A Biophysically-Based Tissue Model for Optimizing Gastric Pacing

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Abstract— **Gastric pacing has been investigated for modulating gastric motility in diseased states. However, to advance this field, new pacing protocols are needed that directly improve gastric motility while increasing the efficiency of existing pacing devices. This study presents a mathematical tissue model for investigating slow wave entrainment during pacing and its comparison with experimental data gathered by high-resolution electrical mapping. The model was used to predict the effect anisotropic conductivities on slow wave entrainment, and the effect of gastric pacing on ectopic dysrhythmias. A diffusion based slow wave propagation model was used, with cell activity modeled as a finite-state machine. Initially, normal slow-wave antegrade propagation was modeled in accordance with experimental data. Then, these simulation parameters were applied to compare the model, in tandem with experimental studies in which an external pacing signal entrains native slow wave activity. The effect of different pacing frequencies on entrainment was demonstrated. Finally, this model was also used for simulating the effect of external stimuli for entraining a distal ectopic focal pacemaker. Two cases were studied with different fiber directions. The results showed that the pacing frequency and orientation of the fibers relative to the stimulation and ectopic site plays a critical role in gastric pacing efficacy.**

Keywords— **gastric electrical stimulation; gastric electrophysiology; entrainment; gastric pacing.**

I. Introduction

Slow wave (SW) activity underpins the phasic contractile activity in much of the gastrointestinal tract (GI) tract. SWs are generated and actively propagated by networks of interstitial cells of Cajal (ICC), which in turn depolarize the adjacent smooth muscle cells [1]. Degradation and loss of ICC have been associated with several GI motility and transit disorders, most notably diabetic gastroparesis and slow transit constipation [1], [2]. Isolated ICC spontaneously excite at intrinsic frequencies and in a declining gradient along the aboral direction of the stomach [3], [4]. However, in the intact tissue, gastric ICC are entrained to the highest single frequency in their syncytium, being a key factor in coordinating stomach contractions [1].

Gastric electrical stimulation (GES) has been applied for many years in attempts to improve motility and symptoms associated with gastroparesis and other motility disorders [5], [6]. New methods are required to improve the efficiency of pacing and its efficacy in modulating motility outcomes. However, there are a vast range of GES parameters that must be tested, such as stimulus location(s), amplitude, pulse width and frequency, currently requiring costly and inefficient animal trials. Mathematical models offer a virtual medium in which hypothetical physiological conditions can be tested *in-silico*, thus presenting an attractive strategy for investigating responses of SW to stimulation [7]. Effects of GES were previously studied on a virtual tissue framework however, that study used a predefined ICC membrane potential trace to represent ICC electrical activity, controlled by an underlying automata algorithm which determined the active or resting state of the surrounding [8]. The method was effective in predicting the entrainment induced as a result of an external stimulus, but, it lacks biophysical detail and thus a realistic tissue electrophysiological basis capable of predictive responses. Modern gastric cell models can predict stimulation responses with high accuracy [9], but these have not yet been applied in tissue stimulations.

Here, we present a tissue model framework for simulating gastric pacing and its effect on entrainment. The model is compared with experimental results and applied to: i) predict the effect of fiber directions and anisotropic conductivities on entrainment; and ii) analyze outcomes of different pacing frequencies.

II. Methods

A. Model Setup

Experimental Data: Simulations were based on high-resolution experimental recordings performed in a weaner pig model [12]. The recordings were obtained using flexible printed-circuit-board arrays (8×24 electrodes; 7.62 mm spacing; total area dimensions ~6×18cm) placed on the serosa of the anterior gastric corpus. Gastric pacing was applied to entrain slow wave activation during mapping. The stimulus was administered using two pacing electrodes connected to a DS8000 multichannel stimulator (World Precision Instruments, Sarasota, FL).

Tissue model setup: The stomach region covered by the electrode array was represented using a finite element mesh

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with a total of 11,041 nodes with inter-nodal spacing of approximately 1 mm. A finite-state machine (FSM) based Corrias and Buist ICC model [10] was used as a description of the cell activity at each solution point. A Mealy finite state-machine approach was developed where the cell behavior depended both on input conditions and the present state. In this method, the cell behavior was modeled as a two state machine and the state transition was determined by: a voltage threshold, intracellular calcium concentration, the non-refractory period and the initial start time which activates the cell model on its own. A bidomain continuum description was used to define the reaction-diffusion phenomena in gastric tissue [7] and the CHASTE software package was used for computing the solutions [11].

B. Simulation Setup

Normal slow wave propagation for validating parameters: Based on experimental recording, a bidomain model was developed with parameters chosen to model the experimental recordings. The surface area to volume ratio, χ = 2,000 cm^{-1}; membrane capacitance, C_m = 2.5 μF cm^{-2}; intracellular conductivities parallel and perpendicular to fiber as σ_{ix} = 0.175 mS cm^{-1} and σ_{iy} = 0.0665 mS cm^{-1}; extracellular conductivities parallel and perpendicular to fiber as σ_{ex} = 0.7 mS cm^{-1} and σ_{ey} = 0.84 mS cm^{-1} and threshold voltage of excitation of cell, V_{th} = -55 mV. A fiber direction was specified to be parallel to the *x*-axis. The diffusion terms were solved with a time step of 0.1 ms and reaction term was solved using the forward-Euler method, also with a time step of 0.1 ms. A SW activity with an intrinsic frequency 3.16 cpm was initiated at the top left corner by allowing that cell to activate at t = 0 s.

Effect of external pacing on slow wave propagation: A threshold stimulus current was introduced, into the simulation setup described previously, with a period of 17 s (3.53 cpm) at the same virtual location as that in the experiment. This current raised the transmembrane potential to the threshold of -55 mV.

Effect of external pacing frequency and entrainment: The simulation setup was the same as previously; however, the stimulus frequencies were varied from 3.2 to 4.2 cpm. In order to define a relationship between different stimulus frequencies and their effect on entrainment, the time taken by the pacing signals to entrain the entire field was noted. The duration of each simulation was 250 s.

Effects of fiber direction on external pacing: Pacing effects were studied with respect to fiber directions (directions of preferred conduction), with the fiber directions at an angle of 45° or 135° to the x-axis. The simulations were performed with the same parameters as used in the previous setup. It was assumed that ectopic activity occurred at around the same location where the stimuli were applied previously, which produced retrograde slow wave propagation at 3.16 cpm. This gastric dysrhythmia was then modulated with an external periodic stimulus at a frequency of 3.5 cpm. The pacing location was top right corner of the model.

III. Results

Normal slow wave propagation for validating parameters: The experimental and the corresponding simulated activation maps for normal antegrade activation, gradual entrainment of the mapped field, and complete entrainment are shown in Fig. 1. The simulated slow wave activity was in good agreement with the experimental recordings. In both virtual and experimental cases, slow waves propagated antegrade with matching conduction velocities. The propagation velocity in the circular direction was 6.42 mm s^{-1}; compared to 4.51 mm s^{-1} longitudinally.

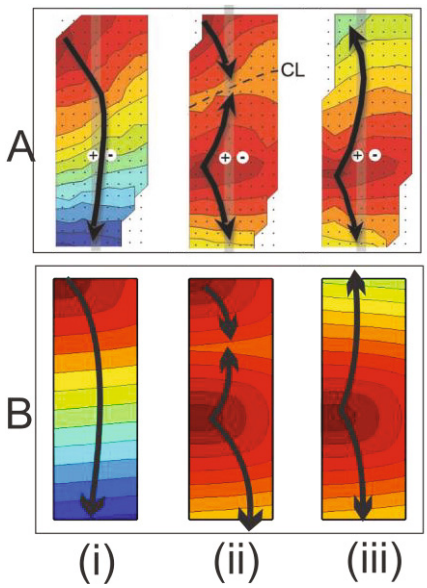

Fig. 1 Activation maps for effects of gastric pacing on entrainment. (A) Experimental recordings and (B) simulation results for (i) normal antegrade propagation. (ii) gradual entrainment by pacing, and finally (iii) entrainment over the entire field. Each color band represents 2 s intervals and red corresponds to 0 s.

Effect of external pacing on slow wave propagation: Slow wave activation maps were obtained as shown in Fig. 1B. The entrained area increased with each cycle as shown in Fig. 1B: (ii) and (iii). The entire field was entrained in 120 s after the onset of stimulus pacing.

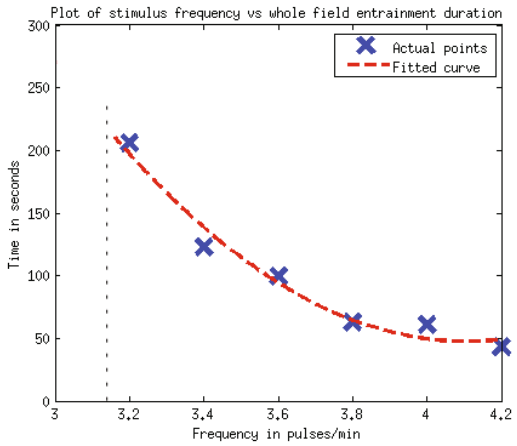

Fig. 2 Time taken to entrain the entire field vs. different pacing frequencies. The natural frequency of the tissue was 3.16 cpm.

Effect of different external pacing frequency and entrainment: Fig. 2. demonstrates the time taken for entrainment of the normal activation pattern (with intrinsic frequency 3.16 cpm) against different pacing frequencies. Pacing with the frequency closest to the native frequency took longer to entrain compared to other values. However, pacing at the highest frequency range was limited by the refractory period value. A stimulus period closest to the refractory period could produce undesirable results such as effective decrease in pacing frequency by a factor of 2. This is because every alternate stimulus might be induced during the refractory period of the gastric cell activity. From the simulation results, the optimal external pacing frequency to quickly entrain the entire stomach was therefore approximately 3.8 cpm. Once entrained, the pacing frequency could be reduced to a frequency close to the natural frequency (3.2 cpm).

Effects of fiber direction on external pacing: The simulated results are shown in Figs. 3 and 4. The gastric dysrhythmia was controlled effectively by external pacing. However, the results indicated that the relative orientation of fiber directions, with the vector from point of ectopic activity and pacing site, had a significant effect on controlling dysrhythmia. In the example shown in Fig. 3, with ectopic activity and pacing site aligned with the fiber directions, entrainment of the entire field was achieved during the 5th activation cycle (Fig. 3E). In contrast, when the orientation of the ectopic activity and pacing site relative to the fiber directions were almost perpendicular, the entrainment was achieved during the 6th cycle (Fig. 4F). These data indicate that effects of fiber direction with anisotropic conductivities on native and entrained wave should be considered when optimizing a pacing location.

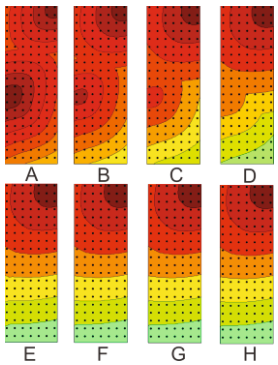

Fig. 3 Activation maps (isochronal intervals of 3 s) during an ectopic activity being entrained by an external stimulus at a frequency of 3.53 cpm. The ectopic activity had a frequency of 3.16 cpm and the fibers were oriented 45° to the horizontal. Maps are shown at 17 s intervals.

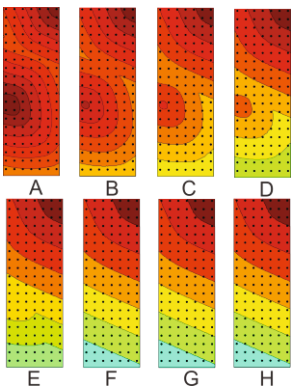

Fig. 4 Activation maps (isochronal intervals of 3 s) during an ectopic activity being entrained by an external stimulus at a frequency of 3.53 cpm. The ectopic activity had a frequency of 3.16 cpm and the fibers were oriented at 135° to the horizontal. Maps are shown at 17 s intervals.

IV. Conclusions

This study presented a gastric tissue model using a FSM based ICC CB model for studying gastric pacing and entrainment. The model was validated for normal slow wave propagation conduction velocity along circumferential and longitudinal direction [12], and then applied for predicting the effects of fiber direction on pacing and SW entrainment. The model successfully simulated normal activation and effects of external stimuli. The results also demonstrated the importance of fiber direction on gastric pacing used for entraining over an ectopic focus.

This model is the first biophysically-based tissue model capable of realistic simulations of gastric pacing, and the first to consider the role of anisotropy in optimizing pacing location. Previous models without a strong biophysical basis

lacked predictive capability [8]. Importantly, the simulations of normal and paced entrainment were in good agreement with the experimental data. However, the simulations used a limited modeling domain and imposed no-flux boundary conditions which do not accurately reflect realistic *in vivo* boundary conditions.

The utility of this model extends to analysis of motility disorders and obesity. In obesity, gastric pacing has been attempted to disrupt normal antegrade slow-wave activity by inducing retrograde events, thereby slowing motility and inducing satiety [13]. This may be achievable without any intolerable side effects [14]. But, current progress has been limited by the need to increase efficiency in pacing protocols and optimize pacing sites. The tissue model presented here provides an ideal platform for rapidly achieving such investigations without the need for exhaustive animal trials.

Another critical question in gastric pacing research is minimizing the power requirement for exciting and initiating ICC pacemaking mechanisms, thus improving the power consumption of implantable devices. In this study, values were chosen to match with the experimental conduction velocities. The arrangement of ICC and resultant anisotropy may be profoundly important in modulating gastric activation patterns, particularly during pacing and dysrhythmia [15]. Further, the contractile activity of the gastric wall arises primarily from smooth muscle cells to which ICC are electrically coupled with gap junction. Hence, orientation of smooth muscle cell [16] fibers is also critical.

In conclusion, we present a model framework that provides a major advance over previously published models. Demonstration of efficacy has been achieved by effectively predicting optimal pacing frequencies and the importance of anisotropic conductivities for rapid entrainment of dysrhythmias. This framework, with further incorporation of anatomical and smooth muscle elements, is anticipated to become an important tool for improving the clinical efficacy of gastric pacing in dysmotility and obesity.

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References

1. K. M. Sanders, S. D. Koh, and S. M. Ward, "Interstitial cells of Cajal as pacemakers in the gastrointestinal tract," *Annu. Rev. Physiol.*, vol. 68, pp. 307–343, 2006.
2. G. Farrugia, "Interstitial cells of Cajal in health and disease.," *Neurogastroenterol motil*, vol. 20 Suppl 1, pp. 54–63, May 2008.
3. R. A. Hinder and K. A. Kelly, "Human Gastric Pacesetter Potential," *Am. J. Surg.*, vol. 133, no. January, pp. 29–33, 1977.
4. J. H. S. T Y el-Sharkawy, K G Morgan, "Intracellular Electrical Activity of Canine and Human Gastric Smooth Muscle," *J. Physiol.*, pp. 291–307, 1978.
5. W. L. Hasler, "Methods of gastric electrical stimulation and pacing: a review of their benefits and mechanisms of action in gastroparesis and obesity.," *Neurogastroenterology and motil*, vol. 21, no. 3, pp. 229–43, Mar. 2009.
6. G. O'Grady, J. U. Egbuji, P. Du, L. K. Cheng, A. J. Pullan, and J. a Windsor, "High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis.," *World J. Surg.*, vol. 33, no. 8, pp. 1693–701, Aug. 2009.
7. L. K. Cheng, G. O'Grady, P. Du, J. U. Egbuji, J. A. Windsor, and A. J. Pullan, "Gastrointestinal system," *Wiley Interdiscip Rev Syst Biol Med*, vol. 2, no. 1, pp. 65–79, 2010.
8. P. Du, G. O'Grady, J. A Windsor, L. K. Cheng, and A. J. Pullan, "A tissue framework for simulating the effects of gastric electrical stimulation and in vivo validation.," *IEEE Trans. Biomed. Eng.*, vol. 56, no. 12, pp. 2755–61, Dec. 2009.
9. P. Du, S. Li, G. O'Grady, L. K. Cheng, A. J. Pullan, and J. D. Z. Chen, "Effects of electrical stimulation on isolated rodent gastric smooth muscle cells evaluated via a joint computational simulation and experimental approach," *Am J Physiol Gastrointest Liver Physiol*, vol. 297, no. 4, pp. G672–G680, 2009.
10. A. Corrias and M. L. Buist, "Quantitative cellular description of gastric slow wave activity.," *Am J Physiol Gastrointest Liver Physiol*, vol. 294, no. 4, pp. G989–95, Apr. 2008.
11. G. R. Mirams, C. J. Arthurs, M. O. Bernabeu, R. Bordas, J. Cooper, A. Corrias, Y. Davit, S.-J. Dunn, A. G. Fletcher, D. G. Harvey, M. E. Marsh, J. M. Osborne, P. Pathmanathan, J. Pitt-Francis, J. Southern, N. Zemzemi, and D. J. Gavaghan, "Chaste: An Open Source C++ Library for Computational Physiology and Biology," *PLoS Comput. Biol.*, vol. 9, no. 3, p. e1002970, Mar. 2013.
12. G. O'Grady, P. Du, W. J. E. P. Lammers, J. U. Egbuji, P. Mithraratne, J. D. Z. Chen, L. K. Cheng, J. a Windsor, and A. J. Pullan, "High-resolution entrainment mapping of gastric pacing: a new analytical tool.," *Am J Physiol Gastrointest Liver Physiol*, vol. 298, no. 2, pp. G314–21, Feb. 2010.
13. J. Yin and J. D. Z. Chen, "Implantable gastric electrical stimulation: ready for prime time?," *Gastroenterology*, vol. 134, no. 3, pp. 665–7, Mar. 2008.
14. S. Yao, M. Ke, Z. Wang, D. Xu, Y. Zhang, and J. D. Z. Chen, "Retrograde gastric pacing reduces food intake and delays gastric emptying in humans: a potential therapy for obesity?," *Dig. Dis. Sci.*, vol. 50, no. 9, pp. 1569–75, Sep. 2005.
15. G. O. Grady, P. Du, N. Paskaranandavadivel, T. R. Angeli, W. J. E. P. Lammers, and S. J. Asirvatham, "Rapid high-amplitude circumferential slow wave propagation during normal gastric pacemaking and dysrhythmias," *Neurogastroenterol Motil*, pp. 299–312, 2012.
16. A. Corrias and M. L. Buist, "A quantitative model of gastric smooth muscle cellular activation.," *Ann Biomed Eng*, vol. 35, no. 9, pp. 1595–607, Sep. 2007.

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