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## Gastrointestinal tract modelling in health and disease

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### Abstract

The gastrointestinal (GI) tract is the system of organs within multi-cellular animals that takes in food, digests it to extract energy and nutrients, and expels the remaining waste. The various patterns of GI tract function are generated by the integrated behaviour of multiple tissues and cell types. A thorough study of the GI tract requires understanding of the interactions between cells, tissues and gastrointestinal organs in health and disease. This depends on knowledge, not only of numerous cellular ionic current mechanisms and signal transduction pathways, but also of large scale GI tissue structures and the special distribution of the nervous network. A unique way of coping with this explosion in complexity is mathematical and computational modelling; providing a computational framework for the multilevel modelling and simulation of the human gastrointestinal anatomy and physiology. The aim of this review is to describe the current status of biomechanical modelling work of the GI tract in humans and animals, which can be further used to integrate the physiological, anatomical and medical knowledge of the GI system. Such modelling will aid research and ensure that medical professionals benefit, through the provision of relevant and precise information about the patient's condition and GI remodelling in animal disease models. It will also improve the accuracy and efficiency of medical procedures, which could result in reduced cost for diagnosis and treatment.

### INTRODUCTION

The gastrointestinal (GI) tract, also called the digestive tract or the alimentary canal, is the system of organs within multicellular animals that takes in food, digests it to extract energy and nutrients, and expels the remaining waste. The major functions of the GI tract are digestion facilitated by motility, secretion and absorption. The various patterns of GI tract function are generated by the integrated behaviour of multiple tissues and cell types. Medical imaging methods such as ultrasonography<sup>[1,2]</sup>, magnetic resonance imaging (MRI)<sup>[3,4]</sup>, and endoscopic ultrasound (EUS)<sup>[5,6]</sup> are well known stand-alone clinical methods that can disclose structural and functional abnormalities of the GI tract. However, a thorough study of the GI tract requires understanding of the interactions between cells, tissues and gastrointestinal organs in health and disease. This depends on knowledge, not only of numerous cellular ionic current mechanisms and signal transduction pathways, but also of large-scale GI tissue structures and the special distribution of the nervous network. A unique way of coping with this explosion in complexity is mathematical and computational modelling; providing a computational framework and Information Communication Technology (ICT) based tools for multilevel modelling and simulation of the human gastrointestinal anatomy and physiology<sup>[7-9]</sup>. Computer-based analysis, visualisation, modelling and simulation are used routinely in fields such as engineering, meteorology or traffic control to understand the behaviour and outcomes of new designs and impact of

external phenomena well in advance of their realisation, thereby avoiding costly failures. In GI tract studies, this approach is not common, mainly because we still lack those models that can emulate the behaviour of the human body. Nevertheless, exploration of the GI tract has dramatically improved by the introduction of cross sectional imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), which have revolutionised the way in which many conditions are diagnosed and treated. The ability to examine, in detail, structures inside the GI tract without resorting to surgery, has allowed clinicians to diagnose problems and plan corrective procedures with a minimum of risk to the patient<sup>[10-11]</sup>. In order to continue this exploration, it will be necessary to complement the traditional approach with an integrative approach that combines observation, theory and prediction across the temporal and dimensional scales, across scientific disciplines, and across the anatomical subsystems, all of which reflect the rather artificial divisions described.

The aim of this review is to describe the currently status of biomechanical modelling work on the GI tract in humans and animals that can be further used to integrate the physiological, anatomical and medical knowledge of the GI system.

## ANATOMY AND FUNCTION OF THE GI TRACT

The GI tract is a continuous channel through the body with the biliary and pancreatic ducts as major side-branches. The GI tract consists of a series of organs, which resemble one another in constitution, being variously arranged as cylinders, spheroids, or intermediate forms. The main functions of the GI tract are transport and digestion of food. The different segments show a large variation in morphology and muscle mechanical properties, i.e. the oesophagus mainly serves to quickly transport the food bolus from the mouth to the stomach where the food in the stomach is stored for some time whilst simultaneously being broken down into smaller components. The GI sphincters serve to separate the GI tract into compartments. However, the gut is also important for immune functions<sup>[12]</sup>. The wall of the GI tract is typically composed of four layers, i.e., the mucosa, submucosa, muscle and serosa (some parts are called the adventitia where there is no epithelium) (Figure 1). The muscle layer consists of an outer longitudinal and an inner circular muscle layer. The collagen-rich submucosa and mucosa layers are inside the muscle layer. Another thin layer of muscle, the muscularis mucosae, exists almost throughout the entire tract. The motions of the GI tract accomplish a net antegrade flow in order to mix the contents and move them across the surface where absorption occurs. The contractile patterns and transit vary greatly from one part of the tract to another. The GI wall movements during digestion and absorption are the consequence of contractions of the two layers of smooth musculature. Contractions of the longitudinal muscle layer shorten

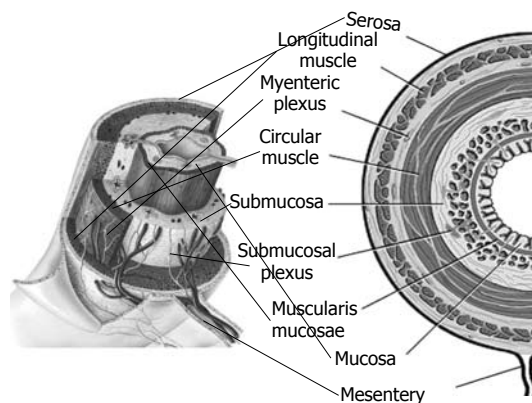


Figure 1 Schematic diagram of the GI tract.

the gut wall, whereas the peristaltic contractions of the circular muscle layer, in contrast, mainly produce forward transit with relatively little mixing. The contractions of circumferential and longitudinal muscles occur together, most of the time. The enteric nervous system (ENS), composed of both the myenteric (inter-muscular) plexus and the submucosal plexus, is distributed in the GI tract from the oesophagus to the internal anal sphincter<sup>[13]</sup>. A network of nerves of the myenteric plexus is embedded in the loose collagen matrix between the longitudinal and circular muscle layers (Figure 1). This set of nerves is essential for the regulation of the contractions of the adjacent musculature. Between the nerve endings and smooth muscle are the interstitial cells of Cajal (ICCs), which have been shown to be critical for the generation and propagation of the electrical slow waves that regulate the phasic contractile activity of GI smooth muscle, and for mediating neurotransmission from enteric motor neurons to smooth muscle cells<sup>[14,15]</sup>. The ENS ensures that the GI tract can fulfil essential tasks even when isolated from the rest of the body. The GI tract is - on the other hand - unable to work normally without the integrative functions of the ENS. Malfunctions of the ENS are increasingly recognized as underlying factors in many GI diseases. The exogenous nerves running together with the sympathetic and parasympathetic nervous systems are also important in regulating blood flow and secretion *etc*<sup>[16]</sup>. They also encode the conscious sensations from the gut such as fullness, urge to defecate and pain<sup>[17]</sup>. Medical imaging methods such as ultrasonography, MRI, and endoscopic ultrasound (EUS) are well known stand-alone clinical methods that can disclose structural and functional abnormalities of the GI tract<sup>[6,18]</sup>. Therefore, modelling analysis based on the anatomy and structure of the GI tract and different imaging methods can be applied to the problems related to function and pathophysiology.

## DISEASE CAUSING TISSUE AND STRUCTURE REMODELLING OF THE GI TRACT

The GI tract, like other hollow organs such as the

Table 1 Diseases causing histomorphological and biomechanical remodeling of GI tract<sup>[19-45]</sup>

Diseases	Species	Test organs	Histomorphometric remodeling			Biomechanical remodeling		
			WT	WA	LT	OA	RES	Stiffness
Type I diabetes	Human	Esophagus	↑	ND	ND	ND	ND	Circ NC Long↑
		Duodenum		ND	ND	ND	ND	Circ NC Long↑
		Esophagus	↑	↑	Mu↑Su↑Ms↑	↓	↓	Circ↑Long ND
	Rat	Duodenum	↑	↑	Mu↑Su↑Ms↑	↓	↓	Circ↑Long↑
		Jejunum	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↑Long↑
		Ileum	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↑Long↑
Type II diabetes	Rat	Colon	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↑Long↑
		Esophagus	↑	↑	Mu↑Su↑Ms↑	↓	↓	Circ↑Long ND
		Stomach	ND	ND	ND	ND	ND	Circ↑
Systemic sclerosis	Human	Duodenum	ND	ND	ND	ND	ND	Circ↑
Ulcerative colitis Fasting	Mice	Colon	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↑Long↑↑
		Duodenum	↓	↓	Mu↓ Su↓	↑	↑	Circ↓ Long↓
		Jejunum	↓	↓	Mu↓ Su↓	↑	↑	Circ↓ Long↓
Low protein diet	Rat	Ileum	↓	↓	Mu↓ Su↓	↑	↑	Circ↓ Long↓
		Duodenum	↓	↓	NC	NC	NC	Circ↓ Long NC
		Jejunum	↓	↓	Mu↓ Su↓	↓	↓	Circ↓ Long NC
Partial obstruction	Mink	Ileum	↓	↓	Mu↓ Su↓ Ms↓	↓	↓	Circ↓ Long NC
		esophagus	ND	ND	ND	ND	ND	Circ↑Long ND
		Jejunum	↑	↑	Mu↑Su↑Ms↑	↓	↓	Circ↑Long ND
Osteogenesis imperfecta	Mice	Esophagus	↓	↓	Mu↓ Su↓ Ms↓	↑	↑	ND
Irradiation	Mice	Rectum	↑	↑	ND	↑	↑	ND
Small bowel resection	Rat	Jejunum	↑	↑	Mu↑Su↑Ms↑	↑	↑	NC
		Ileum	↑	↑	Mu↑Su↑Ms↑	↑	↑	NC
EGF treatment	Rat	Esophagus	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↑Long ND
		Duodenum	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↑Long NC
		Jejunum	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↓ Long↑
	Rat	Ileum	↑	↑	Mu↑Su↑Ms↑	↑	↑	Circ↓ Long↑
		Colon	↑	↑	Mu↑Su↑Ms↑	↑	↑	ND

WT: Wall thickness; WA: Wall cross-sectional area; OA: Opening angle; RES: Residual strain; LT: Layered wall thickness; Mu: Mucosa; Su: Submucosa; Ms: Muscle; Circ: Circumferential direction; Long: Longitudinal direction; ND: Not done; NC: No change.

heart, blood vessels, urinary bladder and the urethra, is functionally subjected to dimensional changes. Hence, biomechanical properties are of particular functional importance. Data on the biomechanical properties are crucial for the understanding of the normal function of the GI tract and dysfunction due to disease because, (1) peristaltic motion that propels the food through the GI tract is a result of interaction of the passive and active tissue forces and the hydrodynamic forces in the food bolus and (2) remodelling of the mechanical properties reflects the changes in the tissue structure that determine a specific sensory-motor dysfunction.

Human studies have documented that diabetes melitus<sup>[19]</sup> and systemic sclerosis<sup>[20]</sup> induce biomechanical GI remodelling. Using different animal models (Figure 2), we have demonstrated that biomechanical and histomorphological remodelling occur in the GI tract due to normal physiological growth<sup>[21,22]</sup>, malnutrition<sup>[23,24]</sup>, inflammation, obstruction<sup>[25-27]</sup>, bowel resection<sup>[28]</sup>, diabetes<sup>[29-33]</sup>, radiation injury<sup>[34]</sup>, collagen changes<sup>[35,36]</sup> and EGF treatment. The morphometric properties are best described at the zero-stress state where no internal or external forces deform the tissue. Furthermore, knowing the zero-stress configuration is essential in any mechanical analysis since it serves as the reference state for computing stress and strain under physiological or pathophysiological conditions. With reference to the zero-stress state, combining

the morphometry data and pressure data, we can compute the stress-strain relationship of the GI wall. The stress-strain distribution mainly reflects the elastic properties of the GI tract. Changes in the elastic properties reflect structural remodelling of the GI wall in different diseases. Therefore, we consider the opening angle of the zero-stress state, residual strain and stress-strain relationship as the most relevant biomechanical parameters to describe diseases causing GI remodelling. Generally, diseases and factors inducing tissue overgrowth, such as diabetes<sup>[37-40]</sup>, obstruction and EGF<sup>[41-45]</sup> treatment, increase GI wall stiffness; whereas factors reducing tissue growth, such as fasting and low protein diet decrease GI wall stiffness. The more collagen in the GI wall, the stiffer the wall is<sup>[20]</sup>, and vice versa. However, the effect of different factors on the opening angle and residual strain of GI tract depend on the changes of layered structure. Fung's hypothesis of non-uniform remodelling states that if the inner wall grows more than the outer wall, the opening angle will increase<sup>[46]</sup> whereas if the outer wall grows more than the inner wall, the opening angle will decrease. Table 1 summarizes the histomorphological and biomechanical remodelling of the GI tract caused by different diseases.

It is well known that mechanosensation is important for GI function. Mechanosensitive nerve endings exist extensively in the GI tract where they serve a critical role in homeostasis. The mechanosensitive afferents in

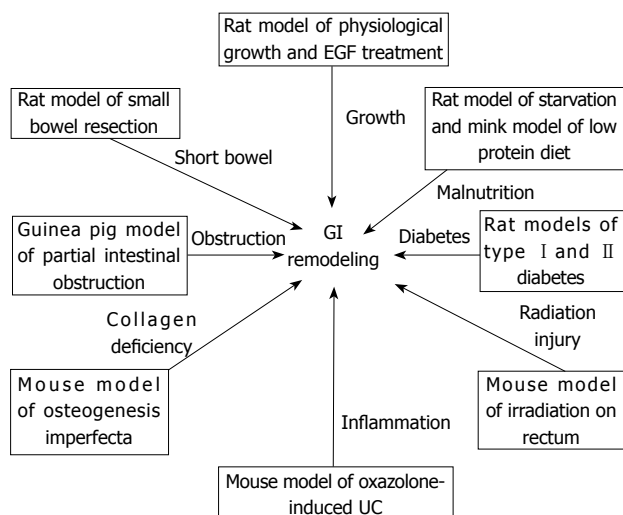


Figure 2 Disease-induced GI remodeling in animal models.

the intrinsic and extrinsic pathways have been described as low-, wide-dynamic- or high-threshold tension-receptors<sup>[12]</sup>. Therefore, the GI tract structure, as well as the stress and strain distribution in the wall, is important for the GI sensory and motor function. The GI wall structure or deformation changes caused by a disease will alter the relative positions of the mechanosensitive afferents (zero setting of the mechanosensitive afferents). The biomechanical remodelling by the disease, such as alterations of residual strain, stress distribution and wall stiffness, will alter the tension and stress distribution of the mechanosensitive afferents. As a result, the perception and motility of the GI tract will also change. Therefore, the morphological changes and biomechanical remodelling of the GI tract are likely to affect the function of mechanosensitive afferents in the GI wall and further affect the motor and sensory functions.

## BIOMECHANICAL MODELLING OF THE GI TRACT

The use of numerical models and, in particular, of finite element models has been extensively studied in the field of soft tissue mechanics because of the potential they offer in the analysis of the mechanical behaviour of morphologically complex structures, with high structural hierarchy and constituents with non-linear behaviour<sup>[47,48]</sup>. The effectiveness of numerical models depends on reliable reconstructions of the morphometry of the anatomical site under investigation, the specific loading and boundary conditions, as well as the definition of constitutive models capable of describing the mechanical response of the single tissues. Gastroenterology research has traditionally been based on experimental approaches rather than on mathematical modelling. Most of the previous modelling efforts in the biological area were in the cardiac and lung field; but, other areas are in now being developed. However, in the past five to ten years several groups have independently started to model the

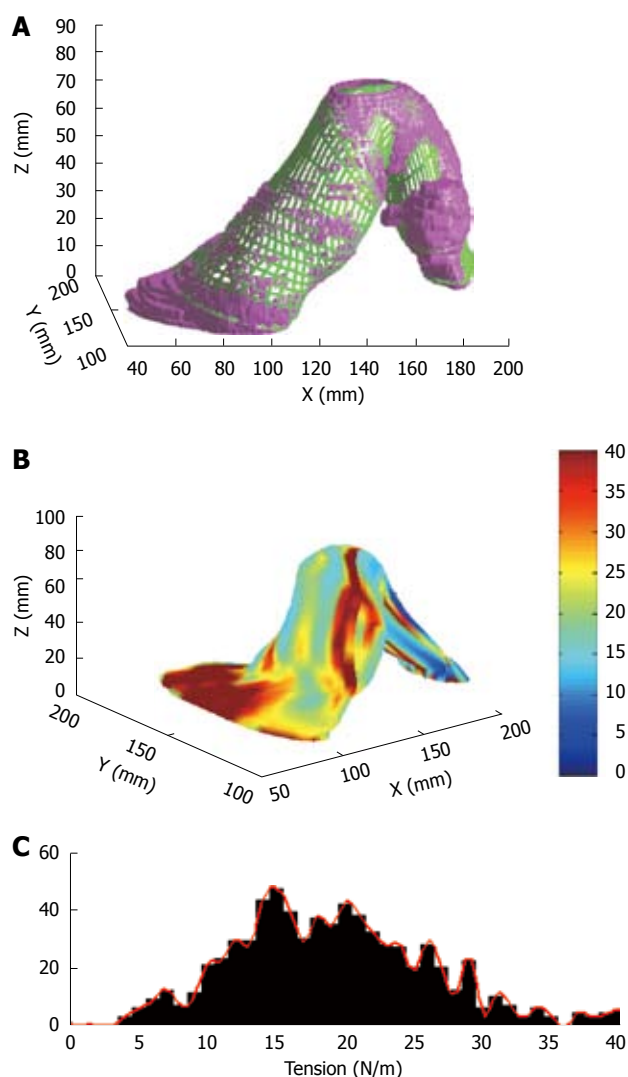
GI tract.

The large morphological complexity of the GI tract and the variability in the different parts of the tract are well known. The complexity increases in the characteristic folds of the connection regions<sup>[49-51]</sup>. With regard to the structural conformation of GI tract tissues, the inner mucosa and submucosa layers are surrounded by the outer muscular and serosa layers. Collagen fibres of submucosa form a complex network and are oriented in different directions. The muscular layers have muscle fibres oriented in the circumferential direction (circumferential muscle layer) or the longitudinal direction (longitudinal muscle layer). As a consequence, the GI tract tissue must be considered as a multi-layered composite material, made up of tissues with different mechanical characteristics<sup>[12,52-54]</sup>. Some of the components show a specific spatial disposition of the sub-structures, such as collagen and muscle fibres, and are studied by means of a constitutive formulation already adopted in other fields for the mechanics of biological tissues, based on the theory of fibre-reinforced materials<sup>[55-57]</sup>. The most current investigations of the GI tissue properties are mainly focused on seeking the constitutive equation and the associated constitutive parameters of the physiological or pathological status. To date, most GI structure and tissue property studies have been based on animal experiments. Medical device development has made it possible to study the mechanical behaviour of the GI tract *in vivo*<sup>[58-62]</sup>.

The methods and current developments in studies of the biomechanical properties of normal and disease remodelled GI tissues have been described in the above sections. Hereafter, the establishment of morphometric-related modelling of the GI tract will be briefly introduced. According to the reconstruction methods on GI modelling, the establishment of the GI models can be divided into *in vivo* medical images-based models, the anatomical-based models and the theoretical analysis-based models.

### *In vivo* medical images-based GI models

Advances in imaging are introduced initially as research tools and subsequently as clinical diagnostic tests. Medical image-based 3-D models of *in vivo* GI organs have characterized the oesophagus, stomach, small intestine, sigmoid colon, oesophageal gastric junction and the rectum, based on cross-sectional imaging using ultrasonography, computed tomography (CT), Functional Luminal Imaging Probe (FLIP) or magnetic resonance imaging (MRI)<sup>[3,4,63-68]</sup>. With the development of the medical devices such as impedance planimetry, it is now possible to record the mechanical parameters such as the luminal pressure simultaneously with the cross-sectional medical images. Therefore, the *in vivo* mechanical behaviour of the organs can be computed on the basis of the reconstructed GI morphometric models and the recorded mechanical parameter. A reconstructed sigmoid-colon model and the corresponding tension and stress distribution on the model are illustrated as an example in Figure 3. Detailed descriptions of *in vivo* GI

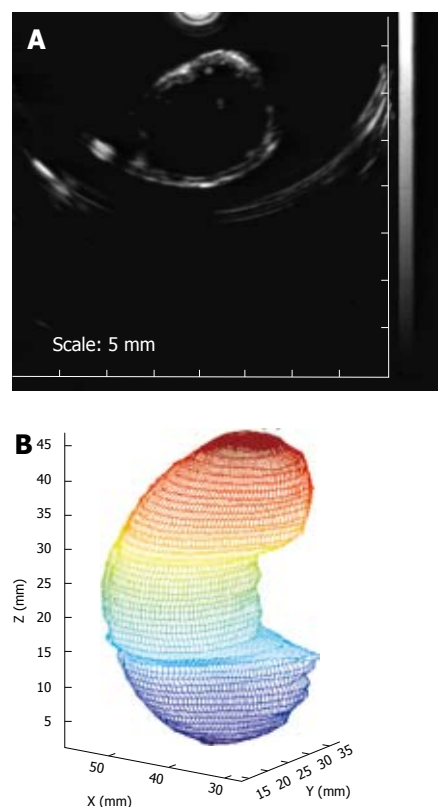


**Figure 3** A reconstructed sigmoid-colon model and the corresponding tension distribution. A: A representative sigmoid colon model with the distension volume of 200 mL. The model with purple colour is the solid model generated directly from the MR images, and the green mesh is the smoothed surface, the comparison between the solid model and smoothed surface indicates that the smoothed model fits well with the original solid model; B: The circumferential curvature distribution on the surface models; C: Tension distribution of the sigmoid colon surface model.

modelling analysis can be found in studies of Liao *et al.*<sup>[66]</sup> and Frokjaer *et al.*<sup>[3,4]</sup>.

### Anatomy-based GI modelling

For modelling analysis using the *in vivo* image based models, only the tension or stress was computed on the basis of three-dimensional surface geometry using the Laplace's equation, and the wall thickness. The tissue structure was, therefore, not taken into account. To aid in understanding of the relationship between the structure and function of the GI tract in healthy and diseased states, an anatomically-based finite element model is needed. The anatomically based visualization GI model is now commercially available, however the GI anatomy based numerical modelling analyses are mainly been done by Andrew Pullan's group so far, and all models were built from the Visible Human Project<sup>[69-71]</sup>. The

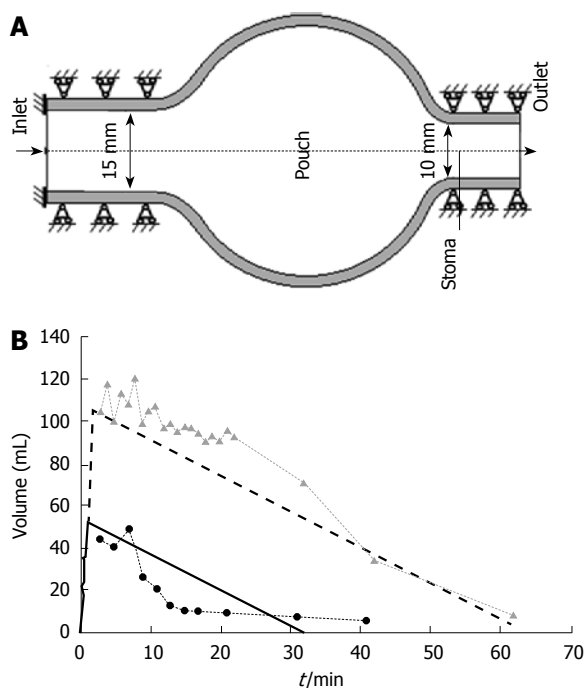


**Figure 4** An example of the anatomically based *in vitro* rat stomach model generated from ultrasonic scanning. A: A representative CT scanning of a cross sectional slice of an *in vitro* rat stomach; B: The reconstructed gastric model on the basis of the CT scanning on the *in vitro* rat stomach. The distance between cross sectional slices was 1 mm, the colour change from blue to red means the increase of the stomach length in z direction.

Visible Human project provided a set of cross sectional images of a human cadaver. On each image, data points around the organ boundary of interest were created and then the geometry models were constructed on the basis of the distinguished data clouds<sup>[71-75]</sup>. The anatomically-based models have now been used to investigate normal and pathological electrical activity of the stomach and small intestine<sup>[71-74]</sup>, the muscle functions on the gastro-oesophageal junction during swallowing<sup>[75]</sup> and the blood flow in the mesenteric arterial system of the human intestine<sup>[69,70]</sup>. An example of the anatomically-based *in vitro* rat stomach model generated from ultrasonic scanning is illustrated in Figure 4.

### Theoretical analysis-based GI modelling

The morphological complexity of the GI organs makes it difficult to build the anatomically-based finite element models. Hence, some numerical models of the GI organs were built on the basis of theoretical analysis by simplifying the complex GI morphometry as a regular geometry such as a circular cylinder for the oesophagus<sup>[52,57,64,68,76]</sup> and a sphere for the stomach pouch<sup>[77]</sup> and some regular tubes for describing the antroduodenal junction<sup>[78]</sup> and the oesophago-gastric junction<sup>[79]</sup>. In the morphometrically-simplified model, most of the biomechanical features such as the tissue structure, tissue properties and bolus flow can be



**Figure 5** A simplified pouch model for describing the gastric emptying of a patient treated for obesity. A: A representative pouch model of mid-sized pouch with stoma diameter of 10 mm, B: Volume history in the filling and emptying phases in the mid-sized and large pouch models with stoma diameter of 10 mm. The solid line represents the mid-sized pouch, and the dotted line the large pouch. Circles and triangles represent volume data of the recorded clinical emptying curve for the mid-sized and large pouch. Pouch and stoma are a small fundic cavity and a corresponding narrow outlet between pouch and the rest of the stomach in gastropasty and gastric bypass procedures for obesity.

expressed mathematically and, thus, the mechanical function of the GI tract can be simulated. The simplified GI tract models have existed for describing the muscle function<sup>[53,68,76]</sup>, food transportation<sup>[77,78,80,81]</sup> and blood flow<sup>[65]</sup> in the GI tract in healthy and diseased situations. A simplified pouch model for describing the gastric emptying of a patient treated for obesity is illustrated in Figure 5 as an example. As can be seen, the emptying curves for the pouch based on the simplified model agree well with the clinical results.

## PERSPECTIVE

GI modelling studies are focused on patient-specific computational modelling and simulation for prediction of disease or early diagnosis by integrating patient specific knowledge and predispositions obtained in biomedical imaging. Modelling studies of the GI tract will advance our understanding of the mechanisms of GI function and diseases, such as dyspepsia and visceral pain. Furthermore, an integrated GI tract simulation model will be beneficial for medical education, and for evaluation of the efficacy and safety of new drugs. The challenge of GI modelling is to develop mathematical and computational models of structure-function relations appropriate to each (limited) spatial and temporal domain, and then to link the parameters of a model at one scale to a more detailed description of structure and function on the adjacent levels. The

present analytical tools can thus be integrated in order to analyze complex structures for understanding biomechanical behaviour in other visceral organs and be further integrated as a global GI model. The mechanical behaviour-related aspects of diseases of the sigmoid colon (diverticular disease, irritable bowel syndrome, *etc*), small bowel (motility disorders), stomach (motility disorders, non-ulcer dyspepsia, *etc*) and oesophagus (oesophagitis, gastro-oesophageal reflux disease, non-cardiac chest pain, *etc*) can be further developed by applying modified versions of the present models.

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