Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2015 ; 2015: 8062–8065. doi:10.1109/EMBC.2015.7320264.

Tissue Specific Simulations of Interstitial Cells of Cajal Networks Using Unstructured Meshes

Shameer Sathar*,

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

Mark L. Trew, 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

Abstract

Gastrointestinal motility is facilitated by specialized pacemaker cells called Interstitial Cells of Cajal (ICC). ICC play a critical role in coordinating normal motility and its degradation in the gastrointestinal tract is associated with many functional motility disorders. Nonetheless, the degree of degradation and associated clinical impact remains unclear. Continuum modeling frameworks offers a virtual mean to simulate the electrical activity, and analyze the ICC activity in both normal and diseased states. Confocal images of the ICC networks were obtained from the intestine of normal mice. In this study, a new approach is presented where meshes of ICC networks were generated using a Delaunay triangulation and used to solve finite-element based reaction-diffusion equations describing gastrointestinal electrophysiology. The electrical activity was simulated on the ICC network and solutions were compared to those of a regular mesh based on individual pixel locations. The simulation results showed the proposed approach to be approximately 80% more efficient than a pixel-based mesh. The difference in activation time for the entire network between the different methods was observed to be around 4% (about 20 ms). The proposed approach will enable efficient examination of the ICC slow wave activity in larger networks and for longer temporal duration that has been previously impossible. This will provide valuable insights relating ICC degradation to gastrointestinal motility disorders.

I. INTRODUCTION

Gastrointestinal (GI) motility represents the coordinated contraction of the GI tract wall necessary for digestion and transportation of food contents. The motility is coordinated by an underlying omnipresent electrical activity termed slow waves. These are initiated and propagated through networks of the interstitial cells of Cajal (ICC) [1]. Isolated ICC from discrete locations excite spontaneously at different intrinsic frequencies; however, in the

*Fax: +64 (0) 9 367 7157; Tel: +64 (0) 9 923 1497; ssat335@aucklanduni.ac.nz.

intact tissue, all the ICC are entrained to a single dominant frequency in the network [2]. ICC network degradation has been associated with several GI functional motility disorders notably gastroparesis and slow-transit constipation [3]–[5].

Even though ICC loss and network degradation have been associated with GI health and motility disorders, the mechanism of how the structure of ICC networks relate to the physiology of GI tract is poorly understood and remains an active subject of investigation [1], [6], [7].

Mathematical models are increasingly been shown to be successful and robust for in-silico analysis of tissue electrophysiology [8]. In-silico models offer a virtual medium in which hypothetical physiological conditions can be tested and are an attractive strategy for analyzing the structure-function relationship of the ICC network [9].

Recently, slow-wave propagation was simulated on a tissue-specific model containing the two-dimensional microstructure of the myenteric ICC network of both normal and artificially degraded ICC networks [9]. The results showed how degradation in the ICC network impairs the slow wave propagation and ultimately motility and transit. However, this model utilized a computational mesh based on the pixels of two-dimensional bitmap images of the ICC imaging data. Consequently, the mesh was not adaptive and the resulting computations were inefficient. An image pixel-based network of size 0.317 mm by 0.317 mm network took about 2 hrs to solve for an activation time of 400 ms [9]. Future studies, with a focus on simulations over larger network (e.g., organ scale) and with the activation time requirements typically in the order of several seconds, will be intractable with pixel-based network models.

In this study, unstructured triangular mesh models of ICC networks are proposed. The proposed model was compared for efficiency and efficacy to a pixel-based model. A biophysically-based continuum modeling framework was used to simulate ICC pacemaker activity, providing a functional electrical comparison.

II. Methods

A. ICC network imaging data

Confocal ICC imaging data was obtained from the proximal jejunum of mice using immunofluorescence staining procedures as previously described [10]. Unbiased thresholding algorithms were used to segment the images to obtain two-dimensional bitmaps of the network structure [7]. The image segments of the ICC were depth-averaged into two-dimensional images representing the entire ICC network structures. This approach was appropriate as the ICC network was relatively thin in the transmural direction ($\sim 10\ \mu\text{m}$) and the majority of the network was planar. The final image was $0.531 \times 0.531\ \text{mm}$ in size sampled at 1024×1024 pixels.

B. Pixel-based simulation model

A regular evenly spaced triangular mesh with each node corresponding to each pixel of the image was generated. The resulting mesh had 1,048,576 nodes (1024×1024) resulting in a

spatial resolution of 0.519 μm as shown in Fig. 1A. The model expresses a substantially higher spatial resolution than previous comparable cardiac simulations (300 μm), that have also used a bidomain continuum modelling framework [11]. Each node in the resultant pixel-based mesh represented either an ICC cell or non-ICC cell, based on the pixel attributes.

C. Triangulation-based simulation model

The two-dimensional image was analyzed for isocontours. A finite element triangular unstructured mesh was constructed using a Delaunay triangulation algorithm over the generated isocontours of the segmented images. A two stage mesh refinement was required to obtain a suitable unstructured triangular mesh and to improve the mesh quality by reducing the element skewness as shown in Fig. 1B. A triangle mesh generator tool [<https://www.cs.cmu.edu/~quake/triangle.html>] was used to build the mesh. Each node in the resulting triangular mesh represented either an ICC cell or non-ICC cell, based on the regional attributes assigned during the segmentation process.

D. Continuum-based modeling and simulation parameters

A bidomain continuum modeling framework was used to model the reaction-diffusion process describing the electrical propagation through the network. The equations relate the transmembrane potentials and extracellular potential in the tissue electrophysiology process. The equations are summarized as in (1) and (2)

$$\nabla \cdot (\sigma_i \nabla V_m) = -\nabla \cdot ((\sigma_i + \sigma_e) \nabla \phi_e) \quad (1)$$

$$\nabla \cdot (\sigma_i \nabla V_m) + \nabla \cdot (\sigma_i \nabla \phi_e) = A_m \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} \right) \quad (2)$$

where i and e subscripts represent the intracellular and extracellular domains respectively. The σ terms are the conductivities, ϕ_e is the potential, A_m is the surface to volume ratio of the membrane, C_m is the membrane capacitance and V_m is the transmembrane potential. The term I_{ion} represents the cellular activity which provides the active response. A finite-state machine (FSM) based ICC model was used to model the cellular activity [12], [13] for ICC nodes in the models. The FSM modeled a voltage-dependent entrainment mechanism where the cellular activity of the ICC was divided into two states of *Active* and *Passive*, with the transition between them determined by V_m , $[\text{Ca}^{2+}]_i$ and a non-refractory period defining the intrinsic frequency of the pacemaker activity. The non-ICC nodes were represented using a passive cell model with a zero active ionic-current. The slow wave activity was initiated at the region marked in Fig. 2A by setting the t_{start} parameter of the ICC model [12] to 0, and a larger t_{start} value ($>$ simulation duration) at other locations.

The intracellular conductivity parameters were set to 0.0012 and 0.12 mS cm^{-1} respectively for non-ICC and ICC regions while the extracellular conductivity parameters were set to

0.0002 and 0.02 mS cm⁻¹. A_m and C_m were given values of 1000 cm⁻¹ and 2.5 μF⁻² respectively. An ODE time-step of 0.1 ms, diffusion time-step of 1 ms was used for the numerical solution process. These ODE and PDE time-steps were selected based on a convergence analysis to obtain a stable solution to the model. The problem was solved for 2000 ms of simulation time using the CHASTE computational package with a conjugate gradient solver and a block-Jacobi preconditioner [14].

III. Results

The activation time map of the simulated electrical activity for the two models is shown in Fig. 2C and Fig. 2D. The activity starts at the initiating site and eventually entrains the entire network in approximately 500 ms. The activation maps show that both the simulations followed a similar activation pattern, although the conduction velocity was faster in the triangulated network compared to the regular-pixel based network.

The activation time over the entire network was compared to quantify the differences in the activation rate. The average V_m was evaluated at each time-step for both simulations and was plotted in Fig. 2B. There is a difference in activation time of 20 ms (4%) for 500 ms of average V_m activation, and a conduction velocity difference of approximately 0.11 mm s⁻¹. A sample V_m plot for point P1 (shown in Fig. 2A) is shown as an inset in Fig. 2B. The regular pixel-based network had 1,048,576 solution points whereas the triangulated based geometry had only 251,313 solution points. The number of solution points was reduced by approximately 80%. The detailed mesh statistics for the unstructured mesh are shown in Table. I. The simulation time for solving the electrical activity over the pixel based network and triangulated network was 111 minutes and 18 minutes respectively using 48 cores on NeSI PAN cluster. This represented an 80% increase in computational efficiency.

IV. Discussion

ICC network degradation is a key reason for GI functional motility disorders. However, quantifying the relationship between the network and function has been constrained due to limitations in experimental approaches. Modeling studies are better alternative in such cases, however they are computationally intensive. In this study, we presented an efficient triangulation based ICC network model to simulate slow wave activity over an ICC network.

The results show that the proposed method is approximately 80% more efficient than pixel based approaches and the differences were within an acceptable limit. The differences in smoothness of the activation maps can be attributed to the coarseness of the visualization data points in the two meshes. A regular pixel-based mesh activation map has data points at a higher resolution than the unstructured triangulation based approach. Further, the data values are linearly interpolated spatially in the unstructured mesh.

There was a difference in the activation time of 20 ms between the models. This difference is only 4% of the activation time, and is thought to arise from variations in the mesh characteristics. Convergence analysis usually produces a curve that varies with mesh resolutions. The propagation velocity for a pixel-based mesh is unique to the particular resolution of 0.519 μm for the given conductivity parameters. Conduction velocities

computed on a more highly refined unstructured mesh were almost identical to the original unstructured mesh. The differences are believed to have negligible effects when unstructured meshes are used for a particular type of study as the comparisons are considered to be relative.

The resolution required for the simulation presented here is limited by the network geometry and the desire to capture the structure accurately. However, from a convergence perspective the resolution is very high compared to a typical cardiac simulation for both regular pixel-based and triangular mesh based models.

Following this development of modeling technique, the consequences of ICC network degradation with functional outcomes in gastrointestinal smooth muscle behavior can be investigated. This was hindered previously due to computational constraints. The non-ICC tissue in the background was assumed to be passive with no active response to the simulated slow waves, whereas this space is partly occupied by smooth muscle cells. A biophysically based smooth muscle cell model which has recently been proposed [15], could be applied within this proposed computing framework. The ICC network-geometries considered in the study were a two-dimensional representation of a 3D image which was depth averaged given the small depth of the tissue. Future work will extend this method on unstructured tetrahedral meshes on isosurfaces of 3D network geometry. Further, this can be extended on to whole organ level. Although, the boundary conditions were assumed to be no-flux across all edges, this assumption is appropriate the study was focused on developing a framework and analyzing its efficiency, rather than direct correlation with a physiological observation.

In summary, this study provides a framework to efficiently analyze the structure-function relationships in an ICC network using high-performance computing resources. The method is anticipated to become an important tool for future large ICC network studies and analyzing the effects of network degradation in GI motility disorders.

Acknowledgments

The authors would like to thank Prof. Jean-Marie Vanderwinden for providing the ICC network imaging data. The author(s) wish to acknowledge the contribution of the NeSI high-performance computing facilities at the University of Auckland and the staff at NeSI and Centre for eResearch.

FUNDING

This work was supported in part by grants from the Riddet Institute, New Zealand, Health Research Council of New Zealand and NIH (R01 DK64775).

References

1. Farrugia G. Interstitial cells of Cajal in health and disease. *Neurogastroenterol Motil.* May; 2008 20(Suppl 1):54–63. [PubMed: 18402642]
2. Huizinga JD, Lammers WJEP. Gut peristalsis is governed by a multitude of cooperating mechanisms. *Am J Physiol Gastrointest Liver Physiol.* Jan; 2009 296(1):G1–8. [PubMed: 18988693]
3. Huizinga JD, Zarate N, Farrugia G. Physiology, Injury, and Recovery of Interstitial Cells of Cajal: Basic and Clinical Science. *Gastroenterology.* 2009; 137(5):1548–1556. [PubMed: 19778538]

4. Grover M, Farrugia G, Lurken MS, Bernard CE, Fausone-Pellegrini MS, Smyrk TC, Parkman HP, Abell TL, Snape WJ, Hasler WL, Ünalp Arida A, Nguyen L, Koch KL, Calles J, Lee L, Tonascia J, Hamilton FA, Pasricha PJ. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology*. May; 2011 140(5):1575–85.e8. [PubMed: 21300066]
5. Wedel T, Spiegler J, Soellner S, Roblick UJ, Schiedeck THK, Bruch H-P, Krammer H-J. Enteric nerves and interstitial cells of Cajal are altered in patients with slow-transit constipation and megacolon. *Gastroenterology*. 2002; 123:1459–1467. [PubMed: 12404220]
6. Ordög T. Interstitial cells of Cajal in diabetic gastroenteropathy. *Neurogastroenterol Motil*. 2008; 20:8–18. [PubMed: 18173559]
7. Gao J, Du P, O'Grady G, Archer R, Farrugia G, Gibbons SJ, Cheng LK. Numerical metrics for automated quantification of interstitial cell of Cajal network structural properties. *J R Soc Interface*. Sep.2013 10(86):20130421. [PubMed: 23804441]
8. Cheng LK, Du P, O'Grady G. Mapping and modeling gastrointestinal bioelectricity: from engineering bench to bedside. *Physiology (Bethesda)*. Sep; 2013 28(5):310–7. [PubMed: 23997190]
9. Du P, O'Grady G, Gibbons SJ, Yassi R, Lees-Green R, Farrugia G, Cheng LK, Pullan AJ. Tissue-specific mathematical models of slow wave entrainment in wild-type and 5-HT(2B) knockout mice with altered interstitial cells of Cajal networks. *Biophys J*. May; 2010 98(9):1772–81. [PubMed: 20441740]
10. Klein S, Seidler B, Kettenberger A, Sibaev A, Rohn M, Feil R, Allescher H-D, Vanderwinden J-M, Hofmann F, Schemann M, Rad R, Storr Ma, Schmid RM, Schneider G, Saur D. Interstitial cells of Cajal integrate excitatory and inhibitory neurotransmission with intestinal slow-wave activity. *Nat Commun*. 2013; 4:1630. [PubMed: 23535651]
11. Pullan, AJ.; Cheng, LK.; Buist, ML. Mathematically Modelling the Electrical Activity of the Heart: From Cell to Body surface and back again. World Scientific Pub Co Inc; 2005.
12. Sathar S, Trew ML, Du P, O'Grady G, Cheng LK. A biophysically based finite-state machine model for analyzing gastric experimental entrainment and pacing recordings. *Ann Biomed Eng*. Apr; 2014 42(4):858–70. [PubMed: 24276722]
13. Corrias A, Buist ML. Quantitative cellular description of gastric slow wave activity. *Am J Physiol Gastrointest Liver Physiol*. Apr; 2008 294(4):G989–95. [PubMed: 18276830]
14. Mirams GR, Arthurs CJ, Bernabeu MO, Bordas R, Cooper J, Corrias A, Davit Y, Dunn SJ, Fletcher AG, Harvey DG, Marsh ME, Osborne JM, Pathmanathan P, Pitt-Francis J, Southern J, Zemzemi N, Gavaghan DJ. Chaste: an open source C++ library for computational physiology and biology. *PLoS Comput Biol*. Jan.2013 9(3):e1002970. [PubMed: 23516352]
15. Corrias A, Buist ML. A quantitative model of gastric smooth muscle cellular activation. *Ann Biomed Eng*. Sep; 2007 35(9):1595–607. [PubMed: 17486452]

Fig. 1.

Finite element meshes of the pixel-based and unstructured triangulation based methods. (A) corresponds to a regular triangular mesh with each pixel in the original image corresponding to a vertex of an element. The small block marked with the white square is zoomed in subsequent figures. (B) corresponds to the process of generating unstructured triangular mesh. The isocontours of the image was obtained using an edge-detection algorithm. A simple triangulation is then applied on the isocontours which is further refined using the Delaunay triangulation based tool 'triangle' [<https://www.cs.cmu.edu/~quake/triangle.html>].

Fig. 2.

Simulation of slow wave propagation over the ICC network. The activity is initiated at the region shown as a white patch in the network (A). (B) shows the plot of average V_m over the entire network and the inset figure corresponds to plot of V_m at a single point P1 (shown in (A)), for both pixel-based and unstructured mesh simulations. The unstructured triangular model activated on an average 20 ms earlier than the structured mesh. (C) and (D) show the activation maps for both meshes.

Table 1

Mesh statistics for the unstructured mesh

Property	Value
Mesh Vertices	251313
Mesh elements	500787
Smallest area	6.2603e-10 mm ²
Largest area	1.8798e-04 mm ²
Smallest edge	2.9154e-05 mm
Largest edge	0.023339 mm