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Electromechanical modeling and simulation of the physiological state of human gastric wall smooth muscle cells

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ABSTRACT

Electromechanical and regular contractions of the smooth muscles of the gastric wall are responsible for grinding, mixing, and propulsion food into the intestines. Lack of proper functioning in contracting the smooth muscle causes digestive disorders. This study aimed to present an electromechanical model for the contraction of smooth muscles of the human gastric wall in the physiological state. In this model, the electromechanical contraction of the smooth muscles is due to the distribution of the electrophysiological slow wave (Due to ionic interaction of cells with extracellular environment and adjacent cells) over 240 cells and 548 links. The results showed that the contraction started at the beginning of the gastric wall and gradually transferred to the end of the wall (pylorus). Also, it was found that the maximum contraction of about 34.7% occurs at the end of the model and near the pyloric sphincter. Finally, the behavior of tissues can be simulated non-invasively using the modeling and their function can be examined under physiological and pathological conditions.

1. Introduction

The mechanical functions of the stomach, including the process of digestion, mixing, and transferring the resulting material to the intestine, play a vital role in the digestive system [1]. Electromechanical contractions of the stomach wall occur due to the distribution of slow waves. In this paper, to better represent the electromechanical contraction of gastric wall muscle used from modeling. This study aimed to simulate and model the electromechanical contractile behavior of

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human gastric wall smooth muscle (HGWSM) in the physiological state by combining two electrophysiological and electromechanical approaches. The electrophysiological approach involves the ionic interactions of each cell with adjacent cells and the extracellular environment and the electromechanical approach involves simulating the behavior of passive and active muscles by elastic and contractile elements, respectively.

Ions transfer occurs through ionic channels, pumps, and exchangers in the presence of electrical and chemical field gradients, which are explained by Ohm's and Fick's laws, respectively [2,3]. Cells interact with the interstitial fluid through their excitable membranes and with neighboring cells through gap junctions. Slow waves are produced by the pacemaker and propagated to adjacent cells [4]. The modeling of gastric wall motility depends on its electrophysiology and electromechanical contractions, which generate peristaltic waves during digestion [5,6]. This wave is produced by pacemaker cells and propagates across the stomach wall (including the corpus, antrum, and pylorus).

Recently, many mathematical studies have been presented on soft tissue contraction in the heart [7,8,9,10] and skeletal muscles [11,12,13]. However, due to the complex structure and function of the gastrointestinal tract, fewer articles have been published to model gastric motility [14]. The production and propagation of electrophysiological stimulation waves in the heart [15], nerve [16], stomach [17,18], and other irritable tissues [19] have been studied by researchers. The electromechanical contractions of the heart tissue were simulated under the electrophysiological wave effects [20]. A tubular model of esophageal peristaltic behavior with mucosal and submucosal layers was presented based on elastic assumptions [21]. An intestinal wall tubular model was proposed considering the Gasser-Ogden-Holzapfel model [22]. Several models have been proposed to simulate intragastric flows based on geometry. These models were simulated assuming deformations independent of the elastic properties of the gastric wall [23]. Food decomposition and digestion in the gastric were studied and simulated using the Euler-Lagrange finite element method [24]. Propagation of slow waves was simulated using CT scan images and electrodes [25]. Diverticulosis stress and strain during colonoscopy have been simulated in the colon [26,27]. Propagation of electric current in the human stomach was presented in the elliptical shape [28]. A cylindrical viscoelastic model was proposed for the gastric muscles based on the electrical pulse [29,30]. The advantage of the present study compared to previous research is considering the electrophysiological interaction of cells with each other and the electromechanical interaction of cells with muscles.

Studies on the electromechanical behaviors of the gastrointestinal tract are of great importance and help to understand the food digestion system. Peristaltic motility of the stomach plays an essential role in the digestion of food, mixing of enzymes, and the propulsion of this content to the intestine [14]. Experimental studies on animals require consideration of a different condition of standardization, calibration, and validation. These researches are costly and time-consuming. Many of these experiments can be summarized using modeling to save time and money.

This paper aimed to model and simulate the physiological state of cells and electromechanical function of the gastric wall smooth muscles. Previous studies have considered the mechanical aspects of muscles and ignored the electrophysiological details of smooth muscles. The novelty of this research compared to previous studies is considering the effect of ion channels, production, and propagation of slow waves on the contraction of smooth muscles of the stomach wall. Using this model, each ion channel can be inhibited by pharmaceutical agents and its effect on slow wave

[31,32,33] and muscle contraction can be investigated in the electromechanical model. In addition, the results of this study can be used in the design of gastric wall implants for secondary stimulation of smooth muscles and improve contractile disorders and dysmotility of gastric muscles [34,35,36,37].

2. Materials and Methods

The electrophysiological behaviors of cells in the neighborhood in the tissue are affected by various factors and conditions. The electrical potential of a cell is the result of ion interaction, connection with adjacent cells, and the extracellular environment. Each of these phenomena has different effects on slow wave production and distribution mechanisms, which can be studied and modeled separately.

Each cell interacts with the extracellular space surrounding it through an excitable membrane [38]. The membrane has several types of mechanisms and channels for each ion. Their electrophysiological performance is completely different from each other. Each of the ion channel receptors in the excitable cell membrane can be sensitive to specific pharmacological factors [39]. Each cell directly connects to the neighboring cells through gap junctions [40]. These connections are also channels between two adjacent cells for the flow of ions [41]. Ions through these channels affect the electrochemical status of adjacent cells [42]. Changes in gap junction characteristics can cause pathological conditions [43]. The ions pass through biological membranes through various mechanisms. The main mechanisms are simple diffusion, channel transport, facilitated diffusion, and active transport [44]. The ion may pass through the membrane at different coefficients under the influence of any of these mechanisms. The passage of ions through excitable channels significantly affects the electrical potential of the membrane sides [2].

Temporal changes in membrane potential can be explained using Eq. (1). This is a nonlinear differential equation with two independent variables. This differential equation is first order and second orders in time and space, respectively. The time rate of change of the cell's electrical potential ($\delta V/\delta t$) is given by Eq. (1) [20,45,46].

$$\frac{\delta V}{\delta t} = \frac{f(V,u)}{C_m} + \nabla(D\nabla V) \quad \textbf{(1)}$$

Where $f(V,u)/C_m$ is the effect of cell interaction with interstitial fluid through the excitable membrane of the cell, $f(V,u)$ is the total ion-exchange currents from the cell membrane, V is the membrane potential, u is the vector of several components of channel activity (activation gating variables and inactivation gating variables) and C_m is the cell capacitance. $f(V,u)$ is a function of all ion currents, ion pump current, exchanger current, leakage current, and excitation current. $f(V,u)$ is described as Eq. (2) [18,20,31,33].

$$f(V,u) = i_{Na} + i_{CaL} + i_{CaT} + i_k + i_{Pump} + i_{Exchanger} + i_{Leakage} + \cdots + I_{stimul} \quad \textbf{(2)}$$

Where i_{Na} is the sodium current, i_{CaL} and i_{CaT} are the L-type and T-type calcium currents, i_k is the potassium current, i_{Pump} is the sodium–potassium pump, $i_{Exchanger}$ is the sodium–calcium exchanger, $i_{Leakage}$ is the leakage current and I_{stimul} is the stimulus current. The stimulus current is considered by Eq. (3) [18,31,33].

$$I_{stimul}(t) = f(t) \quad \textbf{(3)}$$

Where $f(t)$ is a stimulus current applied to the cell as an artificial pacemaker. The rate of Membrane coefficients $\delta u/\delta t$ in Eq. (4) depends on the gating coefficients and the membrane potential of the cell at that time [20].

$$\frac{\delta u}{\delta t} = g(V,u) \quad \textbf{(4)}$$

Where $g(V,u)$ is the electrophysiological function of the ion channel gate. For three-dimensional space, the gradient operator ∇ is described by Eq. (5) [20].

$$\nabla = \frac{\partial}{\partial x} + \frac{\partial}{\partial y} + \frac{\partial}{\partial z} \quad \textbf{(5)}$$

The changes in the electrical potential of the cell due to the ion exchange of the cells with each other through the gap junctions $\nabla(D\nabla V)$ are presented in Eq. (6). The Laplacian vector in the HGWSM model represents the volumetric distribution of the electrical potential of cells in the tissue. This expression can be simplified in the form of Eq. (6) [20,46].

$$\nabla(D\nabla V) = D\nabla^2 V = D(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2})V \quad \textbf{(6)}$$

Where D is the spatial voltage propagation function at any point in the model, ∇ is the gradient operator, and V is the membrane potential [47]. D is the diffusion coefficient of the membrane potential at each point in the gastric tissue and depends on the direction of the fiber. In this model, a homogeneous and isotropic environment is considered. The diffusion coefficient is the same in all directions and indicates the electrophysiological relationship of adjacent cells with each other.

Gastric cell parameters (concentration of sodium, calcium, potassium ions, cell capacitance, and cell volume) were extracted from the gastric study [18]. Each cell was considered a node. Between the nodes, links were assumed as gastric muscle fibers. The electromechanical behavior of each of the links was formed by considering the simultaneous effect of active contraction and passive deformation in interaction with each other. The deformation in HGWSM was due to the distribution of electrical stimulation and tissue elastic behavior. The propagation of the slow wave causes an electromechanical contraction in the structure. Figure 1 shows the HGWSM electromechanical model. This model consists of 240 nodes and 548 links. The cells are arranged next to each other in a rectangular cube structure (six rows, twenty columns, and two floors).

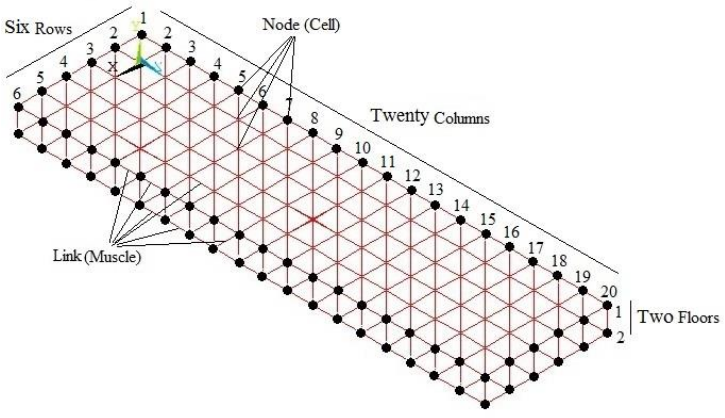

Figure. 1. The HGWSM electromechanical model includes 240 cells (nodes) and 548 muscles (links).

The ionic interactions of each cell with adjacent cells are considered linearly through the gap junctions. Nodes represent the function of cells. Also, nodes cause changes in electrical potential based on electrophysiological exchanges with adjacent cells and the interstitial fluid through their excitable membrane. A simplified Hill's model (Figure 2) was used to describe the electromechanical behavior of links (muscle fibers) in HGWSM. This Hill model consists of the contractile component in series with the elastic component. The elastic and contractile elements model the behavior of passive and active muscles, respectively. Figure 2 shows muscular links between two adjacent cells. Links are models of muscles that can have both active contraction and passive contraction simultaneously.

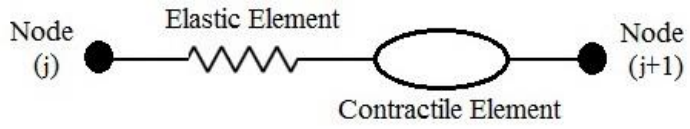

Figure. 2. Simplified Hill model. Nodes (j) and (j+1) symbolize two adjacent cells that are connected by a link. This link contains the elastic element and the contractile element in series.

The HGWSM structure was formed by connecting the links and cells. To simulate the electromechanical behavior of the HGWSM model, the Hill model was added to all muscle fibers. The slow wave propagation causes electromechanical contractions in the contractile element of muscle fibers. The produced contraction force wants to reduce the length of the links, but the connection of links to the neighboring links antagonizes this contraction and a new geometry (concavity in the model) is formed. Finally, the new geometry is the result of the interaction of forces and displacements between all the elements in the HGWSM model.

3. Results

In this paper, the peristaltic behavior of the HGWSM model was presented using electromechanical interaction between cells and muscle fibers. The results of this simulation are similar to the physiological function of the gastric wall. The slow wave distribution causes electrophysiological stimulation of the stomach wall and provides the required contraction movements of the stomach.

Figure 3a shows the results of the slow wave simulation for a single gastric cell. Also, figure 3b shows the results of slow wave simulations on a set of cells along the stomach wall (beginning of the gastric body: BoB, middle of the gastric body: MoB, end of the gastric body: EoB). The electrophysiological wave obtained from the simulation stage included all the phases of the slow wave (initial potential, depolarization, spike, plateau, repolarization, and rest) in Figures 3a for single cell and for HGWSM cells in figure 3b. This wave corresponded to the models of the colon, jejunum, and stomach in terms of phases [18,31,33]. The membrane potential values of the initial, spike, plateau and rest phases were about -70, -36, -42, and -70 millivolts (mV), respectively, which had an acceptable agreement with the potential values of the gastric model membrane [18]. In addition, the result of slow wave propagation on the cell set is consistent with the single-cell model in terms of phases and membrane potential values.

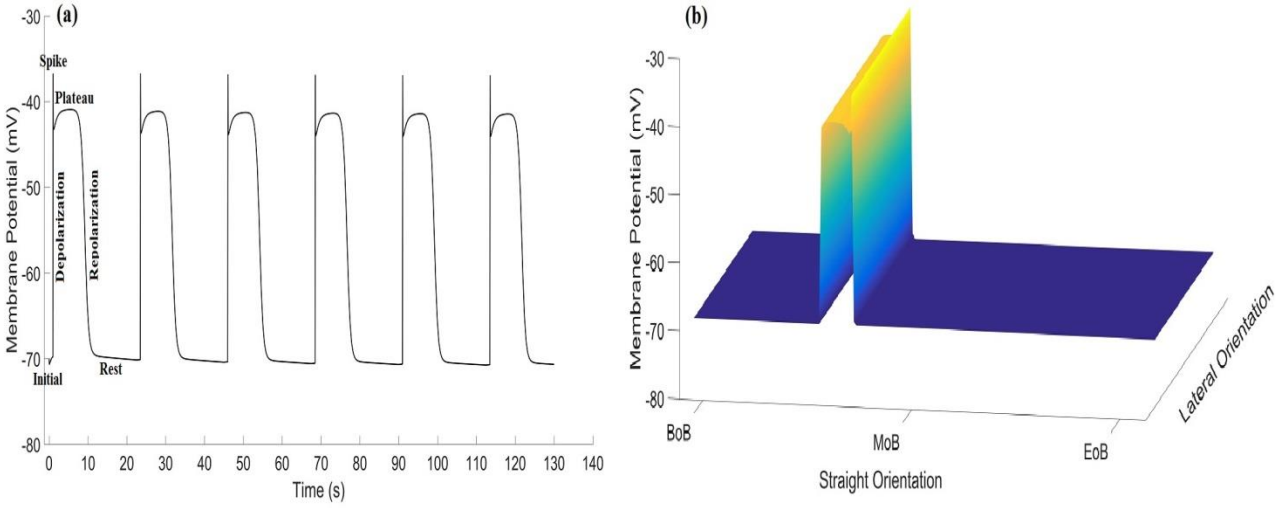

Figure. 3. Slow wave simulations in: a) human gastric smooth muscle cell, b) HGWSM cells between BoB and MoB.

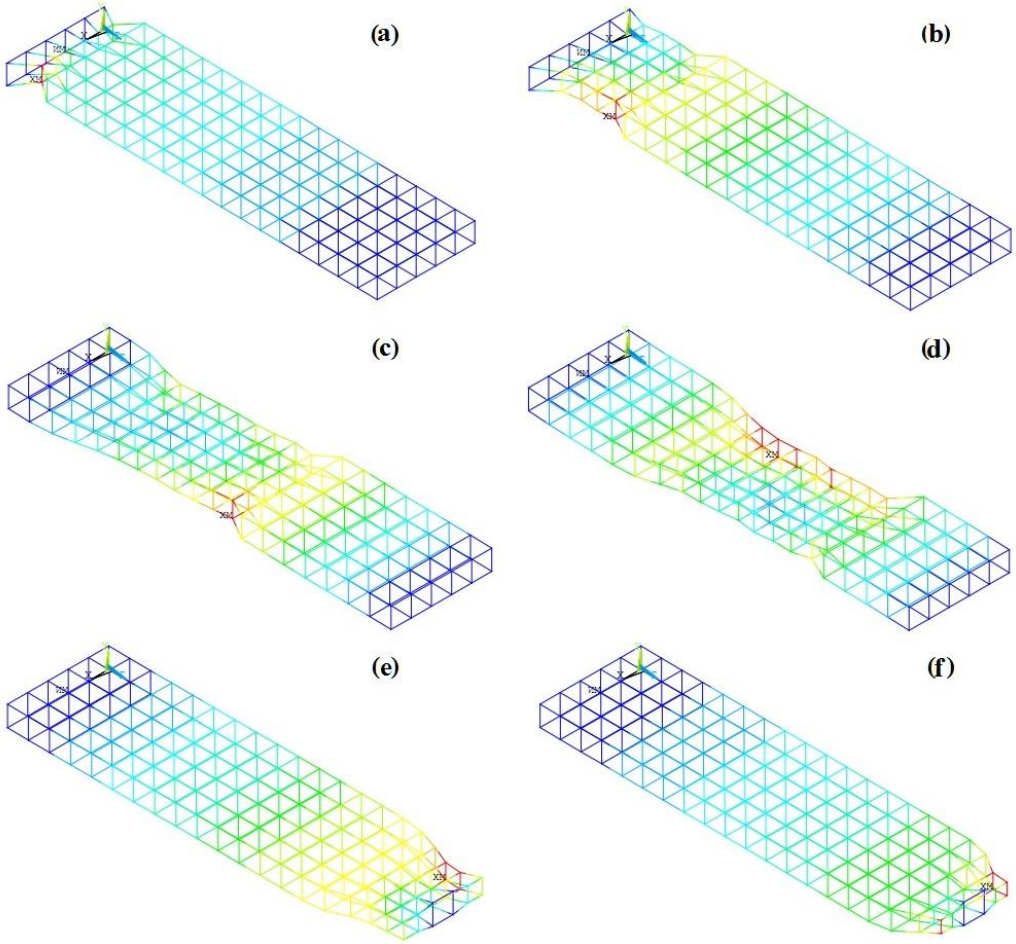

Figure. 4. Electromechanical contraction of HGWSM model: a) Initial Contraction at the beginning of the wall. b) Propagation of contraction at the beginning of the stomach corpus. c) Propagation of contraction at the middle part of the stomach corpus (upper section). d) Propagation of contraction at the middle part of the stomach corpus (lower section). e) Contraction at the antrum. f) End of contraction at the pylorus.

Figure 3a shows the slow wave simulation of a stomach cell in 6 cycles. As it turns out, the slow wave frequency of the stomach cell is about 2.81 cycles per minute. This result was in line with the findings of modeling and laboratory studies on gastric cells [18,48].

The model presented in this paper shows the deformation of HGWSM over several cross-sections during a cycle of gastric activity. The structure of the HGWSM model was considered excitable and flexible. The links in this model have electromechanical interactions with cells. If a link in the model excites and contracts, all links change the length to attain a new equilibrium by interacting with other links.

The simulation results of the HGWSM electromechanical model under physiological conditions are shown in Figures 4a to 4f. The wave of electrical excitation begins in the pacemaker area, located at the junction of the fundus and the corpus (Figure 4a). Figure 4a shows the start of contraction at the beginning of the gastric wall as a concavity in the model. The value of this contraction in the physiological state is about 27.5%. The propagation of contraction along the stomach wall is shown in Figure 4b.

As the slow wave propagates, the contraction reaches the middle of the stomach wall. Figure 4c ,d shows the distribution of contraction in the middle region of the stomach wall in the upper and the lower sections, respectively. While the initial parts of the stomach body have returned to their original state. The stimulus wave continues to propagate in the middle of the body and extends to the antrum and the pylorus. then, the slow wave spreads to the end of the stomach wall to propulsion the contents of the stomach to the pylorus (Figure 4e). Figure 4f shows that the contraction ends at the end of the stomach wall in the pylorus section. This process is repeated at a frequency of 2.81 cycles per minute in the stomach. The results of physiological contraction in different parts of the HGWSM model are given in Table 1.

Table 1. Contraction of the HGWSM model in six parts of the gastric wall in the physiological state.

Parts of the stomach wall	Contraction in physiological state
Initial Contraction at the beginning of the wall	27.5% (Figure 4a)
Propagation of contraction at the beginning of the stomach corpus	21.8% (Figure 4b)
Propagation of contraction at the middle part of the stomach corpus (upper section)	22.3% (Figure 4c)
Propagation of contraction at the middle part of the stomach corpus (lower section)	26.1% (Figure 4d)
Contraction at the antrum	27.7% (Figure 4e)
End of contraction at the pylorus	34.7% (Figure 4f)

The data in Table 1 show that the contraction occurs at the beginning of the gastric body and extends to the middle and end of the gastric body and finally continues to the pyloric sphincter, Where the contents of the stomach are transferred to the beginning of the small intestine. The results showed that the maximum contraction of the gastric muscles in the physiological state at the beginning of the gastric wall is about 27.5% and at the end of the gastric wall (pylorus section) is about 34.7%.

4. Discussion

In this paper, an electromechanical model of HGWSM is presented under the effect of electrophysiological wave propagation. Stimulation was performed by applying the slow wave simulated from the electrophysiological stage of gastric cells on the electromechanical model of

HGWSM. Simultaneous electrophysiological and electromechanical interactions were considered between cells and muscles In this modeling.

The results of electrophysiological modeling of gastric smooth muscle cells showed that the values of the initial potential and the spike potential in the slow wave are about -70 and -36 mV, respectively (Figure 3). These results showed acceptable agreement with previous research [18]. Also, It was consistent with experimental findings from the canine stomach [48]. The slow wave frequency in this simulation was 2.81 cycles per minute (Figure 3a), which is in good agreement with previous research [18,49,50]. While the slow wave frequency in the smooth muscles of the colon and jejunum is about 5 and 6 cycles per minute, respectively [31,33].

The findings of the electromechanical model showed that the distribution of electrophysiological waves is the cause of contraction in the electromechanical model. These results are in line with the findings of modeling wave propagation in the heart tissue [20,51]. The results in the electromechanical model indicated that the contraction occurs at the beginning of the stomach wall, where the slow wave is produced (Figure 4a). In addition, the results showed that less contraction occurs in other parts of the stomach wall than at the beginning and the end of the stomach wall. According to the results of Table 1, it was found that the contraction spreads in the stomach wall and gradually increases towards the end of the stomach wall (from about 21.8% at the beginning of the corpus to 27.7% in the antrum). So that the most contraction occurs at about 34.7% at the end of the stomach, where digested food is pushed into the duodenum and small intestine (Figure 4e, f).

Two-element model of the muscle is considered with the series connection In the electromechanical model. For increased accuracy, a parallel dashpot element can be considered that models the viscous behavior of the muscle. The contractile element behavior in the HGWSM model is linear. The nonlinear behavior of this element can be modeled using more experimental data such as muscle length change rate. The properties of smooth muscle in the stomach (fundus, corpus, antrum, and pylorus) appear to be different [44]. Hence, more realistic results are obtained if different mechanical and anatomical properties are considered for smooth muscle.

In electrophysiological models, the effect of ions on the slow wave can be investigated by blocking the ion channels of smooth muscle cells [32]. Also, It can be examined which ion currents have the greatest effect on the formation of slow waves [52]. Finally, the effect of drug blockers on ion channels can be studied on electrophysiological and electromechanical models.

Using the electrophysiological and electromechanical models of gastric smooth muscle cells can be investigated the behavior of gastric wall muscles. If there are movement and muscle contraction disorders, bioelectronic implants in the stomach wall can be used to generate secondary stimulation. This stimulation forces the muscles to contract to bring the muscle's behavior closer to physiological conditions [34,35,36,37].

In future research and using the results of this study, a three-dimensional anatomical model for the stomach can be made by considering more cells. Since the mechanical properties of gastric tissue are nonhomogeneous and anisotropic [53]. Therefore, by applying mechanical properties to the different parts of the stomach, electromechanical changes can be observed more accurately. If substitute an asymmetric tensor instead of the constant diffusion coefficient, can be studied nonhomogeneous and anisotropic properties of the gastric muscles. In the HGWSM model, the effect of geometric deformation was ignored on the slow wave propagation. Also, interactions of

intragastric fluids were not considered in the HGWSM model. If these interactions are considered in future studies, can observe progress in modeling the gastrointestinal tract and different models can be obtained similar to the heart [54,55,56].

5. Conclusion

Electrophysiological and electromechanical models can simulate the contraction of the smooth muscle of the gastrointestinal tract under various physiological and pathological conditions. The effect of ions on slow wave propagation and tissues contraction can be investigated using these models. The biggest advantage of these models is the non-invasive effect study of ion channels blockade on muscles. By controlling the blockage of ion channels, a pattern for smooth muscle contraction in the physiological state can be obtained and gastrointestinal movement disorders can be brought closer to the physiological state.

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