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Research report

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.

1. Introduction

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

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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. Anoctomin1 has

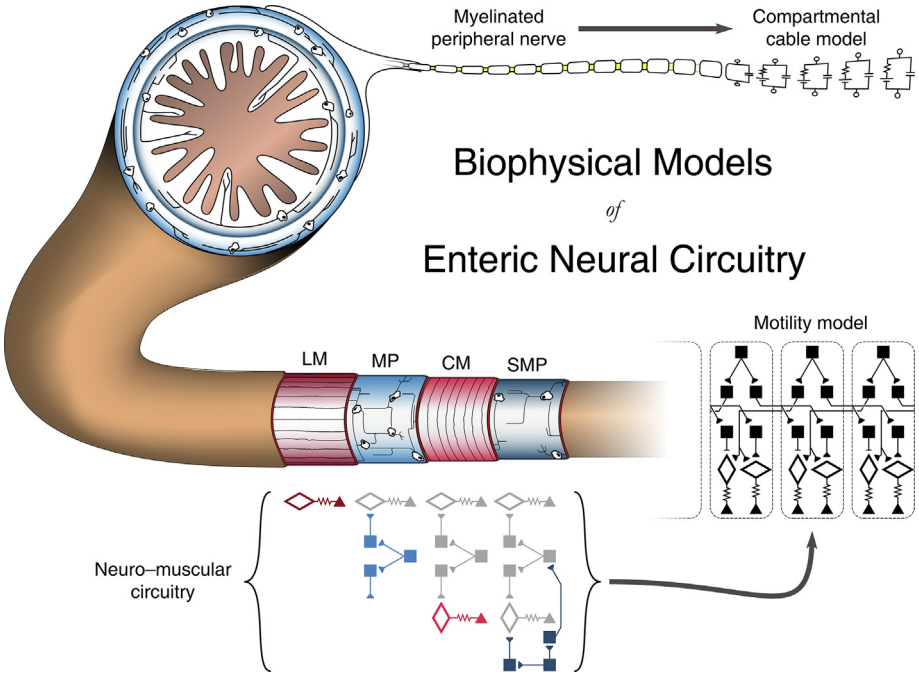

Fig. 1. Biophysical models of enteric neural circuitry. Gastrointestinal motility is the result of coordinated activity of enteric neurons, smooth muscle fibers, and interstitial cells of Cajal. Electrically-active cells form neuromuscular circuits among the layers of the gastrointestinal wall. By interconnecting these cells into networks, we can develop models of gastrointestinal motility.