



# What Is the Future of Impedance Planimetry in Gastroenterology?

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The gastrointestinal (GI) tract is efficient in transporting ingested material to the site of delivery in healthy subjects. A fine balance exists between peristaltic forces, the mixing and delivery of the contents, and sensory signaling. This fine balance is easily disturbed by diseases. It is mandatory to understand the pathophysiology to enhance our understanding of GI disorders. The inaccessibility and complex nervous innervation, geometry and mechanical function of the GI tract make mechanosensory evaluation difficult. Impedance planimetry is a distension technology that assesses luminal geometry, mechanical properties including muscle dynamics, and processing of nociceptive signals from the GI tract. Since standardized models do not exist for GI muscle function in vivo, models, concepts, and terminology must be borrowed from other medical fields such as cardiac mechanophysiology. The review highlights the impedance planimetric technology, muscle dynamics assessment, and 3 applied technologies of impedance planimetry. These technologies are the multimodal probes that assesses sensory function, the functional luminal imaging probe that dynamically measures the geometry of the lumen it distends, and Fecobionics that is a simulated feces providing high-resolution measurements during defecation. The advanced muscle analysis and 3 applied technologies can enhance the quality of future interdisciplinary research for gaining more knowledge about mechanical function, sensory-motor disorders, and symptoms. This is a step in the direction of individualized treatment for GI disorders based on diagnostic subtyping. There seems to be no better alternatives to impedance planimetry, but only the functional luminal imaging probe is currently commercially available. Wider use depends on commercialization of the multimodal probe and Fecobionics.

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## Key Words

Electric impedance; Gastrointestinal tracts; Luminal; Medical devices; Muscle Strength

## Introduction

Proper function of the gastrointestinal (GI) tract requires that its mechanical and mechanosensory operations are normal. However, normal motor behavior in the GI tract includes a good deal of variation because, as a self-regulated mechanical device, it monitors its own functions and modifies them continuously. Examination of

the GI tract encompasses both mechanical events in relation to the physical conditions in the muscular wall and biochemical conditions in relation to the milieu of the lumen. Neural mechanoreceptors in the wall and neural chemoreceptors in the mucosal epithelium receive a variety of kinds of inputs continuously and respond in ways that modify the mechanical functions.<sup>1-6</sup> The GI tract is affected by a variety of diseases.<sup>7</sup> Disturbed mechanical function is sometimes the most conspicuous aspect of the disease. For example for

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the esophagus, this seems natural considering that the esophagus primarily serves the mechanical function of transporting ingested food and fluids to the stomach, or venting air. Esophageal achalasia is perhaps the best known esophageal disease characterized by disturbed mechanical function. This kind of disease is commonly spoken of as the motor disorders of the GI tract.

A fine balance exists between the peristaltic forces generated in the GI tract, the mixing and delivery of the intestinal contents, and sensory signaling. This fine balance is easily disturbed by diseases. Since standardized models do not exist for GI muscle function, models, concepts and terminology must be borrowed from other medical fields such as cardiac mechanophysiology. It is mandatory to understand the complex pathophysiology of the GI tract to enhance our understanding of GI disorders. The inaccessibility, and complex nervous innervation, geometric, and mechanical function of the GI tract makes mechanosensory evaluation difficult. Impedance planimetry is a distension technology that was developed during recent decades.<sup>6,8-10</sup> Impedance planimetry and its applied technologies have made it possible to get insight into luminal geometry, mechanical properties including muscle dynamics, and processing of nociceptive signals from the GI tract.<sup>1,6,8-13</sup>

The current review highlights the impedance planimetric technology, muscle dynamics assessment, and 3 applied technologies of impedance planimetry. These technologies are the multimodal probes that assesses sensory function, the functional luminal imaging probe (FLIP) that measures the geometry of the lumen it distends, and Fecobionics that is a simulated feces providing high-resolution measurements during defecation. These technologies as outlined in the review gives the possibility for researchers in the future to enhance the quality of interdisciplinary research and to gain more knowledge about motor disorders, sensory symptoms and treatment options.

## Gastrointestinal Distension Studies and Impedance Planimetric Technology

In the mid-1980s, there was an increasing recognition that provocative tests were useful in studies of GI function. Such tests would not only measure the background activity in the gut such as the pressure patterns but would also test how the organ reacted to a specific stimulus such as a mechanical stimulus. Several ways exist to stimulate the GI tract mechanically. Simple and physiological methods for distension of the gut such as ingestion of well-defined meals may be useful.<sup>14</sup> However, balloon or bag distension is used more frequently as the mechanical stimulation intensity

can be controlled. For intraluminal bag distension technologies the stimulus will provoke mechanosensitive receptors in the organ wall and thereby test the mechanosensory system. In many studies distensions were based on pressure-volume measurements using latex balloons or the barostat.<sup>15-18</sup> However, there were concerns related to the lack of data on the geometry of the distending balloon or bag. Consequently, the stimulation field and the influence of muscle contractions and relaxations would not be known, as well as lack of reproducibility due to strain softening, and errors in computation of wall tension would be concerns with those technologies.<sup>6,8,19,20</sup>

Impedance planimetry was developed in the late 1980s as an alternative technology for distension of the GI tract. The rationale for the development was many-fold. Most importantly a better tool for assessment of distensibility and for assessment of the mechanical parameters closely associated with mechanoreceptor activation was warranted. Impedance planimetry was less biased by the limitations of the other technologies described above. It was recognized that pressure-diameter or pressure-cross-sectional area (P-CSA) measurements provided a means of assessing the dynamic muscle functional properties as well as passive wall properties at a single location in the GI tract.<sup>6,8,21</sup>

The development of impedance planimetry was inspired from other medical fields. Studies with impedance technology using probes with or without bags had been done in urology in the 1970s based on a theoretical study published by Harris et al<sup>22-24</sup> in 1971. Impedance measurements were also widely used for determination of the volume of the left ventricles of the heart.<sup>25</sup> However, these impedance technologies were not directly applicable for GI distension studies. Modifications were needed in terms of dimensions, electronics, signal processing and distension protocols. The first GI studies using a four-electrode principle were published in 1988.<sup>26</sup> The term "Impedance planimetry" first appeared in a publication from 1991 and have been used since then.<sup>27</sup> The abovementioned developments of impedance technology in urology and the cardiac fields also paved the road for the intraluminal impedance catheters often used in evaluations of gastroesophageal reflux and esophageal clearance.<sup>28</sup>

Impedance planimetry measures P-CSA relations inside the distending bag; ie, the luminal dimension will be measured at the distension site. The principle of CSA measurement is rather simple and based on Ohm's law. Four electrodes are placed on the catheter inside a bag filled with conducting fluid. Two outer excitation electrodes generates a constant alternating current (typically 100 mA at 5 kHz). A pair of detection electrodes located between the excitation electrodes measures the voltage difference between them (Fig.

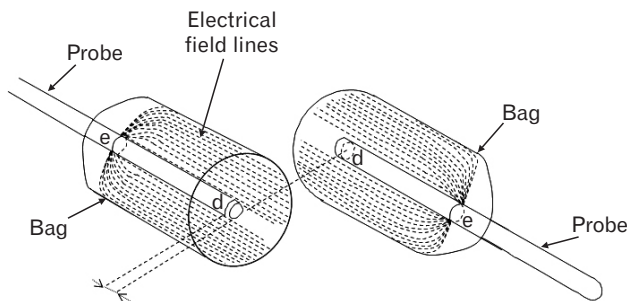
1). The voltage difference is proportional to the CSA multiplied by a calibration constant.<sup>8,26,27,29</sup> Sources of error are well described and can be handled with ease.<sup>8,27,29</sup> The luminal diameter or the inner wall circumference can be computed from the CSA measurement which can be used for computation of mechanical parameters such as tension (the product of the pressure and the radius) and strain (a measure of deformation).

Impedance planimetry was initially used in animal models. These span from physiological studies of distensibility in various parts of the GI tract<sup>26,31</sup> to studies of disease models such as the obstructed opossum esophagus.<sup>32-34</sup> Numerous studies followed in humans. Physiology studies in humans primarily focused on:

- Measurement of real-time tension in the esophagus<sup>35</sup>
- Strain as the most reliable stimulation parameter for the sensory response to distension<sup>13,36,37</sup>
- Demonstration of intestinal tone and its dependency on the interdigestive phases<sup>38,39</sup>
- Variation in distensibility along the esophagus<sup>40,41</sup>
- Esophagogastric junction (EGJ) and anal sphincter measurements.<sup>41,42</sup>
- GI muscle function evaluation (see below)
- Mechanosensation including central integration, sensitization mechanisms, and strain-dependency of mechanoreceptor-mediated responses<sup>43-53</sup> (see the section on the multimodal probe below)
- Preconditioning behavior<sup>37,43,54</sup>

In addition to the numerous multimodal studies listed later in this paper, clinical studies using impedance planimetry focused on the following areas and diseases:

- Hyperalgesia in patients with non-cardiac chest pain (NCCP)<sup>55</sup>



**Figure 1.** Schematic of the impedance planimetry probe. [d] and [e] indicates the detection and excitation electrodes.

- GI tract stiffening in systemic sclerosis<sup>54,56-58</sup>
- Hypersensitivity in IBS and its dependency on pain processing in the central nervous system<sup>59</sup>
- Hypersensitivity and increased tone of the sigmoid in patients with active ulcerative colitis<sup>60</sup>
- Rectal tone changes in patients with spinal cord injury<sup>61</sup>

GI muscle properties are important because the GI tract primarily serves a mechanical function by mixing and transporting the contents to the site of delivery. The muscle delivers the forces that moves the intraluminal matter. Hence, better assessment of GI muscle dynamics is warranted. Impedance planimetry and its applied technologies offer such an assessment which was inspired from cardiovascular studies.

### Advanced In Vivo Muscle Function Studies: From Cardiology to Gastroenterology

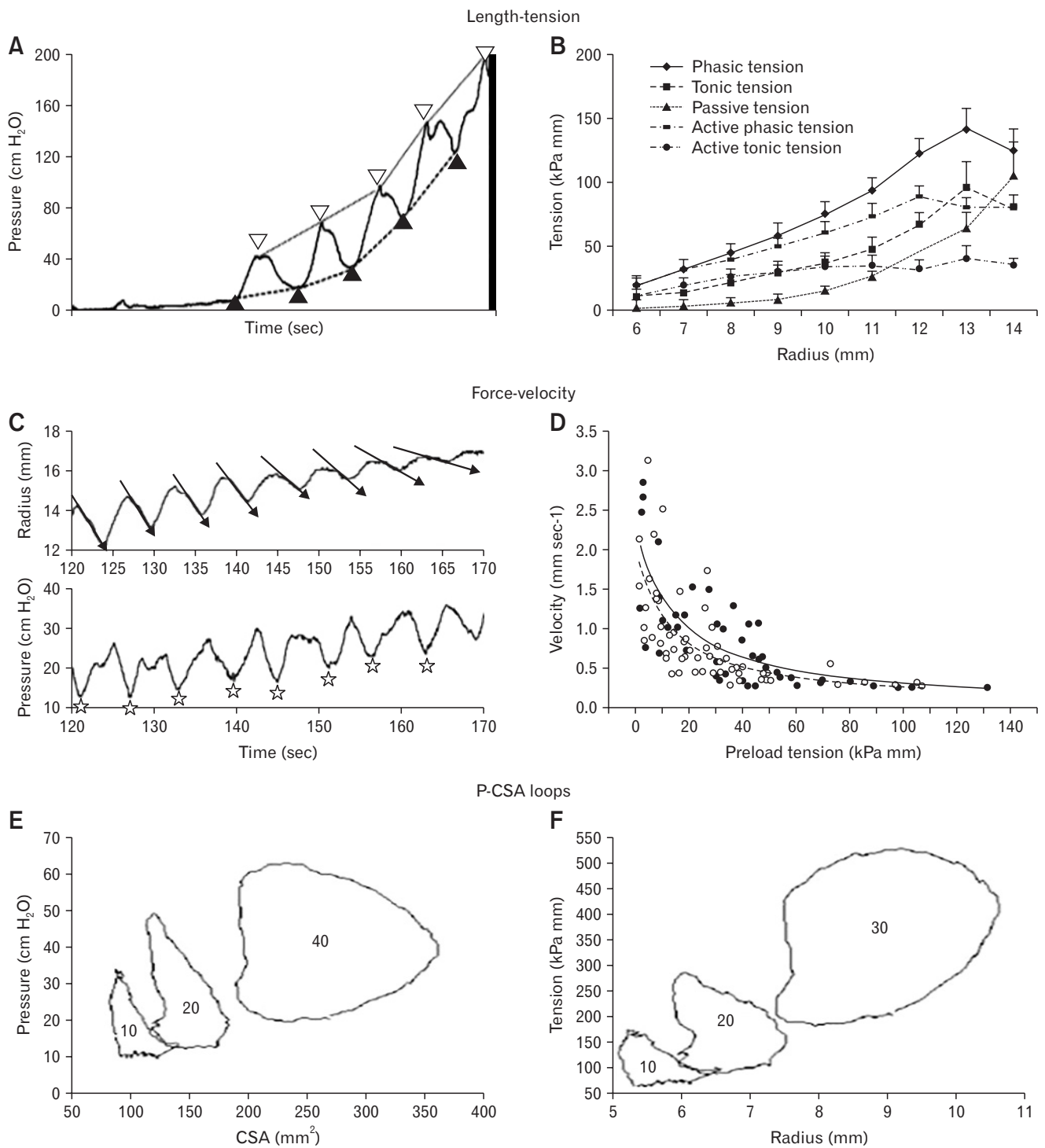
Evaluation of GI muscle function has primarily been based on manometry with analysis of parameters such as contraction amplitude, number of contractions, peristaltic velocity, and patterns of contractions. Impedance planimetric distension data allow much more detailed and structured analysis of contractility. A key feature is that impedance planimetry measures pressure as well as geometric data. Consequently tension and strain can be calculated. These mechanical measures are important for several reasons as outlined below. In GI physiology we can learn from the development of parameters and concepts in cardiac mechanics as listed in Table.

Like the GI tract, the heart primarily serves mechanical functions. The study of muscle and whole organ mechanics in the cardiac field developed way before that in gastroenterology where such studies and concepts yet are in the infancy. It is useful to consider cardiac mechanics and models of the active and passive mechanical behavior for obtaining a better understanding of GI function and remodeling in GI disorders. The table refers to the left side of the heart, ie, the left ventricle and injection of blood into the aorta. The description and concepts are quite basic from a cardiovascular physiology point of view. The interested reader can first seek information in cardiac physiology books.<sup>19</sup> The scientific literature on the topic is abundant and offers further in-depth readings. Obviously, the cardiac models and equations may need modifications to be applied to the GI tract due to differences in anatomy and geometry, but it is evident that there are many similarities and that impedance planimetry offers a new way to assess GI muscle function. Using impedance planimetry, it has been possible to derive parameters such as

**Table.** Gastrointestinal Correlates of Cardiovascular Mechanical Parameters

Parameter	Cardiovascular terminology	Gastrointestinal applications
Preload and the length-tension diagram	Preload is the end-diastolic volume that stretches the right or left ventricle of the heart to its greatest dimensions under variable physiologic demand. It is the initial stretching of cardiac muscle cells prior to contraction. Hence it is related to the end-diastole sarcomere length. Since the ideal length of the cardiac sarcomere cannot be measured in physiological and clinical studies, parameters such as ventricular end-diastolic volume or pressure are used as proxies of preload. The myocardium contracts more powerfully when the end-diastolic volume increases due to a greater number of cross-bridges being formed between the myofibrils. According to the length-tension characteristics of cardiac muscle, this is true up to a point where progressive loss of contractile ability is observed with less cross-bridges due to overstretch.	The esophageal length-tension relation was demonstrated <i>in vivo</i> . <sup>62-64</sup> The total and passive tension showed an exponential increase as function of the change in radius, whereas the active tension increased until it reached a local maximum. Older people had lower maximum active tension and stiffer esophagus. It was suggested that such changes may contribute to the high prevalence of reflux disease in elderly. <sup>64</sup> The preload was associated with the length-tension diagram.
Afterload	Afterload is the end-load against which the heart contracts to eject blood. It can be broken into components: one component is the aortic pressure the left ventricular muscle must overcome to eject blood. The greater the aortic pressure, the greater the afterload on the left ventricle. The other component follows Laplace's law where the tension on the muscle fibers in the ventricular wall is the pressure within the ventricle multiplied by the volume (radius) within the ventricle divided by the wall thickness. Comparing a heart with a dilated left ventricle to a normal heart, the dilated heart must create a greater tension to overcome the same aortic pressure to eject blood because it has a larger internal radius.	Afterload mechanics, ie, the resistance to flow can be described by impedance planimetry and FLIP since distensibility with high-resolution geometric profiling and opening characteristics are assessed. Data are available for healthy subjects and patients with achalasia. <sup>9,65,67,68</sup> FLIP data have been used to compute the flow resistance using numerical models. <sup>69</sup> Analytical models can also be used with assumptions, applying the principles of Hagen-Poiseuille's law. <sup>8</sup>
Force-velocity relations	Force-velocity relationships relate the speed at which a muscle changes its length to the amount of force that it generates. Force declines in a hyperbolic way relative to the isometric force as the shortening velocity increases. The reverse happens when the muscle is stretched, ie, force increases above isometric maximum, until finally reaching an absolute maximum. This has strong implications for the rate at which muscles can perform mechanical work and the power (force x velocity) can be calculated.	Force-velocity and force-power relations have been demonstrated in the normal and diseased esophagus where the velocity of contraction and the force depend on each other in a hyperbolic way. <sup>66,70</sup>
The pressure-volume or P-CSA loop	The cardiac pressure-volume loop has long been used to measure the work done by the heart and its efficiency. A considerable amount of information on cardiac performance can be determined from the pressure-volume plot. Several physiologically relevant hemodynamic parameters such as stroke volume, cardiac output, ejection fraction, and myocardial contractility can be determined from these loops. The pressure-volume area represents the total mechanical energy generated by ventricular contraction.	Since most of the GI tract is tubular, it makes sense to express the loops as P-CSA loops rather than pressure-volume loops. <sup>8</sup> Distension-induced peristaltic contractions resulted in P-CSA loops with relaxation and contraction phases. This demonstrates that GI contractions are sensitive to the initial stretch and to the muscle state. The work increased and propulsive tension increased with the distension pressure. The loops were reduced during butylscopolamine administration. <sup>70</sup> Furthermore, tension-stretch ratio loops in patients with systemic sclerosis were shifted to the left, indicating wall stiffening. Low contraction amplitudes and small P-CSA loops were also features in the patients, resulting in low work output, power output, $\Delta$ tension, and contraction velocity. <sup>56</sup>
Preconditioning	Cardiovascular studies have revealed that biological tissue responds with a strain softening response when repeatedly stretched. <sup>71,72</sup> This process is called tissue preconditioning.	Preconditioning behavior was demonstrated in various parts of the GI tract. <sup>6,8,37,43,54</sup>

FLIP; functional luminal imaging probe; GI, gastrointestinal; P-CSA, pressure-cross-sectional area.



**Figure 2.** Illustration of different gastrointestinal (GI) muscle properties. Panel A shows the bag pressure during distension in the human esophagus and the derived length-tension diagram is shown in panel B. Panel C shown simultaneous radius and pressure measurements during a distension. The arrows show the radius change (slope) during contractions. The slope depends on the degree of distension. The data can be converted to a force-velocity diagram as shown in panel D. Each contraction will result in a pressure-cross-sectional area (P-CSA) loop. This is illustrated in panel E at 3 distension levels (bag pressure of 10, 20, and 40 cmH<sub>2</sub>O). The P-CSA loop can be converted to a tension-radius loop for better comparison between experiments (panel F).

active-passive length-tension diagrams, force velocity curves, pre-load-afterload diagrams, and loop diagrams (Fig. 2).<sup>56,57,62,63</sup> This opened up a completely new way of studying GI muscle properties in vivo,<sup>6,8,9,56,57,64-66</sup> which will likely impact the way GI muscle function is assessed and interpreted in the future. Some clinical implications of this type of analysis have been outlined.<sup>6</sup>

## Specialized Impedance Planimetric Technologies and Their Applications

Three applied technologies of impedance planimetry have been developed. The first technology was developed in the early 2000s for assessing sensory mechanisms. Due to the battery of stimulation modalities, it was named the multimodal probe. The second technology was brought forward a few years later and provided high-resolution geometric measurements, ie, geometric profiling of the distended organ. It was named the FLIP. The third technology based on impedance planimetry is in its infancy but nevertheless show great potential in future anorectal applications. Whereas the multimodal technology and FLIP measure at preselected locations such as in the anal sphincters, Fecobionics provides a variety of measurements during intestinal transport of the device.

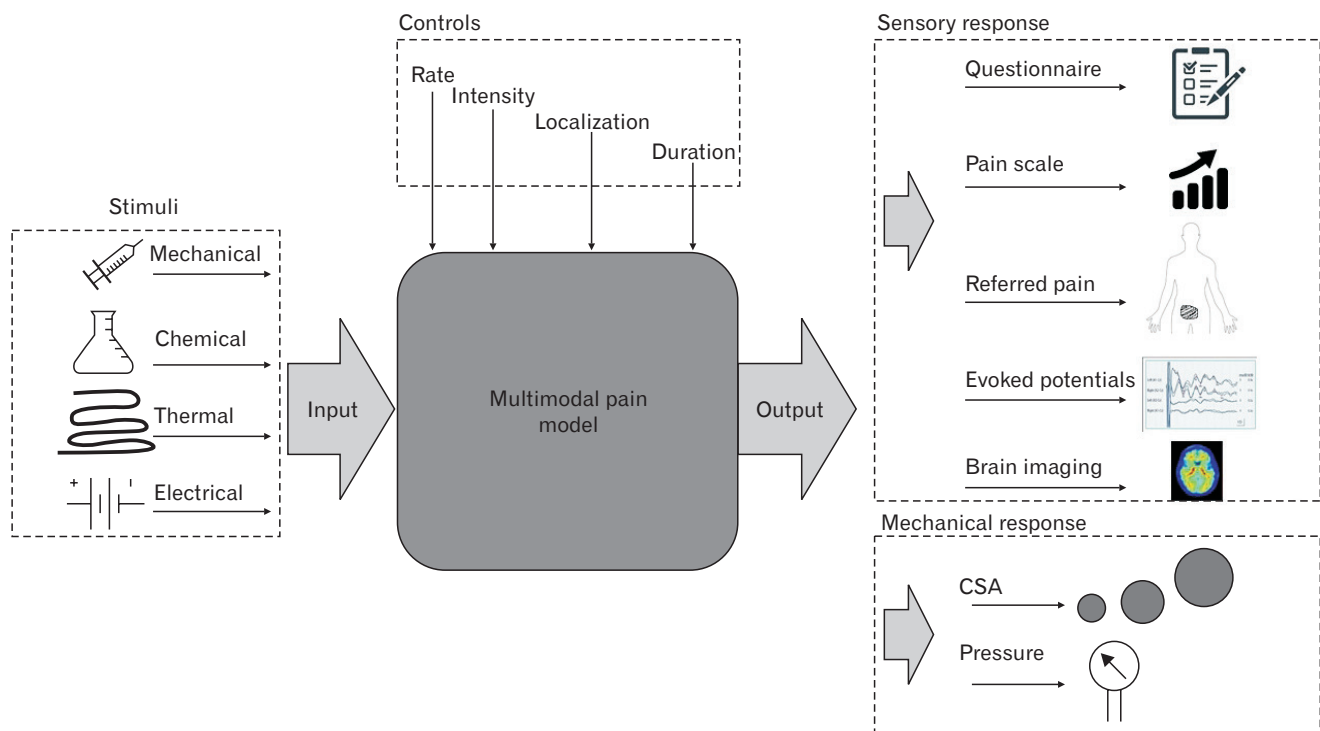
The 3 applied technologies are described separately below.

## The Multimodal Probe

### Background

Visceral diseases are typically associated with unspecific symptoms such as discomfort and pain. The sensory feeling is often vague and patients find it difficult to characterize it, in contrast to the distinct localization in somatic pain. Such GI disorders are commonly encountered in clinical practice with pain as one of the most frequently presented symptoms. Manifest visceral pain originates from a variety of underlying pathologies. Pain is a complex multidimensional experience comprising sensory-discriminative, affective-motivational and cognitive-evaluative components.<sup>73-75</sup> Thus, gastroenterologists are challenged in treating GI pain because the underlying diseases often are difficult to diagnose correctly.

In clinical practice, the symptomatology of underlying diseases is often confounded by complaints relating to psychological, cognitive, and social aspects of the illness as well as systemic reactions such as fever affect the experienced symptoms. Furthermore, pharmacological treatment may cause undesirable adverse effects, which bias the clinical evaluation of the symptoms. Experimental pain models are designed to cover the confounding factors, which then can be turned to advantages in the assessment of basic GI func-



**Figure 3.** Schematic of stimulation and assessment modes in experimental pain models. CSA, cross-sectional area.

tions, mechanisms of disease, and treatment efficacy. Under these controlled facilities, the investigator controls the nature, localization, intensity, frequency, and duration of the applied stimulus, and assesses the quantitative measures of the psychophysical, behavioral, or neurophysiological responses (Fig. 3).<sup>76</sup>

The ideal experimental stimulus to elicit visceral pain in man should be natural, minimally invasive, reproducible, and quantifiable.<sup>77</sup> Preferably the pain should mimic the observations in diseased organs by evoking phenomena such as allodynia and hyperalgesia.<sup>78</sup> Some stimulation methods seem to fulfill these requirements, but most laboratories use their own stimulation paradigms, often without the necessary standardization. The different methods for pain stimulation of the GI tract are based on:

- Mechanical stimulation (see references above)
- Chemical stimulation<sup>79-95</sup>
- Thermal stimulation<sup>96-97</sup>
- Electrical stimulation<sup>98,99</sup>
- Ischemic stimulation<sup>100,101</sup>

Experimental pain models have the advantage that specific receptors and pathways can be selectively activated. Consequently the effect of pathophysiological conditions on such evoked responses can be studied systematically. On the other hand, one major limitation of most experimental pain models in the GI tract is that they mimic only part of the clinical pain mechanisms. This is because experimental pain is relatively short-lasting and without activation of the many peripheral and central nervous mechanisms that are typically activated during diseases. Clinical pain is a sum of many pain mechanisms, where experimental pain based on a single modality recruits only parts of these mechanisms.<sup>13</sup> Therefore, a multimodal testing approach must be used which will increase the probability for activation of a range of relevant neural mechanisms. Especially if the stimulation is relatively long lasting and includes modalities known to evoke peripheral as well as central sensitization, the likelihood that the model will mimic clinical pain is high despite the non-harmful nature of the stimulation. In the GI tract difficulties with access to the organs and technical limitations of the currently available models have made such a multimodal stimulation approach difficult.

Treatment of pain is one of the major challenges in clinical medicine as it is often difficult to evaluate the effect of a treatment because the symptoms of the underlying diseases often confound this assessment. Human experimental pain models offer the possibility to explore the pain system under controlled settings. The

models can also be used to screen the analgesic profiles of drugs targeted to treat pain.<sup>102</sup> Thus, if the patients are individually tested with a sensory testing battery to unravel at which levels the pain system is reacting abnormally, the most appropriate treatment can theoretically be selected.

### Multimodal technology

The multimodal probe consists of a catheter with an impedance planimetric bag for distension (mechanical stimulation). The probe also contains side holes for injection of chemicals above the bag (chemical stimulation), and silver-chloride stimulation electrodes on the catheter or bag for electrical stimulation. Short and long pulsed electrical stimulation signals can be delivered across the electrodes giving current to a maximum of 80 mA or until the pain detection threshold is detected. Furthermore, the water inside the bag can be heated or cooled by recirculating the fluid (thermal stimulation) using a reservoir and pump system, or a thermistor element. Furthermore, the multimodal probe will record the CSA and multiple pressures as well as the study subject report symptoms, the pain level on a visual analog scale, and referred pain areas. Objective sensory information can be assessed by recording evoked potentials from the brain or by imaging technology.

### Multimodal studies

It is out of the scope of this paper to make a complete review of the numerous publications using the multimodal approach. The reader is referred to other literature for a comprehensive review of the studies where the multimodal model have been used.<sup>1,6,11,12,103</sup> In brief, it has been used in different parts of the GI tract to assess the sensory response of controlled stimulations in healthy subjects and in various patient groups. In healthy subjects, sensory responses and mechanisms related to gender, age, and other factors were studied in the esophagus,<sup>44,48-52,79,82,83</sup> small intestine,<sup>37,104,105,106</sup> and large intestine including the rectum.<sup>107,108</sup> Clinical studies have been published on gastroesophageal reflux disease (GERD), non-cardiac (functional) chest pain, and Barrett's esophagus,<sup>45,46,53,79,109-116</sup> and on diabetic gut function.<sup>117,118</sup> In addition, several pharmacological studies were published, in particular related to testing of opioids.<sup>12,102,106,119,120</sup>

### The future for the multimodal technology

It is evident that multimodal assessment offers deep insight into sensory mechanisms due to its multiple controlled stimulation modes and assessment of sensory-motor data. This allows for subtyping of patients which is important for individualized treatment.

At present, no other technology provides such kind of measurements. A prominent example is the capability of the technique to differentiate pain mechanisms in patients with GERD, non-erosive reflux disease (NERD), and NCCP, ie, NCCP, NERD, and GERD patients are normo-, hyper-, and hypo-mechanosensitive, respectively, as well as the differences in acid and thermal sensitivity.<sup>45,46,53,116</sup> The potential for subtyping patients with IBS and functional dyspepsia is obvious and needs to be explored further. Multimodal technology will facilitate the design of subsequent clinical (phase III) studies. Hence, a substitution of the current “trial and error design” with a more mechanism based approach will reduce the economic and human burden in the development of new drugs targeted against GI pain. Furthermore, experimental pain studies would be valuable in phase I studies of potential pain killers, where screening may provide knowledge about analgesic properties and interference with evoked pain mechanisms before the drug enters large clinical studies. This may improve design of phase II and III studies and be directed against patients assumed mainly to suffer from the type of pain where the drug has potential effects. However, the multimodal technology is not yet commercialized and therefore has not gained widespread use. Most publications come from a few specialized research groups. Commercialization is needed for clinical breakthrough.

Future studies should use the multimodal technology in experimental pain stimulation of different patient groups to gain more information about the pain system. Recordings of evoked potentials and non-invasive neuroimaging combined with multimodal technology can be used to explore the mechanisms behind visceral pain transduction, processing and perception in patients with functional GI disorders.<sup>121,122</sup> Together with pharmacological studies, such interventions could lead to a mechanism based treatment approach in patients with visceral pain.

## Functional Luminal Imaging Probe

### Background

GI sphincters have an important role in the control of flow of liquids and solids being transported in the GI tract. Inadequate function of sphincters is the basis of many GI diseases. Perhaps the best examples are the obstructions created by the non-relaxing lower esophageal sphincter (LES) in achalasia and the loose LES associated with GERD. Traditionally, sphincters were studied by pull-through and stationary manometric techniques, by the Dent sleeve and, more recently using high-resolution manometry (HRM).<sup>123-125</sup> Manometry and the Dent sleeve proved useful for

showing transient lower sphincter relaxations, and impaired LES relaxation in patients with achalasia. HRM has gained widespread use in physiology and clinical laboratories. However, valves do not necessarily have to squeeze tight to be competent. Therefore, manometric studies only provide part of the assessment. In fact, manometric data show poor correlation with the strength and competence of sphincters.<sup>126,127</sup> It has long been thought that measurement of sphincter function through resistance to distension is a better approach, now more commonly known as distensibility testing. Measuring the amount of opening or the opening pattern as cross sectional geometry of a valvular region will provide better diagnostic information.<sup>128</sup>

Several attempts were made to measure the geometry of sphincters for assessment of distensibility. Some successful measurements by means of conventional impedance planimetry were made in the LES and the anal sphincter though there were problems placing the rather short bag in the sphincter.<sup>42,129</sup> Groups led by Shaker, Mittal and Pandolfino independently developed other distension devices. However, none of these have become common practice due to limitations caused by use of radiation, technical difficulties, and geometry related factors.<sup>130-132</sup> A major step forward in the development of impedance planimetry was made in 2004 and onwards with designs of probes capable of making multiple CSA measurements in rectal studies.<sup>133</sup> This led to the early FLIP studies by McMahon and coworkers on the EGJ.<sup>65,127,134,135</sup> As outlined below FLIP represents a good practical method to measure distensibility in sphincters and other parts of the GI tract since it easily captures the geometry of the whole sphincter region. For measurement in the GI tract, distensibility is usually defined as the relationship between the minimum CSA in the narrow region and the bag pressure.

### Functional lumen imaging probe technology

The basic principle of FLIP is that of impedance planimetry, ie, measurements of the CSA inside a distending bag from electrical impedance measurements. However, FLIP has many pairs of detection electrodes and therefore can measure a longitudinal series of CSAs inside the bag. Currently the standard is 16 CSA measurements. Since the bag is much longer than the traditional impedance planimetry bags, it is easier to conduct sphincter distension without the bag dislocating to low-pressure zones adjacent to the sphincters. Furthermore, the multiple CSA measurements will ensure that the narrowest part of the sphincter can be captured during the whole distension, even if the catheter and bag slide forward or backwards a bit.

Another important development was made in the analysis and



display of the FLIP data. Firstly, the data were presented as semi-3-dimensional (3D) geometric plots since it is not easy to interpret continuous data streams from numerous channels (Fig. 4). This is the classic FLIP representation which in sphincters will show an hour-glass shape. The early studies in the rectum<sup>133</sup> and EGJ<sup>134,135</sup> also led to the adoption of the color contour plotting technology that was pioneered for HRM by Ray Clouse in the early 1990s.<sup>136,137</sup> This modified plotting technology allows display of the dimensional changes during distension in colour as function of time (Fig. 4).<sup>10</sup> Thirdly, in most studies published, the distensibility was evaluated in terms of very simple measures such as simply looking at the magnitude of the CSA or dividing the CSA with the pressure at a given point of distension.<sup>138-141</sup> This may introduce errors. The opening pressure, the level of distension, and the actual slope of the mechanical data curves must also be taken into account. The sphincter elasticity have in some studies been evaluated in terms of the pressure-strain modulus (elastic modulus  $[E_p] = \text{change in pressure} / \text{change in diameter} \times \text{diameter at a reference state}$ ).<sup>142</sup> Whereas this parameter is clearly more reliable and valid than the distensibility mentioned above, more advanced mechanical parameters should be considered.<sup>6,8</sup> While these biomechanical metrics are important, they are not always obvious to busy clinicians who are under time pressure to make rapid clinical decisions.

## Studies

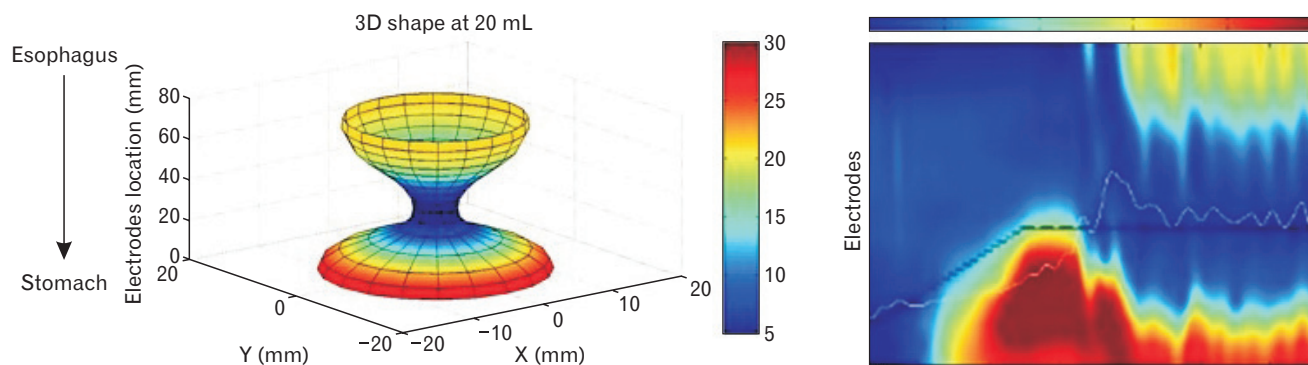
It is out of the scope of this paper to review the numerous publications using FLIP. The reader is referred to other literature for a comprehensive review of FLIP studies.<sup>10</sup> In brief, FLIP has been used in different parts of the GI tract to assess the geometric and mechanical properties in healthy subjects and in various patient groups. Studies have been done in the upper esophageal sphinc-

ter,<sup>143-145</sup> esophageal body in eosinophilic esophagitis,<sup>146,147</sup> EGJ related to achalasia, GERD, Barrett's esophagus, systemic sclerosis, and various treatments such as anti-reflux surgery and peroral endoscopic myotomy (POEM),<sup>146,148-159</sup> pylorus<sup>160</sup> and anal canal related to fecal incontinence, and gender differences.<sup>139,142,161,162</sup>

## The future of the functional luminal imaging probe technology

FLIP is widely available since it was commercialized almost a decade ago. Nevertheless, it is still in its infancy with many physiological, diagnostic and therapeutic aspects yet to explore. No other technology can provide the same kind of dynamic data. FLIP has revolutionized our way of studying sphincters, seems valuable in subtyping of diseases like achalasia and fecal incontinence, and for assessment of the outcome of anti-reflux surgery. There are recent indications that FLIP is better than HRM for assessment of achalasia. Quite a lot of work has accumulated on intraoperative assessment of the efficacy of POEM and Heller myotomy. The future will show if FLIP will truly improve the outcome of endoscopic and surgical procedures. Work is also ongoing in other sphincters and in non-sphincteric regions.

In the future we will hopefully see further improvements of FLIP and analysis of FLIP data. For the catheters, this may range from longer bags to more electrode pairs, better spatial resolution, and multiple pressure measurements. Concerns have been raised about analyzing distension data based on too simple parameters.<sup>6,8</sup> The same concerns are valid for FLIP analysis.<sup>140,141</sup> Studies have been initiated to shed light on distensibility parameters and their value as clinical endpoints. It is also to be expected that the advanced muscle analysis as outlined previously in this paper will be used in FLIP analysis. Much can be gained from the kind of analysis and



**Figure 4.** The typical “hour-glass” representation of functional luminal imaging probe data (top) and a color contour plot (topography) at the bottom. The color scale from blue towards red indicates increasing diameter. The white line is the bag pressure and the heavy black line represents the volume.

FLIP is an eminent technology to provide detailed geometric data of the GI lumen.

## Fecobionics

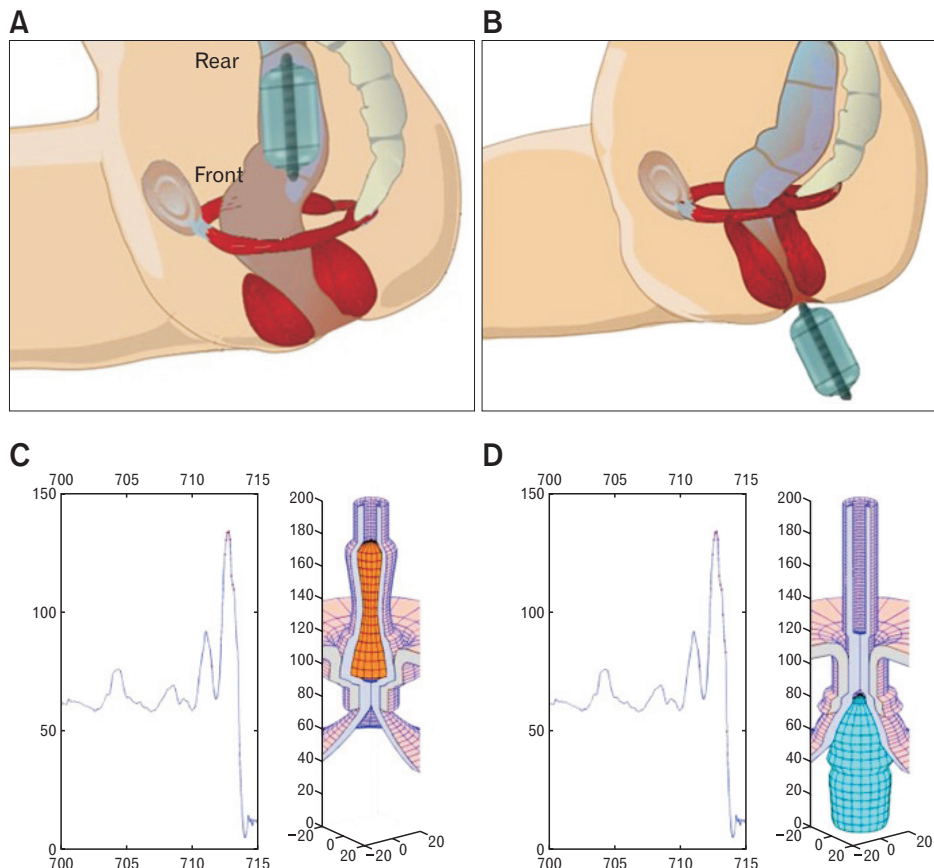
### Background

Defecation is a complex physiological process through which stools are eliminated from the rectum.<sup>163</sup> Defecatory disorders are frequent, especially in the elderly, and affect up to 25% of the population. However, defecatory disorders remain poorly recognized and treated.<sup>164,165</sup> The lack of physiologically relevant and easy-to-use diagnostic tests for identifying the underlying mechanisms is a significant problem. The opening characteristics of the anal sphincter and relaxation of the puborectalis muscle during defecation must be described in detail which is not possible with current technology. For example, the balloon expulsion test does not assess geometry, defecography does not provide information about anorectal pressures, and HRM is not performed during defecation but is a static measurement. Considerable disagreement exists between the results of various anorectal tests and they correlate poorly with symptoms and treatment outcomes.<sup>164-166</sup> Attempts have been made to make

artificial stool for evaluation of defecation such as Fecom<sup>167</sup> but it did not become widely available. A new technology was warranted that would fundamentally rethink the approach to anorectal functional testing.

### Fecobionics technology

Fecobionics is a simulated stool, a biomechanics device, capable of dynamic measurements of a variety of variables during passage inside the gut and during defecation. The development was based on the bionics concept (<https://en.wikipedia.org/wiki/Bionics>). Fecobionics imitates the defecation process and provide geometric mapping and manometric profiles in a single examination. It has the consistency and shape of normal stool. It records pressures, orientation, electrical impedances, and viscoelastic properties during defecation. It is made of a 10 cm long and 12 mm wide core of medical grade resin that contains the electronic sensors and circuit boards. A bag is mounted on the bendable core. Pressure transducers are placed at the front, rear and inside the bag, in addition to 2 gyroscopes for orientation and angle measurements, and impedance electrodes (Fig. 5). A major novelty is the measurement of front and rear end pressures rather than radial pressure during defecation.



**Figure 5.** Schematics of the defecation of Fecobionics are shown (A and B). Simulations from human defecation experiments are shown in the bottom panels (C and D). The color of the Fecobionics bag indicate the pressure in the bag during expulsion, ie, blue is low pressure and orange is high pressure. It was possible to measure impedances, pressures, and bending of the device. The anorectal angle was measured and the shape simulated. The expulsion velocity was computed from the pressure and impedance signals.

Current prototypes are wired and have the battery outside the anus. However, work on making the device wireless is ongoing.

### Fecobionics Studies

Fecobionics is capable of measuring high-resolution pressure and impedance profiles as well as the anorectal angle during defecation.<sup>168</sup> The impedance profiles can be simulated in different ways, ie, as semi-3D plots or video clips or as color contour plots (Fig. 5). The impedance data also allowed calculation of the expulsion velocity. In addition to the impedance plots, promising physiological data were obtained from the pressure sensors which allowed defecation to be divided into 5 distinct phases.<sup>168,169</sup>

### The future of Fecobionics

Fecobionics is in its infancy and not yet Food and Drug Administration approved but nevertheless show very promising results. Successful application have been demonstrated in humans. It is the first intraluminal device measuring a variety of physiological variables during defecation. Especially, the signature from the end-mounted pressure sensors demonstrating 5 phases during expulsion is novel. Since Fecobionics integrates several current tests, it potentially provides simple and inexpensive assessment of a range of defecation biomarkers that will be important in research and clinical practice. Fecobionics holds potential to differentiate patient groups and provide insight into mechanisms of anorectal disorders. Technology-related issues yet to address are making it wireless and improve position determination for identifying the trajectory. Despite the fact that no other device can provide similar recordings, it must be evaluated how Fecobionics compares with other anorectal function tests. Currently it seems that the expulsion time is comparable to that recorded with the balloon expulsion test and the bending angle corresponds to anorectal angles reported in the literature. Hence, Fecobionics data are consistent with existing tests. It is anticipated that the device can replace the balloon expulsion test and HRM but future comparative studies are needed. The clinical future of Fecobionics ultimately depends on its ability to impact on treatment of anorectal disorders. Potential clinical applications are diagnosis and biofeedback training for fecal incontinence and dys-synergic defecation.

### Some Bioengineering Thoughts on Impedance Planimetric Data

The inaccessibility of visceral organs and the unavailability of tissues in many patients with motor diseases, make the modern

investigator turn to the methods of mathematical modeling or numerical simulation to examine the physical processes that operate in GI sensory-motor function. However, modeling and simulation require valid data that can only be obtained from real tissues and experiments. The advances that are mentioned in this review can do much to alter our management of sensory-motor dysfunction in the GI tract in the future. This paper has outlined unique similarities between cardiac and GI muscle behavior assessed by impedance planimetry. They include especially the method that combines distension of an intraluminal bag with the depiction of the length-tension and preload-afterload relationships *in vivo*, the advances in medical imaging and 3D-modeling, and the development of new ways to combine data on the properties of tissues and fluid flow. If we model the data with some simple assumptions, we can predict flow through the luminal region. New technology can advance our knowledge if it is properly applied. This will require, however, a general appreciation for mechanosensory models and simulation.

Publications on impedance planimetry, the multimodal technology, FLIP and Fecobionics demonstrate how profiling and modeling will have a role in future studies in the diagnosis and monitoring and treatment of GI diseases. This in turn will provide better models for the Human Physiome project (<http://physiomeproject.org/>).<sup>170</sup> Recent initiatives such as the GIOME<sup>171</sup> and Esophagiome projects<sup>172</sup> will in time lead to smarter, more precise and tailored medicine and treatments. Models based on impedance planimetric data fits well here.

### Conclusion and Perspectives

Impedance planimetry is a validated distension technology that has given rise to advanced muscle analysis as well as 3 applied technologies. Once a good understanding of the principles of impedance planimetry and its uses in the hollow organs is gained, the researcher can become creative about its applications and their uses. An overview of them as described here may help gain a deeper understanding of the principles involved and inspire the researcher to seek further potential applications within their own area of expertise or interest. Future aspects are described above for each of the applied technologies. Although significant progress has been made in our understanding of GI function such as sphincter dynamics and central processing of GI pain, many questions remain unresolved. For example, our understanding of the differences in EGJ geometry and in the central processing of visceral pain remains nascent. Further application of advances made in other disciplines, such as cardiology, neuroimaging, simulation and modeling, may

be combined with impedance planimetry that may lead to many of these knowledge gaps being addressed and allow the development of routinely clinically applicable techniques that may facilitate individualization of therapy in the future.

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