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Establishing Volumetric Biomarkers
In MRI of the Digestive Tract.

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Published works by staff candidate submitted to the
University of Nottingham
for the degree of Doctor of Philosophy

December 2015
Acknowledgements

I would like to take this opportunity to acknowledge the help and support of my colleagues at the University of Nottingham. In particular Dr Luca Marciani and Prof Penny Gowland who recruited me back in 2008, after my prolonged career break, who have always encouraged and supported me as I have returned to research, culminating in this submission. Also Prof Robin Spiller both for inspiring my interest in the workings of the gut and for framing the questions that MRI had to answer.

The Sir Peter Mansfield Imaging Centre has been a tremendous environment in which to work due to the inclusivity and friendliness of my colleagues coupled with their scientific drive and excellence. I am truly grateful for the support that I have received, both professional and personal, from all the staff and students contained within. There are too many to mention individually but I am indebted to you all.

To Laurence and Ellie who take great pride in their Mum’s achievements, whilst gently mocking the geek within, to John who has loved and supported me for 40 years and to my late Mother and Father who would have been overjoyed to see me attain a PhD towards the end of my working life.

Thank you.
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1. Abstract

This extended abstract describes the background to the 14 research papers that
the author, as staff candidate, is submitting for the award of PhD by published
works. The core part of this work refers to the development of volumetric
biomarkers within the human digestive tract using magnetic resonance imaging
(MRI) and their application to answer novel biomedical research questions. In
particular the author’s work has focussed on applying these techniques within
the human colon and the first two papers (which detail this work) were led and
written by the author. This work was pioneering in its field, the first time that
physiologically undisturbed colon volumes were measured in healthy human
subjects and in patients suffering from irritable bowel syndrome (IBS) and
provided novel insights into the post-prandial symptoms experienced.
Subsequently the effect of an experimental stress on this post prandial response
was evaluated in healthy subjects, also the first time such an effect had been
measured. The third paper, also written by the author, describes her work on
the first clinical application of similar volumetric techniques to assess the
human nasal airways and their response to pharmacological intervention, in
this case the efficacy of a nasal decongestant.

This document seeks to set the gastro-intestinal papers within their scientific
and physiological background and to show their original contribution to the
current understanding of the physiological processes within the human gastro-
intestinal tract.
Between mouth and anus, a complex myriad of mechanical, chemical and biological procedures interact to liquefy and transport food; to break it down into increasingly simpler chemical forms; absorb nutrients and then eject what is no longer required. MRI provides a unique window into the functions and form of this environment at the macroscopic level; a non-invasive tool for detecting and measuring the structure and physical movements of the abdominal organs and their contents, monitoring fluid transport and providing insights into the biological processing therein. This can provide quantitative biomarkers to rigorously assess the normal undisturbed physiology in health and disease and the effect of pharmacological interventions. It is a hitherto relatively unexplored area and it is the development and application of such measurements that form the bulk of the author’s research contained within the presented publications.
2. A brief background to MRI as applied to the gastrointestinal tract

The first MRI image of the human abdomen was obtained in 1977 [1, 2] and since then rapid advances in both MRI theory and technology have led to an imaging modality uniquely able to image the distribution of water and fat in the human body without the radiological risks of high resolution computed tomography (CT). MRI not only provides information on the density of water and fat but on the environment, both physical and chemical, within which the hydrogen nuclei contained in water and fat molecules reside. It is these subtle differences in environment that enables detailed images of form and function within the human body, particularly those organs of predominantly high water content. Thus MRI has, historically, been primarily directed at the human brain where unparalleled detail of the anatomy and function have been obtained [3]. Early imaging techniques were highly susceptible to disturbance from physiological movement, however the development of more rapid imaging techniques has enabled visualisation and measurement of mobile structures such as heart, blood vessels and viscera within the timescale of individual breaths and even heartbeats.

2.1 MRI – a brief semi-classical explanation

The physics of MRI, as applied to in vivo imaging, is described very clearly elsewhere [4] [5] This section seeks to provide a quick background to the
terms and technologies applicable to abdominal imaging, in particular those used in the published works submitted by the author.

2.1.1 NMR
Nuclear magnetic resonance in its most basic form relies on the magnetic properties of atomic nuclei. In most nuclei the magnetic properties of the constituent baryons cancel out giving a net magnetic ‘spin’ of zero. However, when this is not the case then these ‘un-paired spins’ (present in such naturally abundant nuclei as hydrogen, fluorine, sodium and phosphorus) give rise to a net magnetic moment. The application of an external magnetic field will then result in these spins aligning parallel and anti-parallel to the applied field. However the number of spins aligning parallel is slightly greater than those aligning anti-parallel (as it requires more energy to be anti-parallel). This difference in numbers is extremely small and at temperatures concurrent with the human body (and even with an applied field of 1.0 Tesla -approximately 40,000 times the earth’s magnetic field) is only 7 nuclei in one million. This results in a very small net longitudinal magnetisation. However, application of a time varying electromagnetic field (in this case within the radio frequency part of the electromagnetic spectrum) can cause these aligned spins to precess around the direction of the applied field (creating a transverse magnetisation). Absorption of this RF energy is a resonant phenomenon (due to quantum mechanical considerations energy can only be absorbed within very precise frequencies). Thus each of these elements has its own resonant frequency dependent on the nuclear properties of the nuclei and the applied field. For isolated hydrogen nuclei (protons) this resonant frequency is 42MHz at 1.0 Tesla but this frequency can be altered slightly by the structure of the chemical
bonds surrounding the proton (known as a ‘chemical shift’ in frequency and this is the basis for magnetic resonance spectroscopy). For example the protons in a water molecule resonate at a slightly (3ppm) higher frequency than those in a tri-glyceride [6] molecule. A brief pulse of RF energy at the resonant frequency will thus be absorbed and subsequently result in the emission of a small RF field and it is this field that becomes the detected MR signal.

This radiative energy will only last for a short time due to loss of magnetisation from any movement and reorientation of the resonating protons including that caused from physical processes such as collisions. This reduction in energy (and hence the intensity of signal) has an exponential form and is known as free inductive decay (FID). This can be parameterised by the time constants $T_1$ and $T_2$, where $T_1$ is an expression of how quickly the longitudinal magnetisation of the nuclei is reduced (it is the time taken for the signal to reduce to the fraction ‘e’ of its original value (where e= 2.72)) and $T_2$ relates to the decay of the transverse magnetisation. $T_1$ is often referred to as the spin-lattice time constant ($T_1$ is more affected by any chemical bonds surrounding the resonating proton) and $T_2$ as the spin-spin time constant (and is more affected by the degree of magnetic coupling with adjacent protons). $T_1$ and $T_2$ vary with the applied magnetic field ie the values at 1.5T will be different to values at 3T but in biological materials, $T_1$ and $T_2$ are higher in liquids and shorter near large complex molecules[7]. Typical values for human tissues are shown in table (1) [7], more recent in vivo measurements at 1.5 and 3 T can be found elsewhere [8].
<table>
<thead>
<tr>
<th></th>
<th>$T_1$ (ms)</th>
<th>$T_2$ (ms)</th>
</tr>
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<tbody>
<tr>
<td>Water</td>
<td>2000-3000</td>
<td>2000-3000</td>
</tr>
<tr>
<td>Liver</td>
<td>586</td>
<td>46</td>
</tr>
<tr>
<td>Fat</td>
<td>343</td>
<td>58</td>
</tr>
<tr>
<td>Muscle</td>
<td>856</td>
<td>29</td>
</tr>
</tbody>
</table>

**Table 1**: Typical $T_1$ and $T_2$ values at 1.5T [7],

It is possible, by the addition of paramagnetic materials, to manipulate $T_1$ and/or $T_2$, in order to provide additional contrast to that obtained from unadulterated biological tissues. This has led to the development of contrast agents containing gadolinium that can be swallowed or injected into the bloodstream to enhance normal or pathological structures.

2.1.2 MRI

The 3D image produced in MRI relies on subtle shifts in frequency and phase of the resonant absorption/emission caused by variations in the applied magnetic field. Addition of a spatially varying applied magnetic field (or magnetic field gradient) localises the emitting nuclei due to the fact that the frequency of their RF emission changes according to the exact value of the total applied field (frequency encoding). In a similar manner the phase of the emitted RF field will also rely on the location within this spatially changing field (phase encoding). Precisely timed excitation pulses and gradient switches in three dimensions (pulse sequences) can construct echo trains of RF pulses as the precessing magnetic dipoles come in and out of phase. These ‘spin-echo’ or ‘gradient-echo’ trains can then be used to derive spatial and intensity maps (i.e.
the image). Hence the physical principles described result in a map of the location of resonating protons within water and fat, with the subtle differences in signal intensity introduced by density, $T_1$, and $T_2$ changes all delineating the tissues within individual organs of the abdominal cavity and any contents therein.

Since the original 3D imaging of the human abdomen was demonstrated in 1988 [9] there has been an explosion of technical innovations in magnet technology. Scanners capable of imaging the human body with static fields of 1.5T, 3T are now available within the clinical environment (and up to 7T within the research environment). However with higher fields come increasing problems with variations of magnetic susceptibility and motion artefacts and abdominal imaging (with its large tissue and gas contrasts) at the 7T field is in its infancy. Advances in gradient coil design and modes of operation enable fast application of the 2D and 3D image acquisition and this has been coupled with enormous leaps in RF signal processing and computational capability. Data acquisition times have been reduced by orders of magnitude so that it is now possible to acquire high resolution 3D images within seconds and visualise them almost instantly.

The majority of the data in the submitted published works were acquired using the 1.5T Philips Achieva™ scanner based in the Sir Peter Mansfield Imaging Centre at the University of Nottingham. Nasal data were acquired on the 3T scanner and the hyperoxia study (paper 14) used the 7T scanner, also at the Sir Peter Mansfield Imaging Centre.
2.2 Pulse sequences relevant to submitted papers

Imaging the abdomen has different technical challenges to those in brain imaging. The required volumes are larger and there is much more variation in MRI parameters between large blood vessels (e.g. aorta, vena cava, hepatic and portal veins), tissues, free water and gas within the stomach and bowel than within grey and white matter. Imaging of nasal morphometry has similar challenges with the proximity of bone and air-filled spaces. Motional blurring and artefacts from respiration and heart motion and peristalsis are much greater within the abdomen leading to image degradation. Within the often adipose abdomen fat/water chemical shifts can also have an effect. Due to all of these technical challenges it has proved necessary for the development of bespoke imaging techniques for the abdomen with varying sequences of resonating RF, applied field gradients and enhanced signal detection and computation. These differing pulse sequences are optimised to the acquisition of the precise data that is required e.g. high water content or fat imaging, capture of motion or flow etc. The main sequences generally used for these applications at Nottingham and elsewhere (and contained within the published works) are summarised below.

Many of the features of interest within the digestive system are related to fluid secretion, transport and absorption (see section 3) and as such MRI pulse sequences that are sensitive to freely mobile water are useful for the visualisation and measurement of stomach and small bowel contents. Water
has both a long $T_1$ and $T_2$ whereas liver and fat have a much shorter $T_2$ than $T_1$ (Table 1). Therefore a pulse sequence which relies on the transverse $T_2$ relaxation of water (a $T_2$ weighted sequence which generally has a long time between the echoes) will result in an image where the water has a high signal (as there has been less signal decay) and the signal from the surrounding visceral fat and tissue will be much lower (as shown in Fig 1a and b).

![Image of stomach and nasal septum](image)

**Fig 1:** $T_2$ weighted images of a) small bowel [10]

b) nasal structure (paper 3)

A fast spin echo RARE (rapid acquisition with relaxation enhancement) heavily $T_2$ weighted image was used to image and measure fluid volumes in the stomach (paper 5), pancreatic and bile ducts (paper 13), small bowel (papers 5 8 9 11 12) and colon (paper 1). The rapid acquisition and the sensitivity of fast spin echo techniques was also utilised for the imaging and volume measurement of inflamed, water loaded nasal membranes (paper 3).
Other pulse sequences rely on the ratio of $T_1$ and $T_2$ to provide contrast.

Gradient echo sequences (where the re-phasing of the precessing dipoles is achieved by manipulation of magnetic gradients) are more sensitive to small changes in $T_1$ and $T_2$ and a balanced gradient echo sequence has been used to image stomach contents whether food (paper 4 6 7 9 10), foams and gels (paper 4) and gall bladder volumes (paper 13). A similar pulse sequence was used to image ascending colon contents (paper 11) as in Fig 2.

![Fig 2: High resolution balanced gradient echo image of ascending colon (paper 11).](image)

Another way of creating contrast using gradient echo techniques within the abdomen is aided by the chemical shift in resonant frequency between fat and water. Two images are created, the first has an echo time of 2.3ms, designed such that the echoes from fat and water are out of phase (at 1.5T) and the second has twice this echo time so that the echoes from fat and water are in phase. The out of phase image creates a black border at the fat/tissue interface and this often helps to highlight anatomical details within the abdomen (as
seen in fig 3). This sequence was used to provide anatomical landmarks for successful segmentation of the small bowel (papers 5 8 9 11 12) and also for the identification and measurement of the colon (papers 1 2 8)

Fig 3: Dual echo images of human abdomen
a) fat / water out of phase  b) fat / water in phase
(data acquired by author[11])

The pulse sequences used for brain imaging at 7T are very different to those used in GI imaging. There are fewer susceptibility differences, indeed the BOLD technique relies on the small differences between oxygenated and deoxygenated blood to provide information on blood flow within the brain. In this case the emphasis is to achieve a good signal to noise ratio, with high resolution and rapid imaging and a gradient echo planar imaging (EPI) sequence was used (paper 14). Cerebral blood flow was assessed using an arterial spin labelling technique FAIR where RF excitation occurs upstream of the blood flow and signal readout is targeted on regions downstream [12].
3. Context of submitted papers - MRI and the physiology of digestion

The process of digestion has previously been a difficult field to explore. Despite the fact that the alimentary canal is technically outside of the body (it is lined by epithelium) access to its realms historically relied upon invasive procedures, both surgical and endoscopic, that disrupted the very processes to be studied.

The advent of x-ray imaging techniques opened a window onto the undisturbed physiology, particularly when combined with the ingestion/ introduction of highly contrasting materials, such as barium. Although most barium studies are performed to highlight abnormalities within the digestive tract i.e. tumours, hernias, strictures etc. it is possible to highlight the passage of food through the alimentary canal. This could be done directly e.g. swallowing a barium laced meal, or by monitoring the passage of a standard meal by ingestion of radiopaque markers prior to eating. These techniques are more suited to the examination of the upper GI tract where the only preparation required is a period of fasting and the transit times involved are in the region of hours rather than days (and hence require fewer exposures). However greater preparation is required for the examination of the lower digestive tract where the presence of faeces interferes with the visualisation of the bowel. Here fasting and purging
are required to cleanse the colon and frequently gaseous distension of the bowel is also required.

The radiological hazards of such examinations are acceptable within the clinical setting, where examination can provide substantial diagnostic benefit to the patient, but such exposures are unacceptable for the study of basic physiology where serial imaging of healthy volunteers would be required. Gamma scintigraphy techniques, where a radioactive substance is ingested and detected, are used in the clinical setting [6] to assess motor disorders of the upper GI tract and could potentially be used to provide information on the progress and absorption of radio-actively labelled food components e.g. the absorption and dissemination of sugars and/or fats. However the radiological safety requirements, when using these techniques on human subjects, have also restricted their use in basic physiological research.

More recent developments of ingestible wireless pills equipped with camera and chemical sensors have proved particularly useful in examination of the small bowel [13] where traditional endoscopic techniques cannot be used. They provide exquisite insight into the environment in close locality to the devices but lack the ability to see ‘the whole picture’.

Since the advent of rapid imaging techniques [9, 14, 15] using MRI to visualise and monitor the digestive tract is a rapidly expanding field and comprehensive reviews of its use can be found elsewhere [16-18] This section briefly reviews the processes of digestion and the way that these have been
monitored using MRI in order to contextualise the submitted papers within the wider field. Attention is drawn to the work at Nottingham and, in particular, the work of the author, detailed in the submitted papers.

3.1 Upper GI tract

3.1.1 Mouth

Digestion begins with the biting and chewing of food. The act of chewing reduces the size of the food components, releases saliva and prepares a bolus for the act of swallowing. Swallowing requires the coordinated action of the tongue and the oro-pharyngeal structures to propel the food into the oesophageal tract, without the dangers of inhalation. Real-time 2D MRI has been used to assess chewing and swallowing in healthy volunteers, dysphagia patients [19] and acromegaly patients [20] where the larger tongue volumes of the patients (measured in this study) can lead to abnormalities in the swallowing process. In both cases visualisation of the food bolus was enhanced by use of an oral gadolinium contrast agent.

3.1.2 Gullet

Transit of the food bolus down the oesophagus can be hindered by the presence of physical obstruction (due to stricture or pathology) and also relies upon the presence of efficient, coordinated peristalsis and this can be affected by age and disease causing achalasia. Passage into the stomach is regulated by the gastro-oesophageal junction, which not only needs to relax to allow food into the stomach but also prevents reflux of highly acidic gastric contents into the relatively unprotected oesophageal epithelium. MRI has been used to research motility [21], gastro-oesophageal function [22] [23] and reflux [24]
but generally these are routinely clinically assessed using high resolution manometry [25, 26].

### 3.1.3 Stomach

The food then accumulates in the stomach where the lumen stretches to accommodate the volume of food and this stretching is an important part of both function and satiety responses. Failure of accommodation can lead to premature satiety, nausea and dyspepsia. The stretching of the stomach wall is also an important regulator of appetite and hunger, it is the detection of a full stomach that leads to cessation of eating. MRI can provide a radiologically safe method to measure these volume increases (and hence stretching) [27] [28] without the disturbance that balloon inflation methods introduce [29].

The necessary secretion of acid and digestive enzymes from the stomach wall is stimulated by the presence of food and these secretions can also be measured using MRI [30] [31, 32]. Substantial contractile activity is also triggered by food within the stomach, with primarily antegrade peristaltic waves churning and mixing the contents. Distension of the stomach walls will precipitate high motility whereas little or no distension will result in little motility. This ensures efficient and sufficient exposure of contents to the gastric acid and enzymes and promotes the mechanical breaking down of large food particles (antral grinding). Again rapid MRI techniques have been used to visualise and quantify this gastric motility[33] [34] and grinding [35] and establish the effect that factors as meal composition and viscosity [36] have on these functions.
Food resides in the stomach until it is of such a liquid form that it can exit the pylorus and enter the duodenum. The precise timing of this process (usually 1-4 hours) is influenced by many factors and there are many feedback mechanisms that control this process and at least five different sensory receptors have been identified in the mucosa, which respond to mechanical, thermal, osmotic and chemical stimuli. A liquid meal will tend to empty faster than a solid and the emptying rate of a solid meal will depend heavily on the efficiency of the antral grinding. The liquid phase will often empty before the solid phase as the combination of peristalsis and constriction of the pylorus sieves liquid from the more solid particles (antral sieving). A low nutrient meal will empty much faster than a meal high in fat which, when detected in the duodenum slows motility (and emptying) in order to match the available delivery of bile and pancreatic secretions. Any disruption to these mechanisms e.g. due to the nerve damage frequently seen in diabetes, can result in delayed gastric emptying (gastroparesis) with associated nausea, pain and vomiting.

MRI has been used in many studies to assess the gastric emptying process in health [37-40] and disease [41-48] and response to alteration in meal form [49] and pharmacological intervention [50, 51]. Several papers in the author’s submitted published works are concerned with the measurement of gastric emptying using both a manual segmentation as shown in Fig 4 (papers 4, 6, 7, 9, 10) and a semi-automated method (paper 5).
Fig 4: Manual segmentation of stomach volume

(data acquired by author paper 9)

Measurement of the stomach volume as a function of time provides a quantitative estimate of gastric half-emptying time and this can be compared with the subjective responses of human volunteers in terms of satiety and hunger. The ability to discriminate between the volume of liquid or solid stomach contents and the distension due to swallowed air provides indicators as to the predominant mechanisms of satiety.

This is important when meal form has been altered to increase satiety by ‘foaming’ (paper 4) or ‘souping’ (paper 10) or by preventing separation/layering of fat (paper 7). Satiety is also increased when a meal composition has been altered (paper 6), with a high fat meal promoting a greater feeling of fullness despite emptying faster than a high carbohydrate meal. Also consumption of a bread based meal increases the gastric emptying time compared to an equicaloric rice-based meal (paper 9) but did not appear to
affect satiety. There was a similar effect seen with bran additives which also delayed the gastric emptying time (paper 12). In addition, the measurement of the rapid emptying of water into the small bowel provides crucial information for the parameterisation of drug delivery and absorption (paper 5).

3.2 Small Bowel

3.2.1 Duodenum

As a meal enters the duodenum the gall bladder releases bile (and decreases in volume), and the pancreas directly secretes a fluid containing mixture of enzymes and bicarbonate. Both fluids are released from the common bile duct into the duodenum through the sphincter of Oddi. Bile contains water, bicarbonate and bile acids and these acids have detergent action which causes fat globules to break down (emulsify) into much smaller droplets. Emulsification greatly increases the surface area of fat, making it available for digestion by lipases (secreted from the pancreas). Pancreatic secretion is also alkaline to change the pH from the highly acidic environment of the stomach (pH 1.5-3.5) to the slightly more alkaline environment (pH 6-7.4) tolerated by the small bowel. The amount of bile released and pancreatic fluid is generally controlled by feedback from the receptor cells of the enteric nervous system and a highly fatty meal results in increased secretion [52]. Pharmacological intervention can change these secretory processes (and/or affect the function of the releasing sphincter) and paper 13 describes the author’s quantitative assessment of the effect on the gall bladder, common bile duct and pancreatic duct of morphine-neostigmine and secretin in healthy volunteers. Both agents
were found to increase gall bladder volume but the morphine-neostigmine
challenge caused greater distension of the pancreatic duct due to contraction of
the Sphincter of Oddi. The effect of amount and form of fat droplets on bile
release from the gall bladder was also investigated in paper 7 but no difference
was found in the change in gall bladder volumes whether the fat emulsions
were stabilized or whether there were fine or coarse fat droplets present.

3.2.2 Jejunum and Ileum

Upon leaving the duodenum the mixture of food, bile and pancreatic juice pass
into the small bowel, and the rate of transport is now dominated by the
peristaltic activity of the small bowel wall. Both antegrade and retrograde
contractions occur, continuing the mixing process and creating small ‘pools’ in
the convoluted intestinal loops. These ‘pools’ (or pockets) are thereby
gradually moved through the small bowel allowing the absorption of simple
sugars, amino acids and fatty acids, before emptying into the ascending colon
through the ileocaecal valve. Mean transit times for non-nutrient fluids have
been measured [53] at 84 minutes but there is a large natural variation in
addition to those changes caused by meal composition. Large amounts of fat
have been found to increase the small bowel transit time [54, 55] and the
presence of disease or strictures (common in Crohns disease) can also retard
the flow leaving large distended loops of fluid which can be prone to bacterial
overgrowth.

MRI is particularly useful in the study of this region of the digestive tract as
intubation is not only difficult but disturbs these processes (in particular it
increases motility). The liquid nature of the intestinal chyme enables rapid and accurate imaging using T₂ weighted sequences that provide a large contrast with surrounding viscera and fat. Motility studies using a combination of oral contrast agents and unabsorbable hydrogels are reported in health [56, 57], post-surgery [58] and after pharmacological intervention [59, 60]. More recently semi-automated methods of assessing small bowel wall motility in health and Crohns disease have been reported [61-66]. The direct observation of fluid flow in the small bowel has also been described using an MRI tagging technique [62, 67].

The lumen of the small bowel can both secrete and absorb water and pioneering work at Nottingham has established a validated MRI measurement of the volume of free water within the small bowel [10]. This volume measurement has been used to evaluate the effect of bran additives [68], and the author subsequently used this measurement method applied to a bread based meal vs a rice based meal (paper 9) where the bread meal was found to reduce the small bowel water compared to the equicaloric rice based meal. In addition the effect of the form of food on small bowel water has been investigated. A solid/liquid meal was found to increase the small bowel water more rapidly than a ‘souped’ meal (paper 10) - as the liquid phase emptied from the stomach almost immediately- although during the later phase of digestion the total water content was greatest for the ‘souped’ meal. Small bowel water content is also significantly reduced in patients with disordered bowel function such as IBS-D (paper 12), but significantly increased in coeliac disease and scleroderma [69] and constipation (private communication
from C Lam -awaiting publication). The effect of dietary components such as fermentable oligo–di–mono saccharides (FODMAPS) on both healthy volunteers and subjects with bloating is beginning to be explored [11, 70, 71].

In addition the rate and extent of drug dissolution and absorption may be highly influenced by the precise water distribution within the stomach and small bowel and quantification of this distribution was evaluated in 12 healthy volunteers, both in the fasted state and post-ingestion of a 240ml water dose (paper 5). In this case the water formed distinct small pockets within the small bowel of around 5ml.

Evaluation of pharmacological interventions at Nottingham include: - a study on the effects of ondansetron on small bowel water in healthy volunteers [72] and IBS-D patients [73]; the effect of oral polyethylene glycol to speed transit in healthy volunteers (paper 8) and in constipated patients [74] - which caused a fourfold increase in small bowel water from the fasted state; the use of loperamide and simethicone to slow transit in an experimental model of diarrhoea (paper 11) where, despite accelerating the gastric emptying of a mannitol drink the interventions both reduced the amount of small bowel water and increased the oro-caecal transit time compared to a placebo.

3.3 Large Bowel

The large bowel is defined as the section of GI tract from ileocaecal valve to rectum. It consists of 4 regions, the ascending, transverse, descending and the sigmoid colon. It is vitally important for the absorption of nutrients and the
recovery of water and electrolytes as well as the transmogrification of watery intestinal chyme to the solid faecal matter passed to the rectum. [75]

3.3.1 Ascending colon

Upon exiting the small bowel the intestinal chyme enters the ascending colon via the ileocaecal valve. This valve has two functions. Firstly it regulates flow into the colon thereby slowing transit and aiding absorption in the terminal ileum as well as preventing overload of the large bowel (with subsequent rapid transit, poor colonic absorption and diarrhoea). Secondly it acts as a non-return valve to prevent backflow of the bacterially loaded colonic contents into the relatively sterile small bowel. Failure to regulate backflow is thought to lead to overgrowth of bacteria in the small bowel (SIBO) which is associated with rapid transit and malabsorption as well as clinical symptoms such as pain, bloating and diarrhoea [76]. The main function of the ascending colon is to facilitate the efficient fermentation and degradation of so-far unabsorbed complex sugars and fats. The chyme is thoroughly mixed with resident bacteria, which are present in enormous populations (the ‘microbiome’ [77]). This is accomplished by antegrade and retrograde peristaltic contractions that create flow within the large volume of the ascending colon.

Basic physiological data on colon morphology has to date mainly been obtained from resected cadaver specimens, inter-operative measurements or from radiological assessments of the emptied and distended colon. Nottingham has led the way in the measurement of the undisturbed colon using MRI using
a manual 3D segmentation method. An example of the reconstructed volume of the colon is shown in fig 5.

![Colon Segmentation](image)

**Fig 5:** Volumetric reconstruction of segmented colon
(data acquired by author [11])

This has been important in establishing the range of normal fasting values in vivo both in health (75 subjects) and in IBS-D (25 subjects) (paper 1) and coeliac disease and scleroderma [69]. Surprisingly there are no significant differences in these fasted values in healthy subjects compared to those suffering from IBS-D although the post-prandial behaviour of both small bowel water [78-80] and the ascending colon volume (paper 1) has been shown to differ in a manner consistent both with the accelerated transit seen in IBS-D and in the manifest clinical symptoms. These symptoms are often worsened by stress [81] and both psychological and pharmacological treatments of the underlying stress have been reported to be effective in lessening symptoms [82, 83]. Therefore the effect on the small bowel and colon of an ethically acceptable experimental stress (ice cold hand immersion) and a pharmacological stress (corticotrophin releasing hormone-CRH) was evaluated at Nottingham (paper 2) using 36 healthy volunteers. This showed that both
stressors constricted the small bowel and CRH both increased the volume of
the ascending colon and reduced the normal post-prandial expansion and was
associated with the sensation of distension and bloating. Subsequent to this
work (which utilised a laborious manual segmentation of the colon from
surrounding viscera) further development has been reported on semi-
automated techniques to measure these volumes [84] (although a good degree
of manual segmentation is still required). The colon volumes reported in this
study (on 4 subjects) were similar to those previously published by the author.

Fermentation within the ascending colon also produces gas, and this can be
easily visualised using MRI. Abnormal handling of the gas produced has been
implicated in the symptoms [85] such as bloating [86] of both IBS [87] and
constipation [88, 89]. Dietary modification to reduce fermentable sugars have
been reported to improve symptoms in IBS patients [90] and measurement of
colon volumes and gas loading at Nottingham have shown consistent
differential responses to FODMAPs (fermentable-oligo-, di-, mono-
saccharides and polyols) compared to simple sugars in healthy volunteers [71]
with the largest increase in diameters seen in the transverse colon. Recent work
by the author and colleagues at Nottingham with patients reporting bloating
[11] has suggested that it is the sensitivity of the colon to stretching which
differs in patients rather than the amount of gas produced.

3.3.2 Transverse colon
The main function of the transverse colon is the absorption of short chain fatty
acids produced by the fermentation in the ascending colon, (although further
fermentation- including proteins-does take place in this region) and the reabsorption of water and electrolytes from the chyme. It is more mobile than the ascending and descending colon and also exhibits a greater range in form and volume, both in the fasted and fed state (paper 1). The gastro colic reflex has been found to have less effect here than in the ascending colon (paper 1) [91]. Propulsive and mixing activity also continues throughout this region and lack of coordinated motility can lead to slow transit constipation. In contrast, excessive or uncoordinated (or retrograde) contractions can lead to the pain associated with IBS [92], with either diarrhoea or constipation.

### 3.3.3 Descending and Sigmoid Colon

Water and electrolyte absorption continue as the mixture of living and dead bacteria and undigested food residue gradually becomes more viscous and solid faeces form. Approximately 90% of the water is normally reabsorbed within the colon leaving around 100-150ml /day within the faeces. [93]. Faecal material and gas are stored in the mobile, expandable sigmoid colon until preparation for defecation occurs. Certainly large quantities of gas have been observed in this region in our MRI studies [11, 71].

### 3.4 Colo-rectal

#### 3.4.1 Rectum

Around 1 hour prior to defecation antegrade contractile activity increases throughout the whole colon [94] and faeces are propelled through the sigmoid
colon and into the rectum where distension of the rectal walls produces the
desire to defecate and the relaxation of the internal anal sphincter. IBS
sufferers have been shown to have greater sensitivity to this distension [95, 96], experiencing both higher pain and urgency levels.

3.4.2 Defecation

Defecation in healthy subjects is normally a voluntary act involving relaxation of the puborectalis muscle and the external anal sphincter, coupled with an increase in inter-abdominal pressure. Voluntary and involuntary contraction of the rectum then expels the faeces. In cases where defecation is obstructed, either by a functional inability to relax the puborectalis or by physical obstruction due to abnormal anatomy, the inability to empty the rectum leads to constipation and delayed gut transit. Previously investigated by contrast barium and x-ray defecography using MRI is becoming increasingly available, with the advent of scanners where the sitting position is possible within the magnetic field (so-called upright scanners). The rectum is filled with a viscous MRI contrast material and dynamic imaging performed as the act of defecation is attempted. The high resolution moving images of the musculature of the rectum and anus, combined with the surrounding anatomy can provide a great deal of useful information regarding mode of action and efficiency of defecation [97, 98].
3.5 Whole gut transit

The motility of the digestive system varies greatly between individuals, with the time taken to transit from mouth to anus ranging from hours to days\cite{99,100}. This transit time has been found to be significantly altered in irritable bowel syndrome and constipation \cite{79,101}. Work at Nottingham has established a novel MRI method for measurement of whole gut transit time using MRI marker capsules (and compared this technique with that using radio-opaque markers \cite{102}). This has then been used to evaluate the stimulation of colonic motility using a polyethylene glycol bowel preparation in healthy volunteers (paper 8) and in constipated subjects \cite{74}.
4. Gastrointestinal MRI: going forward

The increasing availability of MRI, its acceptability as a non-invasive alternative to CT and the technical advances in spatial and temporal resolution will open up new applications within the digestive tract as increased detail is obtained. Abdominal imaging is moving from 1.5T to 3T both in clinical and research applications and the advent of abdominal imaging at 7T holds the potential of imaging the finer details within the stomach and bowel lumen, as well as more detailed resolution of associated hepatic and pancreatic structures. 7T imaging also holds the potential for more rapid magnetic resonance spectroscopy of gut contents, increasing the understanding of nutrient transport and absorption within these regions.

Improved motion compensation and post-processing will lead to longer image acquisition times not constrained by the duration of a breath hold both improving the signal to noise ratio in images and enabling real-time cine MRI capture of peristalsis in small bowel and particularly in the colon where contractual activity is much less frequent. MRI measurement of flow patterns within these structures could also be useful in the assessment of motility disorders and their response to pharmaceutical intervention, and indeed in the mechanics of drug absorption within the gut.

MRI has contributed greatly to the understanding of gut physiology and function since those simple images were obtained 37 years ago. Nottingham is at the forefront of gastro-intestinal MRI and well placed to drive the techniques and expertise further over the decades to come.
5. List of peer reviewed publications from UoN- including author contribution


This paper was the first to measure colon volumes in the unprepared and undisturbed human colon enabling the evaluation of the normal physiological response to feeding.

Author contribution- Assisting MRI Data acquisition (10%), measurement of colon volumes (100%), analysis (60%) and reporting of results (60%).


This paper used the techniques developed in paper 1 to assess the effect of stress on the large bowel

Author contribution- Assisting MRI Data acquisition (20%), measurement of colon volumes (100%), analysis (60%) and reporting of results (60%).

3. S Pritchard, M Glover, G Guthrie, J Brum, D Ramsey, G Kappler, P Thomas, S Stuart, D Hull, and P Gowland. Effectiveness of 0.05% oxymetazoline (Vicks Sinex Micromist (R)) nasal spray in the treatment of objective nasal congestion demonstrated to 12 h post-administration by magnetic resonance imaging. *Pulmonary Pharmacology and Therapeutics* 27, 121-126, 2014.

This paper was the first clinical trial using MRI to demonstrate the effect of a nasal decongestant in shrinking inflamed nasal membranes in subjects suffering from colds.

Author contribution- Protocol design following own pilot study (30%), subject recruitment (100%), data acquisition (80%), measurement of nasal morphometry (100%) and data analysis (80%) and reporting (50%).


This paper applied the gas/ liquid manual segmentation for the measurement of gastric emptying.
Author contribution- measurement of gastric emptying for inter-observer comparisons


Author contribution- measurement of gastric emptying using semi-automated method (100%).


This paper used the manual segmentation method for gastric volumes (liquid and air) to compare the effect of a high fat and a high carbohydrate meal. 

Author contribution- Assisted MRI data acquisition (20%), measurement of gastric emptying (100%), data analysis (20%) and reporting (20%).


Author contribution- measurement of small bowel water for inter observer comparison


This paper used the colon volume measurement technique developed in paper1 to stratify response to a laxative challenge in healthy volunteers.

Author contribution- measurement of colon volumes (100%)


Author contribution- measurement of gastric emptying (100%), data analysis (10%) and reporting of results (10%).

Author contribution- measurement of small bowel water (100%), data analysis (30%) and reporting (20%)


Author contribution- measurement of gastric emptying and gas content (50%)


Author contribution- Assisting in MRI data acquisition (20%) and measurement of small bowel water in study 2 (healthy volunteers) (100%)


Author contribution- assisted experimental protocol design, MRI data acquisition (50%) and measurement of gall bladder volume, common bile duct and pancreatic duct diameter and length (100%).


Author contribution- responsible for operation of Respiract™ system used for inducing stable hyperoxia and hypercapnia.
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