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Toward the Virtual Stomach: Progress in Multi-scale Modeling of Gastric Electrophysiology and Motility

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Abstract

Experimental progress in investigating normal and disordered gastric motility is increasingly being complimented by sophisticated multi-scale modeling studies. Mathematical modeling has become a valuable tool in this effort, as there is an ever-increasing need to gain an integrative and quantitative understanding of how physiological mechanisms achieve coordinated functions across multiple biophysical scales. These interdisciplinary efforts have been particularly notable in the area of gastric electrophysiology, where they are beginning to yield a comprehensive and integrated *in-silico* organ modeling framework, or 'virtual stomach'. At the cellular level, a number of biophysically-based mathematical cell models have been developed, and these are now being applied in areas including investigations of gastric electrical pacemaker mechanisms, smooth muscle electrophysiology, and electromechanical coupling. At the tissue level, micro-structural models are being creatively developed and employed to investigate clinically significant questions, such as the functional effects of ICC degradation on gastrointestinal electrical activation. At the organ level, high-resolution electrical mapping and modeling studies are combining to provide improved insights into normal and dysrhythmic gastric electrical activation. These efforts are also enabling detailed forward and inverse modeling studies at the 'whole body' level, with implications for diagnostic techniques for gastric dysrhythmias. These recent advances, together with several others highlighted in this review, collectively demonstrate a powerful trend toward applying mathematical models to effectively investigate structure-function relationships and overcome multi-scale challenges in basic and clinical gastrointestinal research.

Acute and chronic digestive disorders remain a major health and economic burden, with substantial uncertainty in their causes and mechanisms.^{1, 2} Concerted research efforts in recent years have led to a better understanding of gastrointestinal (GI) electrophysiological mechanisms in health and in significant digestive diseases such as gastroparesis and functional dyspepsia.^{3, 4} The complexity of the experimental findings has promoted increasing sophisticated mathematical modeling effort, with *in-silico* multi-scale studies now at the forefront of several areas of basic science and clinical research progress.

This review is an extension and update to a previous interdisciplinary review on mathematical modeling of the gastrointestinal (GI) tract,⁵ and is focused principally on the stomach. In a similar manner to the previous review, the current review is organized into a hierarchy of biophysical scales: cellular activities are considered first, followed by tissue, organ and finally whole body level activities. This organization is appropriate because multi-scale modeling by its nature encompasses and quantifies physiological events across vast

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Further Reading/Resources

Hunter P. J. The IUPS Physiome Project: a framework for computational physiology. *Prog Biophys Mol Biol.* 2004 Jun-Jul;85(2–3): 551–69.

spatiotemporal horizons.⁶ Example components from various scales are illustrated for GI electrophysiology in Fig. 1. Modeling efforts to provide comprehensive quantitative descriptions of physiology in health and disease are broadly encompassed under strategic efforts such as the IUPS Physiome Project and Virtual Physiological Human (VPH) project, which have been reviewed elsewhere,⁶ and the work discussed in this review thus comprises collective progress toward a ‘Virtual Stomach’.

This review centers on a number of advances made since the publication of a previous review,⁵ with a particular focus on gastric electrophysiology, where modern modeling techniques have been productively employed to particularly useful effect in recent years. The review also highlights experimental techniques and findings that are relevant to current notable modeling problems, challenges in basic physiological science, and clinical applications.

CELLULAR LEVEL

Interstitial Cell of Cajal Models

Gastric slow waves originate from spontaneous depolarizations of interstitial cell of Cajal (ICC) membrane potentials.⁷ Individual ICC generate slow waves at specific intrinsic frequencies, with a decreasing gradient in the aboral direction.⁸ The mean frequency of gastric slow waves *in-vivo* varies between species, being approximately 3 cpm in humans,⁴ and 3–5 cpm in large animals.^{9, 10} Slow waves from ICC subsequently activate adjoining smooth muscle cells (SMC), which are also under neuronal and hormonal co-regulation, ultimately generating GI motility.²

ICC-ICC Coupling—In the intact stomach and under normal conditions, ICC undergo an ‘entrainment’ process such that the different intrinsic frequencies converge to a single frequency,⁸ i.e., cell-to-cell coupling. The entrainment process causes propagation of gastric slow waves at a speed much lower than typical bioelectrical conduction velocities in the nerves or cardiac muscles. Previous phenomenologically-based models have attempted to simulate the entrainment process by coupling relaxation oscillators in a network and demonstrated a “phase-pulling” effect where the latency between oscillators with different intrinsic frequencies in a bi-directionally coupled network converges to a constant value, thus achieving a consistent propagation pattern^{11, 12}.

Biophysical ICC Model—As more detailed physiological mechanisms regarding the entrainment began to emerge, biophysically-based models that incorporated these mechanisms were required. An example of such an ICC model is a recent cell model developed by Corrias and Buist.¹³ The cell model contains five types of ion conductance governed by the Hodgkin-Huxley type gating variables (two Ca^{2+} conductances, two K^{+} conductance, and one Na^{+} conductance), two Hill type conductances (one Cl^{-} conductance, one Ca^{2+} -extrusion conductance, and one non-selective cation conductance), one Ca^{2+} -dependent K^{+} conductance, and one background K^{+} conductance.¹³ The intracellular domain is divided into a bulk cytoplasm compartment and a pacemaker unit compartment, which includes a mitochondria compartment and an endoplasmic reticulum compartment. The Ca^{2+} kinetics in the pacemaker unit compartment was based on the model developed by Fall and Keizer,¹⁴ and governs the oscillatory intrinsic slow wave activity of the ICC model (Fig. 2b).

ICC Pacemaking Mechanism—The term ‘entrainment’ has also been used to refer to the intracellular convergence of small amplitude depolarizations, termed ‘unitary potentials’, into a single coherent ICC slow wave, which is a different phenomenon, i.e., the ICC pacemaking mechanism.^{15, 16} The concepts underlying these two types of entrainment

activities are not mutually exclusive. It is likely that many of the mechanisms responsible for the ICC pacemaking mechanism, such as ion channels and IP₃-mediated Ca²⁺ release, also play key roles in cell-to-cell entrainment.^{8, 16}

Lees-Green *et al.* recently provided a detailed review of pacemaking mechanisms discovered in ICC and in the context of biophysically-based ICC models.¹⁶ A number of theories of ICC pacemaking have been proposed, and a key motivation of mathematical modeling has been to integrate available data and attempt validation of these theories in an *in-silico* whole-cell environment.¹⁶ In a prominent example, the unitary potential theory of ICC pacemaking has been modeled by Faville *et al.* (Fig. 2a) with a pacemaker unit (PMU) cluster and a bulk cytoplasm model.^{17, 18} The mechanism of action of this model, as originally proposed by Sanders *et al.*,¹⁹ relied on the assumption that the Ca²⁺ released from IP₃R-operated stores in the endoplasmic reticulum could stimulate the uptake of Ca²⁺ by the mitochondria. The uptake was thought sufficient to decrease the local Ca²⁺ concentration near the PMU below the resting level, which would activate a Ca²⁺-inhibited non-selective cation conductance.^{16, 19} However, an intracellular model developed by Means and Sneyd since demonstrated that it was theoretically infeasible to decrease the local Ca²⁺ concentration sufficiently within the physiological range of Ca²⁺ uptake rate into the mitochondria, and the underlying pacemaking mechanism adopted by the model of Faville *et al.* therefore now needs revision.²⁰

A more physiologically-consistent hypothesis of the pacemaking mechanism and entrainment is that Ca²⁺ release from IP₃R-operated stores in the endoplasmic reticulum induces transient inward pacemaker currents.^{8, 16} Voltage-dependent Ca²⁺ entry and IP₃ activation has been successfully modeled in two separate studies.^{21, 22} Both used the whole-cell Corrias and Buist ICC model as the host cell model to test the entrainment mechanisms.¹³ In one study, Du et al. utilized a voltage-dependent IP₃ model component proposed by Imitiaz *et al.* to model a voltage-dependent IP₃ mechanism that accelerates Ca²⁺ cycling in the ICC to invoke slow wave activity.^{22, 23} In another study, Buist *et al.* proposed a voltage-dependent dihydropyridine-resistant pathway to couple the membrane voltage to Ca²⁺ cycling in the pacemaker unit subspace of the whole-cell ICC model.²¹ A Ca²⁺ extrusion mechanism was also incorporated to maintain a long-term homeostasis in the whole-cell model.²¹ The voltage-dependent entrainment mechanisms allowed propagation of slow waves to be modeled at the tissue level (see Section Tissue Level).

ICC Channelopathy Model—A strong correlation between GI symptoms and a sodium ion channel (Na_v1.5) gene mutation has been established in patients with intestinal pseudo-obstruction,²⁴ Brugada syndrome and functional dyspepsia.²⁵ However, the link between the genetic mutation and cell function could not be established directly using patch-clamp recordings from ICC and/or SMC, because the controlled mutations are carried within carrier HEK-293 cells.²⁶ A clear understanding of the effects of channelopathy due to gene mutation on cellular mechanisms that contribute to generation of slow waves would therefore allow detailed analysis on GI functions under pathological conditions and response to pharmaceutical agents. Poh et al. developed detailed Markov description of sodium channels, and simulated the effects of sodium channelopathy by fitting the activation profiles from the HEK-293 cell study and substituting the channel model in the whole-cell ICC and SMC models.^{26, 27} The study demonstrated for the first time a heterogeneous effect of sodium channelopathy on ICC and SMC resting potentials, even though sodium channel kinetics were assumed to be identical in both ICC and SMC.²⁷

Gastrointestinal Smooth Muscle Cell Models

The electrophysiology of SMC has also been an active area of model application. Corrias and Buist developed a SMC model which was parameterized to simulate canine SMC activation (Fig. 2b).²⁸ More recently, a SMC model was published by Poh *et al.* containing seven types of ion conductance, reproducing human jejunal smooth muscle cell (hJSMC) slow wave activity (Fig. 2c).²⁹ An attempt has also recently been made to mathematically evaluate the electromechanical relationship between slow waves and motility in a cell model by Gajendiran *et al.*, which consisted of a bimodular component, and is dependent on intracellular Ca^{2+} concentration (Fig. 2d).³⁰ The model simulated the interaction between Ca^{2+} and calmodulin which activates myosin light-chain kinase (MLCK) in the first module. The pathway of actin-myosin bridge formation, which involves MLCK phosphorylation of myosin, takes place in the second module. The application of this model was recently explored in an initial two-dimensional model of gastric electromechanical coupled activity,³¹ and the need now exists to integrate the functions of ICC, SMC and their electromechanical activity into a fully coupled framework. For example, the hJSMC model was driven by a fitted trace of ICC pacemaker current, whereas the electromechanical model was driven by a fitted trace of intracellular Ca^{2+} concentration. In practice, it has been proposed that Ca^{2+} cycling in the ICC contributes to the intrinsic pacemaking mechanism; the resultant slow wave potential depolarizes the surrounding SMC and activates the Ca^{2+} release mechanisms in the SMC and contractility.³² This electrical coupling mechanism is explored further in the next section.

Electrical Coupling Mechanisms

The electrical coupling mechanisms between ICC-ICC, ICC-SMC, and SMC-SMC are also incompletely understood, making detailed modeling studies uncertain. Hanani *et al.* previously presented a detailed discussion on the experimental evidence regarding potential coupling mechanisms.³³ Electron-microscopic evidence has demonstrated the existence of physical gap junctions between ICC-ICC and ICC-SMC,^{33, 34} and two separate modeling studies have modeled a direct gap junction coupling between ICC and SMC.^{21, 22} However, the distribution of gap junctions in the GI tract is heterogeneous and physiological evidence for their function is inconclusive, particularly between ICC-SMC. Experimental studies have also proposed an interesting stretch-coupled, 'peg-and-socket', interlocking of membranes between the cells during contraction, which could add a dynamic and mechano-sensitive component to the coupling mechanism.³⁵ Furthermore, the increased surface area between these interlocked cell membranes could increase the conductance between ICC and surrounding cells through a field coupling mechanism, and these hypotheses would also be an attractive target for modeling studies.^{8, 33}

Important questions also remain regarding the functional capacity limit of ICC as pacemakers in the GI tract. There may be a tradeoff between the increase in conductance and the effectiveness of entrainment, as previously eluded to in a calcium oscillator coupling study.³⁶ For example, an increase in conductance in the surrounding tissue is likely to dissipate the current faster from the pacemaker ICC. This is another question that could be effectively investigated using mathematical modeling.

TISSUE LEVEL

ICC Distribution and Coordination of ICC Activation

There are inter-regional as well as inter-species variations in the distribution of ICC throughout the stomach, which play an important role in maintaining slow wave propagation and motility.³⁴ Several classes of ICC are identified based on anatomical location.³³ ICC in the myenteric plexus (ICC-MP) and intramuscular compartment (ICC-IM) have been

proposed to underpin gastric slow wave initiation and propagation. In one prominent hypothesis of this sort, Hirst *et al.* proposed that ICC-MP in the guinea-pig antrum drive the initiation and longitudinal propagation of gastric slow waves, exciting ICC-IM in the circumferential muscle at each propagation step, generating secondary slow wave propagation that follows rapidly in the circumferential direction.³⁷ However, this hypothesis does not fit with observed propagation patterns in larger animal models and humans, as revealed by high-resolution (HR) electrical mapping, because circumferential propagation is only normally observed at the pacemaker region in the stomach,^{9, 10, 38} and during gastric dysrhythmia.^{4, 39, 40}

To examine these mechanisms further, a tissue modeling study of gastric anisotropy was recently performed.⁴⁰ An idealized ICC pathway model was developed to test whether a bidirectionally-coupled ICC-MP and ICC-IM network could potentially explain the propagation patterns revealed by HR mapping. In this model (Fig. 3a), as in the original model of Hirst *et al.*,³⁷ ICC-IM preferentially conducted slow waves in the circumferential direction, while conductivity was homogenous in ICC-MP (Fig. 3b). The conductivity in the circumferential direction in the ICC-IM was higher than the conductivity in the ICC-MP. A stimulus was modeled in the middle of these virtual ICC networks to invoke an ectopic pacemaker. When uncoupled, the stimulation invoked slow wave propagation with a uniform circular profile in all directions in the ICC-MP layer, demonstrating that ICC-MP conduction alone cannot explain experimentally-observed patterns (Fig. 3c). On the other hand, if the two layers were bidirectionally-coupled, an elliptical profile around the pacemaker site was reproduced (Fig. 3d), i.e., ICC-IM was required to generate the faster circumferential component, while slower longitudinal conduction occurred in ICC-MP.⁴⁰ The details of ICC and smooth muscle structural heterogeneity and their impact on slow wave propagation await further study before this model can be validated and expanded. For example, humans do not appear to have a well developed gastric ICC-MP layer,⁴¹ and the roles of other ICC classes and SMC should be explored. One possible avenue to generate the required anatomical detail could be through reconstructing a virtual GI tissue block through extended tissue level imaging of the fiber and ICC network structures, as has been utilized to great effect in cardiac modeling.⁶

Tissue-specific ICC Network Models

Damage to ICC during disease is an active area of current research.^{1, 42, 43} Histological and confocal imaging evidence has demonstrated major changes to the ICC network in gastric motility disorders, most notably diabetic and idiopathic gastroparesis,^{4, 41} and ICC density has also been shown to decline during normal aging.⁴⁴ Although staining and confocal imaging techniques are effective for identifying the spatial distributions of ICC and degradation to networks, there are two major problems impeding the use of the imaged ICC networks as an effective data source for tissue models: first, there is a lack of large-scale imaging data and registration techniques for studying spatial patterns of ICC depletion; second, current metrics of ICC depletion only involve nuclei counts and volume computations (e.g.,^{45, 44}), preventing quantitative studies of network geometries. In order to overcome the first of these challenges, Gao *et al.* recently proposed an ICC network generation algorithm adapted from SNESIM, an established geostatistical algorithm used to build numerical models of oil reservoirs.⁴⁶ By extracting structural features of ICC network images provided to the network generation algorithm, these features could be interpolated and replicated to generate large-scale realistic virtual ICC networks across a spectrum of ICC degradation, capturing depletion as well as changes in other structural characteristics (Fig. 4a). Numerical metrics for quantifying the structural properties of ICC networks are also under development.⁴⁶

Efforts to interpret the functional consequences of ICC loss provide a major motivation for tissue modeling studies, including both structural and slow wave propagation models.^{22, 46} The propagation of slow waves through ICC networks and the subsequent depolarization of SMC has been usefully investigated using multi-scale modeling,²² and a number of recent reviews have addressed the concept of using the monodomain and bidomain equations to model slow waves at scales larger than the cellular scale.^{5, 47} The specific arrangement of ICC and SMC sharing a common extracellular space has also led to the development an extended bidomain model, which contains two intracellular domains coupled to a common extracellular domain.⁴⁸ The extended bidomain model presents an attractive strategy for simulating multiple cell types while reducing the dimensionality of extracellular domains to one.

An example of a modeling analysis of the structure-function relationship between ICC network structures and slow wave propagation was demonstrated by Du *et al.*²² The ICC network geometries were obtained from confocal images of ICC from wild-type and ICC-degraded (5-HT_{2B} knockout) mouse jejunum. The bidomain model was used to solve for the slow wave propagation. 'Non-ICC' tissue was assumed to be a current-sink in the modeled domain. A gradient of intrinsic frequencies (2.9–3.0 cpm) was assigned across the modeling domain to demonstrate entrainment (Fig. 4b). This simulation setup has also recently been applied to tissue-specific virtual ICC networks.²² Simulation analyses have quantified differences with regard to the current density in depleted networks, which may help explain experimentally observed reductions in extracellular slow wave amplitude in gastroparesis patients.⁴ One way of indirectly validating such tissue models in future may be through Ca²⁺-fluorescence video imaging of ICC network functions.⁴⁹

WHOLE-ORGAN LEVEL

Gastric Electrophysiological Models

Recent experimental studies have reported multiple types of electrophysiological heterogeneities in the stomach, motivating modeling studies to quantitatively integrate these experimental results at the whole-organ level.^{9, 10, 38, 50} A series of HR electrical mapping studies have reported a highly organized and consistent slow wave propagation sequence, originating from the gastric pacemaker on the proximal greater curvature, and with regional variations in velocity and amplitude as the wave propagates towards the pylorus.^{9, 10, 38} Experimental recordings have also demonstrated electrophysiological differences in the morphological features of gastric slow waves. The gradients of resting membrane potentials can be significant: approximately −45 to −75 mV in the antegrade direction of the stomach and −75 to −62 mV across the gastric wall in the canine antrum.⁵⁰ Recent experimental and modeling studies have attributed this phenomenon to the hyperpolarizing effect of carbon monoxide.^{21, 50} It has been proposed that these gradients play a role in the coordination of SMC during different degrees of contraction.⁵⁰

HR mapping has also been extended to describe gastric slow waves in animal species as well as gastroparetic patients.^{4, 39, 51} In particular, one recent study afforded the first direct high spatiotemporal evidence between human gastric slow wave dysrhythmia and gastroparesis, in which ICC counts were approximately 50% lower than in controls.⁴ A platform that is capable of integrating the experiment data may help to improve the pathogenesis of dysrhythmic slow waves in the whole stomach.

Modeling studies have attempted to integrate these findings and simulate slow wave activation over a subject-specific stomach whole-organ model using the continuum approach.^{5, 52} In a recent study, HR mapping results from the normal human stomach were incorporated into a patient-specific anatomical model.^{38, 53} The geometry of the stomach

was developed based on a finite element description and fitted from a set of pre-operative computer tomography images of a patient.⁵³ A gap-junction coupled ICC-SMC model was used to simulate slow wave activation and the bidomain equations were solved to simulate propagation. The subject-specific whole-organ model incorporated merged activation times of the human gastric slow wave during a single cycle of activity and the electrophysiological gradients from fundus to antrum and across the gastric wall (Fig. 5).

One important observation evident in the updated descriptions of whole-organ gastric slow wave activity is the simultaneous wavefronts occurring in the organ.³⁸ The multiple propagating wavefronts influence the resultant electrical dipole, greatly complicating interpretations of whole-organ activity from far-field recordings taken at the torso (see Section Torso Level).^{54, 55}

Computational Fluid Dynamics Models

Another field of active modeling research in gastric motility, not directly related to electrophysiology, is the study of the flow and mixing behaviors in the stomach using computational fluid dynamic (CFD) techniques. A major aim of these studies has been to investigate the fluid and mechanical forces that drive the distribution and transport of the gastric contents. One clinical motivation for this work is a need to interpret magnetic resonance imaging gastric motility data in gastroparetic patients, which demonstrated that the heterogeneous contraction profiles within the stomach contributed to a significant change in the rate of gastric emptying.⁵⁶ Furthermore, the distribution of the gastric contents has been found to depend on the rheology of the ingesta,⁵⁷ which can be highly visco-elastic and non-Newtonian. The mode and type of forces the ingesta exert on the GI wall can also activate a series of mechano-sensitive mechanisms in the GI tissue that may have consequences in the efficacy of digestion in health and disease. Together, these two factors require a platform that is capable of relating gastric motility to luminal content distribution, in order clarify the relationship between gastric motility and emptying, and further quantify the effects of pharmaceutical agents on gastric motility.

Previous modeling studies have used the CFD techniques to simulate the relationship between gastric wall contraction, luminal contents distribution, and gastric emptying.⁵⁸ In a recent study Ferrua and Singh developed a CFD model in a three-dimensional stomach geometry during gastric contraction.⁵⁹ The antrum model was prescribed to contain a series of phasic contractile waves propagating towards the pylorus according to MRI data.⁶⁰ The stomach was also modeled as a closed system. The CFD model was then used to numerically analyze the dynamics of gastric fluids with different rheological properties.⁵⁹ The laminar behavior of water and honey, both Newtonian fluids, and tomato juice, a non-Newtonian fluid, were studied. The simulated results showed a complex and highly three-dimensional flow profile in the stomach model during contraction.⁵⁹ Although the strongest fluid motions were always predicted within the antrum, a slow but constant recirculation of gastric fluids was also shown to occur in the corpus. Fluid from the fundus was continuously drawn into the antrum along the lesser curvature, and forced back through the core region of the stomach model.

Similar to the issues faced by the electromechanical modeling effort at the cellular level,^{30, 31} there is currently a modeling disconnect between the slow waves, mechanisms of slow wave propagation, material properties, motility, and luminal content distributions. The CFD models discussed above go some way towards relating motility to content distributions, however, these findings await validation, and more work is also needed to integrate elements of mechanoelectrical feedback into the modeling framework, in order to accurately predict the dynamic effects of luminal content on GI motility.

TORSO LEVEL

Far-Field Recording Techniques and Forward Models

Even though recordings obtained from the serosal is a reliable method for assessing gastric slow wave activity,^{10, 38, 63} these methods still have limited clinical utility due to their invasiveness. On the other hand, far-field slow wave recording techniques, such as electrogastrography (EGG),⁵³ present another class of promising techniques for non-invasive diagnosis of gastric dysrhythmias. EGG has been applied in basic research and complemented clinical studies on patients with unexplained nausea, vomiting, and dyspeptic symptoms.⁶¹ Another experimental far-field recording device, called the superconducting quantum interference device magnetometer (SQUID),⁶² has been applied as an alternative method of non-invasively characterizing slow wave activity.

EGG holds potential as a routinely deployable tool to aid the diagnosis of gastric slow wave dysrhythmias and digestive dysfunction.⁶⁴ However, despite a number of studies that showed a clear correlation between the dominant frequency component in EGG and normal gastric slow wave, uncertainty remains about its reliability and specificity.⁶¹ Simultaneous HR mapping and EGG would be one way to validate the relationship between EGG and gastric dysrhythmias. A virtual platform that relates the electrical source of the stomach to the far-field potential field on the torso surface would facilitate this process by identifying morphological features in EGG to the state of slow wave activation in the stomach to directly relate cutaneous recordings to the underlying sources.

Magnetogastrography (MGG) is an alternative method that utilizes the resultant magnetic field associated with gastric slow wave activity, measured via a SQUID setup.⁶⁵ One key theoretical advantage of MGG is that since the layers of tissue in the torso attenuation of magnetic fields by the body is less than that of electrical fields by the body, MGG produce a better signal-to-noise ratio than EGG.⁶⁵ Furthermore, it has been reported that MGG could be employed to pick up the frequency component in a more localized manner than EGG, for example, the frequency-gradient in the intestine.⁶⁵

Both EGG and MGG have been applied to identify characteristics of slow wave propagation and uncoupling of slow waves in the stomach.^{54, 64} There are, however, several common technical and physiological limitations that have prevented EGG and MGG from becoming a routine diagnostic tool. A fundamental limitation has been a lack of understanding about how to interpret the far-field recordings in relation to the state of electrical activation of the underlying organ, partly due to the lack of spatial resolution and reliable signals.⁶⁶ Experimentation regarding this question is challenging, particularly due to the existence of multiple simultaneous wavefronts in the human stomach, as well as the heterogeneity in slow wave characteristics propagation.³⁸ Mathematical modeling presents an attractive alternative strategy for quantifying the relationship between gastric slow waves and EGG or MGG, as detailed modeling analysis can be used to predict morphological and temporal signatures in the EGG or MGG. In the cardiac field, the established forward modeling approach has successfully been applied to relate cardiac electrical activity to the ECG recorded on the torso, in order to optimize the placement of recording electrodes and improve diagnostic sensitivity;⁶⁷ similar aims could be achieved for GI electrophysiology.

A recent modeling study investigated the contribution of the updated gastric slow wave description to EGG and MGG (Fig. 6).⁵³ Furthermore, the effects of an heterogeneous torso on EGG and MGG were also investigated in a separate study,⁶² as previously done in cardiac forward problems.⁶⁸ Interestingly, the modeling predicted a reduction in fat conductivity affected the EGG more than MGG, whereas an increase in fat conductivity affected neither significantly.⁶² This finding highlighted the potential for investigating MGG

using SQUID.⁵⁴ On the other hand, experimental evidence of the exact relationships between gastric slow waves, EGG and MGG remain inconclusive. Further investigations of simultaneous recordings of gastric slow waves and far-field recordings are needed in order to elucidate these relationships, and to better advance the current uncertainty surrounding EGG and MGG as a routine clinical tool.

Inverse Models

Attempts to improve the clinical utility of EGG and MGG have also raised interest in inverse modeling of gastric electrophysiology. In general, a transfer matrix that maps gastric slow waves to EGG and MGG is constructed, and then the inverse of the transfer matrix is computed using an inverse method.^{55, 69} Gastric slow waves can then be reconstructed from far-field measurements. An initial attempt was made to resolve a single dipole from a SQUID recording device, coupled with MRI data of the stomach.⁷⁰ The surface current density (SCD) method has been proposed to be an alternative technique for resolving dipole characteristics such as projection and velocity, provided that the dipole was located within 100 mm of the SQUID sensor.⁵⁴ More recently, another modeling study has demonstrated that multiple activation wavefronts can be successfully reconstructed from a simulated body surface potential field.^{55, 69} Like the heart, GI inverse modeling also faces challenges in numerical solution procedures. Furthermore, EGG and MGG also suffer from weak signal-to-noise ratios and interferences from cardiac electrical activity and respiratory movement artifacts, and MGG requires a highly expensive and extensively shielded magnetometer, limiting its availability to researchers.

COMPUTATIONAL TECHNIQUES

As multi-scale models of physiological processes grow in complexity and scale, a new generation of numerical and simulation techniques have been developed and transitioned into the GI field. Two such simulation platforms are CHASTE and CMISS. CHASTE is a software package that is conventionally used for cardiac simulation but has recently been adapted to solve GI electrophysiological models.^{71, 72} CMISS is another example of a continuum software package that has been applied to solve GI electrophysiological models.^{53, 73} In both environments, systems of differential equations are solved over a geometric mesh using a discrete method, such as the finite element method. The individual environments differ in approach to constructing the geometric mesh and numerical procedural setup. For example, in CHASTE, the geometry is constructed from tetrahedra basis functions, with the elemental node points being the solution points at which cell models are solved.⁷¹ In CMISS, the geometry can be constructed from supra-linear basis functions and the cell models are solved at higher resolution solution points embedded within the geometric elements.⁷⁴ One significant difference between these two packages is the ability of CHASTE to perform distributed computing, which has potential to scale up to larger problems. In another major advance towards a more efficient computational framework, the CMISS project is in the process of being superseded by the Open CMISS project.⁷⁵

Conclusions

Research in gastric electrophysiology and motility, in both basic and clinical science, is progressing rapidly partly due to a series of inter-disciplinary efforts. Among the major challenges of moving forward, one particular problem modelers face is the presence of co-regulating pathways in GI function. There is a complex interplay of pathways operational in health and disease.² For example, ICC loss during gastroparesis is often associated with autonomic and enteric neuropathy as well as SMC pathology,^{1, 2} and it is not always clear in digestive disease how such mechanisms interact to bring about an overall reduction in

motility and symptoms. Future modeling studies will need to incorporate components of neural modulation on slow wave activity and motility, as has been achieved by Chambers *et al.* in the guinea-pig jejunum.⁷⁶

Another major ongoing focus of GI electrophysiological modeling is regarding gastric slow wave dysrhythmias.^{4, 39} Gastric dysrhythmias are associated with several significant functional disorders;⁷⁷ however, the mechanisms underlying dysrhythmias remain poorly understood. Factors contributing to dysrhythmia in gastroparesis may include depletion of ICC, structural changes to ICC networks, or increased fibrosis in the connective stroma,⁷⁸ which can be contributors to an increased heterogeneity in gastric slow wave conductivity. Future modeling studies could incorporate these elements in order to develop mechanistic insights into gastric dysrhythmias. Modeling studies can also incorporate detailed channelopathy models at the cellular level under the multi-scale modeling framework,²⁹ and offer an opportunity to coordinate the electromechanical coupling activity in the GI tissue.

In summary, GI mathematical modeling studies have gained substantially in complexity and accuracy in recent years, across multiple biophysical scales. There are many directions needing continued development and application for the ‘Virtual Stomach’, and the field would benefit from a close collaboration between experimental and modeling investigations in realizing these opportunities.

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Fig. 1.

Multi-scale arrangement of GI electrophysiological models. The spatial scales cover cellular to whole-body levels. The electrophysiological process at each spatial scale can also be over different temporal scales, from milliseconds to hours.

Fig. 2.

Cell model simulations of gastrointestinal slow wave activity. (a) An intestinal ICC model developed by Faville *et al.*¹⁸ (b) Gastric ICC (solid line) and SMC (dashed line) model developed by Corrias and Buist.^{13, 28} (c) An intestinal SMC model developed by Poh *et al.*²⁹ (d) A gastric electromechanical model developed by Gajendiran *et al.*³⁰ showing the relationship between intracellular Ca^{2+} (solid line) and normalized force generation (dashed line) in a SMC.

Fig. 3.

ICC pathway simulations. (a) A two-layer model consisting of ICC-MP and circular ICC-IM networks.⁴⁰ The ICC-MP layer conductivity was homogenous, while the ICC-IM layer conductivity was preferentially in the circumferential fiber direction. (b) Ectopic pacemaking with ICC-IM decoupled from the ICC-MP (shown). Slow waves propagated homogeneously in all directions. (c) Ectopic pacemaking with ICC-IM bidirectionally-coupled to the ICC-MP (shown). ICC-IM assumed the driving network role during circumferential conduction, outpacing and activating ICC-MP, while slower longitudinal conduction occurred through ICC-MP.

Fig. 4.

ICC networks and slow wave propagation. (a) Virtual ICC networks were generated using an adapted SNESIM algorithm with varying degrees of ICC densities in the image field ($636 \times 636 \mu\text{m}$), at 35%, 40%, 45% and 50% density (normal network density). The generated ICC networks are four times the area of the real ICC network image ($318 \times 318 \mu\text{m}$). (b) Demonstration of slow wave entrainment simulations in a real depleted ICC network (35% density) over 120 ms.²²

Fig. 5.

Gastric slow wave propagation simulated in a virtual human stomach model. The sequence of slow wave activations shows that slow waves originate from a pacemaker on the greater curvature of the proximal stomach and then propagates in the antegrade direction towards the gastric pylorus.

Fig. 6. Simulated body surface potential fields (colored field) and magnetic vector fields located at an array above the stomach region (yellow arrows) due to an instance of gastric slow wave activity (as shown in Figure 5).