Published in final edited form as:

Ann Biomed Eng. 2014 January ; 42(1): 177–192. doi:10.1007/s10439-013-0906-3.

Automated classification and identification of slow wave propagation patterns in gastric dysrhythmia

Niranchan Paskaranandavadivel, Jerry Gao, Peng Du, Gregory O'Grady, and Leo K Cheng

Abstract

The advent of high-resolution electrical mapping of slow wave activity has significantly improved the understanding of gastric slow wave activity in normal and dysrhythmic states. One of the current limitations of this technique is it generates a vast amount of data, making manual analysis a tedious task for research and clinical development. In this study we present new automated methods to classify, identify and locate patterns of interest in gastric slow wave propagation. The classification method uses a similarity metric to classify slow wave propagations, while the identification algorithm uses the divergence and mean curvature of the slow wave propagation to identify and regionalize patterns of interest. The methods were applied to synthetic and experimental data sets and were also compared to manual analysis. The methods classified and identified patterns of slow wave propagation in less than 1 s, compared to manual analysis which took up to 40 minutes. The automated methods achieved 96% accuracy in classifying AT maps, and 95% accuracy in identifying the propagation pattern with a mean spatial error of 1.5 mm in comparison to manual methods. These new methods will facilitate the efficient translation of gastrointestinal high-resolution mapping techniques to clinical practice.

Keywords

High-resolution; Activation time map; Gastroparesis; Interstitial cells of Cajal; Extracellular; Pacemaker; Colliding wavefronts; Re-entry; Circular propagation; Mean curvature; Divergence; Conduction block

2 Introduction

The motility of the stomach and intestine is coordinated by bio-electrical events known as slow waves. Slow waves are generated and propagated through a specialized network of cells known as the interstitial cells of Cajal (ICC), which are interlaced throughout the gastrointestinal (GI) musculature¹³. In humans, normal gastric slow wave activity occurs at around 3 cycles per minute (cpm), and originates from the greater curvature of the stomach in the mid- to upper-corpus region, and propagates distally towards the antrum²⁵. Abnormalities in slow wave activity ('gastric dysrhythmias') have been related to major gastric motility disorders such as functional dyspepsia and gastroparesis^{21, 24}.

In recent years, high-resolution (HR) extracellular mapping techniques have provided vital insights to the spatiotemporal profile of gastric slow wave propagations. The major advantage that HR mapping provides, in comparison to sparse extracellular mapping techniques or cutaneous electrogastrigraphy (EGG), is that it enables accurate tracking and quantification of slow wave activation patterns. The spatiotemporal profiles of normal gastric slow wave propagation have now been recorded in detail in animal and human

subjects^{25, 17}, and gastric HR mapping in animal subjects have also identified key classes of abnormal propagation patterns^{18, 28}. Furthermore, a recent study has experimentally shown that in patients suffering from gastroparesis, a disease where the stomach fails to empty normally in the absence of a mechanical obstruction, there are abnormal patterns of slow wave initiation and conduction that can only be reliably detected and quantified using HR mapping²⁴. Detecting and understanding these mechanisms has thus become a major translational research goal across multiple biological and biophysical scales, with significant potential to improve clinical accuracy and efficiency in the diagnosis of gastric disorders^{19, 5}.

To date, all HR mapping studies of gastric dysrhythmia have used manual classification and visual analyses of spatial slow wave propagation patterns^{24, 16}. Manual approaches can miss certain critical features that are pertinent to gastric slow wave dysrhythmia, prone to observer bias, and inefficient. The introduction of guided tools and real time analysis (e.g.,³) would be a major step toward the successful clinical translation of GI HR mapping, by enabling its routine use by clinicians untrained in signal and image processing, as has occurred in cardiac HR mapping³⁷. Our group has presented a semi-automated method for identifying characteristics of slow wave dysrhythmias⁶, but requires *a priori* knowledge about normal propagation patterns, which reduces efficiency and introduces observer bias.

Here, we present novel automated methods to classify slow wave propagations in an intuitive manner using a similarity metric, and to detect patterns of interest in slow wave propagation using divergence, mean curvature and image processing techniques. These tools will allow for normal and abnormal slow wave propagations to be classified in a consistent manner, and will enable the automated detection and visualization of key regions of normal and dysrhythmic slow wave propagation.

3 Materials and Methods

3.1 Recording and signal processing methods

Gastric serosal HR extracellular *in vivo* mapping was performed on cross-breed weaner pigs (n = 6, 32±1 kg) following approval from the University of Auckland Ethics Committee. Weaner pigs are a useful model for gastric dysrhythmia studies because spontaneous episodes of dysrhythmias occur in approximately 50% of these animals during routine intra-operative mapping²⁸, unlike in normal humans. The gastric serosal surface was exposed by a mid-line laparotomy and the method of anaesthesia and physiological monitoring was performed as described by Egbuji *et al.*⁷.

All HR recordings were performed using flexible printed circuit board (PCB) arrays (192–256 electrodes; 0.3 mm diameter gold contacts, 7.62 or 4 mm inter-electrode spacing) which were tessellated and held in place with Tegaderm (3M, Minneapolis, MN)⁴ (Fig. 1(b)). The PCB arrays were gently placed on the serosal surface of the stomach with minimal gastric handling and were held in contact using warmed saline-soaked gauze. Typically, the PCB arrays were placed on the anterior region of the stomach and covered 30–60% of the anterior surface. A five minute period of stabilization was allowed prior to a recording period (9.1±4.7 min). Ten datasets were acquired for this study. The data was recorded using the ActiveTwo System (Biosemi, Amsterdam) with a sampling frequency of 512 Hz. The common mode sense (reference) electrode was placed on the body surface of the lower abdomen. The right-leg drive electrode (ground) was placed on the right hind leg.

The raw data was processed and analyzed in Matlab R2011b (Natick, Massachusetts). The raw signals were first downsampled to 30 Hz and filtered using a moving median filter to eliminate baseline wander and a Savitzky-Golay filter to remove high-frequency noise^{31, 32}.

The slow wave events were identified using a validated automated variable threshold method (Fig. 1(a)), and then clustered into their propagating wavefronts using a validated polynomial-based-surface estimate algorithm^{8,9}. The clustered wavefront was visualized as an activation time (AT) map, which represents the spatio-temporal pattern of slow wave propagation as recorded from the surface of the stomach^{4,8} (Fig. 1(c)). The velocity and amplitude of the slow wave propagation as depicted in the AT map was calculated according to recently validated automated methods^{31,33}.

3.2 Automated classification of slow wave propagations

The goal of the automated classification algorithm was to efficiently quantify the degree of similarity between heterogeneous AT maps. Similar slow wave propagation patterns were categorized into a single class. The representative propagation pattern for each class were computed as an average of the individual AT maps within the class, and these representative propagation patterns were denoted as 'templates'.

A schematic of the automated classification algorithm is shown in Fig. 2. The algorithm assigned the first candidate AT map from the HR recording sequence as a template, and subsequent candidate AT map were compared to all existing templates using a Pearson correlation coefficient (PCC) similarity metric:

$$PCC = \frac{(X - \mu_X)(Y_i - \mu_{Y_i})}{\sigma_X \sigma_{Y_i}} \quad (1)$$

where X is a two-dimensional matrix of times in the candidate AT map, Y_i is a two-dimensional matrix of times in the i^{th} AT template, μ_X and μ_{Y_i} are the associated means, and σ_X and σ_{Y_i} are the associated standard deviations of X and Y_i respectively. If there was no corresponding time value for either the candidate AT map or AT templates, those time values were discarded prior to estimation of the PCC. If the candidate AT map did not cover at least 20% of the electrode array, it was discarded from the classification algorithm.

A PCC threshold (PCC_{th}) of 0.9 was selected by systematically varying this parameter when applied to synthetic data and experimental recordings (see Section 3.4.1) to group similar wave events. That is, if a candidate AT map had PCC greater than 0.9, it was considered to be similar to an existing template. If the candidate AT map had PCC greater than 0.9 for multiple templates, the template with the highest PCC was selected. The candidate AT map was then assigned to the matching template, and the template was updated by averaging the candidate AT map with the template itself at each electrode position. If a candidate AT map had PCC below the threshold of 0.9 across all existing templates, it was considered dissimilar to any existing templates, and it was assigned as a new AT template.

After all the AT maps were assessed by the above classification algorithm, the total number of resultant templates represented the number of propagation pattern modes present in a particular experimental recording. If the recorded data had consistently stable propagation patterns then the result would only be a single AT template. On the other hand, if the recorded data had unstable propagation patterns, then a larger number of AT templates would result. To assess the stability of the slow wave propagation in an experimental recording, the occurrence (Occ) of each AT template was calculated as a percentage:

$$Occurrence(\%) = \frac{I}{N} \times 100, \quad (2)$$

where I is the number of AT maps that were used to construct the template, and N is the total number of AT maps in the experimental recording.

3.3 Identification of slow wave propagation patterns

Once the gastric slow wave propagation pattern modes were acquired as AT templates, a 2D Gaussian low pass filter (size 2×2 and σ as 0.25) was applied to the AT templates to filter any noise accumulated as part of the averaging process from the automated classification method (Matlab functions: *fspecial*, *imfilter*). Regions of interest with key slow wave propagation features were then identified in the AT templates. Three spatial propagation patterns of central interest were: (i) pacemaker (normal or ectopic) activity, (ii) colliding wavefronts, and (iii) conduction block. An explanation of these patterns and justification for their selection as priority patterns is provided in the following sections. Mathematical operations on the velocity vector of the slow wave propagation were used along with image processing techniques to detect regions of interest, as illustrated in the flowchart in Fig. 3.

3.3.1 Pacemaker region (normal and ectopic)—The pacemaker region is a site where slow wave activity originates. Normally, the pacemaker originates from the greater curvature of the mid- to upper-corpus region of the stomach^{25, 17}, but ectopic initiations also occur, causing abnormal slow wave activation patterns⁷. Ectopic pacemakers have been found to underlie dysrhythmic propagation at bradygastric, normal and tachygastric frequencies in animal and human models, causing ‘retrograde’ or aboral propagations^{24, 18, 28, 27}. To detect pacemaker regions from the AT template map, the divergence of the velocity field of the AT templates was computed. The divergence denotes whether the velocity vectors are diverging from a point, or are converging from all directions to a point, as shown in Fig. 4(a) and Fig. 4(b). A threshold of greater than 1 (based on synthetic and experimental data) was used to mark regions that denote the site of diverging velocity vectors from a point, and hence a pacemaker region in the AT template. If there was more than one separate region identified, it indicates the presence of multiple pacemakers. The largest divergence value in each of the separate thresholded regions were chosen as the pacemaker locations. For ease of visualization and localization, the pacemaker origin was dilated using a radius of 10 pixels (4 mm) in a separate field map, as shown in Fig. 4(c).

3.3.2 Colliding wavefronts—A colliding wavefront occurs when two or more slow wave propagation wavefronts propagate into one another. The presence of colliding wavefronts is a key indicator of disorganized conduction sequences^{24, 18, 28, 27}, and can be attributed to one of two scenarios. In the first scenario, there is more than one slow wave pacemaker active, and these sources may ‘compete’ for entrainment of the surrounding tissue, leading to wavefront collisions in a stable or unstable manner. In the second scenario, a slow wave wavefront encounters a region of incomplete conduction block, causing a wavelet to arise, that travels around the block that subsequently collides with the same wavefront.

At a region of a colliding wavefront, velocity vectors of different directions would converge onto a point, and hence would be reflected as a ‘sink’ in the divergence map. A threshold of -0.4 for the divergence map was determined by systematically varying this parameter when applied to synthetic and experimental data, and was found satisfactory for identifying colliding wavefront regions in most cases (see Fig. 5), but with false positives being detected in some cases. Therefore, to further increase the specificity of identification, an inter-pixel watershed algorithm was applied to the AT template (Matlab function: *watershed*)²³. Here the watershed algorithm finds the ridges on the AT map (synonymous to a hilltop of a mountain range), which represent two or more wavefronts intersecting at a point or a plane from opposing directions, denoting a colliding wavefront (See Fig. 5(c)). To

avoid detecting false positives, only ridges with a height (time difference) of greater than 0.15 were retained with certainty. The intersection of areas between the watershed and the thresholded divergence map (Fig. 5(e)) was identified as the region where two or more wavefronts collided (Fig. 5(f)). Both the divergence and the inter-pixel watershed algorithm were used, as this combination provided corroborative detection of a colliding wavefront (Fig. 5(e),(f)). Finally, for ease of visualizing the colliding wavefront, the colliding wavefront region was dilated and morphologically closed (See Fig. 5(g)). If the resultant detected colliding site was less than 200 pixels (corresponding to roughly 30 mm^2), it was considered as a false positive and discarded.

3.3.3 Conduction block—A conduction block is a premature termination of the propagating wavefront, which can arise due to either a functional or anatomical consequence. One of the key characteristics of a reentrant propagation sequence is a conduction block. It has been well established in cardiac electrophysiology that re-entry and functional and anatomical blocks are the basis for many cardiac arrhythmias, some of which may lead to fatal disorganization of cardiac contractions^{1, 34}. Kay *et al.* have used the curvature of the wavefront to understand the drivers and perpetuators of disorganized cardiac arrhythmia patterns, such as spiral activity, wave breakup and colliding activity, in a modelling scenario to be extended for use in optical mapping experiments¹⁴. In the GI field, re-entrant and conduction block patterns of slow wave activity has recently been discovered^{2, 18, 28}, but its clinical significance is yet to be studied in detail¹⁶.

For detection of a conduction block in the gastric AT template, the mean curvature (C_m) of the AT template was used:

$$C_m = \frac{eG - 2fF + gE}{2(EG - F^2)}, \quad (3)$$

where E, F, G are the coefficients of the first fundamental form of the AT map, while e, f, g are the coefficients of the second fundamental form of the AT map¹¹.

During the conduction block, the slow wave does not spread homogeneously due to the tissue being in a refractory state, tissue damage, or loss of ICC. Thus, the slow wave revolves around a functional or anatomical obstacle. In the case of re-entry, it would revolve around the functional obstacle, as well as re-exciting the same circuit of tissue, to initiate continuous slow wave propagation. The pathway around a conduction block can be seen as a large change in curvature at the sites of the AT template (Fig. 6(b)).

In the mean curvature map, the area of conduction on either side of a block can be identified, but the region of interest is actually the region located between the large curvature values, denoting the block. To identify the site of the conduction block, first, areas were identified in the mean curvature map that had values greater than a specified threshold (chosen as 0.015 based on synthetic and experimental data). If there was a conduction block present in the AT map, the identified areas would be on either side of the conduction block (see Fig. 6(b),(c)).

Two separate operations were then performed on the remaining areas. First, a topological skeleton was identified outside of the detected area via the mean curvature threshold (Fig. 6(e)) (Matlab function: *bwmorph*). The topological skeleton is a line that is equidistant to its boundaries and identifies the shape outside of the detected areas. Second, a morphological dilation was performed so that the boundaries of the areas merged (See Fig. 6(d)). The intersection between the merged area and the skeleton formed the site for the conduction

block (Fig. 6(f),(g)). Again for ease of visualization, the identified site was dilated and morphologically closed (See Fig. 6(h)). As the conduction block sites routinely span several millimetres^{28, 18}, areas of identified potential conduction block with less than 100 pixels (corresponding to an area of 16 mm²) were considered false-positives, and were discarded (See Fig. 6(i)).

3.4 Validation of automated classification and identification algorithm

3.4.1 Synthetic data—Synthetic AT maps were developed to test the effectiveness of the classification and identification algorithm. Four scenarios of propagations were created: (i) normal propagation, (ii) pacemaker, (iii) colliding wavefronts, and (iv) a linear conduction block. Normal propagation was created using a linear planar function, while the pacemaker was created using an elliptical function (reflecting the anisotropic nature of gastric conduction, being more rapid circumferentially than longitudinally²⁷). Parameters for the function were chosen to represent gastric slow wave propagation^{33, 28, 25}. Colliding wavefronts were created using two elliptical functions with the source of propagation of two opposing corners of the electrode array with the collision path placed diagonally in the electrode array. To represent a conduction block, a linear forward propagating sequence was created for one half of the array, while the other half of the array was constructed using a linear backward propagating sequence. To simulate realistic AT maps, normally distributed random perturbations of 0.5 s were added to each electrode position of the AT map during the creation of synthetic of slow wave propagation³³.

These four synthetic scenarios were applied to generate five synthetic sequences of AT maps (10 minutes long, i.e. the approximate duration of the experimental recordings). Two of the five sequences of synthetic slow wave propagation had one sequence of propagation representing normal slow wave propagation, while the rest of the 3 test sequences had 2, 3 and 4 different scenarios placed in systematically determined locations to depict dysrhythmic slow wave activity.

3.4.2 Experimental data—Experimental HR gastric slow wave recordings comprised 10 data as stated in Section 2.1. Five of the data sets exhibited exclusively normal propagation, while the other five data sets included dysrhythmic events encompassing the typical range of dysrhythmic propagation patterns^{24, 28, 18}. To further define important spatial characteristics of the slow wave propagation patterns in each data set, the velocity and amplitude distributions were defined for each class of propagation, as identified by the templating system, and these were tested by ANOVA for statistical difference in patterns (threshold $p < 0.05$).

Two expert investigators worked independently to manually classify the datasets (314 AT maps in total) as a benchmark for validation. After the application of the classification algorithm to experimental data sets, the output templates (23 in total) were visually assessed by two expert investigators independently to identify the type of propagation pattern as, either (i) pacemaker, (iii) colliding wavefronts and (ii) conduction block, and to localize the dysrhythmic features regionally.

To assess the accuracy of the automated classification methods, the results were compared against manual assessment of the maps. The same approach was performed to compute the accuracy of the localization algorithm to define the pattern present. To define the error in localizing the pattern of interest in the AT template, the root mean squared distance between the manually marked region and the automatically marked region was calculated.

4 Results

4.1 Synthetic cases

The automated classification algorithm was applied to synthetic gastric slow wave propagation and the algorithm classified all synthetic sequences correctly into their according classes.

The automated identification was applied to the four scenarios of synthetic slow wave propagation and were able to identify the type of propagation and localize it regionally in the AT map as shown in Fig. 7.

4.2 Experimental recordings

4.2.1 Automated classification algorithm—Table 1 presents the results of applying the automated classification algorithm across all experimental slow wave HR recording datasets, including the number of waves analyzed, number of template classes identified in each experiment, and the statistical outcomes of comparing amplitude and velocity profiles between templates. Compared to manual analysis the automated methods classified the AT maps with 96% accuracy. It took between 20–40 minutes to manually review, compare and classify AT maps, whereas the automated algorithm was almost instantaneous, taking less than 1 s.

Application of the algorithm applied to an example dysrhythmic slow wave sequence (Experiment No. 10 in Table 1) is presented in Fig. 8. Fig. 8 shows a ‘mode graph’, which demonstrates the stability of slow wave propagation through time, and indicates AT templates identified throughout the sequence. The example also shows how the frequency of the slow wave propagation can be interpreted from the mode graph. For approximately the first 250 s of this recording, the slow wave propagation was 3.8 cpm and then for the remainder of the recording, the frequency dropped to an average of 1.6 cpm. When the frequency was at 3.8 cpm the AT maps switched classes twice. The switch was from an ectopic pacemaker propagation to a similar pacemaker pattern, but with no conduction to half the field, for one wave, which then reverted back to the ectopic pacemaker propagation. With the drop in frequency, the AT maps switched classes seven times and the patterns of propagation were varied, indicating highly unstable activation.

A further sequence of typical porcine gastric dysrhythmia is demonstrated in Fig. 9(a). In this example, the slow wave propagation reversed its direction from normal antegrade propagation to retrograde propagation, due to the occurrence of an ectopic pacemaker (Fig. 9(b)). The mode graphs shows that these two distinct propagation patterns have the same frequency of 3.3 cpm; this dysrhythmia would therefore have gone undetected by frequency-domain analysis alone (e.g., performed by standard EGG). To further characterise the spatial properties of the sequence, the velocity and amplitude distribution of each of the AT maps belonging to each of the template propagation pattern were plotted as a histogram (Fig. 9(c)). A clear separation in the distributions of the velocity and amplitude characteristics can be seen across the two patterns of slow wave propagation (refer to Table 1 for further data and statistical comparisons -Experiment No. 2).

4.3 Automated identification algorithm

The automated identification algorithm identified the patterns of interest in the AT maps with an average accuracy of 95% with a mean localizing error of 3 pixels (~ 1.5 mm) in comparison to manual identification. The identification algorithm marked all of the pacemaker sites (5/5) and colliding wavefronts (9/9) and all but one conduction block site (6/7). The mean error in localizing the pacemaker site was 3 pixels (~ 1.5 mm), colliding

wavefront site was 2 pixels (~ 1 mm) and conduction block site was 4 pixels (~ 2 mm). Fig. 8 shows an example identification of the pacemaker activity and a conduction block. Fig. 10 shows an example identification of colliding wavefronts. The automated pattern identification algorithm was also applied on individual AT maps in an experimental recording to track the pacemaker site (see Supplementary material 1).

5 Limitations, Discussion & Conclusions

5.1 Limitations

One of the major limitations of the classification method is that it requires the slow wave event to be identified accurately and the AT map to be correctly clustered into propagating wavefronts. Lowering the PCC threshold for the classification algorithm will allow the method to work for imprecisely detected activation times (due to experimental noise). The downside to lowering the PCC threshold is that the method becomes less sensitive at differentiating propagation patterns. An imposed limitation of the classification algorithm was that if less than 20% of the electrode array was mapped, the method was instructed to ignore that map. Thus, it is imperative to have *a priori* knowledge about the existence of the area mapped before utilization of this algorithm (e.g., fundus is known to be electrically silent).

Like the classification algorithm, the identification algorithm has parameters that can potentially be calibrated based on the level of experimental noise present in the AT map. The parameters that can be adjusted for pacemaker detection is the divergence threshold; for colliding wavefront are the divergence threshold and time difference of the watershed algorithm for detection; and for the conduction block site it is the mean curvature threshold. One of the limitations of the automated identification method is that the accuracy of the localization is based on the inter-electrode distance spacing used in the experimental setup. Also, the identification algorithm is unable to differentiate between a functional or anatomical block, or re-entry; and for colliding wavefronts, the potential resultant of merging wavefronts were not identified. Nonetheless, these specific patterns of propagation can be readily interpreted by the end user when presented with the summary of the recording via a mode graph and identified patterns

5.2 Discussion & Conclusions

In this study we have presented two novel automated methods to analyze and characterize spatio-temporal patterns of normal and dysrhythmic gastric slow wave propagation. The first method was an automated classification algorithm to group slow wave AT maps into classes of similar propagation patterns. The second automated method identified specific slow wave propagation patterns and located their key features within the mapped fields. Utilization of these two methods in tandem allows for an accurate quantitative analysis of gastric slow wave activation patterns in an efficient, specific, intuitive and unbiased manner.

Other techniques have been used to analyze HR cardiac mapping studies^{10, 14, 35, 36}. However these methods could not be directly translated to the GI field due to the significantly different characteristics in the spatio-temporal patterns, time course and signals between cardiac and GI electrophysiology^{9, 8}. The automated classification techniques applied here were motivated in part, by the work of Rogers *et al.*³⁵, where correlation was used to cluster cardiac wavefronts, and the multiplicity index used to account for the fraction of activation patterns in the cluster. Identification of the slow wave propagation patterns and regionally localizing it in the AT map was partly inspired by the work performed by Fitzgerald *et al.*¹⁰, where curl and divergence operators were used on spatiotemporal cardiac mapping data to identify cardiac rhythm. In the GI field, a method has been

proposed to study slow wave dysrhythmias via the use of velocity vectors of the slow wave propagation⁶. Although this method is semi-automated, it still heavily relies on the clinician or researcher to manually define the normal slow wave propagation patterns, and can only ascertain if the AT map is normal or abnormal.

The discovery that ICC generate and propagate gastric slow waves, and that ICC are depleted in major gastric motility disorders such as gastroparesis¹², has reinvigorated clinical GI interest in investigating gastric dysrhythmia. Traditional methods of cutaneous EGG have not been widely adopted, partly due to their incomplete specificity and susceptibility to noise³⁰. However, the application of HR mapping is providing a vital advance, and may now be establishing a new era in which gastric electrical diagnostics can meaningfully inform clinical practice^{15, 16}. In particular, the successful recent translation of HR mapping to gastroparesis has proved that, unlike EGG, HR methods generate data that clearly discriminates abnormal patterns of slow wave initiation and conduction in disease states, including when frequency is normal²⁴ (e.g., Fig. 9). We anticipate that the methods developed here will be a further critical step in the clinical translation of HR mapping. Together with a recently developed automated pipeline of filtering, event detection, and spatial mapping³⁸, this current work will now enable clinicians who are unskilled in signal or image processing to apply HR mapping techniques to classify and interpret abnormal initiation and conduction patterns in GI motility patients. This translation will be further facilitated by the anticipated development of endoscopic HR mapping devices.

The automated analysis methods developed here can be used to assess the efficacy of proposed drug therapies for GI dysrhythmias, such as prostaglandin synthesis inhibitors and natural remedies on slow wave activity^{29, 20}. With the emergence of gastric stimulation as a potential treatment option²², these automated methods will allow for immediate assessment of the gastric slow wave activity and can help guide the stimulation protocols. As occurs in clinical cardiology³⁷, the new methods described here could be applied in an online setting to allow clinicians to make an immediate assessment on the efficacy of the treatments such as pacing, and make alterations to the treatment as necessary. This is feasible because the methods were computationally efficient. The rapid processing time is advantageous because the computational overhead is a significant factor for implementation and visualization of online HR data³.

In human gastric HR mapping studies, it has been revealed that during the circumferential propagation that arises in dysrhythmia, local slow wave velocity increases by more than two-fold due to the inherent anisotropy in the stomach²⁴. A concurrent increase in extracellular amplitude also occurs due to increased transmembrane current entering the extracellular space²⁷. Although the effect is less in pigs²⁷, these properties may still be appreciated in Fig. 9 of the current study, where circumferential propagation arises during ectopic initiation. The higher velocity is indicated by the larger spacing of isochrones, and the zone of high velocity corresponded with the zone of higher amplitudes. The ability to accurately detect and identify these important spatial characteristics provides an essential additional level of clinical reliability for the correct detection and interpretation of dysrhythmic activation. For example, the classification method presented here could potentially become over-sensitive in the presence of excessive noise, which may distort the activation time maps^{9, 8}, resulting in a spuriously large number of classes. But if templates of the pacemaker, colliding wavefront and conduction block were not accompanied by these anticipated (and statistically verifiable) physiological velocity and amplitude changes, then such templates can be safely identified as false positive patterns. In future human trials, a library of normal and abnormal slow wave propagation templates could also be developed for the various regions of the stomach, enabling automatic correct discrimination of key dysrhythmic patterns and their sources for clinicians. This step could also stimulate the

development of more advanced algorithms for pattern analysis and identification via the use of neural networks or support vector machines.

In conclusion, the new automated classification and identification methods are anticipated to provide valuable insights into the nature of normal and dysrhythmic slow wave propagation during experimental and clinical recordings. With the ability to map GI HR slow wave activity using laparoscopic techniques intra-operatively²⁶, and potentially endoscopically in the future, the application of these methods will allow analysis in real-time and can facilitate immediate treatment for GI disorders, similar to what routinely occurs in cardiac electrophysiology³⁷. These methods are efficient, accurate, unbiased and intuitive, and their development will facilitate the clinical translation of HR mapping for patients with gastric motility disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by funding from the NZ Health Research Council (New Zealand) and the, NIH R01 grant (R01 DK64775). JG was supported by a University of Auckland Health Research Doctoral Scholarship, a Freemasons Postgraduate Scholarship, and a R. H. T. Bates Postgraduate Scholarship. PD was supported by a New Zealand Postdoctoral Fellowship and a Marsden Fast-Start grant.

References

1. Allesie M, Lammers W, Bonke I, Hollen J. Intra-atrial reentry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. *Circulation*. 1984; 70:123–135. [PubMed: 6723008]
2. Angeli TR, O'Grady G, Du P, Paskaranandavadi vel N, Pullan AJ, Bissett IP, Cheng LK. Circumferential and functional re-entry of in vivo slow-wave activity in the porcine small intestine. *Neurogastroenterol Motil*. 2013; 25(5):e304–14. [PubMed: 23489929]
3. Bull S, O'Grady G, Cheng L, Pullan A. A framework for the online analysis of multi-electrode gastric slow wave recordings. *Conf Proc IEEE Eng Med Biol Soc IEEE*. 2011:1741–1744.
4. Du P, O'Grady G, Egbuji J, Lammers W, Budgett D, Nielsen P, Windsor J, Pullan A, Cheng L. High-resolution mapping of in vivo gastrointestinal slow wave activity using flexible printed circuit board electrodes: methodology and validation. *Ann Biomed Eng*. 2009; 37:839–846. [PubMed: 19224368]
5. Du P, O'Grady G, Gao J, Sathar S, Cheng LK. Toward the virtual stomach: progress in multiscale modeling of gastric electrophysiology and motility. *WIREs Syst Biol Med*. 2013
6. Du P, O'Grady G, Paskaranandavadi vel N, Angeli TR, Lahr C, Abell TL, Cheng LK, Pullan AJ. Quantification of velocity anisotropy during gastric electrical arrhythmia. *Conf Proc IEEE Eng Med Biol Soc IEEE*. 2011:4402–4405.
7. Egbuji J, O'Grady G, Du P, Cheng L, Lammers W, Windsor J, Pullan A. Origin, propagation and regional characteristics of porcine gastric slow wave activity determined by high-resolution mapping. *Neurogastroent Motil*. 2010; 22:e292–e300.
8. Erickson J, O'Grady G, Du P, Egbuji J, Pullan A, Cheng L. Automated gastric slow wave cycle partitioning and visualization for high-resolution activation time maps. *Ann Biomed Eng*. 2011; 39:469–483. [PubMed: 20927594]
9. Erickson J, O'Grady G, Du P, Obioha C, Qiao W, Richards W, Bradshaw L, Pullan A, Cheng L. Falling-edge, variable threshold (FEVT) method for the automated detection of gastric slow wave events in high-resolution serosal electrode recordings. *Ann Biomed Eng*. 2010; 38:1511–1529. [PubMed: 20024624]
10. Fitzgerald T, Brooks D, Triedman J. Identification of cardiac rhythm features by mathematical analysis of vector fields. *IEEE Trans Biomed Eng*. 2005; 52:19–29. [PubMed: 15651561]

11. Gray, A.; Abbena, E.; Salamon, S. Modern differential geometry of curves and surfaces with Mathematica. Chapman & Hall; 2006.
12. Grover M, Bernard C, Pasricha P, Lurken M, Faussone-Pellegrini M, Smyrk T, Parkman H, Abell T, Snape W, Hasler W, et al. Clinical-histological associations in gas-tro paresis: results from the gastroparesis clinical research consortium. *Neurogastroent Motil.* 2012; 24:531–e249.
13. Huizinga J, Lammers W. Gut peristalsis is governed by a multitude of cooperating mechanisms. *Am J Physiol Gastrointest Liver Physiol.* 2009; 296:G1–G8. [PubMed: 18988693]
14. Kay MW, Gray RA. Measuring curvature and velocity vector fields for waves of cardiac excitation in 2-d media. *IEEE Trans Biomed Eng.* 2005; 52:50–63. [PubMed: 15651564]
15. Koch K. The electrifying stomach. *Neurogastroent Motil.* 2011; 23:815–818.
16. Lammers W. Arrhythmias in the gut. *Neurogastroent Motil.* 2013; 25:353–357.
17. Lammers W, Ver Donck L, Stephen B, Smets D, Schuurkes J. Origin and propagation of the slow wave in the canine stomach: the outlines of a gastric conduction system. *Am J Physiol Gastrointest Liver Physiol.* 2009; 296:G1200–G1210. [PubMed: 19359425]
18. Lammers WJ, Ver Donck L, Stephen B, Smets D, Schuurkes JA. Focal activities and re-entrant propagations as mechanisms of gastric tachyarrhythmias. *Gastroenterology.* 2008; 135:1601–1611. [PubMed: 18713627]
19. Lees-Green R, Du P, OGrady G, Beyder A, Farrugia G, Pullan A. Biophysically based modeling of the interstitial cells of Cajal: current status and future perspectives. *Front Physio.* 2011; 2
20. Lien HC, Sun WM, Chen YH, Kim H, Hasler W, Owyang C. Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circularvection. *Am J Physiol Gastrointest Liver Physiol.* 2003; 284:G481–G489. [PubMed: 12576305]
21. Lin Z, Eaker EY, Sarosiek I, McCallum RW. Gastric myoelectrical activity and gastric emptying in patients with functional dyspepsia. *Am J Gastroenterol.* 1999; 94:2384–2389. [PubMed: 10483996]
22. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol.* 2010; 8:947–954. [PubMed: 20538073]
23. Meyer F. Topographic distance and watershed lines. *Signal processing.* 1994; 38:113–125.
24. O'Grady G, Angeli T, Du P, Lahr C, Lammers W, Windsor J, Abell T, Farrugia G, Pullan A, Cheng L. Abnormal initiation and conduction of slow-wave activity in gastroparesis, defined by high-resolution electrical mapping. *Gastroenterology.* 2012; 143:589–598. [PubMed: 22643349]
25. O'Grady G, Du P, Cheng L, Egbuji J, Lammers W, Windsor J, Pullan A. Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping. *Am J Physiol Gastrointest Liver Physiol.* 2010; 299:G585–G592. [PubMed: 20595620]
26. O'Grady G, Du P, Egbuji JU, Lammers WJ, Wahab A, Pullan AJ, Cheng LK, Windsor JA. A novel laparoscopic device for measuring gastrointestinal slow-wave activity. *Surg Endosc.* 2009; 23:2842–2848. [PubMed: 19466491]
27. O'Grady G, Du P, Paskaranandavadivel N, Angeli T, Lammers W, Asirvatham S, Windsor J, Farrugia G, Pullan A, Cheng L. Rapid high-amplitude circumferential slow wave propagation during normal gastric pacemaking and dysrhythmias. *Neurogastroent Motil.* 2012; 24:e299–e312.
28. O'Grady G, Egbuji J, Du P, Lammers W, Cheng L, Windsor J, Pullan A. High-resolution spatial analysis of slow wave initiation and conduction in porcine gastric dysrhythmia. *Neurogastroent Motil.* 2011; 23:e345–e355.
29. Owyang C, Hasler W. Physiology and pathophysiology of the interstitial cells of Cajal: from bench to bedside. VI. Pathogenesis and therapeutic approaches to human gastric dysrhythmias. *Am J Physiol Gastrointest Liver Physiol.* 2002; 283:G8. [PubMed: 12065286]
30. Parkman H, Hasler W, Barnett J, Eaker E. Electrogastrography: a document prepared by the gastric section of the american motility society clinical GI motility testing task force. *Neurogastroent Motil.* 2003; 15:89–102.
31. Paskaranandavadivel N, Cheng LK, Du P, O'Grady G, Pullan AJ. Improved signal processing techniques for the analysis of high resolution serosal slow wave activity in the stomach. *Conf Proc IEEE Eng Med Biol Soc IEEE.* 2011:1737–1740.

32. Paskaranandavadivel N, O'Grady G, Du P, Cheng LK. Comparison of filtering methods for extracellular gastric slow wave recordings. *Neurogastroent Motil.* 2013; 25:79–83.
33. Paskaranandavadivel N, O'Grady G, Du P, Pullan AJ, Cheng LK. An improved method for the estimation and visualization of velocity fields from gastric high-resolution electrical mapping. *IEEE Trans Biomed Eng.* 2012; 59:882–889. [PubMed: 22207635]
34. Pogwizd SM, Hoyt R, Saffitz J, Corr P, Cox J, Cain M. Reentrant and focal mechanisms underlying ventricular tachycardia in the human heart. *Circulation.* 1992; 86:1872–1887. [PubMed: 1451259]
35. Rogers JM, Usui M, KenKnight BH, Ideker RE, Smith WM. A quantitative framework for analyzing epicardial activation patterns during ventricular fibrillation. *Ann Biomed Eng.* 1997; 25:749–760. [PubMed: 9300099]
36. Rogers JM, Usui M, KenKnight BH, Ideker RE, Smith WM. Recurrent wavefront morphologies: a method for quantifying the complexity of epicardial activation patterns. *Ann Biomed Eng.* 1997; 25:761–768. [PubMed: 9300100]
37. Shenasa, M.; Hindricks, G.; Borggrefe, M.; Breithardt, G. *Cardiac mapping*. fourth. Wiley-Blackwell; 2009.
38. Yassi R, O'Grady G, Paskaranandavadivel N, Du P, Angeli T, Pullan A, Cheng L, Erickson J. The gastrointestinal electrical mapping suite (GEMS): software for analyzing and visualizing high-resolution (multi-electrode) recordings in spatiotemporal detail. *BMC Gastroenterol.* 2012; 12:60. [PubMed: 22672254]

(a) Electrode trace with slow wave events marked **(b) Electrode array** **(c) Activation time (AT) map** **Figure 1.**

Gastric HR slow wave recordings on the anterior and posterior surfaces of the porcine serosa near the greater curvature. (a) shows example signal traces from one column of the flexible PCB electrode array which is shown in (b) in the red rectangle. The slow wave events along the arrow in (a) are represented in the activation time map in (c) shown in the black rectangle. The red crosses in the signals in (a) denote the time at which a slow wave event passes under an electrode. The orientation of the PCB electrode array as placed on the serosal surface of the stomach is shown in (b). (c) shows the isochronal AT map (1 s interval) of the slow wave propagating from the top to the bottom of the array.

Figure 2.

Flowchart of automated classification algorithm. A Pearson cross correlation (PCC) was used as a similarity metric to categorize activation time (AT) maps into the matching AT templates depending on a threshold (PCC_{th}).

Figure 3.

Flowchart illustrating the steps taken to identify key regions of interest in the slow wave propagation. Three patterns of interest were: (i) pacemaker (in green boxes), (ii) colliding wavefront (in blue boxes) and (iii) conduction block (in orange boxes). Note that a single activation time map (AT_{map}) may possess more than one key propagation pattern, and the propagation pattern identification algorithm flowchart illustrates this using dotted arrows. The divergence of the activation time map (Div_{ATmap}) was used to identify the pacemaker and colliding wavefront, while the mean curvature of the activation time map ($MeanCurv_{ATmap}$) was used to identify the conduction block.

Figure 4.

Test case showing (a) an AT map with an origin where velocity vectors are diverging and a point where all the velocity vectors are converging. (b) shows the corresponding divergence map of (a). The test case function defining the AT map was defined as $T = aXe^{-a(X-X_0)^2 - a(Y-Y_0)^2}$, where $a=0.25$, X_0 and $Y_0 = 2$. In the divergence map, a positive value (red) indicates a source and a negative value (blue) indicates a sink. In (c) the large divergence value is used to detect a pacemaker site, and for visualization it has been dilated by 10 pixels (4 mm).

Figure 5.

Steps used to denote areas of colliding slow wave wavefronts. (a) shows the isochronal activation map with 1 s intervals. (b) shows the divergence map of (a). (c) shows the result of the watershed of the AT map in (a). (d) shows the overlap of the thresholded area in the divergence map. (e) is the overlap between (c) and (d). (f) shows the resultant intersection of (c) and (d). (g) is the dilation of (f) to clearly illustrate the area of collision.

Figure 6.

Steps used to identify a site of a conduction block. (a) shows an isochronal activation map (1 s interval) which has a pacemaker, as well as a circular propagation with a conduction block, as illustrated by the stacked isochrones. (b) shows the mean curvature map of (a). (c) shows the thresholded map of the mean curvature map. (d) is the where the objects in (c) have been dilated so that the objects merge together, while (e) is the results of the skeleton algorithm of (c). (f) shows the intersection of the of the two images (d) and (e) overlaid, and (g) shows the intersection. In (h) the objects are dilated for clarity. To eliminate erroneous detection and to place physiological limits on the area of the conduction block, any identified objects less than 16 mm^2 or 100 pixels was eliminated as shown in (i).

Figure 7.

Automated identification on synthetic slow wave propagation. The first column shows the synthetic slow wave propagation plotted as an isochronal activation time map (1 s interval). The second column shows the automated identification of the regional characteristics of the gastric slow wave propagation. (a) is a synthetic pacemaker activity. (b) shows two wavefronts colliding across the diagonal in the electrode array. (c) is a zoomed in version of a linear conduction block.

Figure 8.

Mode graph and the AT templates with the key propagation patterns identified and marked. (a) shows the that there are six AT templates that alternated throughout the recording. (b) – (g) shows the AT templates as an isochronal activation time map (1 s interval), their percentage of occurrence, and key features identified, along with a legend at the bottom to intuitively assess the propagation patterns.

Figure 9.

Mode graph and histogram illustrating two classes of propagation present i.e., antegrade and retrograde slow wave propagation. In (a) the mode graph provides information on the order and percentage of propagation pattern occurrence, and frequency of the slow waves. Four of the AT maps are shown in the mode graph. (b) shows the final two templates generated by the automated classification method, with the arrows overlaid to show the dominant propagation direction. The antegrade propagation direction is the longitudinal propagation direction, while the retrograde template shows elements of circumferential propagation. (c) shows the amplitude and the velocity variation across the two classes along with the corresponding histograms.

Figure 10.

Mode graph and the AT templates with the key propagating patterns identified and marked. (a) shows that there are four AT templates and they progressively changed without reverting back to the same pattern. (b) – (e) shows the AT templates as an isochronal activation time map (1 s interval) and the corresponding key features identified. The slow wave activity within the mapped field changed from an antegrade activity to an ectopic pacemaker (with the characteristics of a pacemaker and a colliding wavefront), then to a colliding wavefront pattern alone, before retrograde activity entrained the whole mapped field.

Table 1

ANOVA analysis of amplitude and velocity calculations between different propagation pattern classes in five normal and five dysrhythmic data sets. If there was more than one AT template class, an ANOVA was performed between the calculated velocity and amplitude of the different classes identified to detect statistical differences between patterns. There was a difference in amplitude and velocity across patterns in all dysrhythmic data sets (* = $p < 0.05$).

Experiment No.	1	2	3	4	5	6	7	8	9	10
No. of waves	49	16	46	9	7	44	40	53	22	28
No. of classes	1	1	1	1	1	4	5	6	2	6
Amplitude	—	—	—	—	—	*	*	*	*	*
Velocity	—	—	—	—	—	*	*	*	*	*