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A Multiscale Tridomain Model for Simulating Bioelectric Gastric Pacing

Shameer Sathar,

Auckland Bioengineering Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Mark L. Trew,

Auckland Bioengineering Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Greg O'Grady, and

Auckland Bioengineering Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Leo K. Cheng

Auckland Bioengineering Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand; and Department of Surgery, Vanderbilt University, Nashville, TN 37240, USA. Fax: +64 (0) 9 367 7157; Tel: +64 (0) 9 923 7101

Leo K. Cheng: l.cheng@auckland.ac.nz

Abstract

Goal—Gastric motility disorders have been associated with abnormal slow wave electrical activity ('gastric dysrhythmias'). Gastric pacing is a potential therapy for gastric dysrhythmias, however, new pacing protocols are required that can effectively modulate motility patterns, while being power efficient. This study presents a novel comprehensive 3D multi-scale modeling framework of the human stomach, including anisotropic conduction, capable of evaluating pacing strategies.

Methods—A high resolution anatomically realistic mesh was generated from CT images taken from a human stomach. Principal conduction axes were calculated and embedded within this model based on a modified Laplace-Dirichlet rule based algorithm. A continuum based tridomain formulation was implemented and evaluated for performance, and used to model the slow wave propagation, which takes into account the two main cell types present in gastric musculature. Model parameters were found by matching predicted normal slow-wave activity to experimental observation and data. These simulation parameters were applied while modeling an external pacing event to entrain slow wave patterns.

Results—The proposed formulation was found to be 2 times more efficient than a previous formulation for a normal slow wave simulation. Convergence analysis showed that a mesh resolution of $\approx 0.4 - 0.5\text{mm}$ is required for an accurate solution process.

Conclusion—The effect of different pacing frequencies on entrainment demonstrated that the pacing protocols are limited by the frequency of the native propagation and the refractory period of the cellular activity.

Significance—The model is expected to become an important tool in studying pacing protocols for both efficiency and effectiveness.

Index Terms

conduction axes; gastric pacing; multiscale stomach model; tridomain model

I. Introduction

The phasic contractions in the gastrointestinal tract are controlled and coordinated by an electrical activity termed slow waves. Interstitial cells of Cajal (ICC) generate and propagate these events, within a syncytial cell network. These signals in turn activate the adjacent smooth muscle cells (SMC) [1]. In isolation, ICC excite at a unique intrinsic frequency with a decreasing frequency gradient along the antegrade direction of the stomach [2]–[4]. However, in intact *in-vivo* tissue, ICC are entrained to a single frequency corresponding to the highest frequency present, which is critical for a coordinated motility of the GI tract [1], [4]. Depletion and degradation of ICC networks has been implicated in gastric motility disorders such as gastroparesis and slow transit constipation [5]–[8].

Gastric pacing has been investigated as a potential therapeutic tool that can extrinsically entrain and control ICC frequencies, and therefore, it has been used to improve symptoms and motility in cases of gastroparesis [9], [10]. However, active research seeks to determine the most efficient pacing parameters, such as: stimulus location, and pulse amplitude, width, and frequency. At present, such studies require extensive and expensive trial-and-error experiments with animal models [11].

Mathematical models are increasingly successful and robust for in-silico analysis of bioelectric activity, [12], [13] and are therefore a potentially useful tool for investigating slow wave response to stimulation, prior to focused experimental studies [11]. In systems with a single cell type, balancing current conservation between intra and extra-cellular spaces with membrane electrophysiology results in coupled reaction-diffusion equations, commonly referred to as the bidomain equations. These equations capture electrical anisotropies and heterogeneities, and are considered to accurately represent the underlying biophysics [14]. In the cardiac context they have been widely applied to study electrical arrhythmia and their treatment by external stimuli [15].

In gastric electrophysiology, studies have identified sparse gap junctions mediate communication between intermingled ICC and SMC [16], [17]. An alternative to the single cell type and extracellular space bidomain formulation that accounts for the multiple cell types present in the stomach has been recently proposed by Buist and colleagues [18], [19]. However, this “extended-bidomain” formulation results in non-symmetric systems of equations, limiting the choice of efficient and stable linear solvers.

Gastric experimental observations have indicated that there are preferred directions in the spread of electrical activation [20], [21]. Different layers of ICC, ICC-MY (ICC in the myenteric plexus region between the circular muscle (CM) and longitudinal muscle (LM) layer), ICC-IM (intramuscularly within the CM and LM layers), and ICC-SEP (lying in septa between muscle layer bundles) coordinate anisotropic slow wave propagation [21], [22]. In the model equations, mathematically, the morphology of electrical propagation depends on the principal directions of the conductivity tensors. We are not aware of studies that have incorporated electrical anisotropy into studies of electrical activation in the stomach which solely depends on the conductivity parameters. In cardiac electrical studies, anisotropy is determined by the orientation of the local myocyte long axis and other structural features [23], [24]. These orientations are usually extracted from detailed 3D image reconstructions [23] or at the organ scale from MRI-based diffusion tensor imaging [25]. Such image-based methods are largely unexplored in the gastrointestinal field largely due to the resolution and signal-to-noise challenges of imaging the thin gut wall. An alternative to image based extraction of principal directions are rule-based methods [26], [27].

In this study, we present an efficient anatomically realistic human stomach model for simulating bioelectric pacing activity. Importantly, to simulate the effects of pacing protocols on slow wave activity, we introduce a novel multi-cell tridomain formulation of the governing equations such that the resulting finite element discretization is symmetrical, generating positive-definite systems of linear equations that may be efficiently solved. A rule based method was devised to determine principal axes of activation, taking into considerations all layers of ICC activation, and these were introduced into anisotropic conductivity tensors. Finally, for the first time, normal slow wave activity and pacing induced activity has been efficiently simulated in the context of intermingled ICC and SMC cells with anisotropic axes of electrical conduction.

II. Materials and Methods

The Chaste (<http://www.cs.ox.ac.uk/chaste/>) modelling environment was used for all simulations [28].

A. Tridomain formulation

The problem syncytium is divided into three domains. Domain 1 corresponds to the ICC; domain 2 the SMC; and the third domain the extracellular space. The conservation of current in these three domains can be expressed as [18]:

$$\chi^{(1)} \left(\xi^{(1)} \frac{\partial V_m^{(1)}}{\partial t} + I_{ion}^{(1)}(u^{(1)}, \phi_i^{(1)}, \phi_e) \right) - \nabla \cdot (\sigma_i^{(1)} \nabla V_m^{(1)} + \phi_e) + I_{stim}^{(1)} + \chi^{gap} I_{gap} = 0 \quad (1)$$

$$\chi^{(2)} \left(\xi^{(2)} \frac{\partial V_m^{(2)}}{\partial t} + I_{ion}^{(2)}(u^{(2)}, \phi_i^{(2)}, \phi_e) \right) - \nabla \cdot (\sigma_i^{(2)} \nabla V_m^{(2)} + \phi_e) + I_{stim}^{(2)} - \chi^{gap} I_{gap} = 0 \quad (2)$$

$$-\nabla \cdot (\sigma_i^{(1)} \nabla V_m^{(1)}) - \nabla \cdot (\sigma_i^{(2)} \nabla V_m^{(2)}) - \nabla \cdot (\sigma_i^{(1)} + \sigma_i^{(2)} + \sigma_e) \nabla \phi_e = -I^{totalstim} \quad (3)$$

Here $\sigma_i^{(1)}$, $\sigma_i^{(2)}$ and σ_e are the intracellular conductivity tensors for first and second domain, and the extracellular domain respectively. The variables $V_m^{(1)}$, $V_m^{(2)}$ and ϕ_e are transmembrane potential for first and second domain, and extracellular potential; χ^{gap} and I_{gap} are the surface to volume ratio of the space and the associated gap junction current; I_{ion} with superscripts (1) and (2) are the total membrane ionic current flowing between the respective intracellular and extracellular spaces; and ξ is the membrane capacitance per unit area. The total sum of the applied stimuli is $I^{totalstim}$.

The discrete tridomain system of equations in terms of transmembrane potentials of the two domains is obtained as:

$$\begin{bmatrix} \chi^{(1)} \frac{(\xi^{(1)})}{\Delta t} M + K \begin{bmatrix} \sigma_i^{(1)} \end{bmatrix} & 0 & K \begin{bmatrix} \sigma_i^{(1)} \end{bmatrix} \\ 0 & \chi^{(2)} \frac{(\xi^{(2)})}{\Delta t} M + K \begin{bmatrix} \sigma_i^{(2)} \end{bmatrix} & K \begin{bmatrix} \sigma_i^{(2)} \end{bmatrix} \\ K \begin{bmatrix} \sigma_i^{(1)} \end{bmatrix} & K \begin{bmatrix} \sigma_i^{(2)} \end{bmatrix} & K \begin{bmatrix} \sigma_i^{(1)} + \sigma_i^{(2)} + \sigma_e \end{bmatrix} \end{bmatrix} \begin{bmatrix} V_m^{(1)} \\ V_m^{(2)} \\ \phi_e \end{bmatrix} = \begin{bmatrix} \chi^{(1)} \frac{(\xi^{(1)})}{\Delta t} M V_m^{(1)(n-1)} - \chi^{(1)} M I_{ion}^{(1)} + \chi^{(gap)} M I_{gap} - M I_{stim}^{(1)} \\ \chi^{(2)} \frac{(\xi^{(2)})}{\Delta t} M V_m^{(2)(n-1)} - \chi^{(2)} M I_{ion}^{(2)} - \chi^{(gap)} M I_{gap} - M I_{stim}^{(2)} \\ M I^{totalstim} \end{bmatrix} \quad (4)$$

where M is the mass matrix and K is the stiffness matrix.

A linear system is obtained from FEM spatial discretization method on tetrahedral meshes together with semi-implicit time discretizations [29]. This system of equations is symmetric and positive semi-definite, enabling solution using efficient preconditioned conjugate gradient (*cg*) solver. To date a simple *jacobi* preconditioner has been adequate.

B. Convergence and performance analysis

To test numerical convergence and inform the choice of conductivity parameters, electrical activity in a 100 mm long 1D fiber was simulated. A finite-state machine based Corrias and Buist ICC model (FSM ICC-CB) for ICCs [30], [31], and passive cells with zero active ionic current for SMCs were used for membrane currents. A tridomain simulation was performed with solution points at different spatial resolutions ranging from 0.1–2 mm. The experimentally observed propagation pattern of slow wave activity in the human stomach shows a faster circumferential propagation ≈ 8 –13 mm s⁻¹ than the longitudinal propagation ≈ 3 –5 mm s⁻¹, due to anisotropic properties arising from bidirectional coupling in ICC networks [7], [20]. Thus, two separate tests were performed on extreme cases: one for a slower conduction velocity of ≈ 3 mm s⁻¹ and another for conduction velocity of ≈ 13 mm s⁻¹. Approximate conductivity parameters were initially estimated for a 0.1 mm resolution mesh and later assigned to a coarser mesh to identify a suitable mesh resolution. The conduction velocities were noted for both simulations at different spatial resolutions.

The test with conduction velocity of $\approx 3 \text{ mm s}^{-1}$ was evaluated on a previous non-symmetrical formulation [19] and the new tridomain formulation at a spatial resolution of 0.2 mm. The linear system solution iteration count and time spent was analysed for each solution time-step for the best possible linear solver. The simulations used an absolute tolerance value of 10^{-6} mV for the linear solver.

C. Anatomically realistic stomach mesh

An anatomically realistic stomach geometry was obtained from CT images taken from a human patient using the methods described previously [32], [33]. A cubic Hermite finite element mesh was fitted to the digitized 3D outline of the stomach using an iterative fitting method. The surface of the generated surface mesh was projected normally to obtain a realistic muscle layer thickness of 2.66 mm [34].

The stomach geometry volume was discretized into tetrahedral elements delimited by tetrahedral volume constraint and quality constraint using TetGen (<http://tetgen.berlios.de/index.html>) to obtain a suitable computational mesh.

D. Generating principal axes of conduction

A modified Laplace-Dirichlet rule-based algorithm [27] was used to generate principal conduction axes, necessary for simulating the anisotropic properties of gastric slow wave propagation [20]. In this study, the principal conduction axis for slow wave simulation was assumed to be aligned with the main axis of the stomach (the longitudinal direction), with orthogonal transmural and circumferential axes. Four surface segments (S1, S2, S3 and S4) were extracted from the stomach mesh (shown in Fig. 4) and used to prescribe boundary conditions for computing the conduction axes. The surface segments corresponded to the top of the fundus region, the bottom of the antrum region, the outer serosal surface and the inner mucosal surface.

1) Longitudinal axis—The Laplace's equation was solved on the stomach mesh for a scalar quantity ϕ_1 :

$$\nabla^2 \phi_1 = 0 \quad (5)$$

subject to Dirichlet boundary conditions $\phi_1 = 100$ on S1 and $\phi_1 = 0$ on S2 and no-flux boundary conditions otherwise. The resulting nodal ϕ_1 distribution is used to evaluate the gradient of ϕ_1 at the centroids of the tetrahedral elements. The longitudinal or principal conduction axis is then given by:

$$\vec{\phi}_1 = \frac{\nabla \phi_1}{|\nabla \phi_1|} \quad (6)$$

2) Transmural axis—Laplace's equation was solved for a scalar quantity ϕ_2 subject to Dirichlet boundary conditions $\phi_2 = 100$ on S4 and $\phi_2 = 0$ on S3 and no-flux boundary conditions otherwise. The gradients of ϕ_2 were evaluated at the centroids of the tetrahedral elements. The cross-surface axis direction is then given by:

$$\vec{\varphi}_2 = \frac{\nabla \varphi_2}{|\nabla \varphi_2|} \quad (7)$$

3) Circumferential axis—The longitudinal and cross-surface direction were used to obtain the circumferential axis as:

$$\vec{\varphi}_3 = \vec{\varphi}_1 \times \vec{\varphi}_2 \quad (8)$$

4) Conduction axes orientation tensor—The generated direction vectors $\vec{\varphi}_1$, $\vec{\varphi}_2$ and $\vec{\varphi}_3$ are assembled as 3×3 tensor quantity. The rows in the tensor corresponds to $\vec{\varphi}_1$, $\vec{\varphi}_2$ and $\vec{\varphi}_3$ respectively.

E. Normal slow wave activity

In the full scale stomach simulation of normal slow wave activity, the tridomain formulation was used with parameters as shown in Table I, motivated from a previous study [18]. The conductivity parameters reflect the effect of multiple ICC layers and the resulting impact on the conduction velocity. *In-vivo*, the fundus region is devoid of slow waves and each new wave begins in the corpus region [2], [35]. The fundus region was made inactive by assigning passive cells in both intracellular domains with a initial resting membrane potential of -57 mV [2]. Elsewhere, ICC and passive cells were used for intracellular domains 1 and 2 respectively. The initial V_m value were set to -67 mV for both domains.

The pacemaker region was localized to the greater curvature region just below the fundus, with an intrinsic pacing frequency of $3 \text{ cycles min}^{-1}$ initiated by setting t_{start} parameter of the FSM-ICC CB model to 0 [30]. The t_{start} value was set at all other locations to a larger value, and were therefore entrained by the activity from the pacemaker region. An intrinsic frequency gradient was assigned in the antegrade direction with the frequency values linearly varying from 3 (pacemaker region) to 1.5 (antrum) cycles min^{-1} [3]. The frequency was varied using the non-refractory period parameter of the ICC cell model. The refractory period for the cell model was approximately 10 s for an $[IP3]$ value of 0.0006 mM . Therefore, the non-refractory periods corresponding to $3 \text{ cycles min}^{-1}$ and $1.5 \text{ cycles min}^{-1}$ were evaluated to be 10 s and 30 s respectively. The ODE solver (for the FSM ICC-CB model) time step was set to 0.1 ms and PDE solver time-step was set to 1 ms, a selection based on a convergence analysis to obtain a stable solution.

F. Gastric pacing

Gastric pacing was initiated at the antrum region (indicated in Fig. 5). The pacing was induced extracellularly with amplitude 5 mA cm^{-3} , pulse width 200 ms and frequency of $4 \text{ cycles min}^{-1}$, consistent with established human pacing protocols [9], [10]. The cathode and anode were separated by ≈ 10 mm and were aligned parallel to the circular muscle fibre direction as shown in Fig. 4.

III. Results

A. Convergence and performance analysis

Convergence analysis showed that a more refined mesh was required to capture the slower conduction velocity compared to the higher conduction velocity. Fig. 1 shows that a minimum resolution of $\approx 0.4 - 0.5$ mm was required to accurately represent the slow longitudinal component of the gastric slow wave activity.

The linear solution performance for the tridomain equations (1, 2, 3) was compared to an earlier formulation known as the extended bidomain [19]. The number of iterations and the solving time was reduced by approximately 50% as shown in Fig. 2a and Fig. 2b. The mean linear solver iterations were seen to be 382 and 174 for extended bidomain formulation and tridomain formulation respectively, while the mean time spent on each time-step was found to be 0.03 s and 0.01 s respectively. The minimal spread in the tridomain data suggests that the solution process for tridomain formulation was more numerically stable compared to the extended bidomain formulation.

The tridomain solution framework described here is now available as part of the Chaste project from version 3.3 and can be downloaded from the Chaste website (<http://www.cs.ox.ac.uk/chaste/download.html>).

B. Mesh generation

A realistic 3D stomach tetrahedral mesh was generated from an initial surface mesh (Fig. 3a) using TetGen (<http://wias-berlin.de/software/tetgen/>), based on the mesh resolution requirement informed from the convergence analysis. The tetrahedral mesh had 2,529,627 elements and 497,081 node points as shown in Fig. 3b. The TetGen quality parameter of the generated mesh was set to 0.7, measured as a ratio of the radius of the circumsphere associated with the tetrahedron and the length of the shortest edge.

The boxplot analysis of inter-nodal spacing for each edges in the generated mesh is shown in Fig. 3c. The mesh had a mean edge of 0.32 mm which was accurate enough to capture the numerical solution process as per the convergence analysis.

C. Generating principal axes of conduction

Laplace's equation was solved on the stomach geometry to evaluate longitudinal and cross-surface gradients using the Chaste computational framework. The generated gradients were determined on an element by element basis on the partitioned mesh. The generated vectors $\vec{\varphi}_1, \vec{\varphi}_2$ and $\vec{\varphi}_3$ were corrected for numerical loss of orthogonality as follows:

$$\begin{aligned}\vec{\varphi}_1 &= \vec{\varphi}_2 \times \vec{\varphi}_3 \\ \vec{\varphi}_2 &= \vec{\varphi}_1 \times \vec{\varphi}_3\end{aligned}$$

An enlarged view of the generated principal conduction axes is shown in Fig. 4b–d.

D. Normal slow wave activity

Normal slow wave propagation was simulated with activity starting at the pacemaker region just below the fundus. The activity propagated in the antegrade direction with a velocity of 3 mm s^{-1} and 8 mm s^{-1} along the circumferential direction. The transmembrane potential pattern is shown in Fig. 5a. A maximum of 3 waves was present in the stomach at any point of time. Because of a higher resting membrane potential in the fundus and the preferential spread along the circular direction, the activity initiated from the pacemaker region quickly formed a ring which propagated in the antegrade direction, in accordance with experimental observations [20], [35]. The simulations required 7 hrs to solve 80 s of slow wave activity using 128 threads on the Auckland NeSI Pan cluster with SandyBridge architecture CPUs.

E. Normal slow wave activity and interaction with gastric pacing

Gastric pacing successfully entrained gastric slow wave activity in the model as shown in Fig. 5. The pacing activity progressively took over the antegrade activity by inducing a retrograde propagation. As observed in experimental studies, the retrograde propagation incrementally captured greater portions of the stomach [10], [36], [37].

The site of collision, formed due to the pacing induced activity and the normal antegrade slow wave activity gradually moved proximally, as shown in Fig. 5a. For each successive cycle, the corresponding collision regions are marked as C1, C2 and C3.

The rate at which a region was entrained increased with pacing frequency as shown in Fig. 6. The y-axis indicates the increase in the entrained region in terms of a distance for each successive cycle (e.g. $C2 - C1$). The formation of a collision region was defined by both pacing location and relative frequencies. Fig. 6 shows that for constant tissue electrical properties, the cycle-to-cycle increase in the entrained region was linearly dependent on the pacing interval. Moreover, the pacing protocols were limited by the frequency of the native propagation and the refractory period of the cellular activity. In this case, the native frequency of propagation was $3 \text{ cycles min}^{-1}$ and refractory period was approximately 10 s.

IV. Discussion

This study presents a multiscale 3D stomach model with a realistic biophysically based FSM-CB ICC model and anisotropic conduction for analysing the effects of gastric pacing and its interaction with normal slow wave activity. A key development was to introduce a numerically efficient and stable tridomain formulation. A high resolution mesh was generated with anatomically realistic geometrical properties to accurately solve the numerical problem. A modified Laplace-Dirichlet rule-based method was used to evaluate synthetic principal conduction axes information. Finally, the model was applied to simulate normal slow wave activity and shows the efficacy of predictively evaluating the effects of gastric pacing protocols on slow wave activity.

Previously, attempts have been made to simulate normal slow wave activity on a complete 3D stomach model but their useful predictive capability was not established [19], [33], [38]. Other studies considered a phenomenological-based model that could effectively describe basic biological properties, such as the frequency and amplitude of the slow wave activity;

however, the lack of physiological basis affected their capacity to predict the effects of experimental protocols [11], [38]. More recently, a biophysically based modified Corrias and Buist ICC model was incorporated into a 3D anatomically realistic stomach modeling framework [33]. However, the initial activation times were prescribed a priori and simulated for subsequent cycles - again limiting its predictive capability. Moreover, homogeneous conductivity parameters were used with no principal directions of conductivity [33]. More exhaustive simulations with extended-bidomain formulations have also been performed, but anisotropic conduction was not incorporated in the simulation [19]. This study resolves all of these issues and therefore represents a significant advance in physiologically accurate gastric modeling, with diverse potential applications in integrated electrophysiology, investigating pathophysiology, and therapeutic assessments for electroceuticals and drug design [39].

The tridomain formulation resulted in a symmetric positive definite matrix, improving the simulation efficiency by a factor of two compared to an alternative formulation [19]. Additionally, the solution process was largely stable throughout the entire simulation as shown in Fig. 2a. The human stomach mesh is relatively coarse and a detailed representation of the internal microstructure could yield a mesh ≈ 3 –4 times larger. This will necessitate more efficient solution processes utilizing available high-performance computers as presented here.

The application of extracellular stimuli to the alternative multidomain formulations often encountered numerical problems. The study presented here has only taken into consideration the combination of a *cg* solver and *jacobi* preconditioner. A combination of *algebraic-multigrid* preconditioners and *block-preconditioners* with a *conjugate gradient (cg)* solver can be investigated as a possibly more effective preconditioner-solver combination [40].

Among the possible applications for this model, the current study focussed on a proof of principle evaluation of a single human gastric pacing protocol [9], [10]. No previous studies have modelled gastric pacing on a realistic 3D stomach. Previous biophysical simulation attempts have been limited to a 2D model with FSM-CB ICC model, [30] which although comparatively limited, established the capability of the same ICC model applied here. Importantly, this study also allowed the gastric anisotropy to be simulated for the first time on a 3D model, as experimentally observed [7], [37]. This is a crucial advance in gastric modeling, because anisotropic conductivity has been shown to be a key determinant of arrhythmic conduction patterns and their interactions [7], [20].

The model will be used to optimize pacing protocols for functional motility disorders, including gastroparesis, where therapeutic pacing has already shown promise. Interestingly, gastric pacing is also being investigated for the treatment of obesity, as it attempts to disrupt the normal antegrade activity and induce retrograde events thereby slowing the motility and inducing satiety [41]. Intolerable side effects have not yet been observed through this approach [36].

Currently, progress in this field is limited by the difficulty in determining optimal pacing protocols and optimized pacing sites [42]. The model presented here can be used as an ideal

platform for rapidly progressing such investigations without the requirement of exhaustive animal experiments. Optimal pacing protocols will additionally be important for improving the power consumption of implantable devices.

In this study, the principal conductivity direction was assumed to be aligned along the circumferential direction of the stomach model. The conductivity parameters defined in Table I provide anisotropic diffusion properties in circumferential and longitudinal directions of the realistic stomach with respect to the reference principal axes of conduction. Such an approach is a simplification considering that the stomach has multiple layers (including longitudinal, circular and oblique) with different properties. Future work will investigate the sensitivity of slow wave propagation to variations in the principal conduction axes. Incorporating detailed muscle layer information could ultimately provide greater insights into the effects of microstructure on diseased gastric activity.

In the present study, the conductivities associated with the intracellular domain for both cell types are the same. This implies an equivalent bidomain solution with a sink but with different membrane properties (passive SMC) coupled to the intracellular ICC cell. We have chosen to use a passive cell model primarily for simplicity. This assumption does not obscure the effectiveness of the study as the passive cell with different material properties will act as a load to the ICC cell, which is an advance over a traditional bidomain framework. As experimental investigations progress, anisotropies in the second domain, or SMC electrophysiological properties [43] can easily be incorporated and studied. Finally, the conductivity values associated with the presented model are constant throughout the domain resulting in a constant conduction velocity which is not observed experimentally [35]. A model incorporating with realistic multi-layer information, biophysically-based cell models and varying spatial properties (including conductivity parameters) can now be utilized for future studies. This will provide greater insights into physiological questions otherwise difficult to consider with usual experimental approaches [42].

V. Conclusion

We present, for the first time, a 3D multiscale model for simulating gastric slow waves and gastric pacing, achieved using a novel numerically efficient and stable tridomain formulation. The utility of this model was demonstrated by simulating normal slow wave activity in accordance with experimental observations and then applying the model to gastric extracellular stimulus pulses. With further incorporation of realistic muscle layers, experimental data and pacing validation studies, this model is anticipated to become an important tool for clinical applications especially in defining efficient pacing protocols in dysmotility and obesity.

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Fig. 1.

Convergence analysis for conduction velocities of 3 mm s^{-1} and 13 mm s^{-1} observed experimentally. Figure shows normalized conduction velocities and indicates that a resolution of $< 0.5 \text{ mm}$ is required for velocities of 3 mm s^{-1} .

(a)

(b)

Fig. 2.

(a) Linear solver iterations for each time step ($n = 5000$). Data compared between tridomain and extended bidomain formulation. (b) Time spent on linear solver for each time step ($n = 5000$) comparing the tridomain and extended bidomain formulation. Tips of the whiskers in the box plot represents the maximum and minimum values, the box spans from first to third quartile, the central line indicates the median and '+' indicates the mean.

Fig. 3.

(a) The anatomically realistic stomach mesh is represented in STL surface mesh. (b) The STL mesh was used to generate high quality tetrahedral mesh using TetGen. (c) Internodal spacings for the generated tetrahedral mesh. Median: 0.32 mm, 75% percentile: 0.39 mm, 25% percentile: 0.25 mm.

Fig. 4. Generation of the principal axes of conduction. (a) Stomach mesh geometry. (b) Enlarged view of circular conduction axis direction. (c) Longitudinal conduction axis direction. (d) Cross layer conduction axis direction.

Fig. 5.

Sequence of ICC transmembrane potential distribution at different time instants and V_m traces for ICC at four locations on the greater curvature of the stomach (P1, P2, P3, P4). (a) Normal slow wave activity was entrained by extracellular pacing electrodes (marked in red dots) with pulses of duration 200 ms and amplitude 5 mA, initiated at $t = 56$ s with a frequency 4 cycles min^{-1} . The site of collision (C1, C2, C3) between the normal and paced waves show the gradual increase in the area entrained by the paced activity. (b) V_m vs time plots for points P1, P2, P3 and P4 as marked in (a). The waves are initially entrained to 3 cycles min^{-1} corresponding to the normal slow wave activity. The dashed line corresponds to normal 3 cycles min^{-1} activity.

Fig. 6. The increase in the region entrained for each pacing cycle in the retrograde direction (e.g. $C2 - C1$ shown in Fig. 5a) for a range of pacing intervals.

TABLE I

Tridomain parameters motivated from [18]

Parameter	Value	Units
Intracellular conductivities (ICC), $\sigma_i^{(1)}$	0.0004, 0.03, 0.001	$mS\ mm^{-1}$
Extracellular conductivities, σ_e	0.01, 0.128, 0.001	$mS\ mm^{-1}$
$\chi^{(1)} (ICC)$	200	mm^{-1}
$\chi^{(2)} (SMC)$	100	mm^{-1}
$\xi^{(1)} (ICC)$	0.025	$\mu F\ mm^{-2}$
$\xi^{(2)} (SMC)$	0.010	$\mu F\ mm^{-2}$
χ^{gap}	0.1	mm^{-1}
Intracellular conductivities (SMC), $\sigma_i^{(2)}$	0.0004, 0.03, 0.001	$mS\ mm^{-1}$