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Computational motility models of neurogastroenterology and neuromodulation

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Abstract

The success of neuromodulation therapies, particularly in the brain, spinal cord, and peripheral nerves, has been greatly aided by computational, biophysical models. However, treating gastrointestinal disorders with electrical stimulation has been much less explored, partly because the mode of action of such treatments is unclear, and selection of stimulation parameters is often empirical. Progress in gut neuromodulation is limited by the comparative lack of biophysical models capable of simulating neuromodulation of gastrointestinal function.

Here, we review the recently developed biophysical models of electrically-active cells in the gastrointestinal system that contribute to motility. Biophysical models are replacing phenomenologically-defined models due to advancements in electrophysiological characterization of key players in the gut: enteric neurons, smooth muscle fibers, and interstitial cells of Cajal.

In this review, we explore existing biophysically-defined cellular and network models that contribute to gastrointestinal motility. We focus on recent models that are laying the groundwork for modeling electrical stimulation of the gastrointestinal system. Developing models of gut neuromodulation will improve our mechanistic understanding of these treatments, leading to better parameterization, selectivity, and efficacy of neuromodulation to treat gastrointestinal disorders. Such models may have direct clinical translation to current neuromodulation therapies, such as sacral nerve stimulation.

Keywords

Neurogastroenterology; Computational model; Enteric nervous system; Neuromodulation; Electroceuticals

1. Introduction

Digestion consists of complex and coordinated processes such as motor activity, enzyme secretion, nutrient absorption, homeostasis, and excretion. Digestive processes are regulated

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by the enteric nervous system, which consists of enteric ganglia that form mesh-like plexuses in the wall of the gastrointestinal tract (Furness, 2006). Although the enteric nervous system receives both sympathetic and parasympathetic input, it can regulate digestive function independently of the central nervous system (Gershon, 1999). The autonomous control in the gut is governed by intrinsic reflex circuits which are responsible for complex motility patterns such as peristalsis and segmentation.

Gut motility is a neuromuscular system; it is controlled by a network of interacting enteric neurons, smooth muscle fibers, and intrinsic pacemaker cells. Damage to the nervous system or musculature in the gastrointestinal tract can lead to a plethora of conditions, such as constipation, diarrhea and irritable bowel syndrome, estimated to affect 20% of the population (Lewis et al., 2016). The etiology of these disorders is not always clear, and treatments can be nonspecific. However, biophysical models of the enteric nervous system and gastrointestinal smooth muscle have been developed to understand neuromuscular mechanisms of motility and disease. These models can provide insights into underlying biophysical mechanisms to help improve therapies that employ electrical stimulation to modulate gastrointestinal function.

The purpose of this review is to highlight the recent contributions and challenges of mathematical modeling approaches in neurogastroenterology. This review will focus on current biophysical models in the gastrointestinal system and models of electrical stimulation for modulating gastrointestinal motility. While this review does not focus on neuroendocrine, neuroimmune, or neurocardiac interactions, it should be noted that communication between these systems plays an important role in gastrointestinal function and may have neuromodulatory applications.

2. Biophysical models in the gastrointestinal system

Gut motility is a neuromuscular system coordinated by electrical slow waves and neural reflex loops. Electrical slow waves are coordinated by smooth muscle fibers and intrinsic pacemakers known as interstitial cells of Cajal. Slow waves cause phasic contraction in smooth muscle punctuated by discrete junction potentials delivered by enteric neural circuitry. Motility models consist of interconnected networks of biophysically-defined electrically-active cells (Fig. 1). As new models are developed, it is important to clarify what makes such a model “biophysically-defined”. Such models are a quantitative, often dynamic, description of biological mechanisms (D’Angelo et al., 2013). They depend on carefully designed experiments to derive parameters, such as voltage or current clamp electrophysiology studies. Experiments supporting model parameters can be improved by including a pharmacological dimension, such as using specific ion channel blockers, which lend credibility to parameter selection (Moreno et al., 2016). Finally, new biophysical models, especially those featuring network connectivity would do well to consider including stochastic behavior at the molecular and network levels to simulate noisy action potentials or variability in synaptic connectivity.

2.1. Interstitial cells of Cajal

Here, we review four principal biophysical models of interstitial cells of Cajal: Youm et al. (2006), Corrias and Buist (2008), Faville et al. (2008) and Lees-Green et al. (2014). These models typically describe electrophysiology of interstitial cells of Cajal found in the stomach and small intestine, and they reference experimental data from cardiac, gastric, intestinal, and colonic tissue across a range of species, including mice, guinea-pigs, rats and canine.

The first biophysical model of the interstitial cell of Cajal was introduced by Youm et al. (2006) describing pacemaker activity in the mouse small intestine. The Youm model was adapted from cardiac pacemaker models (Luo and Rudy, 1994; Matsuoka et al., 2003), and describes the membrane potential in classical Hodgkin-Huxley fashion as a function of cell capacitance and dynamic ionic currents. Youm et al. (2006) modified the cardiac models by using parameters reported by Goto et al. (2004) during patch clamp electrophysiology of murine myenteric interstitial cells of Cajal of the small intestine. Some parameters, such as binding constants, conversion factors and rate constants, had to be adjusted empirically in order to reproduce stable and repetitive membrane depolarizations as observed in Goto et al. (2004). The Youm model was loosely validated by comparing spontaneous pacemaker potentials and maximum rate of depolarization between the simulation and patch clamp recordings reproduced from Goto et al. (2004). However, a limitation of the Youm model is the phenomenological description of an “autonomous inward current”, which is biophysically described in later models.

More recently, Corrias and Buist (2008) and Faville et al. (2008) independently developed biophysical models with mechanistic descriptions for initiating pacemaker activity in interstitial cells of Cajal. Both models attribute the “autonomous inward current” described in Youm et al. (2006) as a calcium-inhibited nonselective cation current based on electrophysiology from murine interstitial cells of Cajal of the small intestine (Koh et al., 2002). Primarily, the key difference between the Corrias and Buist model and the Faville model is the Corrias and Buist model uses a single aggregate pacemaker unit instead of multiple pacemaker units as in the Faville model. The advantage of the Faville model is that multiple pacemaker units allows the model to simulate entrainment of unitary potential depolarizations to drive pacemaker activity. However, the underlying mechanisms of these models and the nonselective cation pacemaker hypothesis (Sanders et al., 2006) were later disputed by Means and Sneyd (2010). Means and Sneyd (2010) conducted a spatiotemporal analysis of intracellular calcium dynamics and found that known calcium mechanisms were not sufficient to activate the nonselective cation current, challenging these models and the nonselective cation pacemaker hypothesis.

Finally, Lees-Green et al. (2014) developed a model for small intestinal interstitial cells of Cajal featuring the newly discovered calcium-activated chloride channel, anoctamin1. Anoctamin1 has recently been identified in mouse and human interstitial cells of Cajal (Gomez-Pinilla et al., 2009), and Hwang et al. (2009) found that slow waves were absent in anoctamin1 null transgenic mice. The Lees-Green model included anoctamin1 mechanisms that were developed from whole cell electrophysiology of HEK-293 cells transfected with anoctamin1 (Xiao et al., 2011). The model assumes the transfected anoctamin1 channel

behaves similarly to anoctamin1 expressed in interstitial cells of Cajal, and involves a store-operated calcium channel that responds to depletion of calcium levels in the endoplasmic reticulum. These assumptions are well supported, and the Lees-Green model is the most recent biophysical model of interstitial cells of Cajal based on electrophysio-logical mechanisms for initiating slow waves.

2.2. Smooth muscle fibers

The first biophysical model of smooth muscle fiber electrophysiology was put forth by Corrias and Buist (2007), simulating smooth muscle fibers of the gastric antrum (Corrias and Buist, 2007). Corrias and Buist developed and validated their model by comparing smooth muscle depolarization profiles during experimental recordings from canine gastric antrum (Ward et al., 2004) and during voltage clamp experiments of murine gastric antrum in the presence of pharmacological blockers (Amberg et al., 2002). The Corrias and Buist smooth muscle fiber model is well supported from gastric electrophysiology, and it has since been employed in multiscale computational models to evaluate gastric slow wave propagation (O'Grady et al., 2012).

Since their first smooth muscle fiber model, Corrias, Buist, and colleagues have gone on to develop models of jejunal smooth muscle fibers and colonic smooth muscle fibers based on electrophysiology from human-derived smooth muscle (Poh et al., 2012; Yeoh et al., 2017). The human jejunal smooth muscle model estimated parameters for L-type calcium channels, T-type calcium channels, voltage-sensitive potassium currents and sodium currents based on experimental I–V electrophysiology reported in the literature (Poh et al., 2012). The human jejunal smooth muscle model was validated by comparing simulation results with experimental recordings by Lee et al. (2007). Despite strong evidence and experiment-backed parameters, some experimental data is lacking from this model, such as maximum conductance values. A further limitation of the work is that human jejunal smooth muscle tissue was obtained from morbidly obese patients during gastric bypass surgery. Although it is unlikely that donor obesity impacts intrinsic electrophysiology in jejunal smooth muscle, it is an important consideration in this model.

Yeoh et al. (2017) developed a similar model of human colonic smooth muscle fibers. The human colonic smooth muscle fiber model used electrophysiology data from human colon tissue segments and reported current–voltage characteristics for major ionic conductances contributing to the model. Some parameters such as maximum conductance values were chosen empirically to best align voltage traces between simulations and referenced experimental data (Choe et al., 2010; Rae et al., 1998). The Yeoh and Poh models represent the first biophysical models of smooth muscle fibers to be based on electrophysiology from human tissue. Despite these advancements, the intracellular mechanisms of calcium activity remain phenomenological in these models. Intracellular calcium mechanics in smooth muscle are not fully understood, and research is ongoing (Perrino, 2016).

Further characterization is necessary to integrate electrophysiology models with mechanical models of smooth muscle fibers. Several models have been proposed to describe the excitation-contraction relationship in smooth muscle fibers, but few are biophysically defined and specific to the gastrointestinal system. Gajendiran and Buist (2011) proposed a

model of excitation-contraction coupling based on experimental data from canine gastric smooth muscle. Du et al. (2011) later expanded on this model by coupling smooth muscle fibers to interstitial cells of Cajal. However, there are several assumptions and limitations of the Gajendiran and Buist (2011) model, such as constant concentration of myosin light chain phosphatase and somewhat phenomenological description of intracellular calcium mechanics. Additionally, parameters were estimated empirically from nonmammalian smooth muscle fibers. Nevertheless, the Gajendiran and Buist (2011) model has helped bridge the gap between electrophysiological and mechanical smooth models. With additional experimental data, advanced models of the excitation-contraction relationship will play an important role in developing future motility models.

2.3. Enteric neurons

Enteric neurons have been classically categorized into two physiological categories: S neurons and AH neurons. The most notable characteristic of enteric neurons compared to other neurons are their unmyelinated fibers with slow conduction speeds, and the long after-hyperpolarization exhibited in AH neurons. Early mathematical models of the after-hyperpolarization of AH neurons were initially described by Thomas and Bornstein (Thomas et al., 2000; Thomas and Bornstein, 2003), however these models are pseudo-biophysical and rely on a number of phenomenological descriptions.

More recently, Chambers et al. (2014a) published a freely available model of AH neurons based on electrophysiology recordings from intrinsic sensory neurons of the myenteric plexus in the guinea-pig. The Chambers model of sensory neurons was validated by comparing intracellular voltage traces between experimental data and simulations. The model is well supported and shows similar responses to intracellular stimulation compared to intracellular recordings. However, this model does not reliably describe intracellular calcium dynamics, and it was not able to faithfully reproduce some experimental findings from patch clamp experiments. Further characterization of intrinsic sensory neurons and other enteric neurons will be necessary to comprehensively monitor intracellular calcium behavior.

Most interestingly, models of enteric neurons can be integrated to simulate network effects in enteric neural circuits. Models of enteric networks have been proposed to describe motility reflexes intrinsic to the gastrointestinal system. Early network models began with the work of Miftakhov and Wingate (1994) and Furness et al. (1996), and have since been used to describe complex motor patterns, such as segmentation (Chambers et al., 2008) and migrating motor contractions (Thomas et al., 2004). However, these systems tend to use phenomenological and abstract definitions of neurons and are not well suited to describe the effects of electrical stimulation. Chambers et al. (2014b) have recently reviewed these models of neural regulation of motor events in the gastrointestinal system.

3. Modeling electrical stimulation in the gut

Neuromodulation is being used to treat gastrointestinal disorders (Abell et al., 2015). However, progress in neuromodulation therapy for gastrointestinal disorders is impeded by lack of understanding of the neurogastroenterological circuitry, exemplified by the short

supply of biophysical models. Until recently, most computational models of the gastrointestinal system were not biophysically accurate. Now, computational models of single cells and networks include biophysically-driven mechanisms, and the field is prime for biophysical models of electrical stimulation in the gastrointestinal system.

Electrical stimulation in the gastrointestinal system can be conducted in two ways: direct stimulation of the end-organ and stimulating peripheral nerves that innervate the end-organ (Fig. 2). Electrical stimulation in the gut is primarily designed to improve motility in patients and usually targets the stomach, small intestine, colon, or rectum. This section will highlight gastric electrical stimulation, vagus nerve stimulation and sacral nerve stimulation. Other means of neuromodulation in the gut have recently been reviewed from a clinical perspective (Chen et al., 2017).

3.1. Gastric electrical stimulation

Gastric electrical stimulation is designed to modulate motility or even treat obesity by stimulating the stomach. There are two schools of thought in gastric electrical stimulation: low frequency and high frequency stimulation. Low frequency stimulation, or gastric pacing, is thought to modulate motility by entraining the gastric slow wave. The mechanisms of high frequency stimulation are unclear, and the efficacy of this approach is disputed (Lal et al., 2015).

Computational models of gastric electrical stimulation began with Mintchev and Bowes (1997). The original models were phenomenological until Du et al. (2009) modified the Corrias Buist smooth muscle fiber model to analyze electrical stimulation with in vivo validation. In this work, electrical stimulation was applied by an intracellular current, rather than describing the extracellular stimulation as in clinical applications of gastric electrical stimulation. More recently, Wang et al. (2017) used a combined experimental-theoretical approach analyze the effects of gastric pacing and identify diagnostic metrics for dysrhythmia in the stomach. Novel and well supported computational models will continue to advance the efficacy of gastric electrical stimulation.

3.2. Vagus nerve stimulation

Vagus nerve stimulation is an experimental therapy for treating several gastrointestinal disorders, such as inflammatory bowel disease and obesity (Browning et al., 2017). Although anatomy and function of the vagus nerve are relatively well understood (Stakenborg et al., 2013; Williams and Elmquist, 2012), the relevant pathways and mechanisms of vagus nerve stimulation remain unclear (Berthoud, 2008). Predicting the effects of vagus nerve stimulation and optimizing parameters computationally has proven challenging, despite available models of electrical stimulation of the vagus nerve, largely based on compartmentalized cable model developed by McIntyre et al. (2002).

A consideration of extrinsic peripheral nerve stimulation, as with vagus nerve stimulation and sacral nerve stimulation, is targeted activation of specific fibers. For example, the vagus nerve consists of afferent and efferent fibers with heterogenous populations of varying myelination and fiber diameters, and myelination and fiber diameter contribute to unique stimulus responses and recruitment order among fibers (Yoo et al., 2013). Although the

target fibers of vagus nerve stimulation are disputed, it is recognized that stimulating afferent large diameter fibers contributes to side effects as observed in other indications for vagus nerve stimulation (Ben-Menachem, 2001). Therefore, selective fiber activation is an ongoing objective in vagus nerve stimulation, and computational models have been developed to achieve fiber selectivity. Recently, Guiraud et al. (2016) have reviewed the state of the art technologies for vagus nerve stimulation.

A recent advancement in vagus nerve stimulation uses high frequency stimulation to blockade the vagus nerve, an apparent treatment for obesity (Shikora et al., 2015). However, the mechanisms and efficacy of this treatment are disputed; Pelot et al. (2017) developed a computational model of vagus nerve stimulation that challenge the mechanisms of vagal blockade as a treatment of obesity. Further computational modeling and experimental analysis will advance our understanding of target pathways for vagus nerve stimulation and ultimately improve clinical efficacy.

3.3. Sacral nerve stimulation

Sacral nerve stimulation is being used to treat constipation and fecal incontinence, among other disorders (Carrington et al., 2014). The mechanisms of sacral nerve stimulation therapy are not clear, and it is not clear if sacral nerve stimulation acts through central, autonomic, and/or enteric circuits.

Computational models are common for peripheral nerves, and they often include methods of electrical stimulation. However, there are very few models of electrical stimulation that are specific to the sacral nerve. One particular model compares the current density and electric field of sacral nerve stimulation between implanted electrodes and transcutaneous electrodes (Hirata et al., 2013). In this model, Hirata et al. (2013) use anatomically-derived models of human sacral nerve roots and surrounding tissue to determine electric field and current density. While this is an example of the benefits computational modeling for neuromodulation, this model does not include end-organ effects of sacral nerve stimulation.

Modeling the effects of sacral nerve stimulation using biophysical models may be a useful approach for identifying the mode of action or relevant pathways in this therapy. Further, such models might prove clinically beneficial if they were to include end-organ effects and even disease states. Computational models may provide the opportunity to identify new stimulation patterns for symptom-specific treatment. As with other neuromodulation therapies, such as spinal cord stimulation for treating neuropathic pain (Zhang et al., 2014), it is possible that different stimulation patterns can activate specific mechanisms and neural circuits in the gastrointestinal system.

4. Challenges to neuromodulation models in the gut

Biophysical models of interstitial cells of Cajal, smooth muscle fibers, and enteric neurons have established the foundation for modeling neuromodulation therapy in the gastrointestinal system. The transition away from phenomenological models is a necessary step for modeling electrical stimulation. However remaining challenges limit the existing models of neuromodulation in the gut, and models would be improved by a quantitative

description of intracellular calcium dynamics, biophysical electro-mechanical coupling in muscle fiber models, deterministic network connectivity, and a functional understanding of peripheral innervation of end-organs.

Gut motility is a neuromuscular system, and both neural and muscular systems respond to electrical stimulation. Existing computational models for treating gastrointestinal disorders are often constrained to either the muscular system or enteric nervous system, exclusively. One limitation of existing models is reconciling the effect of electrical stimulation between both of these electrically-active systems. For example, an existing model by Du et al. (2009) predicts the effect of gastric electrical stimulation on motility using biophysical models of smooth muscle fibers and interstitial cells of Cajal. However, this and other gastric electrical stimulation models do not include biophysical neuron models, despite evidence that gastric electrical stimulation activates neurons in addition to smooth muscle fibers and interstitial cells of Cajal (Sun et al., 2006; Xu et al., 2008).

Peripheral nerve stimulation for the treating visceral disorders are advancing. Models of peripheral nerve stimulation often include spatially-extended models of electrical stimulation in a compartmentalized cable equation. Although these models predict nerve fiber response to electrical stimulation, they frequently shy away from assessing end-organ effect. Many peripheral nerve stimulation models claim to optimize stimulation parameters for maximal nerve fiber activation or suppression. However, without modeling the symptoms or disease in the end-organ, such as a biophysical model of the stomach or colon, the parameters cannot be optimized as a specific therapy. Modeling end-organ response to peripheral nerve stimulation is the focus of recent NIH and DARPA initiatives, such as SPARC and ElectRx programs. In order to advance clinical neuromodulation for treating gastrointestinal disorders, such as impaired motility, it will be necessary to develop integrated biophysical models that include neural and muscular systems.

Further, gastrointestinal function relies on other neural interactions that are not discussed in this review, such as neuroendocrine, neuroimmune, and neurocardiac circuitry. Gastrointestinal modeling would greatly benefit from characterization and mathematical models that describe these systems. For example, Riz and Pederson have developed biophysical models of L-type enteroendocrine cells and human pancreatic b-cells (Riz et al., 2014; Riz and Pedersen, 2015), but these models have yet to be integrated into multiscale and integrated modeling efforts. A better understanding of complex neural interactions in the gastrointestinal system will drive model development and could lead to opportunities for mechanistic insight and drug discovery.

5. Integrated neuromuscular models for neuromodulation

Advanced models that pose direct clinical translation for treating gastrointestinal disorders will integrate neural and motor components. Symptoms relating to dysmotility, such as slow gastric emptying, constipation, and fecal incontinence, are the most common targets for neuromodulation (Carrington et al., 2014; Chen et al., 2017). Neuromuscular models for neuromodulation would improve efficiency of these therapies by exploring and optimizing parameters, identifying modes of action, and providing insight for off-target side effects as

has been observed in vagus nerve stimulation and deep brain stimulation (Arle et al., 2016; McIntyre and Foutz, 2013).

Recently, we developed a neuromuscular model to determine the effects of colonic electrical stimulation on colon transit time (Barth et al., 2017). Our model included direct electrical stimulation of the end-organ, which was comprised of enteric neurons, smooth muscle fibers, and interstitial cells of Cajal in an interconnected network. The model revealed that low frequency sine wave had a greater prokinetic effect on motility compared to traditional pulsatile stimulation, which was validated in awake, freely behaving rats. The model further provided mechanistic insights into optimal gastro neuromodulation conditions. Importantly, this neuromuscular model was capable of improving parameters for treating slow transit constipation.

Despite recent neuromuscular models, there remains a clinical need for additional models of neuromodulation therapy in the gastrointestinal system. Many electrical stimulation therapies focus on stimulating peripheral nerves that innervate the end-organ, and these systems have yet to be modeled. Peripheral nerve models integrated with neuromuscular motility models have great potential impact; they could pose direct clinical translation with symptom-specific parameter optimization. Further, such models might offer mechanistic insight into these therapies and predict off-target side effects.

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Fig. 1.

Biophysical models of enteric neural circuitry. Gastrointestinal motility is the result of coordinated activity of enteric neurons, smooth muscle fibers, and interstitial cells of Cajal. Electrically-active cells form neuromuscular circuits among the layers of the gastrointestinal wall. By interconnecting these cells into networks, we can develop models of gastrointestinal motility.

Neuromodulation *in the* Gastrointestinal System

Fig. 2.

Neuromodulation in the gastrointestinal system. Electrical stimulation in the gastrointestinal system either stimulates the peripheral nerves innervating end-organs or stimulates the end-organ directly. Examples of neuromodulation in the gut include vagus nerve stimulation, gastric electrical stimulation, intestinal electrical stimulation, colonic electrical stimulation, and sacral nerve stimulation.