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Accelerometer-Based Assessment of Intestinal Peristalsis: Toward Miniaturized Low-Power Solutions for Intestinal Implants

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ABSTRACT Intestinal electrical stimulation via implants is already used to treat several disorders like constipation or incontinence. Stimulation parameters are most often empiric and not based on systematic studies. One prerequisite to evaluate effects of intestinal electrical stimulation is a direct assessment of intestinal motility. Some common methods are strain gauge transducers or manometry. With both the methods, it is not possible to record the exact 3-D movement. Therefore, we established a new method to record gastrointestinal motility with ultraminiaturized accelerometers, directly glued to the outer surface of the stomach, small intestine, and colon. With this technique, we were able to record precise local motility changes after electrical stimulation. Due to the low energy demand and the small size of the system, it is potentially useful for chronic measurements at multiple sites of the intestinal tract. We will present our first results regarding stimulation-dependent motility changes using up to eight implanted accelerometers in an acute pig model.

INDEX TERMS Accelerometer, intestinal electrical stimulation, intestinal implants, motility, peristalsis.

I. INTRODUCTION

Persitaltic waves of the intestinal tract are important to propagate nutritions in order to extract nutrients during the passage. Several diseases are associated with malfunctioning peristalsis, as for example chronic intestinal pseudo-obstruction (CIPO) [1], slow-transit Constipation [2] and obesity [3], [4]. Intestinal Electrical Stimulation (IES) has emerged as treatment option to influence peristalsis [5]. Depending on the exact stimulation parameters, peristalsis can be amplified or inhibited [5]. The pig is a well established model system for gastrointestinal motility due to its similarity to human physiology. Several methods and stimulation protocols have been tested in the porcine model. Manometric measurements through a cecal fistula revealed a postprandially increased motility index in the range of 2-4cpm, which is similar to that reported for human [6]. Chronic measurements of colonic motility in awake behaving pigs showed that 54% of contractile activity is in the range of 2-4cpm [6]. Increased activity can be seen after meals and in the morning whereas activity was minimal during night [6]. The mean time for 50% gastric emptying for liquid and pellet systems is in the range of 1.4-2.2h in the pig [7]. Total transit time is in the range of 50h [7]. Strain gauge transducers are frequently used to characterize peristaltic activity. Ileo-Caecal-Colonic motility was investigated by means of chronically implanted strain gauge transducers and simultaneous videofluoroscopy [8]. Individual Intestinal segments differed markedly regarding contractile patterns as well as motor function [8]. Retrograde transport could not be observed in the colon of pigs [8]. Ileal motility was characterized by aborally propagating giant contractions (about 3.9 cm/s) at intervals of about 7 minutes, migrating motor complexes with repetitive peristaltic waves occurred at intervals of about 132 minutes [8]. Due to haustral movements, the Caecum showed clustered contractions and peristaltic contractions for propulsion of digesta into the colon [8]. Long peristaltic

waves occurred in the proximal colon with velocities between 2.8 cm/sec in the centripetal loop and 5.7 cm/sec in the centrifugal loop [8].

With sequential electrical stimulation by three chronically implanted electrodes in the caecum of farm pigs a reduction of the mean transit time from 34h to 19h was observed [9]. In contrast, direct colonic stimulation with electrodes in caecal seromuscular layer (8-10V, 1000μs pulse width, 120Hz, 10-30s, 7-15mA) of anesthetized pigs modulated caecal motility and provoked propagating colonic contractions [10]. Duodenum Electrical Stimulation (DES) has successfully been used to reduce body weight in pigs [3]. Gastric emptying is delayed by DES, depending on the dose and stimulation parameters, continuous but not intermittent DES accelerated small bowel transit and only DES with 100% duty cycle (in contrast to 40% duty cycle) reduced body weight gain in obese pigs [3]. Inhibitory effects of intestinal stimulation have also been observed in an acute model. In an acute study with three stimulation sites located in the serosa of the descending colon, sequential electrical stimulation elicited propulsive activity [11]. The best stimulation parameters were a pulse duration of 3ms and a current of 15mA [11]. Electrical stimulation always evoked off colon contractions [11]. Furthermore, nitrergic as well as cholinergic pathways are involved in the response to electrical stimulation [11].

With respect to specific diseases, it is important to establish specific and standardized stimulation protocols with a reproducible effect on peristalsis. In order to do so, basic research with chronically implanted devices at different positions of the intestinal tract are necessary. These devices must be capable of stimulation but also of direct assessment of the movement caused by peristaltic waves. Two important prerequisites are extreme miniaturization and low power demand.

There are several ways to measure the intestine motility:

- surface movement
- intestinal pressure
- gut wall stress

In most cases pressure or stress were used. To measure the pressure, a manometry catheter is positioned in the intestinal tract [11], [12]. Stress is measured with strain gauge transducers, that were fixed on the serosal surface [6], [8]. The surface movement can also be detected directly with small reflectors applied at the intestinal surface [10]. Regarding the important future aspect to integrate the measuring system into an implantable device, our boundary conditions were ''small size'', ''low power consumption'' and ''microcontroller compatibility''. Because of the size and the power consumption we decided to use an integrated circuit based accelerometer from Memsic (MXR9500G/M) [13] that is DC-coupled and therefore enables the detection of very slow movements as they occur in case of peristalsis. Common accelerometers start with 0.1 up to 1.0Hz, that might be too high for the intended application. The MXR9500G/M is able to detect accelerations separately in three axis (x-, y- and z-direction). The Memsic sensor has a very special unique measurement system. The operation is based on the symmetry of an internal thermal field. When the sensor is moved or the position has statically changed, the field becomes asymmetrical. The reception of this phenomenon is very sensitive and allows to measure static and dynamic accelerations, so that we were able to detect very slow movements. The upper frequency was 17 Hz with the standard -3dB amplitude decrease.

II. MATERIALS & METHODS

The integrated circuit has a dimension of 7x7x1.8mm and was soldered on a 1mm thick printed circuit board (pcb) with the final dimension of 8x11mm. To protect the sensors against moisture, they were completely encapsulated with kwik sil (WPI) and an integrated piece of mull as an anchor point for gluing it at the bowel surface (Fig. 1A).

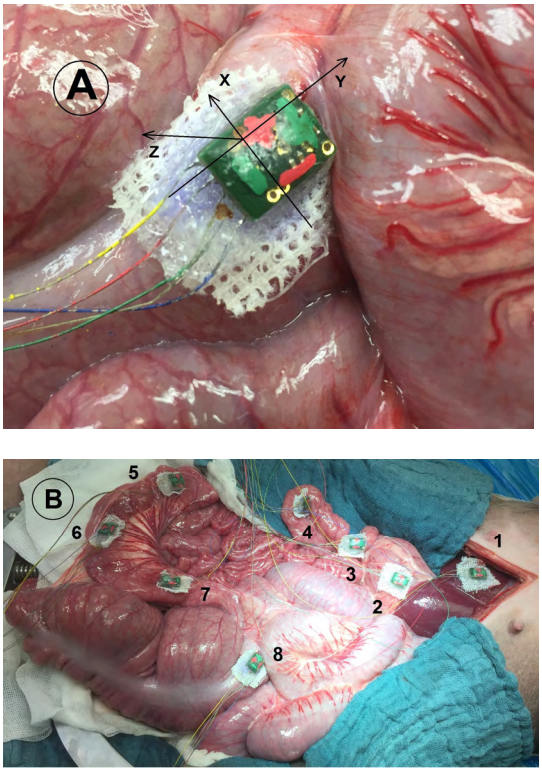

FIGURE 1. Modified accelerometer (A) to be used as an intestine movement sensor at the positions 2 - 8 (B). Accelerometer 1 was used as a respiratory detector.

The units were fixed at the bowel with a special glue (vetbond, 3M). The orientation of the accelerometers were all the same and was always in line with the bowel course. Positive values were associated with oral (y), right (x) and up (z), whilst negative values are associated with anal (-y), left (-x) and down (-z).

In total we used eight accelerometers (Fig. 1 B). One of them (Fig. 1 B 1) was applied on the liver to detect the breathing. Because the abdominal cut ended at the sternum, the liver was directly mechanically coupled with the lung movement and represented the influence on the bowel very good. Therefore we decided to apply the sensor at this position. With this

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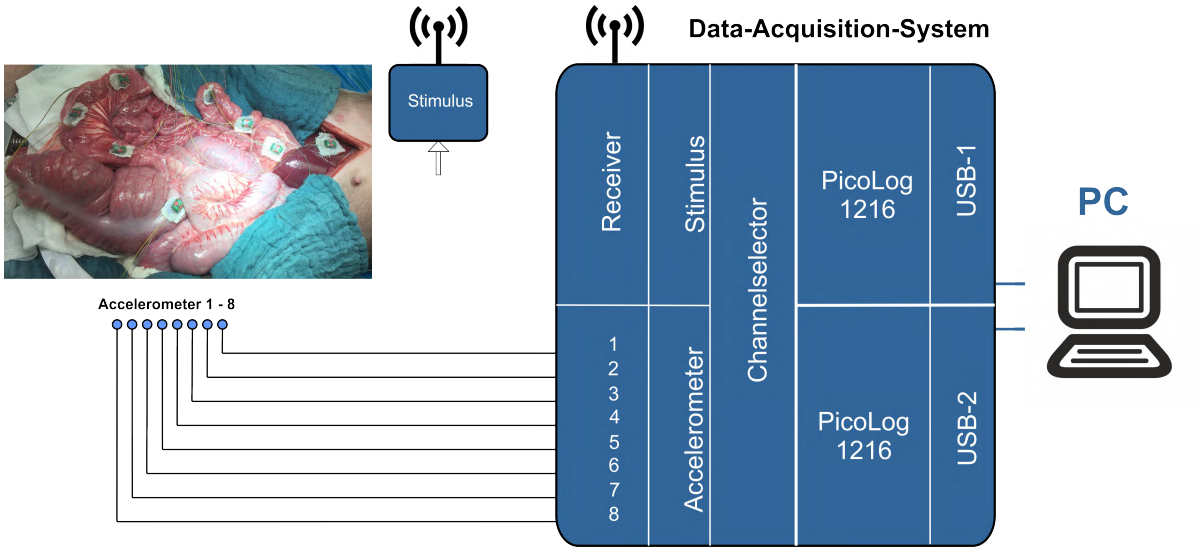

FIGURE 2. Block diagram of the data acquisition system.

TABLE 1. Sites of Accelerometers 1-3 used for analysis.

Acc1 site of stim	Acc2 site of stim	Acc3 site of stim
Duodenum prox	Duodenum dist	Small int prox
Small intestine proximal	Small int medial	Small intestine distal
Small intestine medial	Small intestine distal	colon
gut	Duodenum prox	Duodenum dist

signal the respiratory interference to the intestine movement could be detected. The accelerometers were placed from oral to anal, starting at the gut, ending at the colon. Data were extracted for the stimulation site (gut, duodenum and small intestine) and for the three directly following aboral accelerometers.

To get a marker for later data analysis, a further electrode near by the stimulus electrode was placed. The stimulus signal was measured with a biosignal amplifier that was wirelessly connected to the data acquisition system. The measuring system had no connection to ground and was completely electrically decoupled from the data acquisition system. This is also the case for the accelerometers, because of the non conductive encapsulation.

The signals of the radio receiver and of all movement sensors were connected to a special developed interface board that supplies the accelerometers with power and combined the eight accelerometer sensors with the stimulus signal (Fig. 2). The output signals were digitized by two PicoLog 1216 (Pico Technology) analog to digital interfaces which were connected to a pc by USB. Over all we had 25 input channels that were digitized with 1000 samples per second. The software interface was able to handle both units simultaneously, so that the synchronization was ensured. Additionally we recorded the stimulus with both units.

III. ANIMAL EXPERIMENTS

All procedures were approved by the local ethics committee (#23 177-07/G 17-1-008), and followed the European and the German national regulations (European Communities Council Directive, 86/609/ECC; Tierschutzgesetz). All animal procedures were performed in accordance with the [Medical Center of the Johannes Gutenberg-University Mainz] animal care committee's regulations. 3 pigs (pietrain; 30 +/− 5kg bw) were premedicated with azaperone intramuscularly (2mg/kg weight; Stresnil, Janssen-Cilag), Midazolam (0,3-0,5 mg/kg weight; Ratiopharm) und atropine (0,033 mg/kg weight)) before anesthesia was initiated with intravenous sodium thiopental (5 mg/kg bolus followed by an intravenous infusion (10 mg/kg/h). After intubation, pigs were mechanically ventilated with a Dräger respirator Servo 900b (oxygen-air: FiO2 0.27; pCO2 controlled). Prior to instrumentation, piritramid was administered intravenously (7.5-mg bolus) and maintained by an intravenous infusion (0.25 mg/kg/h). Arterial and central venous lines were introduced via the femoral artery and vein. A suprapubic catheter was introduced into the bladder. Heart rate and oxygen saturation were continuously measured using electrocardiogram, pulse oximetry, and capnometry. Ventilation was adjusted according to repeated blood gas analysis. For volume substitution Ringer solution (10 ml/kg) was constantly infused during the operation. The experimental procedure was kept constant, throughout the experiments. Stimulation parameters are as follows: amplitude: 30mA, stimulation time 30s, pause

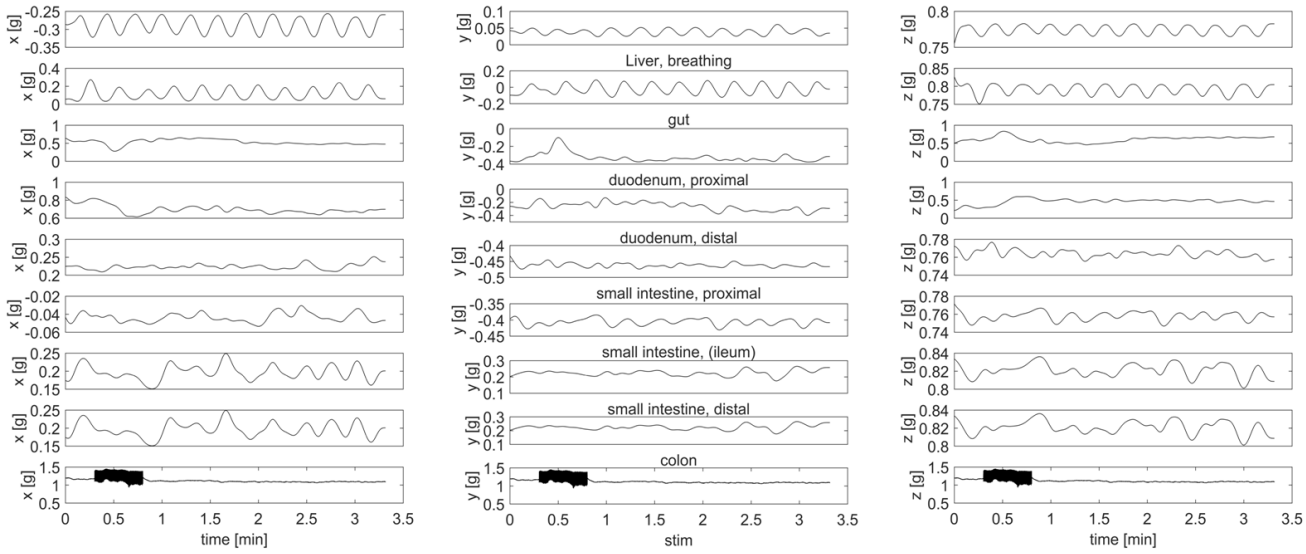

FIGURE 3. x-, y- and z-acceleration [g] for 8 consecutive positions of the intestinal tract during and after electrical stimulation of the duodenum (third channel from top) with 30Hz and 500μs pulse width. An enhanced acceleration can be seen during stimulation in the duodenum. Bottom channel visualizes the stimulus artefact.

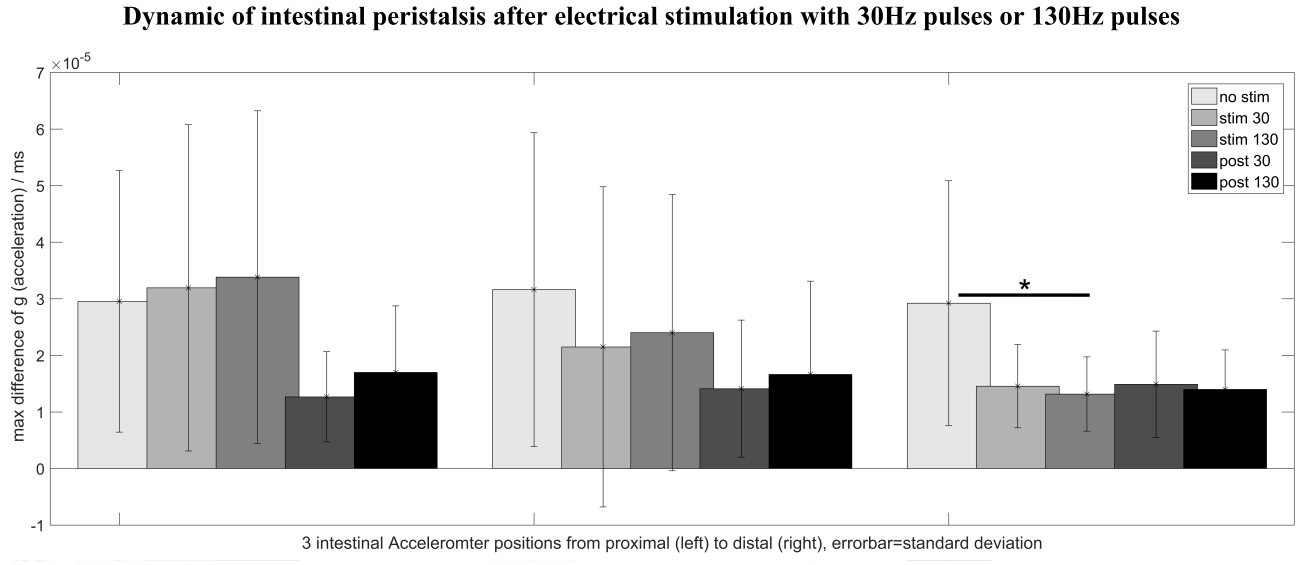

FIGURE 4. Maximal difference of acceleration during, before, and after stimulation for 3 consecutive sites of the intestinal tract, starting at the point of electrical stimulation and in aboral direction. A significantly reduced acceleration can be seen three accelerometers apart from the point of stimulation in aboral direction during stimulation in case of a 130Hz stimulus.

between two stimulation runs: 3 minutes, pulse width 1000μs or 500μs, frequency 30Hz or 130Hz.

IV. STATISTICS AND DATA ANALYSIS

To extract relevant information without breathing rhythm (6-8 cpm), data were filtered with the function filtfilt (with a 3rd order Hamming window, butter, matlab 2016b, mathworks). A low pass filter in the order of 0.1Hz (6cpm, Wn=0,0002) was chosen. Acceleration was extracted for all three axis from raw data and used for further analysis.

For analysis, we pooled data from 6 different intestinal locations from two pigs (n=12). Accelerometer (Acc) one was always the point of stimulation (stim), Accelerometer two was the accelerometer adjacent to the stimulation site in aboral direction and accelerometer three follows accelerometer two in aboral direction. Different positions were pooled (Table 1).

Maximal difference was calculated for normalized data and the sum of x-, y- and z-acceleration. A control situation before stimulation was compared to acceleration during stimulation (40s) and after stimulation (40s).

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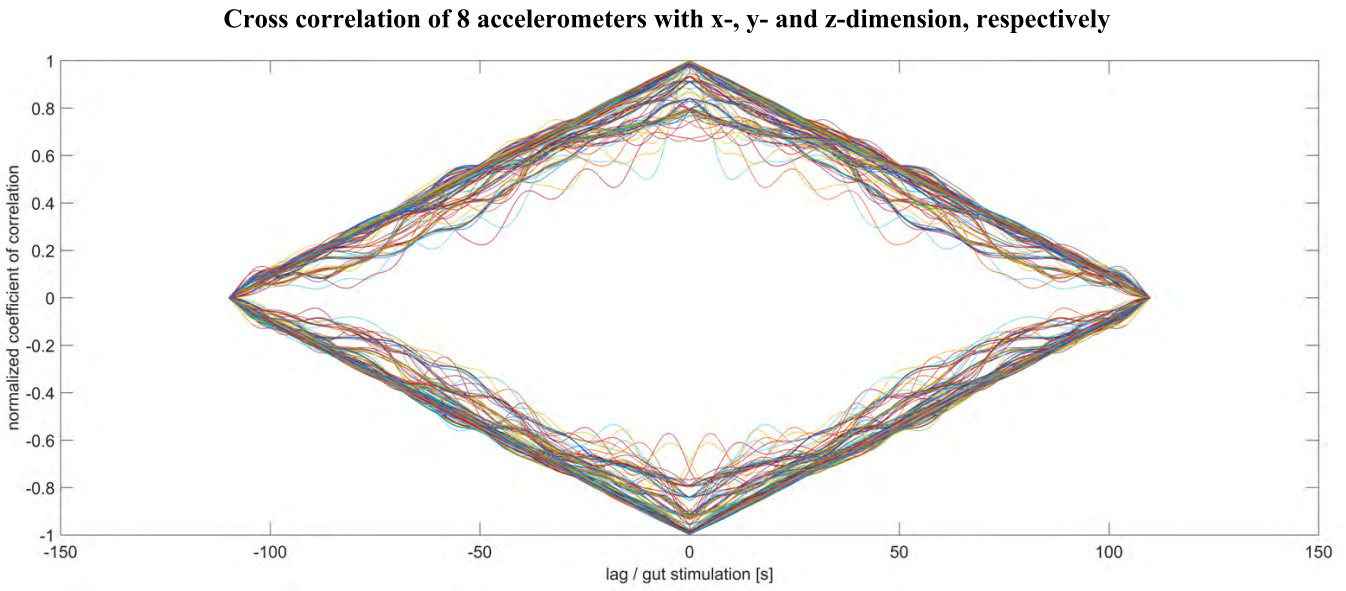

FIGURE 5. Cross correlation between all accelerometer channels (x, y and z separately) during and after electrical stimulation of the gut. Maximal cross correlation is always seen for zero time lag.

TABLE 2. [data-set C_diff1 INTAKT dif s2s3] results of the multiple comparison and Kruskal-Wallis tests: Accelerometer 1.

Group1	Group2	Lower CI	Dif Groups	Upper CI	p-value
No_stim	Stim_30	-19,45	0	19,45	1
No_stim	Stim_120	-19,45	0	19,45	1
No_stim	Post_30	-2,70	16,75	36,20	0,13
No_stim	Post_120	-8,70	10,75	30,20	0,56
Stim_30	Stim_120	-19,45	0	19,45	1
Stim_30	Post_30	-2,70	16,75	36,20	0,13
Stim_30	Post_120	-8,70	10,75	30,20	0,56
Stim_120	Post_30	-2,70	16,75	36, 20	0,13
Stim_120	Post_120	-8,70	10,75	30, 20	0,56
Post_30	Post_120	-25,45	-6	13,45	0,92

TABLE 3. [data-set C_diff2 INTAKT dif s2s3] results of the multiple comparison and Kruskal-Wallis tests: Accelerometer 2 If the confidence interval (CI) does not contain zero, the difference is statistically significant.

Group1	Group2	Lower CI	Dif Groups	Upper CI	p-value
No_stim	Stim_30	-7,86	11,58	31,03	0,48
No_stim	Stim_120	-11,53	7,92	27,36	0,80
No_stim	Post_30	-1,95	17,50	36,95	0,10
No_stim	Post_120	-3,11	16,33	35,78	0,15
Stim_30	Stim_120	-23,11	-3,67	15,78	0,99
Stim_30	Post_30	-13,53	5,92	25,36	0,92
Stim_30	Post_120	-14,70	4,75	24,20	0,96
Stim_120	Post_30	-9,86	9,58	29,03	0,66
Stim_120	Post_120	-11,03	8,42	27,86	0,76
Post_30	Post_120	-20,61	-1,17	18,28	1,00

For each group (Acc1, Acc2, Acc3) a Kruskal-Wallis test was used to estimate possible differences of intestinal acceleration between groups (before, during and after stim). A multiple comparison test was chosen to calculate exact statistical relations between groups (matlab 2016b, mathworks). If the confidence interval does not contain zero, the difference

TABLE 4. [data-set C_diff3 INTAKT dif s2s3] results of the multiple comparison and Kruskal-Wallis tests: Accelerometer 3.

Group1	Group2	Lower CI	Dif Groups	Up per CI	p-value
No_stim	Stim_30	-0,78	18,67	38,11	0,07
No_stim	Stim_120	2,30	21,75	41,20	0,02
No_stim	Post_30	-0,95	18,5	37,95	0,07
No_stim	Post_120	-0,03	19,42	38,86	0,05
Stim_30	Stim_120	-16,36	3,08	22,53	0,99
Stim_30	Post_30	-19,61	-0,17	19,28	1,00
Stim_30	Post_120	-18,70	0,75	20,20	1,00
Stim_120	Post_30	-22,70	-3,25	16,20	0,99
Stim_120	Post_120	-21,78	-2,33	17,11	1,00
Post_30	Post_120	-18,53	0,92	20,36	1,00

is statistically significant (Tables R2-R4, significant result shaded in grey).

V. RESULTS

We were able to show a direct effect of intestinal electrical stimulation onto the acceleration of intestinal movement at the side of stimulation (Fig. 3). Besides this direct effect, no acceleration could be detected after stimulation and at aboral positions from the stimulation site. In Fig. 4 a statistically significant reduction of maximal difference of acceleration can be seen for the third accelerometer in aboral direction from the point of stimulation with 130Hz stimulus during stimulation (statistics in Tables 2-4).

By trend, an inhibited motility can be observed for all conditions despite the direct effect of stimulation at the site of stimulation (Fig. 4). Furthermore, maximal cross correlation is always apparent during stimulation (Fig. 5).

VI. CONCLUSION

In conclusion, we were able to demonstrate that special accelerometers are useful to measure intestinal peristalsis with very high accuracy in x-,y- and z-acceleration at a defined point of the intestinal tract. The data derived from our system differ profoundly from measurements which can be achieved by well established, non-invasive diagnostic tools like the SmartPill® [15]. The SmartPill® must be swallowed and passes the intestinal tract by passive movement with peristalsis. During the passage, data like pH, temperature and pressure are sent by radiotelemetry to a receiver unit [16]. In contrast, our system gives very precise, local information of a x-, y- and z-movement. This is especially important to supervise effects of intestinal electrical stimulation and can not be achieved by floating systems like the SmartPill®, even though the latter system is extremely useful to assess transit time. Furthermore, the accelerometer system can be used to adjust intestinal electrical stimulation by giving feedback information about downstream effects to the implanted stimulation unit. For this purpose, the measurement system must be fixed to defined points of the intestinal tract. Due to the risks associated with surgical procedures, the accelerometer system is intended as an assistance system for implanted intestinal pacemakers. Until now, no systems are available which give feedback information about the outcome of electrical stimulation by implanted intestinal pacemakers. This kind of feedback is mandatory, because of changing physiological parameters which influence peristaltic movements, as for example food intake [17], sleep-wake-cycle [18], stress [19] or the microbiome [20].

In the preclinical context, the accelerometer system can be used to achieve very accurate movement data which make 3D reconstructions of peristalsis possible. Such computer simulations may be beneficial for teaching purposes, surgery schedules and basic research. We found, that our high energy stimulation elicits reduced peristalsis in aboral direction from the stimulation site, which is in good agreement with former findings [5]. It was not possible to elicit or entrain peristaltic waves. This finding substantiates the need for further research in order to consider side effects of intestinal electrical stimulation apart from the direct site of stimulation under physiologic conditions without anesthesia in a chronic pig model with implanted devices. The accelerometers described in our work are well suited to supervise stimulation effects because they are of very small size and have low power consumption, two important prerequisites for the integration in implantable intestinal pacemakers.

The step from the preclinical level to the clinical setting will require some adjustments of the system. To allow minimally invasive implantation, the system must be wireless and energy autarkic. Currently we are working on an inductive power supply system, which might be useful for this purpose. Additionally, the encapsulation must certainly be changed towards materials which are tested for medical implants, like ceramic. Fixation method then depends strongly on the encapsulation material, most likely the system must be sutured to the outer wall of the intestine. The amount of sensors needed surely varies, depending on the clinical case. In general, the entrainment or inhibition of peristaltic waves can be assessed by three sensors placed at different locations

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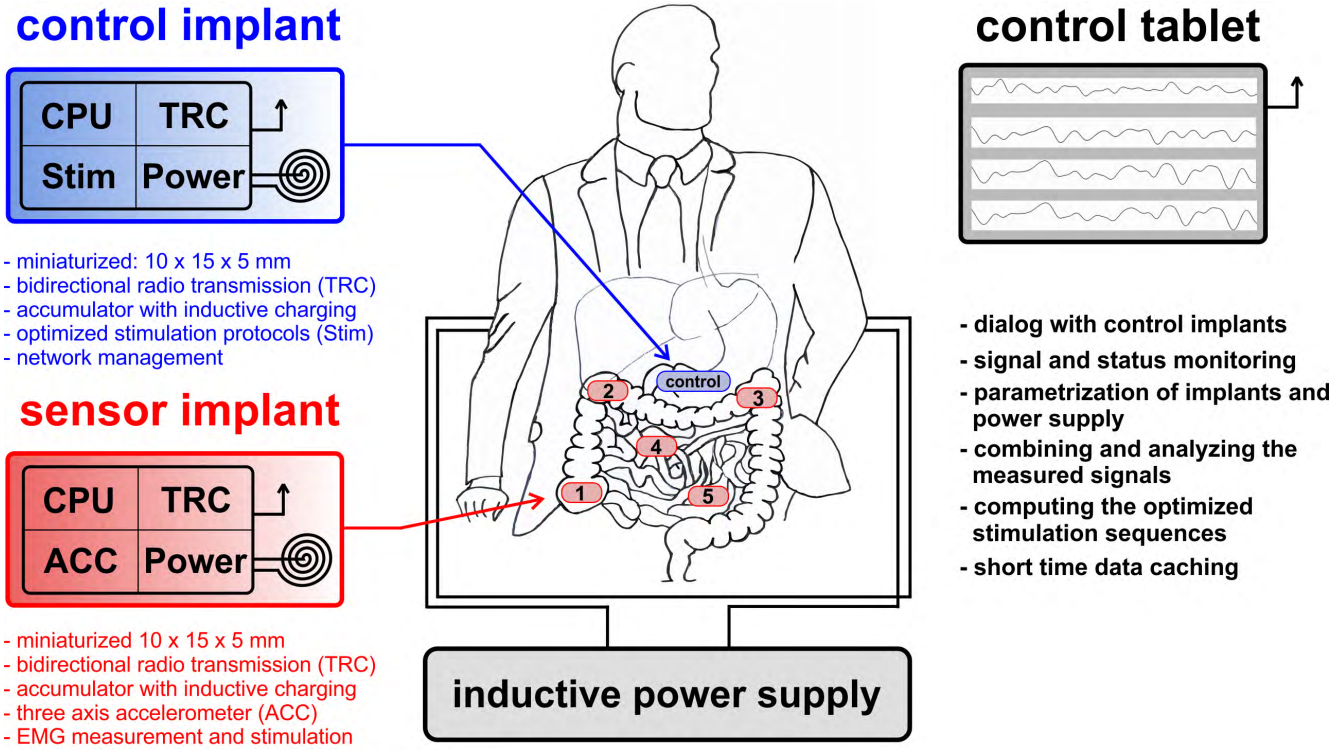

FIGURE 6. **Future medical application realized as wireless body area network. The control implant consists of a CPU with integrated radio transceiver unit and inductive power supply. It communicates with the sensor implants, processes the measured data and implements a stimulation protocol for possible feedback stimulation of intestinal muscles. Besides acceleration, EMG could be detected with the sensor implants. The control tablet serves as monitor, data memory and parameterization unit for the physician.**

on the intestinal tract, as shown in this study. The system would allow objective assessment of IES driven peristalsis for the first time and it might be possible to adjust the stimulation by direct feedback from the sensor system as proposed for wireless body area networks (WBANs) [14]. The proposed design for such a system is shown in Fig. 6.

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