ORIGINAL ARTICLE

Simulation of A Gastric Smooth Muscle Cell Model Utilizing the Electrophysiological Parameters of Colon Cell

Hossein Taghadosi [1], Farhad Tabatabai Ghomsheh [2*], Aydin Farajidavar [3]

[1] *Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran*

[2] *Pediatric Neurorehabilitation Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran*

[3] *Department of Electrical and Computer Engineering, New York Institute of Technology, Old Westbury, New York, USA*

*Corresponding Author: Farhad Tabatabai Ghomsheh
Email: fa.tabatabai@uswr.ac.ir

Received: 2022 April 03/ Accepted: 2022 June 15

Abstract

Purpose: Mathematical simulating and computer modeling of cells in organs help to better understand cells' interactions and tissues' functions. The purpose of this paper was to model and simulate the excitable membrane of gastric cells. In this simulation, the current physiological functional descriptions of the gastric cells have been used, and at the same time, the electrophysiological characteristics of similar cells in the gastrointestinal tract have also been considered.

Materials and Methods: To obtain a mathematical model for the stomach Smooth Muscle Cells (SMCs), the properties and electrophysiological parameters from the SMCs in the colon were used in the simulation of the stomach SMCs. Using the sensitivity analysis method, the effective parameters and values for simulating the electrophysiological behavior of the excitable gastric cell membrane were obtained for different phases of slow-wave (such as Depolarization, Spike, Plateau, Repolarization, and Rest). Also, the Action Potential Duration (APDs) method in four modes of 10, 20, 50, and 90 percent of APDs was used to evaluate the estimation of the effect of sensitivity analysis on the slow-wave of the studied cells.

Results: The findings showed that the greatest effect of the stimulation current parameters was on the slow-wave duration and frequency. In addition, the greatest effect of ion channel parameters was observed on the plateau_phase in the slow-wave. Based on these methods, the resulting slow-wave pattern and its frequency (2.8 cycles per min) were in line with the experimental observations for gastric SMCs.

Conclusion: The mathematical model obtained from the model of colon SMCs accurately represented the electrophysiological behavior of the stomach cells.

Keywords: Gastric Smooth Muscle Cell; Excitable Membrane; Electrophysiological Model; Sensitivity Analysis; Action Potential Duration.

DOI: https://doi.org/10.18502/fbt.v10i3.13148

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Coordinated activity of the enteric nervous system, interstitial cells, and Smooth Muscle Cells (SMCs) results in gastric motility, which is essential for digestion. SMCs are activated by the Interstitial Cells of Cajal (ICCs), which results in the bioelectrical activity of the gut, termed slow-wave [1-3]. Disruption in slow-waves is known to result in functional gastric disorders such as gastroparesis and functional dyspepsia.

Between 60 and 70 million people in the United States suffer from gastrointestinal disorders [4]. In many of these cases, non-surgical evaluation and non-invasive precision techniques can be provided to help with clinical evaluation and electrophysiological analysis [5]. Modeling provides an ideal environment for interpreting *in vivo* recorded information, guiding the experimental studies, and developing hypotheses.

Many researchers have looked into gastrointestinal tissues to provide a variety of electrophysiological, mathematical, and computer simulations for the cells. Lang *et al*. provided a simple mathematical model for the autonomic electrical activity of the SMCs [6], while Skinner *et al*. conducted research on the mechanism of pumps and exchangers in smooth muscle models [7]. Miftakhov *et al*. proposed mathematical formulas for numerical simulation of small bowel movements, and Aliev *et al*. proposed computer simulation of intestinal electrical activity [8, 9]. Corrias and Buist provided an electrophysiological model for gastric SMCs [10, 11]. In another study, Suzuki studied the electrical activity and the production of slow-waves in the stomach and intestines of mice [12]. Rhee *et al*. examined the pacemaker activity of the actual tissue of the human stomach in different parts of the stomach [13]. Poh and Yeoh *et al*. conducted research on the electrophysiological modeling of the SMCs of the jejunum and colon, respectively [14, 15].

For gastrointestinal tract cells, separate electrophysiological models can be designed and presented according to their characteristics. There are billions of cells in the human gastrointestinal tract, the diversity of which is enormous in terms of electrophysiological properties [16]. Providing an electrophysiological model on each of these cells requires extensive laboratory research (such as preparing standard laboratory conditions, patch-clamps technique on human or animal cells, computer simulations, and the use of various mathematical formulas); given that providing these conditions is very time-consuming and costly. To save time and reduce costs, one can deduce the electrophysiological properties of a particular cell from cells with similar characteristics using the sensitivity analysis method.

Sensitivity analysis methods tell us how the uncertainty in the output of a mathematical model can be divided and allocated to different sources of uncertainty in its inputs [14, 17] by considering the output waveform of the SMCs from various experimental works [10, 14, 15], in this paper, we intend to obtain an electrophysiological model of the SMCs from the neighboring cells. This paper shows how the electrophysiological model of SMCs (such as the stomach) can be obtained from similar cells (such as the colon) using the sensitivity analysis method.

2. Materials and Methods

2.1. Cell Model

Due to the structural similarities of the channels, exchangers, and ion pumps in the excitable membranes of the smooth muscles of the stomach and colon, the model proposed in the study by Yeoh *et al*. was selected for our study [15] and electrophysiological parameters were approximated from the colon cell.

Similar electrophysiological parameters were selected to approximate and their values were compared with gastric parameters. These values were optimized using the sensitivity analysis method. With this method, other effective parameters were identified and their effect was investigated on the slow wave curve of the stomach cell. Finally, the Groupe Spécial Mobile (GSM) cell parameters were approximated from the colon cell. Figure 1 shows the intended model of the GSM cells.

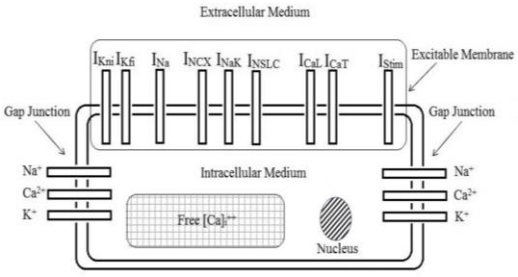

Figure 1. Schematic view of the proposed stomach cell model including calcium (I_{CaL}, I_{CaT}), potassium (I_{Kni}, I_{Kfi}), sodium (I_{Na}) ion channels, sodium-calcium exchanger (I_{NCX}), sodium-potassium pump (I_{NaK}), leakage current (I_{NSLC}), stimulus current (I_{stim}) and gap junction

By examining the slow-wave curve caused by membrane potential changes in both colon [15] and stomach cells [10], it was found that the difference between the two curves is in the slow-wave phases. From following criteria have been used to investigate the differences between the phases of two slow-wave curves: a) initial potential value, b) the slope of depolarization, c) spike potential value, d) valley potential value, e) plateau potential value, f) the slope of the repolarization, g) resting potential value, and h) the duration of the slow-wave cycle [14, 18]. These criteria are shown in Figure 2.

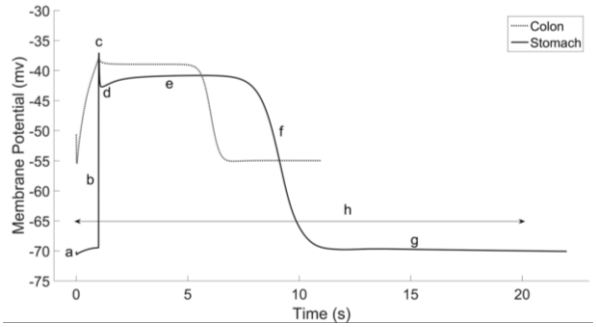

Figure 2. Slow-waves in the colon (dotted line) and stomach (solid line) cells. a) Initial_phase, b) Depolarization_phase, c) Spike_phase, d) Valley_phase, e) Plateau_phase, f) Repolarization_phase, g) Resting_phase, and h) Duration of slow-wave cycle

2.2. Sensitivity Analysis

To investigate the effect of each of the variables (a) to (h), the sensitivity analysis method was used on each of the ion channel parameters, pumps, and exchangers. Sensitivity analysis shows how the model changes with varying parameters [14]. This method reveals which parameters are more important and have a greater impact on model predictions and behavior. Using this method, the value of the effective parameters can be investigated and corrected. In addition, the insignificant and ineffective parameters can be eliminated [17].

Using the sensitivity analysis method on the slow-wave curve of the colon cell, it was investigated that some parameters of ion channels and stimulus current parameters in different parts of slow-wave production have a direct effect on the morphology of the electrical activity [14]. Ion channel and stimulus current parameters of the gastric cell were approximated from the colon cell, and their results are given in sections 3.1 and 3.2, respectively.

2.3. Gastric Excitable Cell Membrane Parameters

Changing electrophysiological properties of the SMC membrane are important factors influencing the formation of action potential and slow-wave occurrence between the two cells. Based on this, the values of the parameters related to the stomach SMCs (Table 1) were considered from the research of Corrias and Buist [9].

2.4. Ionic Current Parameters

In the cell membrane, there are several channels, pumps, and exchangers that are responsible for transporting ions through the cell. By changing the concentration of ions inside and outside the cell, various currents are generated. The main cell current (I_{ion}) has been resulted from all of these ionic currents passing through the cell membrane (Equation 1) [15]. The formula used for the

Table 1. Stomach SMC parameters [10]

Parameter	Description	Value(Units)
$[Ca^{2+}]_o$	Extracellular_calcium_concentration	2.5(mM)
$[Na^{+}]_i$	Intracellular_sodium_concentration	10(mM)
$[Na^{+}]_o$	Extracellular_sodium_concentration	137(mM)
$[K^{+}]_i$	Intracellular_potassium_concentration	164(mM)
$[K^{+}]_o$	Extracellular_potassium_concentration	5.9(mM)
V_m	Membrane potential	-70(mM)
C_m	Cell_membrane_capacitance	77(pF)
V_c	Cell_volume	3.5(pL)
A_c	Cell_surface_area	0.000041(cm^2)

model is as follows and the specifications for each current are given in Table 2 [15].

$$I_{ion} = I_{Kni} + I_{Kfi} + I_{CaL} + I_{CaT} + I_{Na} + I_{NCX} + I_{NaK} + I_{NSLC} \quad (1)$$

The ionic currents used in this paper are based on the currents of the colon SMC, due to the structural similarity of the excitatory membrane of the cells in the smooth muscles that exist throughout the gastrointestinal tract. For this model and according to the currents in the colon cell membrane, two types of potassium channel, two types of calcium channel, one type of sodium channel, one pump, one exchanger, one leakage channel, and one stimulus current were considered.

In Equation 2, the SMC membrane of the stomach for the model was introduced as an electronic circuit, including the total current (I_{total}) of the cell (summation of the current of all ion channels (I_{ion}) and the stimulus current (I_{stim})) [19]. Stimulus current is considered the current generated by the ICC network [15].

$$I_{total} = I_{ion} + I_{stim} \quad (2)$$

The Hodgkin-Huxley formula (Equation 3) was used to calculate changes in membrane potential (V_m) over time. Here C_m is the cell membrane capacitance.

$$\frac{dV_m}{dt} = -\frac{I_{total}}{C_m} \quad (3)$$

2.5. Sensitivity Analysis of Electrophysiological Behaviors of the Excitable Membrane of the Gastric Cell

In this simulation, first, the electrophysiological parameters of the gastric cell were placed in the colon model. Then a modified colon model was simulated by sensitivity analysis of stimulation current and was considered as the Primary-State (P-S). The approximate model close to the stomach model was obtained by re-optimizing the parameters and was considered as the Middle-State (M-S). Finally, the electrophysiological behavior of the gastric cell (stomach model) was obtained by correcting the gating and stimulus parameters of the ion channels and was considered as the Final-State (F-S).

2.6. Quantitative Analysis of the Action Potential

To describe the quantitative changes in each of the slow-wave curve segments, the parameters were considered in order of importance, as shown in Figure 3.

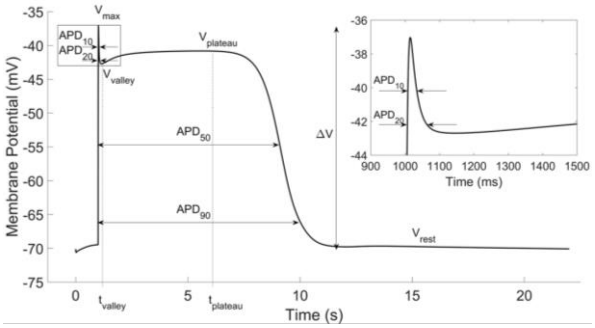

Figure 3. Effective parameters in slow-wave. V_{max}: Maximum membrane potential value in the spike_phase, V_{valley}: Minimum membrane potential value in the valley_phase, t_{valley}: Time of occurrence of the V_{valley}, $V_{plateau}$: Maximum membrane potential value in the plateau_phase, $t_{plateau}$: Time of occurrence of the $V_{plateau}$, V_{rest}: Minimum membrane potential value after the repolarization_phase, ΔV: Difference between V_{max} and V_{rest}, Action Potential Duration (APD_{10}, APD_{20}, APD_{50}, APD_{90}): The time duration that the voltage remains above a certain APD's line

Table 2. Ionic currents of the Colon SMC [15]

Ion Current	Description (Units)
I_{ion}	Main Current Cell (pA)
I_{Kni}	Non-inactivating Potassium Channel (pA)
I_{Kfi}	Fast-inactivating Potassium Channel (pA)
I_{CaL}	L-type Calcium Channel (pA)
I_{CaT}	T-type Calcium Channel (pA)
I_{Na}	Sodium Channel (pA)
I_{NCX}	Sodium-Calcium Exchanger (pA)
I_{NaK}	Sodium-Potassium Pump (pA)
I_{NSLC}	Non-selective Leakage Current (pA)

The maximum value of membrane potential (V_{max}) occurs at spike_phase after passing depolarization_phase, and immediately the membrane potential experiences a limited drop to V_{valley} at time t_{valley}. Then the wave enters the plateau_phase, during which it increases to a maximum of $V_{plateau}$ at the time of $t_{plateau}$. It then goes through the repolarization_phase and reaches the minimum membrane potential at the V_{rest}. Also, (ΔV) is the difference between the maximum and minimum membrane potentials.

Action Potential Duration (APD) is the duration of time that the voltage stays above a certain line$_x$. To calculate APD$_x$, the ΔV is divided into ten equal parts. Then, the duration above the line$_x$ is reported [20, 21]. Its concept is shown in Figure 3 for APDs 10, 20, 50, and 90. To analyze the different_phases in slow-wave, it is necessary to compare all three states (Table 3).

Table 3. Three states intended for comparison

State (Abbreviation)	Description
Primary-State (P-S)	Modified Colon
Middle-State (M-S)	Approximation
Final-State (F-S)	Stomach

Two cases have been used to compare the three models mentioned in the text. Case1: Comparison between (P-S) and (M-S). Case 2: comparison between (P-S) and (F-S).

3. Results

3.1. Ion Channel Parameters

The values for each parameter of the ion channels of the colon cell have been varied using the sensitivity analysis method from initial_values (colon) [15] to middle_values (approximation) and final_value (stomach) to match the slow-wave shape of the stomach cell. The results of changing each of these parameters are given in Figure 4 and Table 4.

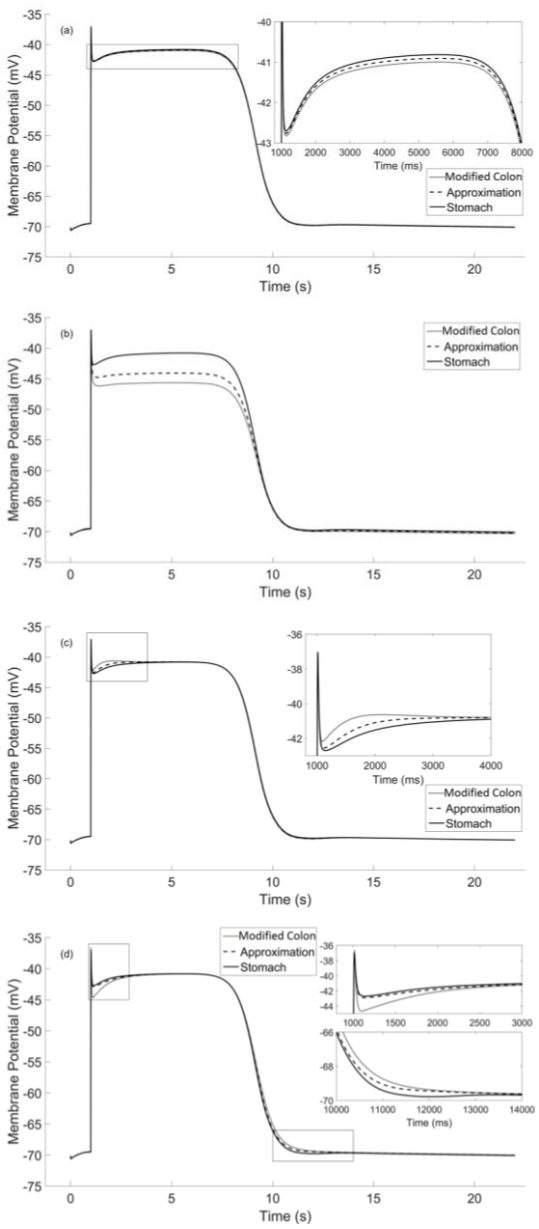

Figure 4. Changes in maximum_conductance and time_constant coefficients of the ion channels by Sensitivity analysis for Modified Colon (dotted line), Approximation (dashed line), and Stomach (solid line). a) G_{Kni}: Maximum_conductance of $Channel_{Kni}$. b) G_{CaL}: Maximum_conductance of $Channel_{CaL}$. c) τ_{f-po}: Time_constant_coefficient of $Channel_{Kfi}$. d) τ_{d-CaT}: Time_constant_coefficient of $Channel_{CaT}$

Table 4. Effective ion channel parameters in three states (Modified Colon, Approximation, and Stomach)

Parameter (Units)	Description	P-S [15]	M-S	F-S
G_{Kni}(nS)	Maximum_conductance of $Channel_{Kni}$	40	39.5	39
G_{CaL}(nS)	Maximum_conductance of $Channel_{CaL}$	8.3	5.325	2.35
τ_{f-po}(-)	Time_constant_coefficient of $Channel_{Kfi}$	0.388	0.744	1.1
τ_{d-CaT}(-)	Time_constant_coefficient of $Channel_{CaT}$	0.044	0.472	0.9

As can be seen in Figure 4, the variables G_{Kni}, G_{CaL}, $\tau_{f\text{-}po}$, and $\tau_{d\text{-}CaT}$ influence the membrane potential value, the plateau_phase value, the valley_phase value, and the resting potential value of slow-wave, respectively.

The highest percentage of influence on properties of slow-waves from modifying G_{Kni}, G_{CaL}, $\tau_{f\text{-}po}$, and $\tau_{d\text{-}CaT}$ are shown in Table 5. Columns 1 to 3 show the affected properties from the highest to lowest, respectively. For example, when changing $\tau_{f\text{-}po}$ from the P-S to M-S, the $t_{plateau}$ changes more than 100% compared to P-S. These changes for APD_{10} and t_{valley} are 9.6% and 2.2%, respectively.

According to Table 5, the highest effect of ion channel parameters in both cases (Case1 and Case 2) is on *APD* during slow-wave's spike_phase, and then on $t_{plateau}$, and finally, on t_{valley} and V_{valley}.

Figure 4a shows that the G_{Kni} parameter has a small effect (≤1%) on $V_{plateau}$, V_{max}, and V_{valley} in case1 and case2. The greatest effect of 0.1mV (≤1%) decrease in case1 and 0.2mV (≤1%) decrease in case2 on $V_{plateau}$ was obtained. Figure 4b shows the changes of G_{CaL} increased APD_{20} by 14ms (30.4%) in case1 and increased the spike_phase by 7060ms (≥100%) in case2. Figure 4c shows the changes of $\tau_{f\text{-}po}$ greatly increased $t_{plateau}$ by 3164ms (≥100%) in case1 and increased $t_{plateau}$ by 3469ms (63.3%) in case2 and decreased APD_{10} by 2ms (6.9%) in the spike_phase in both cases. Figure 4d shows the changes of $\tau_{d\text{-}CaT}$ increased APD_{20} by 6635ms (≥100%) in case1 and increased 6619ms (≥100%) in case2. Also, it increased APD_{10} by 6ms (30%) in case1 and increased by 7ms (35%) in case2. Modification of $\tau_{d\text{-}CaT}$ has a small effect on V_{valley} by 0.5mV in both cases.

3.2. Stimulus Current

Stimulation current affects the total current of cells, which in turn efficacy of the formation of slow-wave. For this purpose, a colon stimulation current was used, which is very similar to a gastric cell in terms of electrophysiological properties.

To extract the gastric slow-wave, the values of each of the colon cell stimulation current parameters were varied using the sensitivity analysis method from the initial_value (colon) to the middle_values and the final_value (stomach). The results of changing each of these parameters on a slow-wave pattern are given in Figure 5 and Table 6.

As can be seen in Figure 5, the variables V_{rest}, t_{slope}, t_1, and t_2 influence the amplitude of slow-wave, the slope of the repolarization_phase, the duration of the plateau_phase, the slope of the depolarization_phase, respectively.

The highest percentage of influence on properties of slow-waves from modifying V_{rest}, t_{slpoe}, t_1, and t_2 are shown in Table 7. Columns 1 to 3 show the affected properties from the highest to lowest, respectively. For example, when changing V_{rest} from the P-S to M-S, the APD_{20} changes more than 100% compared to P-S. These changes for APD_{10} and V_{max} are 28.2% and 20.8%, respectively.

Table 7 shows that the greatest effect of stimulus current parameters in both cases is on the *APD* in the spike_phase and repolarization_phase. The second greatest effect is on $t_{plateau}$ and $V_{plateau}$. Finally, the stimulus current parameters have a great effect on V_{max}.

Table 5. Comparison of change in slow-wave properties based on the ion channel parameters in three states (Modified Colon, Approximation, and Stomach)

Parameter	Case1: M-S vs. P-S			Case2: F-S vs. P-S		
	1st	2nd	3rd	1st	2nd	3rd
τ_{f-po}	$t_{plateau}$ ≥100%	APD_{10} 6.9%	t_{valley} 2.2%	$t_{plateau}$ 63.3%	APD_{10} 6.9%	$\mathbf{t_{valley}}$ 4.5%
τ_{d-CaT}	APD_{20} ≥100%	APD_{10} 30%	V_{valley} 3.4%	APD_{20} ≥100%	APD_{10} 35%	$\mathbf{V_{valley}}$ 4.4%
G_{Kni}	$V_{plateau}$ ≤1%	V_{max} ≤1%	V_{valley} ≤1%	$V_{plateau}$ ≤1%	V_{max} ≤1%	$\mathbf{V_{valley}}$ ≤1%
G_{CaL}	APD_{20} 30.4%	t_{valley} 5.2%	APD_{10} 4.3%	APD_{20} ≥100%	t_{valley} 18.6%	$\mathbf{APD_{10}}$ 17.4%

Figure 5a shows the changes of V_{rest} increased APD_{20} by 2856ms (≥100%) in case1 and 7082ms (≥100%) in case2. These changes also, increased APD_{10} by 4ms (28.2%) and 13ms (92.9%) in case1 and case2, and decreased V_{max} by 5.4mV (20.8%) and 10.9mV (42.1%) in case1 and case2, respectively. Figure 5b shows the changes of t_{slope} decreased $t_{plateau}$ by 962ms (13.1%) and 1755ms (23.9%) in case1 and case2, respectively. These changes also decreased APD_{20} by 262ms (3.4%) in case1 and 524ms (6.7%) in case2. Figure 5c shows the changes of t_1 increased APD_{20} by 1508ms (36.8%) and 3012ms (73.6%) in case1 and case2, respectively. These changes also increased $t_{plateau}$ by 1085ms (32.5%) and 2258ms (67.7%), increased APD_{50} by 1500ms (29.9%)

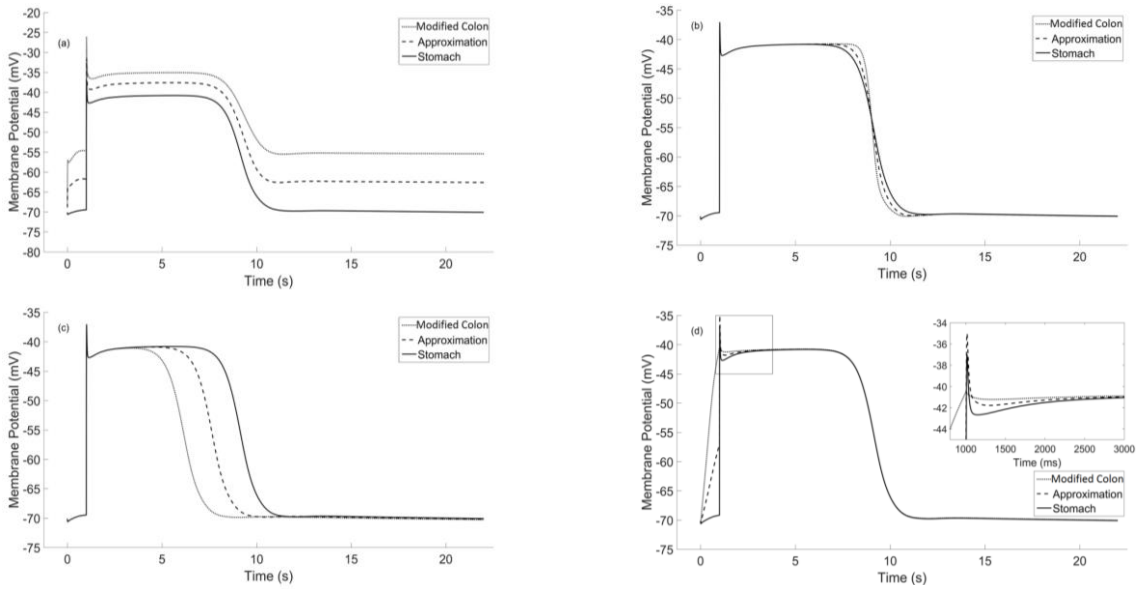

Figure 5. Changes in stimulus current parameters by Sensitivity analysis for Modified Colon (dotted line), Approximation (dashed line), and Stomach (solid line). a) V_{rest}: Resting potential, b) t_{slpoe}: Repolarization_phase gradient, c) t_1: Plateau_phase Duration, and d) t_2: Depolarization_phase gradient

Table 6. Effective stimulus current parameters in three states (Modified Colon, Approximation, and Stomach)

Parameter (Units)	Description	P-S [15]	M-S	F-S
V_{rest}(mV)	Resting potential	-62.8	-75.8	-88.8
t_{slpoe}(ms)	Depolarization_phase gradient	0.2	0.35	0.5
t_1(ms)	Duration of the plateau_phase	6	7.5	9
t_2(ms)	Repolarization_phase gradient	1	30	100

Table 7. Comparison of change in slow-wave properties based on the stimulus current parameters in three states (Modified Colon, Approximation, and Stomach)

Parameter	Case1: M-S vs. P-S			Case2: F-S vs. P-S		
	1st	2nd	3rd	1st	2nd	3rd
V_{rest}	APD_{20} ≥100%	APD_{10} 28.2%	V_{max} 20.8%	APD_{20} ≥100%	APD_{10} 92.9%	$\mathbf{V_{max}}$ 42.1%
t_{slpoe}	$t_{plateau}$ 13.1%	APD_{20} 3.4%	APD_{90} 3.1%	$t_{plateau}$ 23.9%	APD_{20} 6.7%	$\mathbf{APD_{90}}$ 6.3%
t_1	APD_{20} 36.8%	$t_{plateau}$ 32.5%	APD_{50} 29.9%	APD_{20} 73.6%	$t_{plateau}$ 67.7%	$\mathbf{APD_{50}}$ 59.8%
t_2	APD_{10} 99.6%	APD_{20} 14.3%	V_{max} 13.6%	APD_{10} 99.6%	APD_{90} 9.5%	$\mathbf{V_{max}}$ 8.5%

and 3001ms (59.8%) in case1 and case2, respectively. Figure 5d shows the changes of t_2 decreased APD_{10} by 7232ms (99.6%) and 7235ms (99.6%), and increased V_{max} by 5.5mV (13.6%) and 1.9mV (8.5%) in case1 and case2, respectively.

The parameter determining the time of occurrence of a slow-wave per minute is one of the most important parameters in the stimulus current. The period of slow-wave in the colon is approximately 5 cycles-per-minute (cpm) [15], while the period in the stomach is 3 cpm [10]. By changing the t_{period} during stimulation current from the P-S value of 11.8 milliseconds to the M-S value of 17.15 milliseconds and the F-S value of 22.5 milliseconds, this rate decreases to less than 3 cpm (Table 8), which is approximately according to laboratory results [10] for gastric cells (Figure 6).

Table 8. Repeat interval of a slow-wave cycle (cpm: cycles-per-minute) in three states (Modified Colon, Approximation, and Stomach)

State	P-S	M-S	F-S
t_{period}	11799 (ms) 5.1 (cpm)	17150 (ms) 3.5 (cpm)	22500 (ms) 2.8 (cpm)

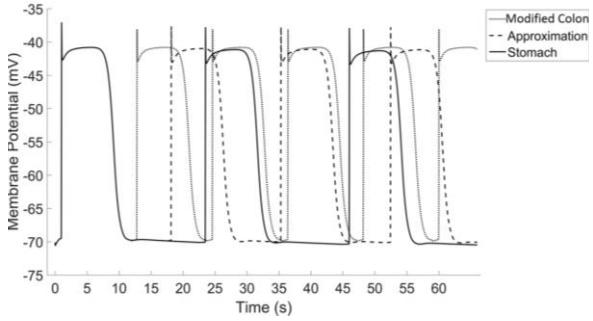

Figure 6. The time difference between repeating a slow-wave cycle by Sensitivity analysis for Modified Colon (dotted line), Approximation (dashed line), and Stomach (solid line)

4. Discussion

The purpose of this study is to obtain the electrophysiological models of a specific cell, i.e., stomach SMC, from another type of cell (colon SMC), which has similar properties and characteristics. We were able to extract the parameters of the gastric cell using the sensitivity analysis method.

Despite the wide variety in the family of gastrointestinal cells, these cells have structural similarities and similar properties, such as the existence of similar SMCs, common ion channels, and similar electromechanical movements [22]. The model obtained in this study was validated using the available data and models, and compared with the electrophysiological patterns of the SMC of the stomach [10].

In similar research, it seems that the reasons for selecting, simplifying, or eliminating some factors are as follows: 1) The parameters did not change much on the different_phases of he slow-wave diagram resulting from the changes in membrane potential. 2) The parameters did not have a significant effect on APD. 3) Quantitative and sufficient empirical information on the characteristics of SMCs has not been available to researchers.

In different species of animals, significant differences between tissues in the gastrointestinal tract have been reported in terms of slow-wave shape and frequency, which have been attributed to different underlying cellular mechanisms [10]. Because the classification of all GI cells is tedious and may not be possible [23], it is suggested to use inferential approaches to obtain mathematical models for each cell. The principles discussed in this paper can be used to deduce the electrophysiological behaviors of other stomach cells.

The difference between this work and other publications on stomach SMC modeling is using electrophysiological estimation and approximation approach to similar cells and optimizing cell parameters, as the same results were obtained at the outputs of the slow-wave curve in the stomach. Using the sensitivity analysis method and finding the effective parameters of the channels and the stimulus current, one middle-model of transition from the colon to gastric conditions were obtained. Then, reusing this method and modifying the effective parameters of ion channel current and stimulation of the final gastric model was achieved.

The presence of chloride currents in the SM (Smooth Muscle) gastrointestinal tract has not yet been fully explained [10] and we, therefore, did not consider the chlorine channel, which could be the basis for future research on the effect of chlorine current on the stomach slow-wave.

As shown in Figure 4, the L-type calcium and potassium channels appear to play a significant role in determining the plateau_phase. However, the effect of L-type calcium channel is greater and its changes cause the plateau_phase displacement of about 5mV,

while the I_{Kni} shows changes of about 0.5mV on the plateau_phase.

Based on the results which are shown in Figure 5, it seems that the parameters of stimulus current have a greater effect on the duration of phases and the slope of depolarization and repolarization_phases (Figure 5b, d). In the plateau_phase, the rate of membrane potential changes is controlled by the potassium and calcium ions (Figure 4a, b). Similarly, the t_1 increases the duration of the plateau_phase (Figure 5c) and the t_{period} prolongs the time of occurrence of a slow-wave cycle (Figure 6).

According to Table 5, it appears that the L-type calcium current, in addition to the potential changes in the membrane of the plateau_phase, has been very effective in the APD created in the spike_phase and has increased the APD. The parameters $\tau_{f\text{-}po}$ and $\tau_{d\text{-}CaT}$ are also very effective in the_phases of the valley and the plateau and the time of their occurrence, they are also very effective on the APD in the spike_phase and have significantly increased it. According to Table 7, the V_{rest} parameter is very influential on the spike_phase APDs. It also has a moderate effect on the membrane potential difference due to the difference in voltage value in the spike_phase and the resting_phase. Parameter t_{slope} has the greatest effect at the time of occurrence of the plateau membrane potential, and t_1 has a moderate effect on the APD of the spike_phase and the middle part of the repolarization_phase due to changes in the duration of the plateau_phase. Parameter t_2 is very effective on the APD_phase of the spike. It seems to be due to the short time and value of the potential of the spike_phase and the lack of a valley_phase in the slow-wave curve of the colon cell, as well as increase in the depolarization_phase rate in the other two curves. It should be noted that t_{period} is the most important parameter among the stimulus current parameters because it affects the number of slow-wave cycles in one minute. In the colon, a slow-wave occurs at the rate of 5 cpm [15], while the rate in the stomach is 3 cpm [24].

In the future, this approach will provide a way to develop neural and hormonal interventions in electrophysiological behaviors of modeled cells by considering neural cell parameters. The development of a complementary ICC model and subsequently combining it in the simulation of multicellular tissue levels allows for a better understanding of the underlying mechanisms of electrophysiological abnormalities seen in arrhythmias and other gastric disorders [10, 25]. Modeling helps to provide a physiological mechanism for gastric arrhythmias and other gastric disorders in addition to a tool for predicting the pathological prognosis and a better understanding of the electrophysiological behavior of gastric cell membranes. Although the results presented here follow empirical data, much work needs to be done to establish the electrophysiological models of the stomach as a reliable tool for examining the pathophysiological aspects of this tissue in the same way as for the heart [7, 26-28].

The development of gastrointestinal cell modeling in combination with biometric measurements [29, 30] can be the basis for the control algorithms embedded in modern closed-loop electrical stimulator devices for the stomach [2, 3, 31].

5. Conclusions

Using the sensitivity analysis method and the approach of matching the electrophysiological function, it is possible to obtain the electrophysiological model for the gastric cell from the colon cell with relatively high similarity, which indicates the physiological behavior of the excitable membrane of the gastric cell. In addition, this method can be used to model other cells of the gastrointestinal tract.

Acknowledgements

We are grateful to Dr. J. w. Yeoh and Dr. M. L. Buist for their insight. The authors received no financial support for the research, authorship, and publication of this article.

References

1- Aydin Farajidavar, "Bioelectronics for mapping gut activity." *Brain Research*, Vol. 1693pp. 169-73, (2018).

2- Amir Javan-Khoshkholgh *et al.*, "System and methodology to study and stimulate gastric electrical activity in small freely behaving animals." *Bioelectronics in Medicine*, Vol. 2 (No. 3), pp. 127-38, (2019).

3- Amir Javan-Khoshkholgh and Aydin Farajidavar, "Simultaneous Wireless Power and Data Transfer: Methods to Design Robust Medical Implants for Gastrointestinal Tract." *IEEE Journal of Electromagnetics, RF and Microwaves in Medicine and Biology*, (2021).

4- ML Buist, LK Cheng, R Yassi, LA Bradshaw, WO Richards, and AJ Pullan, "An anatomical model of the

gastric system for producing bioelectric and biomagnetic fields." *Physiological Measurement*, Vol. 25 (No. 4), p. 849, (2004).

5- Gary Tse, Eric TH Lai, Alex PW Lee, Bryan P Yan, and Sunny H Wong, "Electrophysiological mechanisms of gastrointestinal arrhythmogenesis: lessons from the heart." *Frontiers in Physiology*, Vol. 7p. 230, (2016).

6- RJ Lang, C Rattray-Wood, and ME Holman, "A simple mathematical model of spontaneous electrical activity in a single smooth muscle cell." *Japanese Journal of Pharmacology*, Vol. 58p. 371P, (1992).

7- FK Skinner, CA Ward, and BL Bardakjian, "Pump and exchanger mechanisms in a model of smooth muscle." *Biophysical Chemistry*, Vol. 45 (No. 3), pp. 253-72, (1993).

8- Rubin R Aliev, William Richards, and John P Wikswo, "A simple nonlinear model of electrical activity in the intestine." *Journal of Theoretical Biology*, Vol. 204 (No. 1), pp. 21-28, (2000).

9- RN Miftakhov, GR Abdusheva, and J Christensen, "Numerical simulation of motility patterns of the small bowel. 1. Formulation of a mathematical model." *Journal of Theoretical Biology*, Vol. 197 (No. 1), pp. 89-112, (1999).

10- Alberto Corrias and Martin L Buist, "A quantitative model of gastric smooth muscle cellular activation." *Annals of Biomedical Engineering*, Vol. 35 (No. 9), pp. 1595-607, (2007).

11- Alberto Corrias and Martin L Buist, "Quantitative cellular description of gastric slow wave activity." *American Journal of Physiology-Gastrointestinal and Liver Physiology*, Vol. 294 (No. 4), pp. G989-G95, (2008).

12- Hikaru Suzuki, "Cellular mechanisms of myogenic activity in gastric smooth muscle." *The Japanese journal of physiology*, Vol. 50 (No. 3), pp. 289-301, (2000).

13- Poong-Lyul Rhee *et al.*, "Analysis of pacemaker activity in the human stomach." *The Journal of physiology*, Vol. 589 (No. 24), pp. 6105-18, (2011).

14- Yong Cheng Poh, Alberto Corrias, Nicholas Cheng, and Martin Lindsay Buist, "A quantitative model of human jejunal smooth muscle cell electrophysiology." *PloS One*, Vol. 7 (No. 8), p. e42385, (2012).

15- Jing Wui Yeoh, Alberto Corrias, and Martin L Buist, "Modelling human colonic smooth muscle cell electrophysiology." *Cellular and Molecular Bioengineering*, Vol. 10 (No. 2), pp. 186-97, (2017).

16- Harvey Lodish, Arnold Berk, S Lawrence Zipursky, Paul Matsudaira, David Baltimore, and James Darnell, "Molecular cell biology 4th edition." *National Center for Biotechnology Information, Bookshelf*, Vol. 9(2000).

17- Terry Bahill, Bioengineering--biomedical, Medical, and Clinical Engineering. *Prentice Hall*, (1981).

18- Peter J Blair, Poong-Lyul Rhee, Kenton M Sanders, and Sean M Ward, "The significance of interstitial cells in neurogastroenterology." *Journal of Neurogastroenterology and Motility*, Vol. 20 (No. 3), p. 294, (2014).

19- Alan L Hodgkin and Andrew F Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve." *The Journal of physiology*, Vol. 117 (No. 4), p. 500, (1952).

20- Ursula Ravens *et al.*, "Application of the RIMARC algorithm to a large data set of action potentials and clinical parameters for risk prediction of atrial fibrillation." *Medical & Biological Engineering & Computing*, Vol. 53 (No. 3), pp. 263-73, (2015).

21- Yvonne Richter, Pedro G Lind, and Philipp Maass, "Modeling specific action potentials in the human atria based on a minimal single-cell model." *PloS One*, Vol. 13 (No. 1), p. e0190448, (2018).

22- Graeme Duthie and Angie Gardner, Physiology of the gastrointestinal tract. *John Wiley & Sons*, (2006).

23- Michael Bárány, Biochemistry of smooth muscle contraction. *Elsevier*, (1996).

24- Gregory O'Grady *et al.*, "Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping." *American Journal of Physiology-Gastrointestinal and Liver Physiology*, Vol. 299 (No. 3), pp. G585-G92, (2010).

25- Gregory O'Grady, Tim H-H Wang, Peng Du, Tim Angeli, Wim JEP Lammers, and Leo K Cheng, "Recent progress in gastric arrhythmia: pathophysiology, clinical significance and future horizons." *Clinical and Experimental Pharmacology and Physiology*, Vol. 41 (No. 10), pp. 854-62, (2014).

26- AR Arshi, M Mahmoudian, and F Tabatabaei, "Bond Graph Modeling of Pharmacodynamic Effect of Group 1A Anti-Arrhythmia Drugs on Ventricular Purkinje Cell Membrane Ionic Channels." *SIMULATION SERIES*, Vol. 33 (No. 1), pp. 407-11, (2001).

27- Ching-hsing Luo and Yoram Rudy, "A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes." *Circulation Research*, Vol. 74 (No. 6), pp. 1071-96, (1994).

28- H Zhang *et al.*, "Mathematical models of action potentials in the periphery and center of the rabbit sinoatrial node." *American Journal of Physiology-Heart and Circulatory Physiology*, Vol. 279 (No. 1), pp. H397-H421, (2000).

29- Aydin Farajidavar, Gregory O'Grady, Smitha MN Rao, Leo K Cheng, Thomas Abell, and JC Chiao, "A miniature bidirectional telemetry system for in vivo gastric slow wave recordings." *Physiological Measurement*, Vol. 33 (No. 6), p. N29, (2012).

30- Niranchan Paskaranandavadivel, Rui Wang, Shameer Sathar, Gregory O'Grady, Leo K Cheng, and Aydin

Farajidavar, "Multi-channel wireless mapping of gastrointestinal serosal slow wave propagation." *Neurogastroenterology and Motility*, Vol. 27 (No. 4), pp. 580-85, (2015).

31- Rui Wang *et al.*, "A miniature configurable wireless system for recording gastric electrophysiological activity and delivering high-energy electrical stimulation." *IEEE journal on emerging and selected topics in circuits and systems*, Vol. 8 (No. 2), pp. 221-29, (2018).