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Magnetic tracking of gastrointestinal motility

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Abbreviations

GI = gastrointestinal, HRM = high resolution manometry, MRI = magnetic resonance imaging, MTS-1 = motility tracking system-1, 3D-Transit = Motilis 3D-Transit system, ROM = radio-opaque markers, WMC = wireless motility capsule, DM-1 = type 1 diabetes mellitus

Abstract

Objective: Capsule-based methods for assessment of gastrointestinal (GI) motility have seen great improvements in recent decades. The most recent development is the electromagnetic Motilis 3D-Transit system (3D-Transit). The aim of this paper is to review and discuss the development and technical properties of magnetic tracking of GI motility.

Approach: We performed a comprehensive literature review on magnetic tracking in GI research.

Main results: The Motility Tracking System was the first capsule based magnetic system to be used in GI motility research. However, the potential of the system was hampered by its stationary and hospitalizing nature. This led to the development of the electromagnetic Motilis 3D-Transit system. The 3D-Transit system is a portable system that allows for assessment of both whole gut and regional transit times and contraction patterns in a fully ambulatory setting in the patients' home environment with only minor restrictions on movements. The spatiotemporal resolution of 3D-Transit allows assessment of segmental colonic transit times and permits an analysis of gastric and colonic movements with a degree of detail unrivalled by other ambulatory methods, such as the Wireless Motility Capsule. Recently, robust normative data on 3D-Transit have been published.

Significance: This review provides a current perspective on the use of capsule-based magnetic tracking systems in GI research and how they represent a potentially valuable clinical resource for GI physicians and in GI research.

Introduction

Gastrointestinal (GI) motility is a product of numerous and sophisticated autonomic functions. These include hormonal, muscular, and myoelectrical mechanisms. The interstitial cells of Cajal are responsible for the phasic contractile activity of the GI tract, by spontaneous generation of slow waves that spread throughout the smooth muscle cells of GI wall [1]. Disorders of GI motility, such as gastroparesis, constipation, and the irritable bowel syndrome occur when these critical controlling mechanisms of GI motility may not function properly. They affect up to one-third of the general population, and constitute a significant healthcare and socioeconomic burden and cause substantial decrease in quality of life of those affected [2-4]. GI dysmotility manifests as abdominal pain, nausea, bloating, vomiting, diarrhea, as well as infrequent and incomplete rectal evacuation [5, 6]. Such symptoms are often associated with delayed or accelerated GI transit or uncoordinated peristaltic activity in one or more segments of the GI tract [7, 8].

Motility assessment of the gut is usually performed either by measuring transit times (indices of content flow in the GI tract) or pressure amplitudes and frequencies (indices of GI contractions) [9]. Myoelectrical activity of the GI tract can be measured non-invasively using dense arrays of electrodes like the electrogastrography method for gastric evaluation and high-resolution electrical mapping for the remaining GI tract [10, 11].

Established and emerging methods for evaluation of GI motility are listed in Table 1. Principal methods for the evaluation of motility in the stomach and duodenum are primarily scintigraphic gastric emptying (GE), antroduodenal manometry, and the wireless motility capsule (WMC; SmartPill™, Medtronic, MN, USA) [12, 13]. Principal methods for evaluation of motility in the small intestine and/or colon include antropyloroduodenojunal manometry, hydrogen breath tests, radio-opaque markers (ROM), colonic scintigraphy and colonic manometry [14-18]. All these methods are well established in clinical practice, but all have their recognized limitations (Table 1). For example, the ROM method for assessing whole gut transit lacks standardization, depends on the compliance of the patient, and exposes the subject under study to ionizing radiation. Moreover, it only gives a rough temporal estimate of the transit time through the intestines [19]. Hydrogen breath tests are subject to several sources of error, as small bowel bacterial overgrowth is associated with motility abnormalities and lactulose markedly accelerates transit of the small intestine [9, 20]. Scintigraphy is expensive, time-consuming, involves exposure to radiation, and is restricted to specialized centers [21]. More importantly, these methods only provide snapshots of GI transit rather than single continuous measurements [9]. High resolution manometry (HRM) provides continuous recording of GI pressure waves within a specific region of the GI tract, usually the esophagus, antroduodenal region, or the distal colon and rectum. HRM, however, is invasive, time-consuming, and require specialized centers because of high technical requirements [9].

Magnetic resonance imaging (MRI) is an emerging technique for assessment of small intestinal [22] and colonic [23] contractions as well as orocecal and whole-gut transit times [24]. Unfortunately, MRI is costly and does not allow for ambulatory evaluation.

The purpose of this topical review is to outline the current use of magnetic tracking in GI research. Accordingly, we conducted a comprehensive search (March 1st 2020) in PubMed for the years 1980–2020 using the following search terms: ‘‘gastrointestinal motility method”, “3D transit”, “magnetic tracking”, and “motility tracking system”. Only papers written in English were included. Reference lists in the papers were read for any missed papers in the search.

— Table 1 near here —

Historical perspective of magnetic tracking in gastrointestinal motility research

Early studies from the 1990’s have used magnetic markers as a non-invasive tool for tracking of movements within the GI tract. Weitschies et al. used the seven channel DC superconducting quantum interference device (Biomagnetic Technologies Inc., San Diego, USA), which consisted of multiple highly sensitive magnetic sensors. The system used magnetically marked pellets enclosed in a cylindrical silicone capsule. The device proved itself accurate, but required a shielded environment and was heavily expensive [25, 26].

The MTS-1 was first described in 2005 by Stathopoulos et al., who demonstrated it possible to obtain a 3D configuration of the gut and dynamics of the magnet displacement (velocity, transit time, length estimation, rhythms) [27]. Hence, the MTS-1 was a promising tool in gastroenterological research. However, it was severely limited by its stationary nature that confined the subject to stay still in a specially designed bed during the entire investigation.

This led to the development of an ambulatory system, 3D-Transit. Though sharing many principal characteristics with MTS-1, 3D-Transit is fundamentally different as it replaces the permanent magnet in the capsule with an electromagnetic transmitter system. 3D-Transit was first described in 2014 by Haase et al., who proved the system feasible in healthy subjects and correlating well with whole gut transit times assessed by ROM [28].

Capsule-based technologies for assessment of gastrointestinal motility

Over recent decades, there has been a growing interest in capsule-based technologies providing information on whole-gut and regional GI transit times through the tracking of one or more capsules during

their passage through the GI tract. Such methods may be useful in clinical settings for diagnostic evaluation and management of unexplained GI symptoms or when a generalized or multiregional motility disorder is suspected. Furthermore, they can provide valuable insights into normal and pathological GI physiology [7].

The WMC system is the most used and currently the only commercial available capsule-based system for evaluation of GI motility [29]. It features an ingestible capsule that measures pressure, pH, and temperature as it passes through gut. The WMC system is considered the method of choice in situations where multiregional or whole gut motility disorders are suspected as it allows for ambulatory assessment of gastric emptying, small intestinal transit time, colorectal transit time, and whole gut transit time [30-33]. The location of the WMC is primarily determined by stereotypical changes in pH at the pylorus and ileocecal junctions as well as temperature change (drop on expulsion from the body). This enables an assessment of regional gut function (stomach, small bowel, large bowel), but more precise measurement is limited as the capsule location *within* each GI region is unknown at any time point. Accordingly, detailed information on segmental colonic transit is, for example, not available [29, 34].

The PillCam (Pillcam SB video capsule; Given Imaging, Yokneam, Israel) is an endoscopic capsule system, normally used to diagnose intraluminal epithelial diseases in the small bowel. By means of a computerized endoluminal image analysis of the small bowel, the system allows for detection of wall dynamics and movement of content, and thus provides a noninvasive, simple procedure for automatic identification of intestinal motor dysfunction. Accordingly, the system can automatically discriminate between hypodynamic and hyperdynamic motor disorders, displaying a higher sensitivity than manometry [35-37]. However, the system is currently restricted to research and does not provide any data on GI transit, as with manometry.

The original motility tracking system-1 (MTS-1, MTS Record, Motilis, Lausanne, Switzerland) was developed to allow for detailed spatiotemporal tracking during passage through the GI tract. It consists of a small magnet (Ø 6 x 15 mm, weight 0.9 g) which is continuously tracked by a stationary detector [27]. The system has been validated and used in several studies to assess GI motility in patients with liver cirrhosis and portal hypertension, cystic fibrosis, neuroendocrine tumors, spinal cord injuries, and systemic sclerosis [38-42]. The major shortcoming of the method is its non-ambulatory nature, requiring the subject under study to be immobile during recordings. The system was last used in a clinical study in 2014 [43] and has been replaced by the newer 3D-transit system (3D-Transit, Motilis Medica SA, Lausanne, Switzerland).

3D-Transit is a completely ambulatory, non-invasive tool to assess both whole-gut and regional transit times as well as movement patterns within the GI tract. Using a body-worn detection matrix, the system simultaneously tracks the precise position and general orientation of up to three electromagnetic capsules

from ingestion to expulsion. Given its ambulatory nature and the electromagnetic technology, it is possible to perform the examination in the home environment, under near-normal physiological conditions [28].

General principles of MTS-1 and 3D-Transit

During recording, an iterative algorithm in the software converts the electromagnetic field into five spatiotemporal coordinates displayed on the computer: three position coordinates (x, y, z) and two angle coordinates (θ, φ) (Figure 1B). The x, y, and z represent the three-dimensional spatial position, thus being a reflection of GI transit time between two anatomical positions. The θ and φ represent orientation coordinates with respect to the four sensors in the detector, thus being a surrogate measure of contraction frequency. Using the dedicated software, all movements of each capsule are converted into detailed scalar and vectoral representations. Velocity of movements and orientation of the capsules reflect progression dynamics of the luminal content in the GI tract. Changes in position angles reflect contractile activity in the GI tract [27, 44, 45].

Assessment of regional gastrointestinal motility requires easy interpretation of specific anatomical landmarks. Hence, four landmarks must be recognized: 1) ingestion, 2) pyloric passage, 3) ileocecal passage, and 4) the exit of the capsule. Recognition is carried out by examination of the 2D-plot alongside detection of changes in contraction frequencies (Figure 1B).

Whole gut transit time is defined as the time between capsule ingestion and it being expelled from the body. The latter is confirmed by a centered vertical drop followed by a signal loss from the capsule. The signal loss is due to the capsule having exited the body and thus exceeding the maximum distance to the detector required for connection. This corresponds with time of a bowel movement noted in a diary kept by the subject under study. Gastric emptying time is defined as the time from ingestion of the capsule until pyloric passage. Small intestinal transit time is defined as time from the pyloric passage until ileocecal passage.

Pyloric passage is characterized by cessation of the 3 min^{-1} contraction frequency typical for the stomach [46], the appearance of the duodenal arch, and the beginning of 8-11 contractions min^{-1} typical for the proximal small intestine [47]. Similarly, ileocecal passage is characterized by change from a 6 min^{-1} contraction frequency typical for the distal ileum to a 3 min^{-1} typical for the colon [48, 49], and the occurrence of a short fast movement in the lower right quadrant [45].

Contractility patterns in the stomach are analyzed with specialized Motilis software (MTS Tool, Motilis, Lausanne, Switzerland). Mean contraction frequencies in the stomach can be calculated using the rotations of the capsule. Frequency peaks are identified using a convolution of the fast Fourier transforms with the "shape of a peak" described by a Gaussian function is applied. To avoid a Doppler effect whereby

contraction frequencies intensify due to higher velocities of the magnet, only frequencies obtained during stagnation of the magnet are used [45].

Data are analyzed on a computer running customized software (MTS Record, Motilis, Lausanne, Switzerland) showing a real-time position and orientation of the magnetic capsule. Both systems accommodate for artifacts introduced by respiration and movements by use of accelerometers and respiratory belts. These measures are subsequently filtered out during the post-processing of the data [27, 44, 45]. It should be noticed that both the recording and analysis methods of 3D-Transit are still under development and there are progressive improvements underway regarding both software and hardware.

— Figure 1 near here —

Motility Tracking System 1 (MTS-1)

Technical properties of MTS-1

MTS-1 consisted of a magnetic capsule, a detection matrix, and dedicated computer software. The capsule measured Ø 6 x 15 mm, weighed 0.9 g and contained a permanent cylindrical magnet with a composite density of 1.8 g cm^{-3}. The detection matrix consisted of 4 x 4 magnetic field sensors separated by 5 cm and placed in front of the abdomen with the umbilicus as an anatomical landmark. The system was stationary and thus confined the subject under study to stay in a specially designed wooden bed during investigations. Before starting measurements, the matrix was calibrated by off-setting the earth's magnetic field [45].

Use of MTS-1 in research

The use of MTS-1 was identified in 11 studies over an 9-year period (2005–2014) as listed in Table 2. The first clinical study was carried out in 2009 by Hiroz et al., who used the system to track colonic motility in healthy subjects [44]. A validation of pyloric and ileocecal passage was later carried out in 2011 by gluing the magnet to a PillCam (PillCam, Given, Yoqnaem, Israel). This showed that the MTS-1 was a reliable and precise tool to determine pyloric and ileocecal passages. Furthermore, mean contraction frequencies of 2.85 (± SD 0.29) min^{-1} in the stomach and 9.90 (± SD 0.14) min^{-1} in the small intestine corresponded well to those published with other methods [45].

Worsøe et al. used the MTS-1 to examine potential effects of sacral nerve stimulation on gastric and small intestinal motility in patients with fecal incontinence [50]. The study followed a randomized double-blind crossover design with patients being assigned to either a week with or without sacral nerve stimulation, followed by an investigation with MTS-1. This led to the finding that turning off sacral nerve stimulation does not have any measured effects on gastric or small intestinal motility patterns. Using a

similar crossover design in patients with irritable bowel syndrome, Fassov et al. also found no effects of sacral nerve stimulation on gastric emptying and small intestinal transit time [43].

Fynne et al. used MTS-1 to determine orocecal transit time and gastric emptying in patients with neurogenic bowel problems due to spinal cord injury [40]. Importantly, patients had a significantly prolonged upper GI transit time, whatever the spinal cord injury being high or low ($p < 0.01$). Hedsund et al. described GI motility in patients with cystic fibrosis. Contraction frequencies of the stomach and small intestine were normal, but the magnet reached the cecum after 7 hours in only 20% of patients as compared to 88% of controls [41]. This can be explained by the distal obstruction syndrome, with stasis in the distal small intestine due to excessively low viscosity of mucus in cystic fibrosis [41].

Karlsen et al. examined patients with moderately severe liver cirrhosis and portal hypertension [38]. Previous studies in these patients had used ROM or lactulose breath tests, the latter which is limited to investigation of orocecal transit times. The use of MTS-1 thus permitted the authors to distinguish between gastric emptying and small intestinal transit time, detecting no difference in gastric emptying, but surprisingly a significantly faster transit through the proximal small intestine in cirrhotic patients than in healthy controls [38]. In another study with MTS-1, Gregersen et al. found similar faster transit times of the small intestine in patients with neuroendocrine tumors [39]. Contrary to these findings, Fynne et al. found patients with systemic sclerosis (SSc) to have a significantly reduced transit time through the proximal small intestine [42].

Clinicians in pediatric gastroenterology face diagnostic difficulties as conventional methods like ROM, scintigraphy, and PillCam™ involve radiation or the discomfort of swallowing a large pill (11 x 26 mm). Therefore, Hedsund et al. trialed the used of the smaller MTS-1 capsule (6 x 15 mm) in healthy children aged 7-12. Despite having the inherent restriction of being non-ambulatory, the MTS-1 allowed minimally invasive evaluation of GI motility in children [51].

— Table 2 near here —

3D-Transit electromagnetic capsule system (3D-Transit)

Technical properties of 3D-Transit

3D-Transit consists of a wireless electronic capsule for ingestion, an extracorporeal portable detector containing four sensors, and a computer with display and analysis software (Figure 1). The capsule emits a magnetic field modulated at a given low frequency, which allows to filter out the earth's magnetic field and background noise from the surroundings. This feature enables 3D-Transit to be a portable system assessing

both whole gut and regional transit times and contraction patterns in a fully ambulatory setting in the patients' home environment with only minor restrictions on movements.

Each capsule measures 21.5 mm x 8.3 mm with a density of 1.6 g/cm^2. Capsules emit a signal with a sampling rate of 10 Hz or 5 Hz. Recording at 10 Hz will in theory make it easier to distinguish capsule movement from signal noise. However, all "real" movements are easily shown even at 5 Hz, which is more than enough to calculate movement velocity and movement distances. The lifetime of the battery within the capsule is approximately 48 hours with a sampling rate at 10 Hz. Adjusting the sampling rate to 5 Hz will double the lifetime of the battery to approximately 96 hours. The increased recording duration at 5 Hz outweighs the potential lower signal/noise-ratio when studying subjects with suspected long GI transit times, e.g. patients with constipation. Most of the studies using 3D-Transit have recorded with a sampling rate of 5 Hz.

Capsules are synchronized, hence they have no interference with each other. This enables the system to simultaneously record up to three capsules without any interference impediments, even if residing in the same part of the GI tract [28]. By the use of wireless Bluetooth communication, the movements and changes in orientation can be monitored in real time on a computer while also being stored on a memory card within the detector. At the end of the investigation, data are downloaded to the computer. These are then analyzed and used to determine total and regional gastrointestinal transit times and contractile patterns by the use of dedicated software (3D-Transit, Motilis, Lausanne, Switzerland).

The detector has an inbuilt accelerometer for identification of posture changes and body movement artifacts. Likewise, a thoracic belt registers breathing movements. This is particularly convenient during analysis of data from the small intestine where slow wave contractile frequency (9 min^{-1}) is close to breathing frequency. Both are also stored on the memory card and can be monitored in real time.

Due to electromagnetic noise from the surrounding environment possibly affecting the wireless connection between the capsule and the detector, the minimal distance allowable from external electronic devices (e.g. old computers with spinning magnetic hard drives) is approximately 40 cm. There are no restrictions regarding cell phones or tablets as these do not interfere with the connection. To gain reliable data, the detector should be worn continuously throughout the study and only be removed briefly, e.g. when a shower is needed [28].

Data analysis of 3D-Transit

The 3D-Transit software contains an *overview* function which depicts the full recording with shifts in contraction frequencies plotted against time (time-frequency plot), thus aiding the analysis (Figure 1A). A recent refinement of 3D-Transit data analysis now enables a much more detailed computation of transit

times through four segments of the colorectum. This is done by assessing six distinct anatomical landmarks in the colon: (i) start of the colon, (ii) hepatic flexure, (iii) midpoint of the transverse segment, (iv) splenic flexure, (v) end of the descending colon, and (vi) end of the rectum. The 3-dimensional position data can be visualized after down sampling the data from 5-10 datapoints per second using an algorithm that plots data points when the capsule moves 5 mm within a 3 minutes period (see Figure 2B). Due to the threshold set by the 5 mm distance, the plotting algorithm enables visualization of time points of slow movement and fast movement without showing much non-movement data.

This enables investigators to define transit through six colonic segments: 1) Caecum/ascending colon, 2) transverse colon, 3) descending colon, 4) rectosigmoid colon, 5) total right colon, and 6) total left colon (see Figure 2) [52]. Further, because 3D-Transit allows for highly detailed tracking of the capsules through the entire colon, the system can detect capsule movements that through post-processing can be classified according to movement length, velocity, and direction [53]. The capsule movement through the colon was analyzed using an estimated 'centerline' of capsule progression on to which all capsule position data points were projected [54]. Antegrade and retrograde activity was then analyzed and classified according to thresholds proposed by Hiroz et al. and from analysis of the data distribution of capsule velocity and displacement length in recordings of healthy volunteers [44]. Colonic motility was classified as five specific movement patterns (see Table 3) [53].

No data has been reported on the time-consuming aspect of data analysis. However, from our group's experience, analysis of regional transit times takes approx. 30 minutes while segmental colonic transit times requires approximately 2 hours.

— Table 3 near here —

— Figure 2 near here —

Use of 3D-Transit in research

Fifteen studies were identified using the 3D-Transit over a six-year period (2014–2020), as listed in Table 5. In healthy volunteer studies, use of the 3D-Transit capsule has provided normative values for region-specific gastric, small intestinal, and segmental colonic GI transit times [52, 55]. In volunteer and patient studies, the system has provided detailed information on colonic motility not available by any other ambulatory method [53, 56-58]. In clinical studies, the 3D-Transit system has been used to investigate transit times and movement patterns in patient groups including those with severe ulcerative colitis, Parkinson's disease, idiopathic gastroparesis, diabetes mellitus, and carcinoid diarrhea [55, 57, 59-61].

Further, the system has shown itself valuable to evaluate the effects of different medications on the GI tract [56, 58, 62-64].

— Table 5 near here —

Normative values

Based on recordings from 132 healthy subjects, Sutter et al. established normative data for gastric motility assessed with 3D-Transit [55]. The median gastric emptying time (GET) was 2.7 hours, reproducing previous results found with WMC (3.2 hours) [65]. Gastric contractions were detectable for a median of 92% of the time. Their median frequency was 3.1 min^{-1} which corresponds very well to those described by electrogastrography and antroduodenal manometry [66]. A representative examination of capsule progression through the stomach is shown in Figure 3.

— Figure 3 near here —

Haase et al. assessed GI motility during sleep monitored by polysomnography and found that the amplitude of gastric contractions decreased with the depth of sleep (light sleep versus deep sleep). Moreover, basal colonic activity decreased significantly across sleep stages and was significantly less during deep sleep and light sleep compared with wake periods [58].

In 2019, Nandhra et al. used 3D-Transit to establish normative values for total and region-specific GI and segmental colonic transit times [52]. Recordings were pooled from nine previously published clinical studies carried out between 2012 and 2017, totaling 111 healthy adults [28, 53, 59-61, 63, 64, 67, 68]. They found median transit times as presented in Table 4.

These correlate well with those found by Wang et al. using WMC [65]. Nandhra et al. also analyzed for influence of gender, age, and BMI. Increasing age was significantly associated with longer colonic transit time and whole gut transit time while increasing BMI was associated with longer whole gut transit time [52]. Female gender was associated with longer transverse and descending colonic transit time but shorter rectosigmoid colonic transit time. The authors found good to excellent inter- and intra-rater reliability of the segmental colonic transit times [52].

Whole gut and colorectal transit times were found to cluster in groups separated by approximately 24 hours. Notably, most capsules (38%) were expelled between 06:00 and 08:00, regardless of the group. Furthermore, capsules ingested in the evening trended towards a longer colorectal transit time than capsules ingested in the morning [28, 53]. This reflects that whole gut transit time (and colonic transit time)

is dependent on morning defecation habits as commonly seen in healthy individuals [65]. It also supports the knowledge of the non-continuous nature of GI transit [52]. Additionally, Kalsi et al. demonstrated that inter-rater and intra-rater reliability was high to excellent when performed by experienced raters whereas inexperienced raters had low to fair reliability [69]. This emphasizes that differences in transit times are caused by biological variations rather than methodological issues and that raters must be adequately trained.

In the recent years, there has been an improvement in the 3D-Transit software algorithm, based on the analytical software for the stationary MTS-1. Besides detailed segmental colonic transit times, the software now enables detailed analyses of colonic movement patterns [44, 53]. Hence, Mark et al. reanalyzed recordings on healthy subjects from three previous studies and published their results in a comprehensive series of papers on colonic motility [28, 44, 53, 59, 64]. They found that capsule movement velocities varied greatly, ranging from 180 cm min^{-1} (antegrade displacement) to -180 cm min^{-1} (retrograde displacement), and peaked in three groups: fast antegrade (50 cm min^{-1}), slow antegrade (0.5 cm min^{-1}), and slow retrograde (-0.5 cm min^{-1}). Moreover, Interestingly, recordings with comparable colorectal transit times could represent highly variable types of capsule progression through the various segments (Figure 4) [53].

A recent cine-MRI study also reported quantitative data of antegrade and retrograde contraction velocities, although they observed more retrograde activity using their novel imaging approach [70].

— Figure near 4 here —

3D-Transit studies in patients

Gregersen et al. were the first to use 3D-Transit in a group of patients suffering from bowel dysmotility [59]. In patients with carcinoid diarrhea due to neuroendocrine tumors, the authors found the median whole gut transit time to be about 50% that of healthy subjects while small intestinal transit time was 86.4% of normal and median colonic transit time only 29% of normal. Corresponding to this, patients with carcinoid diarrhea had significantly more long fast antegrade colonic movements and their antegrade colonic movements covered twice the distance observed among healthy subjects [53, 59].

In patients with diarrhea caused by severe ulcerative colitis, Haase et al. surprisingly found a prolonged median whole gut transit time of 44.5 hours compared to 27.6 hours in healthy subjects [60]. This was mainly due to extended transit through the right side of the colon. Likewise, there was a strong trend towards a prolonged transit in the small intestine. The conclusion drawn from this study was that severe inflammation of the distal colon inhibits motility in more proximal segments of the gut [60].

Klinge et al. investigated patients with type 1 diabetes mellitus (DM-1) and symptoms of enteric neuropathy [57]. They found the median whole gut transit time to be more than twice longer in patients with DM-1 (72.3 hours) as compared to healthy controls (28.9 hours). Total colonic transit time was increased by 235%, mainly due to prolongations of transit through the right colon. This was mainly caused by an increased number of slow retrograde movements observed in the colon of patients [57].

In patients with Parkinson's disease, Knudsen et al. found prolonged transit time of the proximal colon, allied to a reduction in fast antegrade movements. Patients also displayed significantly longer small intestinal transit times, while no difference was seen in gastric emptying time [61].

3D-Transit in pharmacological studies

A common side-effect of opioid use is constipation. Four studies have assessed gastrointestinal aspects of opioid treatment in healthy volunteers using 3D-Transit [56, 62-64].

Poulsen et al. compared the impact of opioids on regional GI transit in a double-blind, crossover trial with healthy subjects assigned to either oxycodone or placebo for five days. They found significantly prolonged cecum-ascending, rectosigmoid, and total colonic transit times [64]. Mark et al. subsequently found a significant reduction in long fast antegrade movements and an increase in slow antegrade movements in the oxycodone group. Finally, the oxycodone group had a significantly decreased capsule movement velocity compared with the placebo group [56].

Olesen et al. examined the alleviating effects of the peripherally-acting opioid antagonist naloxegol on oxycodone-induced constipation [62]. Naloxegol significantly reduced colonic transit time by 23% compared to placebo. Of segmental colonic transit times, only rectosigmoid colonic transit time was significantly reduced compared to placebo [62]. Like the study by Poulsen et al., data were further processed, and it was found that naloxegol decreased the number of slow antegrade movements. Fast antegrade movements were also of a longer distance in the naloxegol group than in the placebo group [56].

Mark et al. suggests that increased transit times during opioid treatment can be attributed to a decrease in long fast movements, despite an increase in the number of slow antegrade movements [56]

Finally, Poulsen et al. compared the effects of slow-release naloxone and the osmotically acting laxative macrogol 3350 (both administered with slow-release oxycodone to induce bowel dysfunction) in a randomized, double-blind, crossover trial. Both drugs seem to have comparable effects on GI transit as no difference was found in regional GI transit times nor segmental colonic transit times [63].

The 3D-Transit motility measurements have been shown to detect motility disturbances induced by pharmacological interventions, however the clinical value of such information of motility patterns may be difficult to understand as of now. Additional studies in relevant patient groups may find interesting

associations between clinical parameters and the number, distance or velocity of different motility patterns.

Challenges and limitations of 3D-Transit

Assessing gastrointestinal motility with electromagnetic capsule-based methods, such as the 3D-Transit system, is challenging due to data loss, manual analysis, lack of availability, and the non-direct measurement of GI contractions. Data loss has been reported in between 13.3% and 21% of recordings [52, 53], mainly due to loss of transmission signal and poor recording quality. This issue may be circumvented to an extent if subjects under study are urged to reduce their physical activity during recording, though true, inactivity may itself impact motility of the gut.

Manual analysis of the 3D-Transit recordings is a limitation, especially if performed by inexperienced investigators [69]. However, when performed by adequately or highly trained investigators the system has shown excellent intra-rater and inter-rater reliability [52]. Furthermore, manual extraction of data from each recording is heavily time-consuming. Both drawbacks inform the need for automatization of the system to ensure consistency and to improve the speed of processing.

Another obvious limitation to the 3D-Transit system is its lack of approval from the US Food and Drug Administration and the European Union through CE-marking. 3D-Transit is thus currently restricted to use in research facilities and is not commercially available.

Finally, a limitation inherent to all telemetric capsule systems, is the lack of information at segments where the capsule is not present, which means that assessment of contractions is only carried out at the exact location of the capsule(s) and important information may be missed. Additionally, the 3D-Transit system does not directly measure the pressure amplitude of contractions. Both of these limitations are overcome by HRM, where changes in pressure in each centimeter of the colon are directly measured, though clearly HRM is a much more invasive method [71]. A validation study comparing 3D-Transit and HRM must be done to directly associate motor patterns recorded with the 3D-Transit system.

Future perspectives

Electromagnetic tracking of GI motility shows great promise as a future clinical diagnostic tool. 3D-Transit is the only available tool to provide simultaneous assessment of GI transit and movement patterns, and thus aid in characterizing and diagnosing GI diseases and the effects of treatment. Another potential advantage of capsule-based magnetic tracking is its ability to potentially determine the velocity at which medication

reach a specific segment of the GI tract, although further studies are needed to compare size and composition of the pills and the 3D-Transit capsule.

3D-Transit also holds promising potentials for pediatric gastroenterology as a minimally invasive procedure. As described, a previous study has applied the MTS-1 system in healthy children, but studies validating the use of 3D-Transit in the pediatric population are warranted.

Conclusions

3D-Transit shares similarities with the wireless motility capsule (WMC) as they are both capsule-based, ambulatory, and minimally invasive. Both methods enable assessment of regional transit times throughout the gut, which is essential as most motility disorders affect more than a single region of the GI tract. The 3D-Transit system, however, differs in two essential ways. Its spatiotemporal resolution allows assessment of segmental colonic transit times. Moreover, the 3D-Transit system permits an analysis of gastric and colonic movements with a degree of detail unrivalled by other ambulatory methods. Recently, robust normative data have been published. The system still holds notable limitations. It is neither CE approved nor generally commercially available. Data analysis need further improvement and automatization before the system can be widely adopted in clinical practice.

Legends for illustrations

Figure 1: Motilis 3D-Transit system

The 3D-Transit system. A) Overview function: The frequency of contractions helps determine pyloric and ileocecal passages by changes in gastrointestinal contraction frequency. Pyloric passage is found around the increase from 3 to 9–12 contractions min^{-1}, and ileocecal passage is found around the decline from approximately 6 to 3 contractions min^{-1}. B) 3D-Transit recording of a single capsule as seen in dedicated 3D-Transit software. Pyloric passage of electromagnetic capsule (yellow line). The position (x, y, z) and orientation (θ, φ) of the capsule are displayed. The 2D-plot (x, y) in the upper left corner displays movement through the duodenal arch and is monitored and verified with respect to changes in trajectory and loss of three contractions min^{-1} (arrows) characteristic of gastric motility.

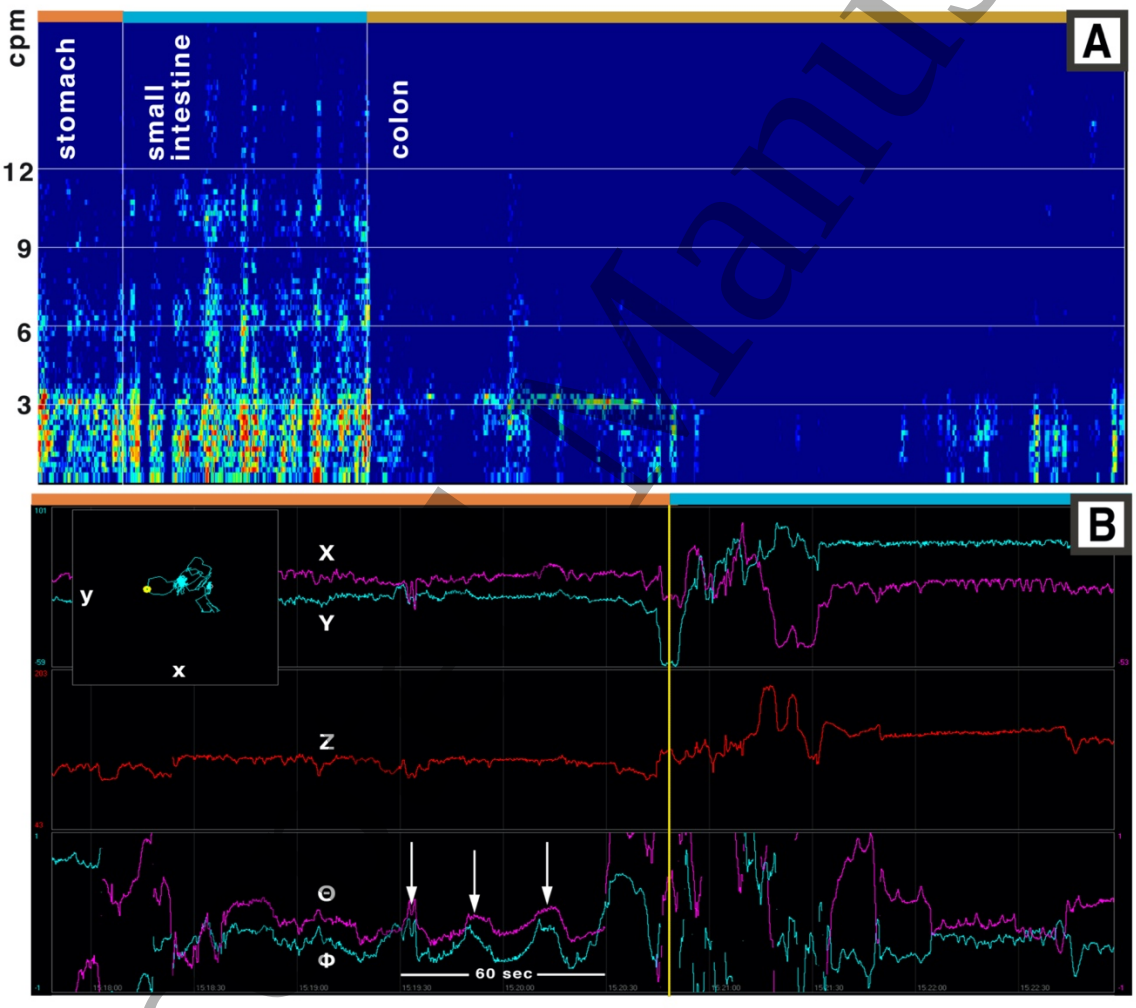

Figure 2: Colonic anatomy and landmarks.

Graphical overview of colonic anatomy and the colonic progression of a 3D-transit capsule. A) Colonic anatomy with segments and six distinct anatomical landmarks marked according to the 3D-Transit analysis: (I) Ileo-cecal passage, (II) hepatic flexure, (III) midpoint of the transverse colon, (IV) splenic flexure, (V) end of the descending colon, and (VI) distal end of the rectum. B) Graphical presentation of processed colonic data from a healthy male. Arabic numerals specify location of the capsule in relation to hours spent in the colon.

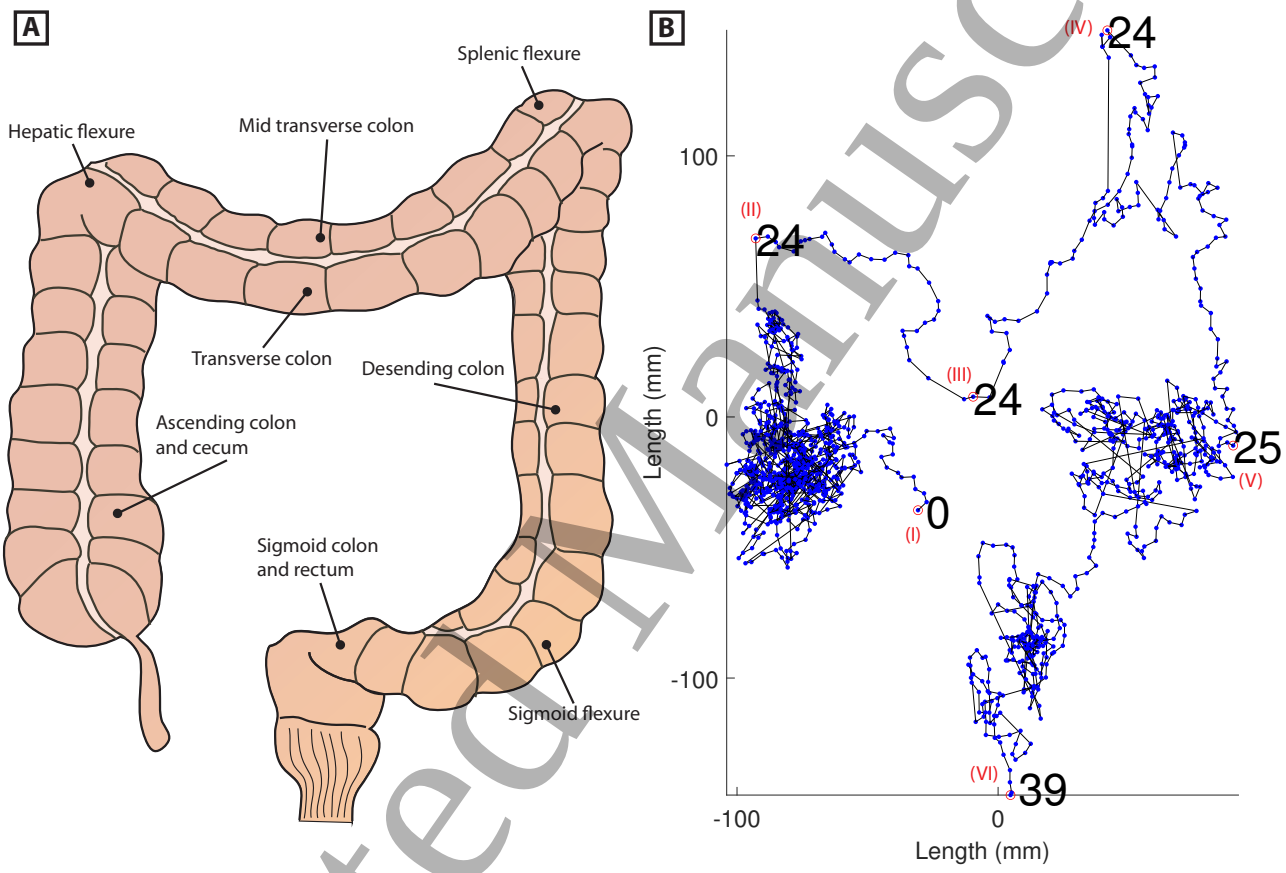

Figure 3: Gastric emptying time

3D-Transit recording from a healthy subject displayed in two projections. The capsule mostly resided in the antrum of the stomach. Position of the capsule at 20-min intervals is marked with Arabic numerals, connected by the dashed blue line.

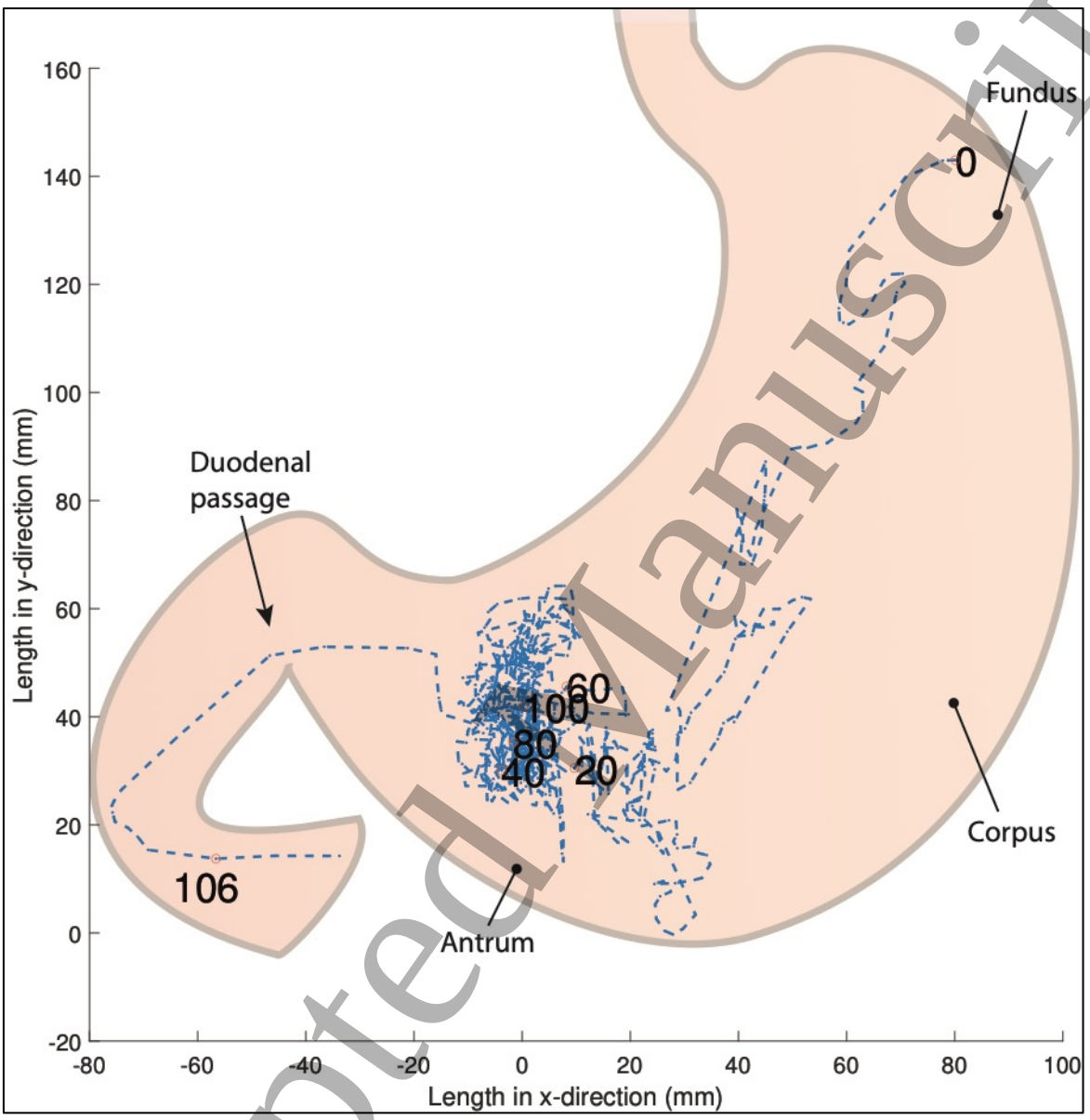

Figure 4: Progression through the colon

Three types of colonic progression patterns recorded with the 3D-Transit system. Anatomical position in colon is represented by the distance in cm from cecum to the rectum (*Y*-axis) plotted against time in hours spent in the colon (*X*-axis). Analysis of progression patterns are divided into fast progression (red), slow progression (blue), and very slow/no progression (black). A) Typical example of recording in a healthy young male with a normal progression pattern and a total colonic transit of just below 20 hours. B) Representative sample of recording in a patient with diarrhea demonstrating a fast progression pattern and a total colonic transit time below 6 hours. Two long fast antegrade movements accounts for approx. 40-50 cm, respectively. C) Recording from a representative male with opioid-induced constipation demonstrating a slow progression pattern during the first 90 hours and a long fast antegrade movement for the last 50 cm. Total colonic transit time was approx. 70 hours.

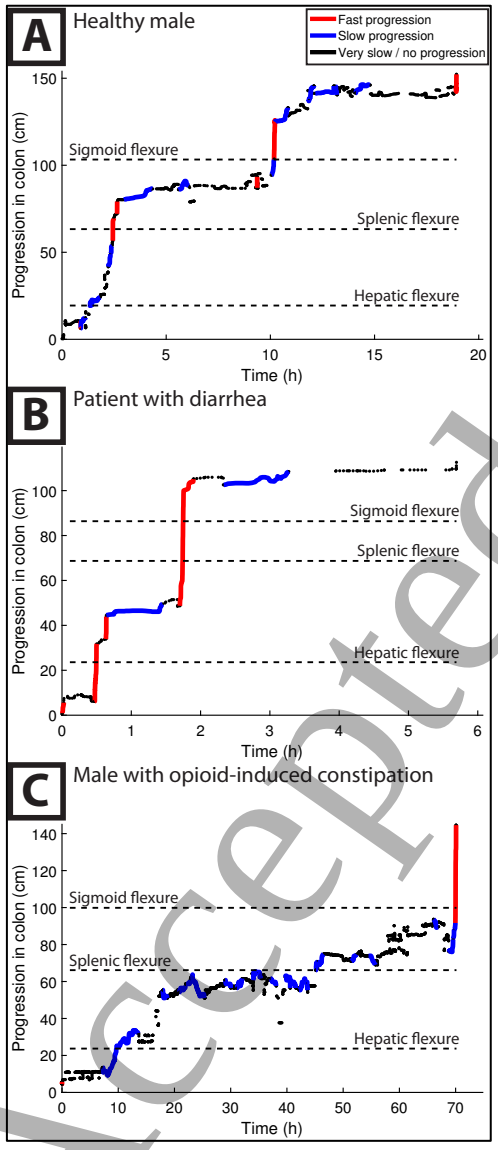

Table 1: Established and emerging methods to assess gastrointestinal motility

Advantages and disadvantages of established and emerging methods to assess gastrointestinal motility.

Table 1: Established and emerging methods to assess gastrointestinal motility				
	Method	**Measurement in the gastrointestinal tract**	**Advantages**	**Disadvantages**
Established	Standard radio-opaque markers (ROM)	Whole gut transit times Segmental colonic transit times (derived)	Minimally invasive Inexpensive Poorly standardized Easy interpretation of data	No direct information on colonic transit time Intake of markers depends on the compliance of the patient
	Scintigraphy	Gastric emptying time Small intestinal transit time Colonic transit time	Minimally invasive High reliability	Subject irradiation Time consuming Difficult data analysis Expensive Limited to specialized centers
	Antroduodenal manometry	Motility patterns in stomach and duodenum	High reliability Radiation free	Invasive Lacks standardization Time consuming Limited to specialized centers
	High-resolution manometry (HRM)	Motility patterns in esophagus, stomach, duodenum, and colon	Radiation free High resolution assessment of motility	Invasive Expensive Difficult data analysis Bowel preparation (colon)
	Wireless motility capsule (SmartPill)	Whole gut and regional transit times	Minimally invasive High standardization Easy to perform Robust normative data Radiation free Ambulatory	No information on segmental colonic transit times
	Hydrogen breath test	Orocecal transit times	Non-invasive High standardization Inexpensive Radiation free	Confounding pitfalls Does not distinguish between gastric emptying and small intestinal transit
Emerging	MRI motility assessments	Whole gut and regional transit times Colonic and small intestinal motility patterns	Non-invasive No radiation exposure	No standardization Expensive Difficult data analysis
	Endoluminal image analysis	Motility patterns in the small bowel	Non-invasive Operator-independent High sensitivity	No information on GI transit times Restricted to research Requires further validation
	3D-Transit system	Whole gut and regional transit times Segmental colonic transit times Motility patterns in the stomach and colon	Minimally invasive Radiation free Ambulatory Provides both motility and transit data under near normal physiological conditions Robust normative data	No standardization Difficult data analysis Not commercially available

Table 2: Previous studies with MTS-1

List of studies using the motility tracking system (MTS-1) and their main findings. Abbreviations: GI, gastrointestinal; GE, gastric emptying; SITT, small intestinal transit time; CTT, colonic transit time.

Table 2: Previous studies with MTS-1		
Author (year)	**Subjects investigated (n)**	**Main findings**
Stathopoulos et al. (2005) [27]	Healthy subjects (n=10)	MTS-1 proved feasible in healthy subjects
Hiroz et al. (2009) [44]	Healthy subjects (n=20)	MTS-1 allowed detailed tracking of capsule movements within the colon
Worsøe et al. (2011) [45]	Healthy subjects (n=8)	MTS-1 was validated against PillCam.
Worsøe et al. (2012) [50]	Patients with fecal incontinence (n=8)	No effects of sacral nerve stimulation on GE and SITT
Fassov et al. (2014) [43]	Patients with irritable bowel syndrome (n=20)	No effects of sacral nerve stimulation on GE or SITT
Fynne et al. (2012) [40]	Patients with neurogenic bowel problems due to spinal cord injury (n=19) Healthy controls (n=15)	Patients with spinal cord injury had prolonged GE Basic contraction frequencies of the stomach and small intestine were unaffected by spinal cord injury
Hedsund et al. (2012) [41]	Patients with pancreatic insufficiency caused by cystic fibrosis (n=10) Healthy controls (n=16)	Patients with cystic fibrosis had distal obstruction syndrome in the small intestine
Karlsen et al. (2012) [38]	Patients with bowel problems due to liver cirrhosis and portal hypertension (n=15) Healthy controls (n=18)	Patients with moderate cirrhosis had faster than normal transit through the proximal small intestine
Fynne et al. (2011) [42]	Patients with systemic sclerosis (n= 15) Healthy controls (n=17)	Patients with systemic sclerosis had prolonged SITT
Gregersen et al. (2011) [39]	Patients with carcinoid syndrome due to neuroendocrine tumors (n=12) Healthy controls (n=12)	Patients with carcinoid syndrome had faster than normal SITT and WGTT
Hedsund et al. (2013) [51]	Healthy children (n=21)	Regional contraction frequencies and transit times in healthy children were determined and corresponded well to those previously observed in adults

Table 3: Colonic motility movement patterns

Colonic motility classified from the five predominant types of movement patterns [53].

Table 3: Colonic motility movement patterns		
Colonic movement	**Distance**	**Velocity**
Long fast antegrade	> 10 cm	> 10 cm min^{-1}
Fast antegrade	4–10 cm	> 4 cm min^{-1}
Slow antegrade	> 4 cm	< 4 cm min^{-1} > 4 cm h^{-1}
Slow retrograde	< 4 cm	< 4 cm min^{-1} > 4 cm h^{-1}
Fast retrograde	< 4 cm	> 4 cm min^{-1}

Table 4: Normative values for gastrointestinal transit times assessed with 3D-Transit

Normative values for total and region-specific gastrointestinal transit times, based on 111 healthy adults [52].

Table 4: Normative values for gastrointestinal transit times assessed with 3D-Transit		
Gastrointestinal region	**Transit time (hours:min)**	**95% CI (hours:min)**
Gastric emptying time	2:41	2:29–3:06
Small intestinal transit time	4:47	4:20–5:06
Colonic transit time	21:06	18:39–23:54
Whole gut transit time	28:52	25:37–30:48

Table 5: Previous studies with 3D-Transit

List of studies using the Motilis 3D-Transit system and their main findings. Abbreviations: GI; gastrointestinal, GE, gastric emptying; WGTT, whole gut transit time, SITT, small intestinal transit time; CTT, colonic transit time; CATT, caecum ascending transit time; DM-1, type 1 diabetes mellitus.

Table 5: Studies using the 3D-Transit system

	Author (year)	Subjects investigated (n)	Main findings
Studies with healthy subjects	Haase et al. (2014) [28]	Healthy subjects (n=20)	3D-Transit proved feasible in healthy subjects. Good correlation of WGTT assessment between 3D-Transit and ROM
	Mark et al. (2017) [67]	Healthy subjects - 3D-Transit + MRI (n=25) - 3D-Transit x 2 (n=21)	3D-Transit proved accurate determination of colorectal length compared with MRI and between days
	Kalsi et al. (2018) [69]	Healthy subjects (n=36)	Rating of 3D-Transit recordings require adequate training
	Nandhra et al. (2019) [52]	Healthy subjects (n=111)	3D-transit used to establish normative reference values for region specific GITT and CTT
	Sutter et al. (2020) [55]	Healthy subjects (n=132)	3D-transit used to establish normative reference values for gastric motility
	Mark et al. (2019) [53]	Healthy subjects (n=34)	3D-transit used to establish normative reference values for segmental colonic motility established
	Haase et al. (2015) [58]	Healthy subjects (n=9)	3D-Transit combined with polysomnography allows investigation of associations between sleep patterns and GI motility
Studies with patients	Gregersen et al. (2015) [59]	Patients with carcinoid diarrhea due to neuroendocrine tumors (n=7) Healthy controls (n=15)	Patients with carcinoid diarrhea had increased WGTT in different segments. Patients had increased frequency of pansegmental colonic movements
	Haase et al. (2016) [60]	Patients with severe ulcerative colitis (n=20) Healthy controls (n=20)	Patients with severe ulcerative colitis had prolonged WGTT, significantly in the proximal colon
	Knudsen et al. (2017) [61]	Patients with Parkinson's disease (n=22) Healthy controls (n=15)	Patients with Parkinson's disease had significantly increased SITT and CATT
	Klinge et al. (2020) [57]	Patients with type-1 diabetes mellitus (DM-1) (n=18) Healthy controls (n=20)	Patients with DM-1 had increased GE, CTT and WGTT Patients with DM-1 had an increased number of retrograde movements
Pharmacological studies	Poulsen et al. (2016) [64]	Healthy subjects (n=25)	3D-Transit proved feasible in a pharmacological study Oxycodone treatment increases GI transit time in different GI segments
	Olesen et al. (2019) [62]	Healthy subjects (n=24)	Oxycodone-induced increase in WGTT and CTT is reversed by naloxegol
	Poulsen et al. (2018) [63]	Healthy subjects (n=20)	Oxycodone-induced increase of GI transit time is equally alleviated by naloxone and macrogol 3350
	Mark et al. (2019) [56]	Healthy subjects (n=59) combined from [62] and [64]	Increased GI transit time during opioid treatment is caused by a decrease in long fast movements rather than uncoordinated peristalsis

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