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Mechanics of the stomach: A review of an emerging field of biomechanics

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Mathematical and computational modeling of the stomach is an emerging field of biomechanics where several complex phenomena, such as gastric electrophysiology, fluid mechanics of the digesta, and solid mechanics of the gastric wall, need to be addressed. Developing a comprehensive multiphysics model of the stomach that allows studying the interactions between these phenomena remains one of the greatest challenges in biomechanics. A coupled multiphysics model of the human stomach would enable detailed in-silico studies of the digestion of food in the stomach in health and disease. Moreover, it has the potential to open up unprecedented opportunities in numerous fields such as computer-aided medicine and food design. This review article summarizes our current understanding of the mechanics of the human stomach and delineates the challenges in mathematical and computational modeling which remain to be addressed in this emerging area.

KEYWORDS

digesta, gastric electrophysiology, gastric mechanics, gastric wall, multiphysics model

1 | INTRODUCTION

Healthcare problems related to the stomach are among the most important causes of morbidity in industrialized countries. For example, healthcare costs of obesity have nearly doubled from \$79 billion in 1998 to \$147 billion in 2008 in the United States,[1,2] where in 2010, the prevalence of obesity was an estimated 36% (17% in the EU[3]). More than 250 000 bariatric surgeries are performed per year in the United States and EU together[4,5] with a cost of €5000-€15 000 per procedure.[6,7] The economic footprint of gastro-esophageal reflux disease (GERD) amounts to an estimated \$20 billion/year in the United States.[8] Moreover, 10%-45% of the general population suffer from dyspepsia (indigestion),[9] which seriously compromises individual well-being and economic productivity. These highly prevalent health problems are closely linked to gastric mechanics (ie, mechanics of the stomach). For example, obesity can be permanently resolved by irreversible changes of gastric geometry and mechanics as performed in bariatric surgery.[10] GERD results from a misbalance between intragastric pressure and closing pressure of the sphincter between stomach and esophagus. Dyspepsia is often related to control disturbances of gastric smooth muscle.

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ABBREVIATIONS: ACW, antral contraction wave; DPM, discrete particle method; GERD, gastro-esophageal reflux disease; ICC, interstitial cell of Cajal; ICC-IM, intramuscular ICC; ICC-MY, myenteric ICC; MRI, magnetic resonance imaging; PDGFRα^+, platelet-derived growth factor receptor α positive; SMC, smooth muscle cell; SPH, smoothed particle hydrodynamics.

Perhaps even more importantly, the stomach and its mechanics play a key role not only in the digestion of food, one of the most essential processes in living organisms, but also for drug administration. Around 70% of all drugs are administered orally, and their processing and effectiveness thus depend crucially on gastric mechanics.[11–13]

This tremendous importance of gastric mechanics is not at all reflected by current research efforts as is best revealed by a comparison with cardiovascular mechanics. Healthcare costs of cardiovascular diseases ($149 billion in the United States in 2008[14]) are comparable to the ones related to the stomach. However, in the program of the 8th World Congress of Biomechanics in 2018 with more than 4500 presentations common cardiovascular keywords* are found 414 times, whereas prominent keywords related to the stomach† do not appear at all. Hundreds of experimental articles about cardiovascular tissue mechanics over the last decades are contrasted by just a small number of articles on experimental gastric tissue mechanics. The situation is similar in modeling. Three-dimensional computational fluid mechanics was first applied to arteries around 1990,[15,16] to the stomach only in 2007.[17] Computational models incorporating fluid-structure interactions were developed for the vasculature already in the mid-1990s.[18] Recently pioneering steps in this direction have been taken for the intestine[19–21] but no such model has been proposed for the stomach so far. In short, modeling of the stomach lags around 20 years behind modeling of the cardiovascular system.

Several reasons have delayed the progress of gastric compared to cardiovascular biomechanics, in particular the sophisticated and for a long time poorly understood electrophysiology of the stomach,[22] the complex mechanics of *digesta* (ie, food undergoing digestion) compared to blood, and the limited understanding of neural and hormonal mechanisms controlling gastric mechanics. Over the last decade, substantial progress has been made in all these fields,[22–39] and rapid advances in computational power allow addressing even complex multiphysics problems nowadays.

Benefitting from these recent advances, the time has come now to tackle one of the still open big questions of biomechanics, which is the development of a comprehensive mathematical and computational multiphysics model of the stomach, which allows for detailed in-silico studies of the mechanics and mathematical principles governing the digestion of food in the stomach. Such a model has the potential to open up new horizons and unprecedented opportunities in numerous fields such as computer-aided medicine and food design. This review article is intended to provide a comprehensive summary of our current understanding of the mechanics of the human stomach. It may serve as a convenient starting point in particular for applied mathematicians and engineers who have interest to start research in this emerging area of biomechanics.

2 | ANATOMY AND PHYSIOLOGY OF THE HUMAN STOMACH

The human gastrointestinal tract is composed of several roughly tube-like organs in series (cf. Figure 1). Food enters via the mouth and is swallowed through the esophagus into the stomach, passing through a muscular cuff (the lower esophageal sphincter) that opens during swallowing. In the stomach, the digesta are stored, mixed, diluted with gastric juice, and mechanically as well as chemically disintegrated. Subsequently, they are released at a tightly controlled rate through the pylorus, a rhythmically opening muscular cuff, into the duodenum,[40] the first part of the small intestine. After the small intestine, where most nutrients are extracted, digesta pass through the large intestine where more nutrients, ions and in particular water are extracted, leaving nearly solid feces, that are excreted through the anus. Positions in the gastrointestinal tract are denoted by the terms proximal (closer to the mouth) vs distal (closer to the anus).

The stomach is as a J-shaped muscular bag curved in the frontal plane (cf. Figure 1). Its volume is determined by the amount of stored digesta and normally ranges between 25 mL in the fasted and 1500 mL in the fed state.[11] After a typical meal of ~1000 mL, the stomach measures around 30 cm along its greater curvature and exhibits a maximal width of around 10 cm. [41] Anatomically, the stomach can be divided into three regions (from proximal to distal): fundus, corpus or body, and antrum (cf. Figure 2). While the gross histology is consistent throughout the organ (cf. Figure 2), the regions of the stomach can also be distinguished based on their detailed histological properties.[42] The fundus is a muscular bag that relaxes upon ingestion of food to increase its storage capacity (gastric accommodation). Peristaltic muscular contraction waves, that is, ring-like contraction that constrict the stomach circumferentially, running from the corpus through the antrum to the pylorus, are mixing and grinding the food in the distal part of the stomach (cf. Figure 3). Temporal coordination of these so-called antral contraction waves (ACWs) with the aperture of the pylorus controls release of the digesta into the duodenum.

2.1 | Gastric lumen: Fluid mechanics and chemical reactions

Mastication breaks solid food down into small fragments that are mixed with saliva in the mouth[43] and, after swallowing, with gastric juice in the stomach. Digesta in the lumen (ie, inside space) of the stomach can be modeled as in general non-Newtonian fluids, carrying a solid phase of particles (cf. Figure 3) and fibers.[44–46] In general, one distinguishes between three types of gastric mixing processes, that is, solid-solid, solid-liquid, and liquid-liquid mixing, depending on the consistency of the digesta.[47]
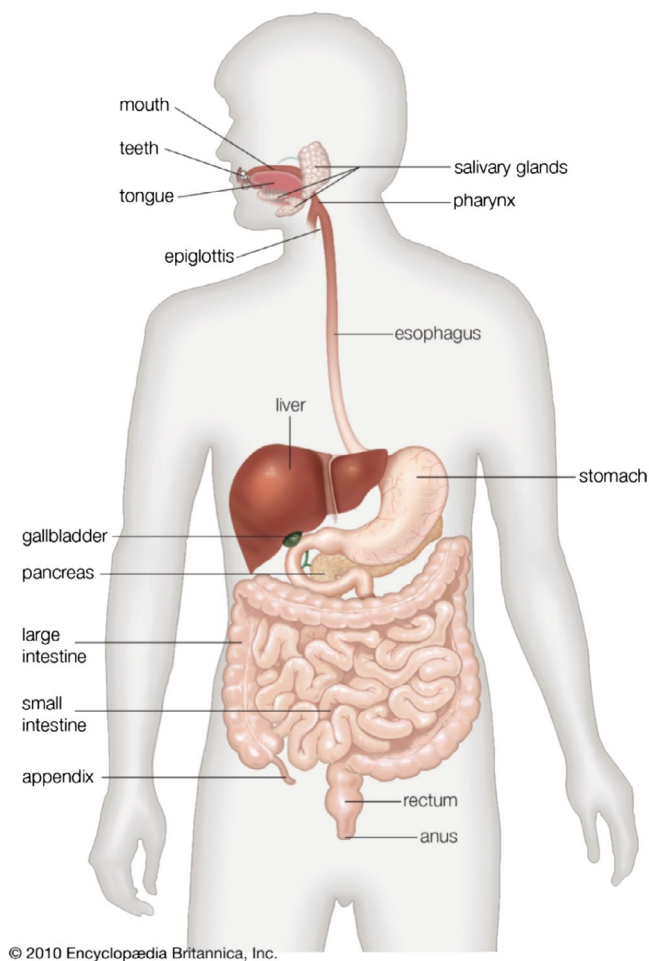
**FIGURE 1** Major regions of gastrointestinal tract from mouth to anus[‡]

In the stomach, solid particles are disintegrated by fragmentation (cleavage into smaller pieces of roughly similar size) and erosion (abrasion of the surface by fluid shear stress).[43,46,48] For tough small particles—like carrot or nut particles of a few millimeters in diameter—erosion dominates.[49] Chemical reactions tenderize the food matrix, promoting thereby both mechanical fragmentation and erosion. Disintegration reduces the size of food particles over time following an exponential, sigmoidal, or delayed sigmoidal function, depending on the rate of simultaneous swelling of the particles due to absorption of gastric juice.[46]

2.2 | Gastric wall: Solid mechanics

The gastric wall is around 3-4 mm thick and is comprised of four major layers, the mucosa, submucosa, muscularis, and serosa.[50,51] Wall elasticity and stress can be divided into a passive part, determined by the strain of elastic fibers mainly in the submucosa and muscularis, and an active part governed by the (adaptable) tone of smooth muscle fibers mainly in the muscularis. The muscularis consists of up to three sublayers (the oblique, longitudinal, and circumferential sublayer) with muscle fibers oriented in respective directions (cf. Figure 2).

One of the primary functions of the stomach is storage of ingested food until it is further processed in the intestine. Gastric volume between the fasted and postprandial state can change by a factor of 60 by unfolding and stretching (by up to ∼160%[52]) of the gastric wall. The mechanics of gastrointestinal tissue is much less explored than the one of cardiovascular tissue. There have been a few papers on the constitutive behavior of the esophagus,[53–57] small intestine,[58–64] and large intestine,[58,61,65–71] and around 20 on the mechanical properties of the gastric wall.[61,72–89] These revealed that the constitutive properties and thickness of the different layers of the gastric wall differ significantly between different regions of the stomach, corresponding to their respective physiological functions. Most papers on gastric tissue mechanics report results of uniaxial tests only,[61,72–76,79,80,87] which are insufficient to characterize the biaxial deformation (in both circumferential and longitudinal direction) observed in vivo, noting the in general significant anisotropy of gastric tissue.[73,88]

Recently, a study identified for the first time the quasi-static passive biaxial mechanical properties of porcine gastric tissue.[88] The authors conducted biaxial tests including seven different stretch ratios of tissue patches extracted from the three main regions of the stomach, that is, fundus, corpus, and antrum. Experimental data was fitted to a Fung-type strain energy function

Regions of the stomach
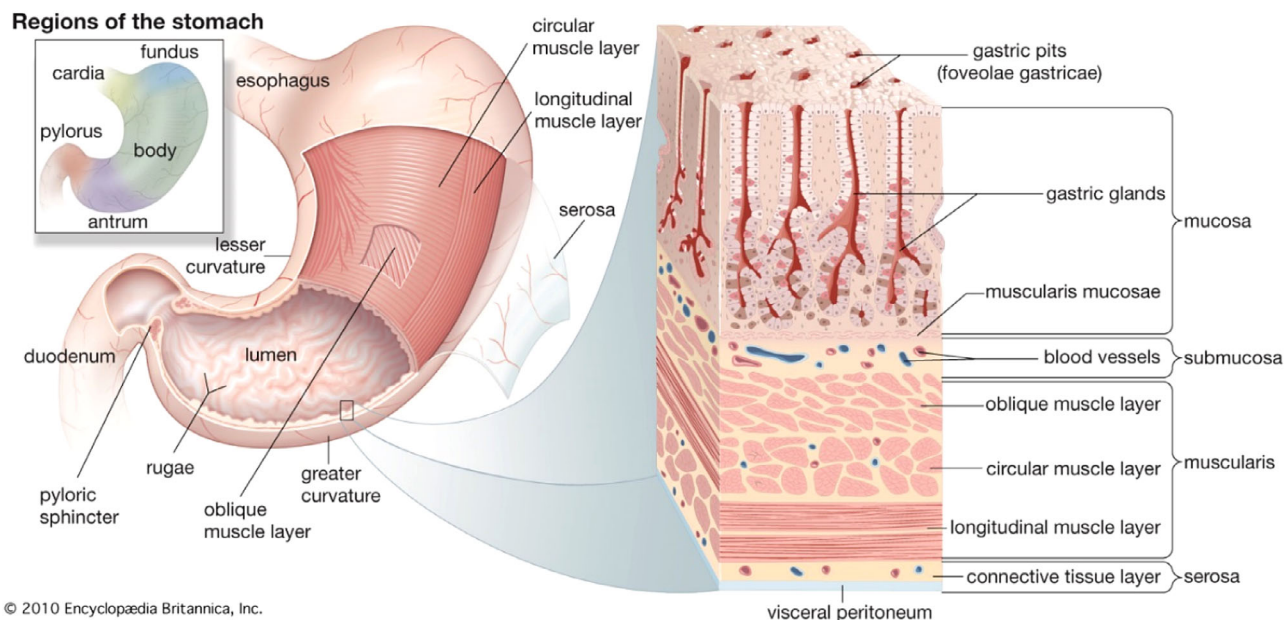
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FIGURE 2   Structure of human stomach (left) and gastric wall (right)§

(cf. Section 3.2). The study confirmed a pronounced anisotropy of gastric tissue. In addition, it showed that the three regions of the gastric wall exhibit specific mechanical properties consistent with their respective physiological functions. However, the study did not conduct layer specific biaxial experiments and was limited to porcine tissue.

Another recent study investigated extensively the active mechanical properties of porcine fundic smooth muscle tissue.[89] The study quantified the force-length and force-velocity relations of fundic smooth muscle strips. Additionally, the dependency of force generation on preceding length changes, so called history effects, was examined. Notably, the study suggested the importance of history-dependent effects for the physiological function of the fundus, that is, mainly gastric accommodation (cf. sSection 2.3.1). While ref. [89] presented extensive data on the active properties of porcine gastric smooth muscle, the experiments were limited to fundic tissue, omitting corporal and antral tissue. Corporal and antral regions might, however, show different active mechanical properties adapted to their specific physiological functions, that is, mixing and grinding of ingested food as well as emptying toward the duodenum (cf. Section 2.3).

Unfortunately, experiments with animal tissue[61,73,74] are not directly applicable to humans due to significant interspecies differences.[74] Only two authors reported biaxial mechanical tests of human gastric tissue.[77,78,81] Focussing on equibiaxial, highly dynamic load only,[81] does not provide sufficient data to establish, for example, a nonlinear strain energy function for gastric tissue. Like ref. [81], also refs. [77, 78] studied only passive elasticity, neglecting the role of smooth muscle tension, and did not examine differences between the layers of the gastric wall.

Despite significant recent progress, there is still a pressing need for more experimental data about the mechanics of the human gastric wall, distinguishing between different regions, wall layers as well as active and passive elasticity and anticipating the complex physiological deformations of the stomach. Nevertheless, there exists already at least a basic collection of published experimental data about the mechanical properties of the gastric wall that can serve as a reasonable basis for mathematical and computational modeling.

2.3 | Gastric wall: Electrophysiology and electromechanics

In general, changes of the gastric geometry by contraction or relaxation of the smooth muscle in the muscularis of the gastric wall are referred to as gastric motility. One can distinguish three kinds of gastric motility: gastric accommodation, gastric mixing and emptying via ACWs, and migrating motor complexes.

2.3.1 | Gastric accommodation

The reflex leading to gastric muscle tone reduction predominantly in the proximal stomach after ingestion of food is called gastric accommodation (cf. Figure 3). It enables the stomach to expand its volume without significant increase of intragastric pressure. Thereby, gastric accommodation supports the physiological function of (temporary) food storage.[36,37,90] Gastric accommodation comprises two main responses: receptive and adaptive relaxation.[91,92] Eating stimulates the oropharynx and esophagus which triggers the relaxation of smooth muscle in the proximal stomach shortly after (within seconds). This response
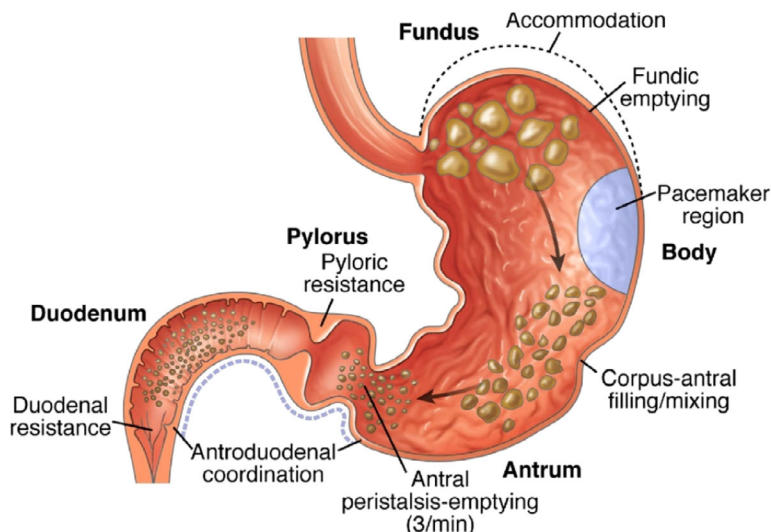
FIGURE 3 Schematic representation of gastric motility patterns including accommodation and antral contraction waves resulting in mixing and grinding of luminal content[¶]

is called receptive relaxation. Adaptive relaxation is a slower mechanism adjusting fundic muscle tone in response to gastric and duodenal distension and increased gastric intraluminal pressure. Possibly nutrient sensing in the duodenum also plays a role. Consequently, the specific properties of the ingested food influence adaptive relaxation.[93] Impaired gastric accommodation is often associated with gastric disorders like GERD and dyspepsia.[9] Normal muscle tension is restored during gastric emptying.[94]

2.3.2 | Antral contraction waves

The motility pattern responsible for gastric emptying and gastric mixing (cf. Figure 3) is at its core the same: antral peristalsis or ACWs. ACWs appear as ring-shaped muscular contractions of the gastric wall which move along the stomach. They make the antrum act as a peristaltic food pump.[40,94] The complex interplay between pyloric opening and closing and arriving ACWs on one hand mixes and grinds digesta and on the other hand regulates gastric emptying, that is, the release of gastric content into the duodenum.

ACWs are controlled by periodic electrical signals, called slow waves, propagating through the gastric wall. The underlying electrophysiology is similar to the heart[95] but yet significantly more sophisticated due to a complex interplay between at least two cell types: smooth muscle cells (SMCs) and interstitial cells of Cajal (ICC).[6,22,96] SMCs are responsible for generating the mechanical force leading to contractions of the gastric wall. ICC are largely responsible for generating the electric signals that stimulate contractions of SMCs. In the following, we will discuss some details of this big picture. In corpus, antrum, and pylorus, a dense network of ICC can be found at the myenteric plexus which is a branching network of cells in the space between the longitudinal and circumferential sublayer of the muscularis. ICC located there are called myenteric ICC (ICC-MY). ICC-MY are not present in the fundus.[97] In all regions of the stomach, ICC can be found inside the longitudinal and the circumferential muscle layers, so called intramuscular ICC (ICC-IM). In addition to ICC, also platelet-derived growth factor receptor α positive (PDGFRα^+) cells are located at the myenteric plexus and inside the muscle layers. They play a role in controlling gastric electrophysiology by transducing input signals from the enteric nervous system. Both PDGFRα^+ cells and ICC-IM are found in close proximity to the endings of enteric motor neurons.[96,98–101] SMCs, ICC and PDGFRα^+ cells are coupled electrically via gap junctions, effectively forming a multicellular syncytium. This syncytium plays the role of the pacemaker system for gastric motility. Additionally, it acts as the mediator for regulatory inputs from the enteric nervous and endocrine systems[96,102] and mechanical stimuli. Slow waves are generated by ICC-MY which harbor biochemical pacemaker units.[33,96,103–108] Anoctamin 1 (Ano1) calcium-activated chloride channels have been identified as key pacemaker channels in ICC-MY and are essential for slow wave generation.[109–112] Another important mechanism for pacemaker activity is calcium-induced calcium release from intracellular stores into microdomains close to the plasma membrane.[96,104,105,108,113] Within the ICC network, slow waves are propagated actively via a voltage-dependent mechanism involving T-type calcium channels and calcium-induced calcium release from the endoplasmic reticulum.[108,113–115] However, slow waves conduct only passively to the surrounding SMCs.[96,116] SMCs are not capable of actively generating slow waves. Instead, SMCs get depolarized by arriving slow waves such that calcium entry through (voltage-gated) T-type calcium channels is initiated.[104,105] The resulting increase of intracellular calcium constitutes the initial step of a complex biochemical excitation-contraction mechanism[117–119] which is essential to translate

the rhythmic electrical pacemaker activity of ICC-MY into the iconic ring-shaped ACWs. Slow waves decay quickly in tissue lacking a network of ICC-MY.[6,102] The fundus lacks ICC-MY and is thus electrically largely quiescent. While slow waves are nonintermittently generated by ICC-MY, smooth muscle contractions occur only if appropriate neural,[4] endocrine[120] and mechanical[121] inputs coincide with the electrical excitation. The transduction of inputs from the enteric nervous system is realized by the PDGFR$\alpha^+$and ICC-IM.[122–124] Additionally, ICC-IM are electrically coupled to ICC-MY indicating their relevance in transmitting slow waves from ICC-MY deeper into the muscle layers. ICC also play an important role in mechanotransduction via stretch-activated currents.[121,125,126] Despite substantial research efforts, many details concerning the complex biophysical mechanisms that control the generation and propagation of slow waves within the multicellular electrophysiological system of the stomach remain unknown.

Individual ICC generates slow waves at a cell-specific intrinsic frequency. An important feature of the ICC-MY network is the proximal to distal intrinsic frequency gradient describing the fact that the intrinsic frequency decreases from approximately 3 cpm (cycles per minute) at the proximal corpus to 0.8-1.8 cpm at the distal antrum. In an intact network, ICC synchronize their activity to the highest intrinsic frequency within the network, a process called entrainment. The precise way how the myriad ICC are entrained in a single wave remains controversial[26,32,127,128] and forms a promising future application area for mathematical modeling. Sensitivity of ICC-internal processes to surrounding electric potential may play a role.[32,129] Therefore, the region with the highest intrinsic frequency is referred to as the pacemaker site. In the human stomach, it is located at the proximal corpus on the side of the greater curvature (cf. Figure 3).[30,43] Frequency gradient and entrainment are essential features for the formation of the physiological slow wave propagation pattern on the organ level.[130] Recent progress in high-resolution electrical mapping techniques has facilitated the identification of slow wave propagation patterns in health and disease.[29,30,131–137] In the healthy human stomach, slow waves are initiated at the pacemaker site (cf. Figure 3) at a frequency of $3cpm$ and from there propagate distally toward the pylorus. Increased circumferential propagation velocity ensures the rapid formation of a closed ring. Slow waves do not spread proximally from the pacemaker site such that the fundus is void of slow wave activity. Between three and four slow waves travel toward the pylorus at a spacing of approximately 60 mm at the same time. Slow waves are unable to pass the pylorus. Therefore, the pylorus acts as separator for the electrical activity of the stomach and the small intestine.[138]

A frequent health problem is gastric dysrhythmia, that is, improperly coordinated slow waves that result in uncoordinated ACWs.[26,139] Over the past years, various types of gastric dysrhythmias have been identified and successfully linked to different functional disorders of the stomach including gastroparesis and GERD.[140,141] To disclose its still poorly understood physiological origin, two avenues of research appear promising: first, the development of biophysically more accurate mathematical models of gastric electrophysiology, second, a careful computational examination of the coupling between electric slow wave propagation and gastric solid and fluid mechanics, noting the pronounced mechanosensitivity of the ICC.[142] The second approach could significantly benefit from a comprehensive computational multiphysics model of the stomach (cf. Section 3).

2.3.3 | Migrating motor complexes

Gastric accommodation and ACWs are the dominant forms of gastric motility in the postprandial stomach (ie, directly after a meal). By contrast, in the fasted stomach between meals so-called migrating motor complexes are observed. They sweep indigestible solids from the stomach through the intestine by means of very strong electromechanical contraction waves. They are typically repeating every 120 minutes.[45] So far, most of the publications concerning gastric mechanics focus on the postprandial rather than the interdigestive stomach, although models of migrating motor complexes may be of great use for computer-aided drug design.

2.3.4 | Examination of gastric motility

The current gold standard to assess gastric accommodation is the so-called gastric barostat,[90] an inflatable balloon that is placed in the (proximal) stomach and connected by a tube through the esophagus to an external air supply which ensures a given constant pressure. If gastric smooth muscle relaxes by gastric accommodation, the volume of the balloon will increase as additional air can be accommodated at the given pressure. This increase of volume is a, though only coarse, measure of gastric accommodation. The gastric barostat is fairly invasive[143] and time consuming and thus often not well-tolerated by patients. Moreover, it alters ACWs and secretion of gastric juice, making a simultaneous evaluation of normal gastric motility and digestion impossible. Some variations of the gastric barostat (imposing, for example, not a constant pressure but volume or wall tension[144]) share the same drawbacks. It has therefore been suggested to replace it by a less invasive procedure such as the measurement of the intragastric pressure[90] (for which a small manometric catheter suffices) or the imaging of postprandial gastric volume (using, eg, magnetic resonance imaging [MRI]).[145] However, neither alone can characterize gastric accommodation. On one hand, intragastric pressure cannot fully characterize gastric accommodation because for a given ingested volume it also depends on the (unknown) individual anatomy. On the other hand, the gastric volume measured by imaging is primarily determined by the ingested volume (plus some gastric juice) rather than by muscular relaxation.[37,143,146,147] The latter can only roughly be

estimated from changes of gastric volume over time by emptying.[147] Therefore, the gastric barostat is still the clinical gold standard to assess gastric accommodation.

ACWs are assessed in clinical practice by antroduodenal manometry. It requires time-consuming placement of a manometric catheter in the stomach and duodenum and can presumably detect by far not all contractions accurately (and also perturbs normal gastric function). Again, imaging has been discussed as a noninvasive alternative.[148–154] However, a standardized interpretation of imaging data is still lacking (despite some suggestions like the gastric motility index[155]), which prevents clinical application so far.[147,156]

3 | MATHEMATICAL AND COMPUTATIONAL MODELING

3.1 | Gastric lumen: Fluid mechanics of the digesta

Examination of gastric fluid mechanics in vivo and ex vivo is difficult and often nearly impossible due to technical hurdles and ethical concerns, especially in humans. In vitro models have greatly helped to advance our understanding of gastric fluid mechanics[157–160] but can hardly mimic the real gastric geometry and motility.[41] Therefore, first computational fluid dynamics models of the stomach were developed around 15 years ago. After first attempts in two dimensions,[40,161,162] in 2007, the first three-dimensional (finite element) model[17,41,49,163–165] was proposed (and slightly modified in ref. [166]). Recently, a promising smooth particle hydrodynamics (SPH) computational model developed originally for the intestine[19,20,167] was applied also to a stomach-like geometry examining gastric motility and emptying.[168,169] These computational models revealed important patterns in gastric flow. For low viscosity[40,161] dominant retrograde jets in the antrum, circulatory flow between the ACWs, and a so-called "stomach road," along which gastric emptying occurs predominantly, were reported. In contrast, for higher viscosity more ordered patterns prevail.[164,170] The importance of buoyancy[170] and antral recirculation[166] for gastric mixing were disclosed by different techniques.[161,164,165] Food disintegration has been studied so far only using highly simplified models (assuming, for example, a fixed amount of erosion each time a particle is passing through an ACW[17]).

Despite their great merits, all current computational models of the human stomach suffer from several important limitations:

- The gastric wall is modeled as rigid and its deformation during ACWs, if modeled at all, is kinematically prescribed. It is experimentally well confirmed that altered properties of the digesta[17,151,171–178] or also altered gastric geometry[179] can significantly change gastric flow, motility, and emptying. Current models with a prescribed wall motion can by design not account for these dependencies and do thus not allow predictive simulations of the impact of substantial parameter changes in the stomach. Such predictive simulations would require coupled multiphysics models accounting for interactions between flow of the digesta and viscoelasticity and electrophysiology of the wall.
- Current models have never been applied with person-specific in vivo geometries and associated data about gastric motility (ie, muscular contractions).
- Mechanical and chemical food disintegration is currently not modeled explicitly. The effect of gastric juice is generally neglected despite its significant impact on food disintegration and thus also on the time-dependent viscosity of the digesta and gastric flow.

In general, the fluid flow in the gastric lumen is assumed to show laminar and incompressible behavior[41,49,164] being expressed by a balance of mass and a balance of momentum in Eulerian form

$$\nabla \cdot \boldsymbol{u} = 0 \tag{1}$$

$$\rho \left(\frac{\partial \boldsymbol{u}}{\partial t} + \boldsymbol{u} \cdot \boldsymbol{\nabla} \boldsymbol{u} \right) = -\nabla p + \nabla \cdot \boldsymbol{\tau} + \rho \boldsymbol{g} \tag{2}$$

with fluid density ρ, velocity field $\boldsymbol{u}$, pressure p, gravity g, and viscous stress tensor $\boldsymbol{\tau}$. The viscous stress tensor $\boldsymbol{\tau}$ is typically expressed in terms of the strain rate tensor $\boldsymbol{E} = \frac{1}{2}(\boldsymbol{\nabla} \boldsymbol{u} + (\boldsymbol{\nabla} \boldsymbol{u})^T)$. As a first approximation, dilute digesta can be modeled as a Newtonian fluid, which is characterized by a linear relationship of the strain rate tensor $\boldsymbol{E}$ and the viscous stress tensor $\boldsymbol{\tau}$ via a dynamic viscosity μ:

$$\boldsymbol{\tau} = 2\mu\boldsymbol{E}. \tag{3}$$

The fluid viscosity of gastric juice in the stomach typically varies from 0.01 to 2 Pa·s.[45] Experiments in vitro showed that the viscosity of digesta decreases within 40 minutes from a maximum of 17 Pa·s to 2.2 Pa·s[180] caused by intragastric dilution[45] with gastric juice. While the assumption of a Newtonian fluid may be appropriate as a reasonable approximation for dilute digesta, there are obviously many cases were it appears not applicable. Then a non-Newtonian fluid with a nonlinear relation between strain rate and shear stress has to be assumed, typically with shear thinning behavior.[45,49,164]
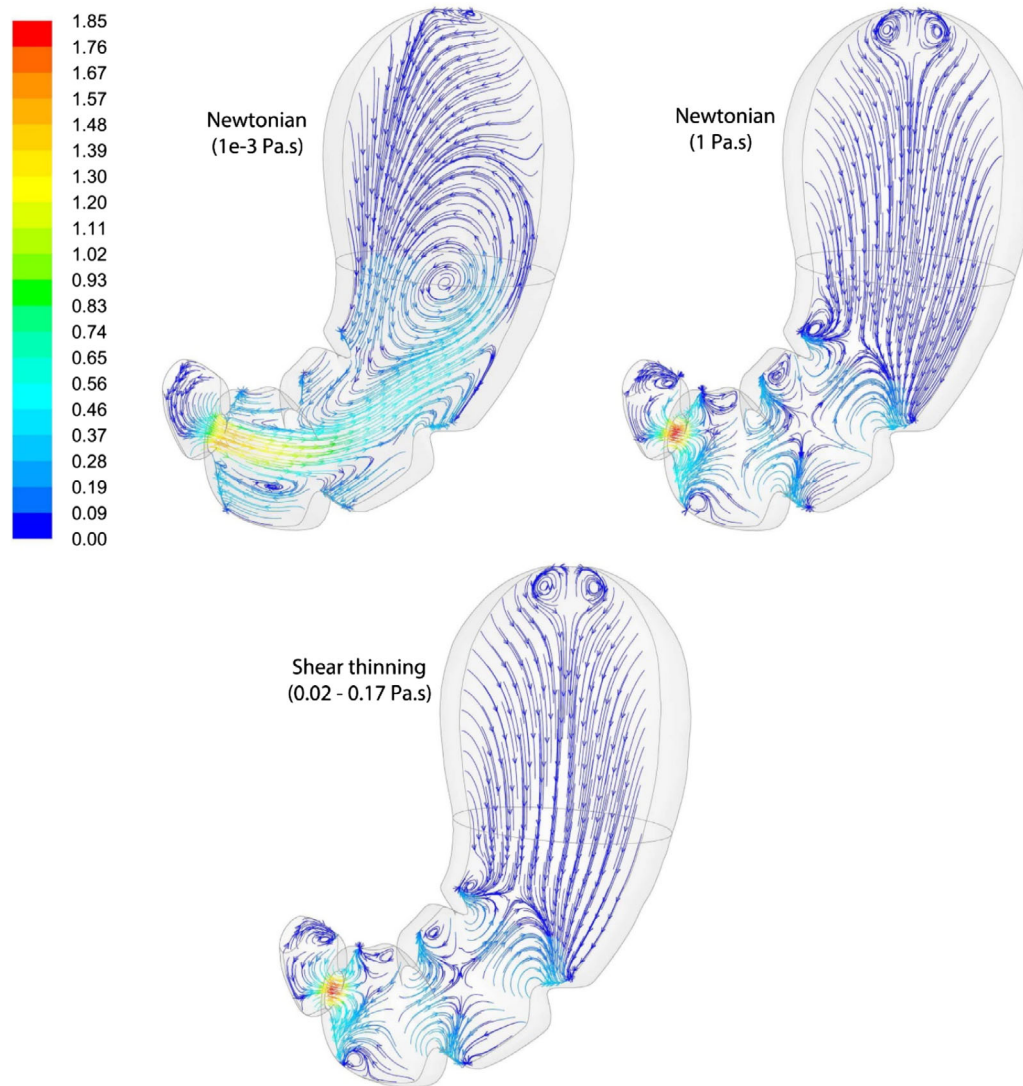
FIGURE 4 Simulation results of a three-dimensional gastric model: streamlines for different rheological properties of the fluid during ACWs, colored by velocity magnitude (cm/s)$^{\parallel}$

Another intricacy to be considered in modeling gastric fluid mechanics is the multiphasic nature which digesta often exhibit. In general, they are a mixture of solid and liquid phases (Figure 4).

Two common approaches to model dispersed multiphase flows as observed in the gastric lumen are the discrete particle method (DPM) and the Eulerian multifluid model.[181,182] The Eulerian multifluid model (also called Euler-Euler model or two-fluid model [TFM]) describes different phases as homogenized, interpenetrating fluids. It allows arbitrarily high volume fractions of the solid phase, but requires the derivation of suitable constitutive relations from kinetic theory. Assumptions or approximations typically applied in this derivation often compromise the quantitative reliability of the approach. This difficulty is avoided by the DPM where particle-particle interactions can directly be modeled by soft sphere or hard sphere contact algorithms. However, for high volume fractions of the solid phase, the DPM suffers from numerical problems.

A promising approach to model multiphase flows specifically in the gastric lumen is the method of smoothed particle hydro-dynamics (SPH), which has already been successfully applied in computational modeling of the small intestine.[167] SPH, first introduced in refs. [183, 184], is a mesh-free computational method, which is by its Lagrangian nature[185,186] particularly suitable for modeling multiphase flows and flows with large deformations of the fluid domain, which both occurs in the stomach.

So far, multiphase flow in the stomach has been addressed only phenomenologically by an Euler-Euler model.[165] More realistic models (eg, using particle-based methods as DPM or SPH) still remain wanted.

3.2 | Gastric wall: Solid mechanics

Continuum mechanical modeling of gastric tissue considerably lacks behind the modeling of other soft tissues. Gregersen and Kassab[187] were among the first to suggest a generic exponential stress-strain relation in gastrointestinal tissue. Still

continuum mechanical modeling attempts of the passive properties of gastric tissue largely remain restricted to Fung-type exponential strain energy functions ψ of the form

$$\psi = \frac{1}{2}c(e^{b_1 E_{11}^2 + b_2 E_{22}^2 + 2b_3 E_{11} E_{22}} - 1) \tag{4}$$

with the ij-components E_{ij} of the Green-Lagrange strain tensor $\boldsymbol{E}$ and where $c > 0$ defines a spatial energy density and b_i, $i = 1 \dots 3$ are nondimensional material parameters.[88] One of the major drawbacks of simple, phenomenological Fung-type exponential strain energy functions is that they do not distinguish between the structural components of the tissue. Structurally based constitutive models have however been shown to be superior for other tissue types, for example, for vascular tissue.[188]

In 2009, Gao and colleagues[189] proposed a component-specific duodenal wall model distinguishing between the passive contributions of elastin and collagen fibers and the active tension created by smooth muscle fibers. The passive model consisted of a single linear-elastic elastin fiber and multiple parallel linear-elastic collagen fibers with distributed unstressed lengths. The collagen fibers were assumed to carry zero stress below a certain length. The smooth muscle model was based on a logarithmic strain energy function combined with a phenomenological muscle tone function. While a component specific modeling approach seems promising, the assumption of linear fiber elasticity adopted in ref. [189] may be questioned.[73,75,88]

A promising approach modeling gastric tissue might be to adapt the structurally based anisotropic hyperelastic strain energy function originally developed by Holzapfel et al. for the arterial wall.[188] For this model has already been found to be suitable for various collagenous soft tissues. The general idea of this modeling approach is to describe each tissue layer by an additively decomposed strain energy function of the type

$$\psi = \psi_{vol} + \underbrace{\psi_{iso} + \psi_{aniso}}_{\text{isochoric}} \tag{5}$$

where the indices *vol*, *iso* and *aniso* indicate the volumetric, the isotropic deviatoric and the anisotropic deviatoric part, respectively. The volumetric part in (5) can as a first approximation for soft tissues often be chosen such that it models nearly incompressible material behavior. For the individual summands in (5), various formulations have been proposed in the context of constitutive modeling of soft biological tissues in the gastrointestinal tract and related organs. For example, Sommer and colleagues[57] studied esophageal tissue. They modeled the isotropic elasticity contribution, which presumably mainly results from the elastin matrix in the tissue, by a Neo-Hookean function

$$\psi_{iso,NH} = \frac{c}{2}(\overline{I_1} - 3) \tag{6}$$

where $c > 0$ is a stress-like material parameter and $\overline{I_1} = \text{tr}(\overline{\boldsymbol{C}})$ is the first invariant of the modified Cauchy-Green tensor $\overline{\boldsymbol{C}} = J^{-\frac{2}{3}} \boldsymbol{C}$ with Cauchy-Green tensor $\boldsymbol{C}$ and determinant of the deformation gradient J.[190] Gizzi and colleagues[191] used a Mooney-Rivlin like function to describe the isotropic elasticity contribution of intestinal tissue. The isotropic contribution in (5) then becomes

$$\psi_{iso,MR} = \frac{1}{2}(c_1(\overline{I_1} - 3) + c_2(\overline{I_2} - 3)) \tag{7}$$

where c_1, c_2 are stiffness related material parameters, $\overline{I_1} = \text{tr}(\overline{\boldsymbol{C}})$ is the first and $\overline{I_2} = \frac{1}{2}(\text{tr}(\overline{\boldsymbol{C}})^2 - \text{tr}(\overline{\boldsymbol{C}}^2))$ the second invariant of the modified Cauchy-Green tensor $\overline{\boldsymbol{C}}$ as defined above.

Both refs. [57, 191] use Fung-type exponential strain energy functions to describe the anisotropic elasticity contribution from collagen fibers. This contribution can be modeled by

$$\psi_{aniso} = \sum_{i=1}^{N} \frac{k_{1,i}}{2k_{2,i}}[\exp\{k_{2,i}(\lambda_i^2 - 1)^2\} - 1] \tag{8}$$

where the index i indicates the ith fiber family out of a total of N fiber families; $k_{1,i} > 0$ are stress-like material parameters, $k_{2,i} > 0$ are dimensionless material parameters and λ_i is the elastic stretch of the material in direction of the ith fiber family.

While the above-mentioned formulations have been used successfully to describe the passive constitutive behavior of various fibrous soft biological tissues,[192–195] their applicability to gastric tissue still needs to be carefully evaluated. For this purpose, suitable experimental data from multiaxial layer-specific tensile tests are required. In particular, detailed mathematical models of smooth muscle tension in the gastric wall still remain to be developed. To this end, work on similar tissues such as vascular smooth muscle[196] or smooth muscle of the urinary bladder[197,198] may serve as a guideline.

3.3 | Gastric wall: Electrophysiology and electromechanics

In contrast to the heart where propagation of electrical signals and excitation contraction both are realized (mainly) by cardiomyocytes, in the stomach, these functionalities are fundamentally split among at least two cell types: generation and propagation

of slow waves is realized by ICC. SMCs get electrically excited by slow waves and transform these signals into mechanical responses (cf. Section 2.3.2). Mathematical descriptions of gastric electrophysiology should take into account its multicellular nature including the complex coupling between the structural components. A computational model of gastric electrophysiology must address phenomena across multiple length and time scales. On the cellular scale, the triggering and modulation of slow waves which are essentially oscillations of the transmembrane electric potential must be described. This is possible either phenomenologically, using a simple oscillating system of ordinary differential equations,[139,199] or by detailed biophysical cell models.[33,34,127,128,200,201] In biophysical cell models, the spatiotemporal scale associated with the description of the kinetics of ion channels and other intracellular mechanisms is even smaller than the one of the processes on the cellular level. All contributions of one type of ion channel are typically compiled to a single, averaged contribution instead of modeling all ion channels of a type individually.[202] There have been detailed reviews of existing biophysical cell models of gastric electrophysiology.[203,204] Only the parameters of biophysical models have a direct biophysical interpretation and are thus appropriate for the detailed exploration of the cellular and subcellular foundations of gastric electrophysiology. Yet, even phenomenological models of gastric electrophysiology are sufficient to reproduce and study the phenomenon of slow waves in realistic geometries when combined with models of electric wave propagation through the gastric wall. Such models in general rely on partial differential equations describing the transport of electric potential through the gastric wall. These partial differential equations can be solved, for example, by finite element discretizations.[22,35] Three increasingly general models have been proposed to model the propagation of electric signals through the gastric wall: the monodomain,[139,191,199,205] bidomain,[206–210] and extended bidomain (also called tridomain)[211–213] model, where the first one is sufficient to model slow waves qualitatively and the last one allows the detailed examination of even advanced phenomena such as external electric stimulation of the stomach. The three models mainly differ in the number of incorporated cell types and the description of the coupling between the cells. From the extended bidomain formulation the bi- and monodomain models may be regained under special simplifying assumptions. The extended bidomain model explicitly models the intracellular space of two different cell types, smooth muscle cells and ICC, as well as a shared intercellular space. These three spaces are coupled via electric currents. Based on the principle of conservation of total current, the extended bidomain model leads to the equations

$$\nabla \cdot (\boldsymbol{\sigma}_i^{(1)} \nabla \phi_i^{(1)}) = A_m^{(1)} \left(C_m^{(1)} \left(\frac{\partial \phi_i^{(1)}}{\partial t} - \frac{\partial \phi_e}{\partial t} \right) + I_{ion}^{(1)} - I_{stim}^{(1)} \right) + A_{gap} I_{gap} \tag{9}$$

$$\nabla \cdot (\boldsymbol{\sigma}_i^{(2)} \nabla \phi_i^{(2)}) = A_m^{(2)} \left(C_m^{(2)} \left(\frac{\partial \phi_i^{(2)}}{\partial t} - \frac{\partial \phi_e}{\partial t} \right) + I_{ion}^{(2)} - I_{stim}^{(2)} \right) - A_{gap} I_{gap} \tag{10}$$

$$\nabla \cdot (\boldsymbol{\sigma}_e \nabla \phi_e) + \nabla \cdot (\boldsymbol{\sigma}_i^{(1)} \nabla \phi_i^{(1)}) + \nabla \cdot (\boldsymbol{\sigma}_i^{(2)} \nabla \phi_i^{(2)}) + I_{stim}^{ext} = 0 \tag{11}$$

where the superscripts (1) and (2) are used to distinguish between the two cell types (ICC and smooth muscle cells) and the subscripts i and e denote quantities related to the intracellular and extracellular space, respectively. The three principle unknowns are the intracellular electrical potentials $\phi_i^{(1)}$, $\phi_i^{(2)}$ and the extracellular potential ϕ_e. $\boldsymbol{\sigma}_i^{(1)}$, $\boldsymbol{\sigma}_i^{(2)}$, and $\boldsymbol{\sigma}_e$ are the associated conductivity tensors. $A_m^{(1)}$, $A_m^{(2)}$, and A_{gap} are surface to volume ratios describing either the amount of cell membrane surface per reference volume (index: m) or the amount of cell membrane surface per reference volume covered by gap junctions between the cells. $C_m^{(1)}$ and $C_m^{(2)}$ are the capacitances of the cellular membranes. $I_{ion}^{(1)}$ and $I_{ion}^{(2)}$ are the total sum of all ionic membrane currents for each cell type. The individual ionic conductances are described by functions of the three principle unknowns and additional internal variables. $I_{stim}^{(1)}$ and $I_{stim}^{(2)}$ are stimulus currents into the respective cells and I_{stim}^{ext} is the total external stimulus current into the extracellular space. I_{gap} describes the current through the gap junctions connecting ICC and SMC, often modeled as an ohmic conductance depending on the difference between the intracellular potentials.

There are multiple ways of reducing the extended bidomain model to a simple bidomain model. The most natural way is the simplifying assumption that only one cell type plays a significant role for propagation of electric signals in the tissue. Mathematically, this means $A_m^{(2)} = A_{gap} = 0$. Then, the second equation of the bidomain model can be dropped and together with it the superscripts distinguishing between cell types because only one cell type remains important. The bidomain equations then follow naturally from (9)-(11) as:

$$\nabla \cdot (\boldsymbol{\sigma}_i \nabla \phi_i) = A_m \left(C_m \left(\frac{\partial \phi_i}{\partial t} - \frac{\partial \phi_e}{\partial t} \right) + I_{ion} - I_{stim} \right) \tag{12}$$

$$\nabla \cdot (\boldsymbol{\sigma}_e \nabla \phi_e) + \nabla \cdot (\boldsymbol{\sigma}_i \nabla \phi_i) + I_{stim}^{ext} = 0. \tag{13}$$

To account for the involvement of the two cell types while using the bidomain tissue formulation (12)-(13), one needs to resort to a geometrically explicit description of the separate tissue layers.[206,208,210]
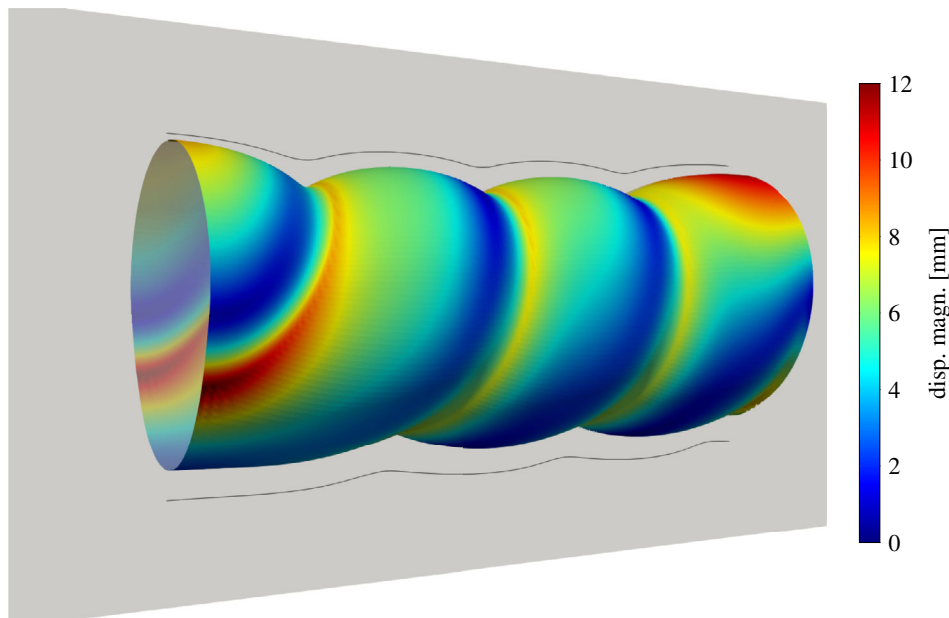
FIGURE 5 Simulation results of an active-strain electromechanics model applied to study ACWs on an idealized cylindrical geometry. The model can represent coordinated propagation of the ACWs based on the underlying entrained slow waves**

The numerical solution of the bidomain and extended bidomain models are both computationally challenging and expensive.[213–215] Therefore, the so called monodomain model remains a popular alternative. Again, there are multiple ways of deriving a monodomain formulation from the (extended) bidomain model.[216] One possibility is to assume equal anisotropy of the extra- and intracellular conductivity tensors, that is, a simple proportionality relation between both. Another possibility is to assume a highly conductive extracellular space, that is, ., $\sigma_e \gg \sigma_i^{(1)}, \sigma_i^{(2)}$. Following the latter approach, it is straight forward to arrive at the following coupled monodomain models (one for each cell type) for gastric electrophysiology:

$$\nabla \cdot (\sigma_i^{(1)} \nabla \phi_i^{(1)}) = A_m^{(1)} \left(C_m^{(1)} \frac{\partial \phi_i^{(1)}}{\partial t} + I_{ion}^{(1)} - I_{stim}^{(1)} \right) + A_{gap} I_{gap} \tag{14}$$

$$\nabla \cdot (\sigma_i^{(2)} \nabla \phi_i^{(2)}) = A_m^{(2)} \left(C_m^{(2)} \frac{\partial \phi_i^{(2)}}{\partial t} + I_{ion}^{(2)} - I_{stim}^{(2)} \right) - A_{gap} I_{gap.} \tag{15}$$

In a recent contribution, ref. [139] has shown that many of the key phenomena of physiological and pathophysiological gastric slow wave propagation such as entrainment, anisotropic conduction patterns, and dysrhythmias can be appropriately modeled by a simple monodomain model (Figure 5).

Gastric electrophysiology and wall mechanics are closely related, for example, via mechanosensitive ion channels in the membrane of the ICC.[142,217] Disregard of this interplay severely limits nearly all current models of gastric electrophysiology.[35] In an initial attempt to examine the interplay between mechanics and electrophysiology in the stomach, Brandstaeter and colleagues[139] have used an active-strain electromechanics formulation to couple electrical slow waves unidirectionally to a continuum mechanical membrane model. With their phenomenological approach, the authors were able to represent the coordinated propagation of ACWs on an idealized stomach geometry as well as the effect of gastric dysrhythmias on the mechanical contractions of the muscle tissue.

The two only coupled electromechanical models of the stomach proposed so far[52,139] still do not yet incorporate fluid mechanics and thus the important effect of fluid-structure interactions on wall deformation. Combining gastric electrophysiology, fluid mechanics and solid mechanics within a coupled multiphysics model of the whole stomach remains one of the greatest challenges in the field and can be hoped to pave the way to significant insights into gastric mechanics and motility in health and disease.

4 | FUTURE APPLICATIONS AREAS

Detailed mathematical and computational models of the human stomach have the potential to provide insights that may lead to important progress in several application areas ranging from medicine to food industries. In this section, we will briefly illustrate a selection of these potential applications.
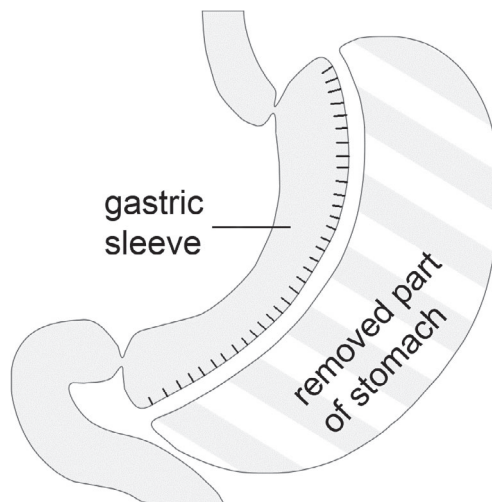
FIGURE 6 sleeve gastrectomy reduces gastric volume by around 75% by stapling, leaving a narrow gastric sleeve

4.1 | Obesity and bariatric surgery

Conservative therapies against obesity, such as a change of life style or medication, seldom reduce body weight by more than 10%, leaving bariatric surgery often as the only option in cases of morbid obesity.[218] Bariatric surgery directly changes gastric geometry and mechanics, but has recently been discovered to induce also subtle biochemical long-term changes such as genetic switches and altered gastrointestinal microbiota.[10] The inability of pharmacological measures to produce such long-term changes suggests a remarkable interplay between mechanics and biochemistry in the gastrointestinal tract which remains poorly understood but might be the key to effective therapies of obesity. Currently, more than 250 000 bariatric surgeries per year are performed in the United States and EU together.[4,5] They typically reduce the effective gastric volume (eg, by downsizing, confining, or bypassing) and pay off within 2-4 years thanks to vastly reduced health care costs.[7] Over recent years, sleeve gastrectomy (cf. Figure 6) has become the by far dominant bariatric surgical procedure in the United States with a market share of around 60% in 2014[219] (compared to only 17% in 2011 [4]). A similar global trend is expected, noting that sleeve gastrectomy is increasingly considered the definitive bariatric operation.[179] Currently, sleeve gastrectomy is performed in practice in a largely heuristic way. Computer-aided planning of these surgical interventions has a significant potential to reduce adverse side effects and is thus an important future application area of mathematical and computational multiphysics models of the human stomach.

4.2 | Dyspepsia

Dyspepsia (indigestion) is one of the most frequent health problems with a prevalence estimated between 10% and 45%.[9] Often an organic reason such as a peptic ulcer or GERD can be diagnosed. However, between 5% and 10% of the general population suffer from so-called functional dyspepsia, where no organic reason can be identified. Several conditions associated with functional dyspepsia are closely related to gastric mechanics such as increased sensitivity to gastric distension, insufficient gastric accommodation, and delayed gastric emptying (possibly owing to antral hypomotility). Clinically, it is important to distinguish reliably at least between the latter two cases, because muscle relaxing drugs may improve gastric accommodation but impair ACWs and thus gastric emptying, while prokinetic agents would have the opposite effect.

As a highly prevalent and yet fairly unspecific problem, functional dyspepsia is likely to have often not only one single cause but rather to result from an unfavorable combination of several factors. Detailed computational multiphysics models of the stomach could help to unravel the interplay between these factors and identify new therapeutic strategies.

4.3 | Food, satiation, and satiety

Satiation and satiety are thought to be mainly governed by mechanoreceptors in the stomach and nutrient sensing in the intestine[220–222] and both have been shown to contribute to total satiation nearly additively.[220] For a given nutrient content, satiation and satiety can therefore be maximized by maximal stimulation of the gastric mechanoreceptors. It remains controversial whether these sense strain or stress[144,223–231] and currently both should be taken into consideration. In either case, however, designing food so as to maximize gastric retention time appears a promising way to maximize satiation. This idea has already been pursued in a few experimental studies[232–236] as an approach to tackle obesity. This approach fits with a generally rapidly increasing interest in food design[233,237] and can be elegantly combined with other approaches from process engineering.[238,239]

A computational multiphysics model of the stomach could help to speed up the progress in this field significantly by replacing time-consuming and costly experiments by fast and cheap in-silico studies.

5 | CONCLUSIONS

Gastric mechanics is a highly promising field of biomechanics. However, modeling of the human stomach at the moment lags around 20 years behind modeling of the cardiovascular system. So far, there exists no computational multiphysics model of the human stomach combining gastric electrophysiology, fluid mechanics of the digesta, and solid mechanics of the gastric wall. The development of such a model has long been impaired by a limited understanding in these fields and a limited availability of robust computational methods enabling convenient simulations of such complex multiphysics problems. Additionally, research effort in the individual fields has been unevenly distributed in the past, that is, a stronger focus has been put on gastric electrophysiology compared to gastric solid mechanics. In recent years, substantial progress has been made in all mentioned fields, now providing a deeper knowledge and more computational resources to develop and apply a computational multiphysics model of the human stomach.

A general computational multiphysics model of the human stomach bears great potential to serve as a valuable tool for examining the link between gastric mechanics and health problems such as functional dyspepsia, GERD, or morbid obesity, and for developing new therapies. Additionally, a computational multiphysics model of the human stomach could be applied to examine gastric motility, for example, migrating motor complexes, which could support future computer-aided drug design.

These promising application areas are expected to stimulate over the next years fast growing research efforts dedicated to mathematical and computational modeling of the stomach.

ENDNOTES

* *Cardio, cardiac, vascular, heart, coronary, aneurysm, artery, arteries, arterial, athero/arteriosclerotic.*
† *Stomach, gastric, gastro, oesophagus, esophageal, esophagus.*
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§ By courtesy of Encyclopaedia Britannica, Inc., copyright 2010; used with permission.
¶ Reprinted from ref. [91]. Copyright (2009), who adapted from Lacy, B. E., Koch, K. L., Crowell, M. D., Chapter 10: Manometry. In: Schuster atlas of gastrointestinal motility in health and disease, Schuster, M. M., Crowell, M. D., Koch, K. L., eds. Second edition 2002, BC Decker Inc., 135-150, both with permission from Elsevier.
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