MATHEMATICAL PHYSIOLOGY OF THE GASTROINTESTINAL SYSTEM - THE IMPORTANCE, THE PROBLEMS, THE SOLUTIONS

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Contents

Summary

This review starts with introductory notes on the gastrointestinal physiology, mainly focused on the electrophysiology of the smooth muscle cells and of the interstitial cells of Cajal. A brief account of the disorders related to impairment of gastric motility is also given. The core of the review is formed by the presentation of various mathematical models of the electrical activity in the gastrointestinal tract. Phenomenological models and biophysically-based models at the single-cell level are presented, both for the muscle cell and the interstitial Cajal cell. The monodomain and bidomain models are then discussed. These models are used to represent the electrical activity at the organ level (e.g., the stomach) and are based on the continuum approach. The section that follows is devoted to the experimental validation, and illustrates experimental

techniques for recording the electrical activity from the GI tract. A brief account of the mathematical models of the mechanical events in the intestine and the stomach was given, which includes the models of absorption. The review concludes by an indication on the future direction of the research.

1. Gastrointestinal Physiology

The human body is typically characterized into 12 major organ systems: cardiovascular, endocrine, gastrointestinal (GI), immune, integumentary (skin), lymphatic, muscular, nervous, reproductive, respiratory, skeletal, and urinary. However, in reality the 'division of labor' between the organ systems is not absolute. For instance, the nervous and endocrine systems also exert a fair degree of control over the functions of the GI system. In this review, we focus our discussion specifically on the physiology of the GI system, and for the most part will therefore conceptually isolate the GI system from the effects of other organ systems.

The major functions of the GI system are digestion, absorption, excretion and protection. Digestion is the process by which ingested food is broken down into basic nutrients and water, ready for absorption and subsequent use in the functions, repair, and growth of bodily tissues. The GI system is best described as a series of 'tubes', (known as the GI tract), into which secretions and excretions from the pancreas and liver drain (Figure 1).

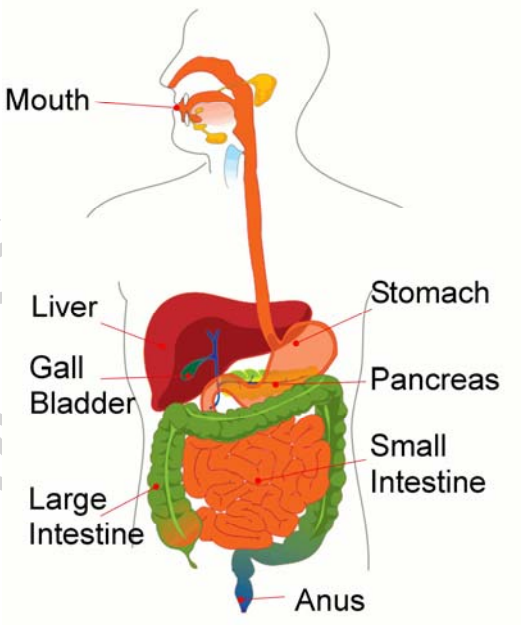

Figure 1. The gastrointestinal (GI) system. The initial breakdown of food begins in the mouth. The stomach mixes ingested food with gastric secretions (acid and digestive enzymes), further grinds the food into fine particles, and releases the contents at a controlled rate into the small intestine. The pancreas and liver release digestive enzymes and bile respectively into the upper small intestine, to aid digestion of proteins, carbohydrates and fat molecules. Bile is stored in the gall bladder prior to release. The long, densely folded small intestine surface absorbs most nutrients and water from digested food. The large intestine is concerned primarily with desiccation and

compaction of waste material and undigested food contents, which are defecated through the anus.

The process of digestion begins from the moment a bite is taken. Food is first masticated (chewed) and mixed with saliva (which contains digestive enzymes), then swallowed through the esophagus to reach the stomach. The stomach is the most dilated portion of the GI tract, and serves as a storage receptacle. Inside the stomach, food is mixed with gastric acids and enzymes, and forcefully broken down into fine particles, which are release to the small intestine at a controlled rate. The digesting food from the stomach is known as chyme. Chyme is continuously propelled along the intestines while absorption of nutrients and water takes place through the densely folded small intestine wall. The digestive process concludes with the defecation of any unabsorbed food contents, together with excreted waste material, through the anus.

The GI wall consists of a number of distinct layers of tissue. Not all parts of the GI tract have the same composition, but the general structure includes those layers shown in Figure 2. The mucosa is the layer on the luminal side (the inner most side) of the GI tract. This layer consists of epithelial tissues lining the lumen of the GI tract, underpinned by a thin layer of smooth muscle (SM) known as the muscularis mucosa. The next layer, deep to mucosa, is the submuscosa, which mostly consists of loose connective tissue, large nerve trunks, and blood vessels. Beyond the submucosa lies the muscularis externa, a thick muscular coat responsible for peristalsis. In the stomach, the muscularis externa consists of SM arranged in three layers: outer longitudinal, inner circular and innermost oblique. The circular layer contains SM fibers arranged in rings around the GI tract, while the longitudinal layer contains SM fibers aligned in the direction along the tract. Contractions of the muscularis externa result not only in peristalsis, but also the mixing movements which are employed by the stomach and intestines to mix the luminal contents with glandular secretions, and in the case of the stomach, to grind contents into small particles (a process termed 'trituration'). The outermost layer of the GI tract is the serosa, which mainly consists of connective tissue, and serves as a structural outer coat.

A key feature of the digestive process is the continuous propagation of the luminal contents along the GI tract, in a movement known as peristalsis. Thus, the physiology underlying peristalsis is one of the most important aspects to the GI system. Among GI functions, this review is primarily concerned with the problem of motility, where most mathematical modeling has focused to date. Understanding of physiology of GI motility is augmented via mathematical models, which represent the biological processes using sophisticated systems of mathematical equations. Before we discuss the modeling techniques in detail, it is important to describe the physiology of GI motility (Section 1.1-1.2) and the problems of impaired gastric motility (Section 1.3).

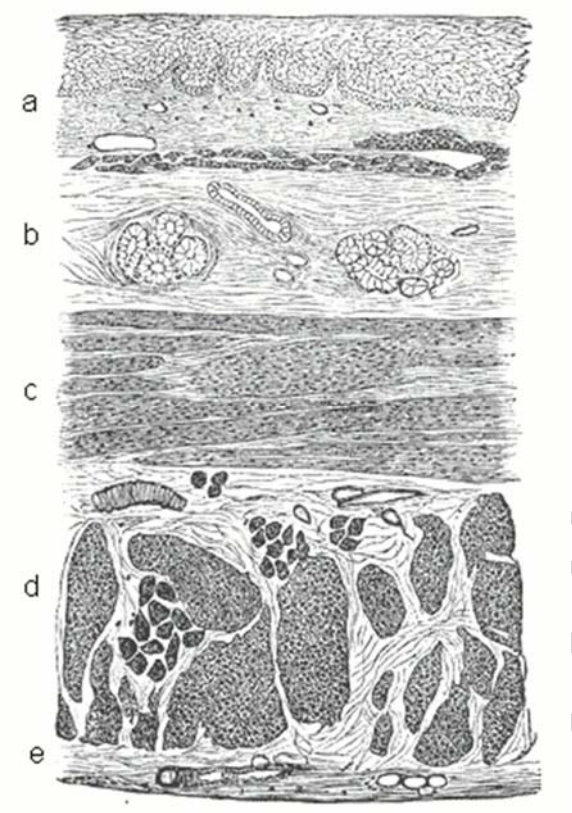

Figure 2. A cross section of the gastrointestinal tract reveals four major layers: (a) closest to the luminal surface is the mucosal layer, which consists of a layer of epithelial cells, the lamina propria, and the muscularis muscosae. (b) the next layer is the submucosa, which contains connective tissues, nerves, and blood vessels. The muscularis externa lies deep to submucosa, and contains SM fibers aligned in (c) the circular (transverse) direction, and (d) longitudinal direction. (e) the outermost layer is the serosa, which contains mostly connective tissue.

1.1. Smooth Muscle Cell Electrophysiology

The SM layers contain smooth muscle cells (SMCs). The SMCs in the GI tract are arranged in bundles, usually 2 to 5 μm in diameter and 20 to 500 μm in length. A SM layer contracts in the direction of its fibre orientation. Like all cells, SMCs are enveloped by cellular membranes which act as semi-permeable barriers, creating an intracellular niche known as the cytoplasm. The constituents of the cytoplasm include many chemicals and cellular organelles, of which most important to peristalsis are charged particles known as ions, notably calcium ions (Ca^{2+}), potassium ions (K^{+}), and sodium ions (Na^{+}).

As occurs in all cells, there are a number of ion channels embedded in the membranes of SMCs, which act as selective passageways for the flow of ions into and out of the cells. As these ions accumulate inside cells, an electrical gradient develops across the cell membrane. This electrical gradient is known as the membrane potential (V_m). There is a V_m at which the net flux of ions due to the difference in concentration is

counteracted by the flux of ions due to V_m, i.e. a V_m where the ions are in electrochemical equilibrium, and hence where the net flux of ions is zero. The V_m at this point is known as the resting membrane potential (RMP), which for SMCs is around -70 mV.

Preceding a contraction, the SMC ion channels activate to allow an additional flux of ions across the cell membrane. This flux results in a change in V_m, also known as a 'slow wave', which is an event of fundamental importance in the physiology of peristalsis (Figure3a). The initial influx of Ca^{2+} and Na^+ rapidly depolarizes V_m towards -30 mV, and then as Na^+-type channels inactivate, Ca^{2+}-type channels remain open, which maintains V_m at a plateau phase. The subsequent inactivation of Ca^{2+}-type channels and prolonged activation of K^+-type channels repolarizes V_m back to the RMP. For more information on the electrophysiology of ion channels, see the Chapter: *Cell excitability*. The occurrence of slow waves is periodic, occurring at approximately 3 cycles-per-minute (cpm) in the human stomach, 12 cpm in the duodenum and 8-9cpm in the terminal ileum. Slow waves do not occur in the large intestine.

SM contractions are triggered by the influx of Ca^{2+} during depolarization and the plateau-phase, which activates a series of cellular contractile reactions (termed cross-bridge cycling). Slow waves spread through the walls of the stomach and intestines in a coordinated fashion and control GI mechanical activity leading to peristalsis. Mechanical activity is also controlled by intramural plexuses and that slow wave may have a permissive role for the development of contractions. Slow waves are oscillations in the membrane potential which make it more likely for a contraction to occur (Figure3a). A slow wave is not always indicative of peristalsis, however, if the amplitude of the slow wave does not exceed a certain V_m threshold (Figure3b), then contractions will not occur (or sometime very weak contractions).

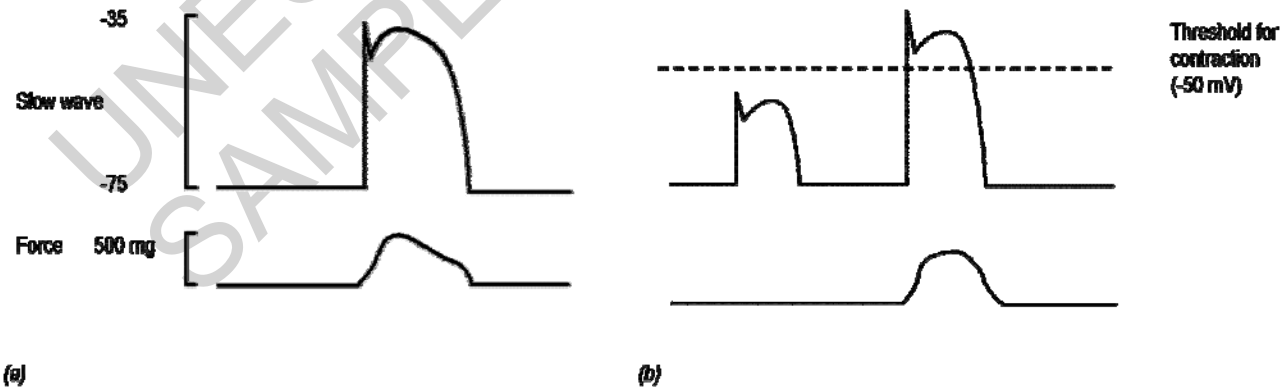

Figure 3. (a) The relationship between contraction and the membrane potential of a canine stomach. The contractile force increases as V_m depolarizes. (b) If the depolarization exceeds a threshold (dashed line) the contractile force becomes stronger. The slow waves with amplitude lower than the threshold do not result in large scale contractions.

1.2. Electrophysiology of the Interstitial Cells of Cajal

It was previously assumed that slow waves were generated autonomously by the SMCs. This view was challenged by the discovery of the interstitial cells of Cajal (ICCs), which reside in intermittent spaces within and in between the SM layers along the GI tract (Figure 4). The ICCs were first described as "nerve-like cells at ends of motor neurons in organs innervated by peripheral nerves" by the Spanish Nobel prize laureate Santiago Ramón y Cajal in 1911. Exactly how the ICCs coordinate slow waves is one of the more controversial topics in the history of GI electrophysiology. Given the limited understanding of the electrophysiology in the early 1910s, the discovery of ICCs went largely unnoticed by the scientific community. Indeed, they were largely forgotten until the 1970s, when the introduction of electron microscopy allowed the morphology of ICCs to be inspected in much greater detail than was possible with conventional light microscopy. Using electron microscopy, histologists found that ICCs are positioned close to the SMCs and nerve terminals along the GI tract (Figure 4a).

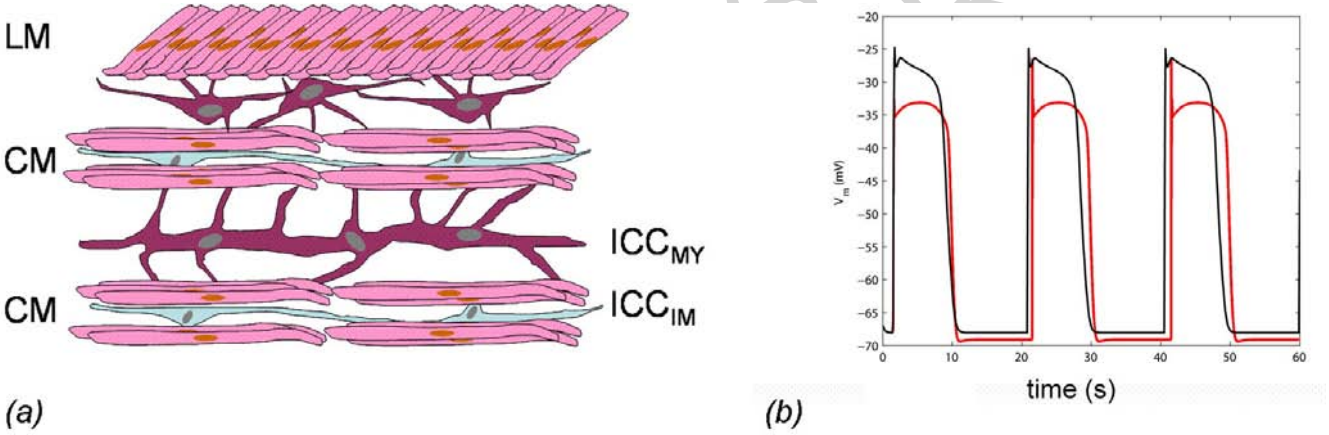

Figure 4. (a) The interstitial cells of Cajal (ICCs) are positioned in close proximity to the smooth muscle cells (SMCs) in the GI wall. There are two types of smooth muscle (SM) layers, the longitudinal layer (LM) and circular layer (CM). A third layer (oblique layer, not shown) may also be present. The ICCs that lie in between the SM layers are known as the myenteric ICC (ICC_{MY}), and the ICCs that are intermingled within the SM layers are known as the intramuscular ICC (ICC_{IM}). The ICCs coordinate peristalsis by generating a pacemaker potential which depolarizes the membrane potentials (V_m) of SMCs and activates the contractile elements in the SMCs. (b) Simultaneous intracellular recordings of ICCMY and a nearby circular SMC showing simulated pacemaker potentials (black) and slow waves (red) occur synchronously at 3 cpm.

The close association of ICCs with the nerve terminals once again reignited the hypothesis that ICCs are involved in neurotransmission of contractions of SMCs. However, even though there was circumstantial morphological evidence of ICCs occurring at the electrically active regions along the GI tract, the mechanisms by which ICCs coordinate the slow waves could not be established, due to the difficulty of isolating ICCs from tissues under experimental conditions. A breakthrough occurred in the early 1990s, when a group of scientists from Japan and America discovered, by accident, a method of manipulating the expression of ICCs in new born mutant mice.

These scientists noticed pathological gastric and intestinal peristalsis and, more importantly, lack of slow wave activity in mutant mice devoid of ICCs. Subsequent work by many researchers has now confirmed that ICCs are responsible for slow wave activity, through spontaneously generated omnipresent periodic electrical events known as pacemaker potentials. The pacemaker potentials conduct passively from the ICCs to the SM layer, where slow waves are triggered by the pacemaker potentials (Figure 4b).

There is some ambiguity in the terms used to describe the pacemaker potential; some literature, for example, refers to it as the slow wave. For clarity, we define pacemaker potentials to be the electrical activity of the ICCs, and slow waves to be the electrical activity of the SMCs. Much effort in the past decade has been devoted to identifying the properties of individual ion channels in ICCs and SMCs and how the collaboration of these ion channels affect the cellular mechanisms of both ICCs and SMCs in different regions along the GI tract.

In isolated cell cultures, ICCs generate pacemaker potentials at different intrinsic frequencies, but in an intact network frequencies of the ICCs congregate to a single frequency in a process known as entrainment. Normal peristalsis of the stomach is dependent on the entrainment of ICCs in the following manner: first, a pacemaker potential is generated in a region of ICCs along the greater curvature of the stomach. This pacemaker potential conducts passively to adjacent regions of the ICC network. The receiving regions respond by generating pacemaker potentials of their own. As a result the pacemaker potentials are continually being regenerated and conducted actively throughout the ICC network in the stomach. Entrainment ensures that the strength of pacemaker potentials is not lost as they propagate for distances up to many centimeters in the stomach. The intestines also contain many ICC pacemaker sites, from which pacemaker potentials are entrained at a decreasing rate in a piece-wise manner along the intestines. Without entrainment, the electrical rhythm of both the ICC network and SM layer becomes disorganized and consequently peristalsis may be impaired. Indeed, this is widely considered to be a fundamental factor in many gastric hypomotility disorders such as gastroparesis; this will be discussed in the following section (section 1.4).

The mechanisms that lead to entrainment are still not completely understood. There are currently two main views: voltage-dependent intracellular Ca^{2+} oscillation, and voltage-dependent Ca^{2+} entry. Both views acknowledge that entrainment is achieved through release of Ca^{2+} from intracellular stores known as the endoplasmic reticulum (ER). Ca^{2+} is released from the ER in response to the increasing level of an intracellular chemical precursor known as inositol 1,4,5- triphosphate (IP_3) .

The first view holds that oscillation of the IP_3 level is voltage-dependent. In this view, depolarization of V_m by an entrainment pacemaker potential triggers Ca^{2+} release, and generation of pacemaker potentials in the receiving ICC. The second view argues that IP_3 levels are not influenced by V_m directly. Instead, a small amount of Ca^{2+} enters the ICC via a voltage-dependent calcium channel. This Ca^{2+} is localized in a subspace close to the ER, where it induces more Ca^{2+} release from the ER by up-regulating the levels of IP_3. The second view also argues that while there is circumstantial evidence for IP_3 synthesis being voltage-dependent, it is currently technically impossible to measure

cell-to-cell IP_3 concentrations in the ICCs during entrainment. It is probable that the second view has more physiological merit, as the phenomenon of highly localized concentrations of Ca^{2+} has been imaged using confocal imaging technique close to the intracellular space between ER and mitochondria in SMCs, and other types of tissues.

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Bibliography

1. Aliev RR, Richards W, and Wikswo JP. (2000). A Simple Nonlinear Model of Electrical Activity in the Intestine. Journal of Theoretical Biology 204: 21-28. [The first cell model that differentiates the functions of gastrointestinal interstitial cells of Cajal and smooth muscle cells].

2. Berne RM, Levy M, N, Koeppen BM, and Stanton BA. (1998) Physiology: Mosby. [A good introduction to general physiology].

3. Cheng LK, O'Grady G, Du P, Egbuji J, Windsor JA, and Pullan AJ. (2010) Gastrointestinal System. Wiley Interdisciplin Rev Syst Biol Med 2(1): 65-79. [A technical review on the existing modeling techniques in gastrointestinal electrophysiology].

4. Corrias A and Buist ML. (2008). A quantitative cellular description of gastric slow wave activity. In: Am J Physiol Gastrointest Liver Physiol. [An update-to-date biophysically-based mathematical cell model of the interstitial cell of Cajal].

5. Corrias A and Buist ML. A quantitative model of gastric smooth muscle cellular activation. Annals of Biomedical Engineering 35: 1595-1607. [An update-to-date biophysically-based mathematical cell model of gastric smooth muscle cell].

6. Everhart JE. (1994). Digestive diseases in the United States: Epidemiology and impact. U.S. Department of Health and Human Services, edited by National Institutes of Health of Diabetes and Kidney (NIDDK) Diseases. Washington, DC: U.S. Government Printing Office. [A clinical study of the cost, frequency, medical care, mortality, and general recommendations of digestive diseases in the United States].

7. Faville RA, Pullan AJ, Sanders KM, and Smith NP. (2008). A biophysically based mathematical model of unitary potential activity in interstitial cells of Cajal. Biophys J 95: 88-104. [An update-to-date biophysically-based mathematical cell model of the interstitial cells of Cajal].

8. Hirst GD and Edwards FR. (2006). Electrical events underlying organized myogenic contractions of the guinea pig stomach. J Physiol 576: 659-665. [A comprehensive description of the gastric slow wave activity in guinea-pig stomach].

9. Koh SD, Ward SM, Ordog T, Sanders KM, and Horowitz B. (2003). Conductances responsible for slow wave generation and propagation in interstitial cells of Cajal. Curr Opin Pharmacol 3: 579-582. [A discussion of the role of the interstitial cells of Cajal in slow wave generation].

10. Lammers WJ, Michiels B, Voeten J, Ver Donck L, and Schuurkes JA. (2008). Mapping slow waves and spikes in chronically instrumented conscious dogs: automated on-line electrogram analysis. Med Biol Eng Comput 46: 121-129. [A description of the experimental recording method and signal processing techniques of serosal slow wave recording].

11. Liao D, Zhao J, and Gregersen H. (2005). Regional surface geometry of the rat stomach based on three-dimensional curvature analysis. Phys Med Biol 50: 231-246. [This study presents an analysis of the geometry of a virtually generated stomach model].

12. Melville J, Macagno E, and Christensen J. (1975). Longitudinal contractions in the duodenum: their fluid-mechanical function. Am J Physiol 228: 1887-1892. [A mechanical analysis of the contractions in the intestine].

13. Pal A, Brasseur JG, and Abrahamsson B. (2007). A stomach road or "Magenstrasse" for gastric emptying. J Biomech 40: 1202-1210. [A novel modeling analysis of the fluid dynamics in the stomach].

14. Pullan AJ, Buist ML, and Cheng LK. (2005). Mathematically modelling the electrical activity of the heart: from cell to body surface and back again. Singapore: World scientific publishing Co. Pte. Ltd. [A comprehensive technical book on cardiac electrical activity modeling].

15. Sanders KM, Koh SD, and Ward SM. (2006). Interstitial cells of cajal as pacemakers in the gastrointestinal tract. Annu Rev Physiol 68: 307-343. [A comprehensive review of gastrointestinal slow wave activity, with focus on the role of the interstitial cells of Cajal].

16. Sanders KM and Ward SM. (2006). Interstitial cells of Cajal: a new perspective on smooth muscle function. J Physiol 576: 721-726. [A comprehensive review of gastrointestinal slow wave activity].

17. Sarna SK, Daniel EE, and Kingma YJ. Simulation of slow-wave electrical activity of small intestine. Am J Physiol 221: 166-175, 1971. [One of the earliest slow wave mathematical model].

18. Wang YR, Fisher RS, and Parkman HP. (2008). Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995-2004. Am J Gastroenterol 103: 313-322. [A clinical study on the prevalence of gastroparesis in the United States].

19. Yao SK, Ke MY, Wang ZF, Xu DB, and Zhang YL. (2005). Visceral response to acute retrograde gastric electrical stimulation in healthy human. World J Gastroenterol 11: 4541-4546. [This study presents an example of gastric electrical stimulation therapy].

20. Yu LX and Amidon GL. (1999). A compartmental absorption and transit model for estimating oral drug absorption. Int J Pharm 186: 119-125. [A modeling study of the kinetic of drug absorption in a multiple compartmental model].

Biographical Sketches

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Dr. Leo Cheng: Leo is a principal investigator at Auckland Bioengineering Institute. He has an extensive background in modeling cardiac electrical activity. He is currently leading the research project of modeling gastrointestinal electrical activity.

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Dr. John Egbuji: John is a trained M.D. The topic of his research is characterization of human gastrointestinal electrical activity.

Dr. Gregory O'Grady: Greg is an advanced surgical trainee and a lecturer at the Department of Surgery at Auckland. His research topic is a rational foundation diagnosis and management of gastric disorders through continuum modeling.

Professor Andrew Pullan: Andrew is a professor of engineering at the University of Auckland. He is the dean of the Department of Engineering Science and holds a conjoint professor position in the department of surgery, Vanderbilt University. Andrew leads many world-leading research modeling projects of the electrical activities of cardiac, skeletal muscular and gastrointestinal tissues.