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Implantable Functional Gastrointestinal Neurostimulation

A. S. Jurkov, *Student Member, IEEE*, A. Arriagada, *Graduate Student Member, IEEE*, and M. P. Mintchev, *Senior Member, IEEE*

***Abstract*—Neural Gastrointestinal Electrical Stimulation (NGES) is a new microprocessor-based method for invoking gastric or colonic contractions by generating multi-channel, high energy, high frequency waveforms. It has been shown that when applied to the lower stomach, NGES offers the possibility for enhancing propulsive peristalsis for the treatment of gastric motor dysfunctions, or for producing retrograde peristalsis for the treatment of obesity. When applied to the colon, NGES can be utilized either for propulsive control in severe constipation or for invoked retrograde contractility. This paper briefly discusses the implementation of an implantable neurostimulator and summarizes the performance of the NGES technique in acute tests on experimental animals and humans, and in chronic tests on animals. These experimental tests indicate that NGES is successful in accelerating gastric emptying of both liquids and solids, and in producing strong, externally-controlled, retrograde contractions.**

I. INTRODUCTION

A. Gastrointestinal Electrical Stimulation

Gastrointestinal Electrical Stimulation (GES) is a method for electrically manipulating the lower stomach or colon as a possible treatment for gastric motor dysfunction [1] and control in severe constipation by enhancing propulsive peristalsis [2], or for retrograde control of gastrointestinal contractions, for example for the treatment of obesity [3]. Various GES techniques have been proposed [4], including gastric pacing [5], low-energy high-frequency stimulation [6] and neural gastrointestinal electrical stimulation (NGES) [7]–[9].

Gastric pacing is a technique which stimulates the stomach at a frequency slightly higher then the natural electrophysiological frequency, entraining gastric electrical activity (GEA) [5] or the "slow waves" [3]. However, the results associated with this technique have been modest, possibly due to the fact that intrinsic rather than extrinsic control remains the dominating factor determining the overall gastric motility index [10], [11].

Low-energy, high-frequency stimulation [6] is another GES technique, which does not entrain GEA because it stimulates the stomach at frequencies significantly higher than the natural electrophysiological frequency. This method has shown some improvement in the mechanical activity of canine stomachs [6], but did not clearly demonstrate the ability to invoke contractions. Antiemetic effect associated with this technique has been reported when treating gastroparetic patients [12], but the possible mechanisms for this phenomenon are yet to be verified and explained [13].

In contrast to the previous methods, NGES generates multi-channel, high energy, high frequency waveforms that can directly invoke contractions which can move gastric content in a controlled fashion depending on the synchronization between the stimulating channels [7], [8]. NGES overrides any spontaneously-existing electro-mechanical events in the gut and does not entrain the intrinsic slow waves. By stimulating the local network of cholinergic neurotransmitters, repeated local contractions can be produced [14]. This stimulation technique has been successful in accelerating gastric emptying of both liquids and solids [7], [8], [15] and in producing strong, externally-controlled, retrograde contractions [9]. NGES is considered the most promising technique for externally-controlled recreation of impaired gastrointestinal motility, since it is the only method resulting in the production of strong, lumen-occluding contractions [4].

B. Functional Multi-channel Neurostimulation

NGES utilizes multi-channel, high frequency (20–500 Hz) and high energy stimulating waveforms to generate synchronized contractions that can move gastric or colonic content in controlled fashion and in both directions. The stimulating voltages are delivered through pairs of serosal electrodes implanted circumferentially and subserosally (Fig.1, Fig.2). NGES causes smooth muscle contractions by inducing the intramural cholinergic fibres to release acetylcholine.

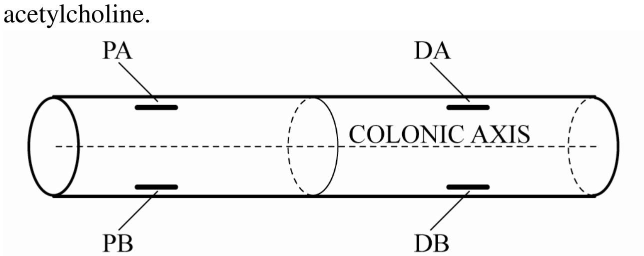

Fig.1. Electrode placement on the colon for two-channel NGES: PA – active proximal electrode, PB – reference active electrode, DA – active distal electrode, DB – reference distal electrode.

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A. S. Jurkov is with the Department of Electrical and Computer Engineering, University of Calgary, Calgary, AB T2N 1N4 Canada (phone: 403-220-2298; e-mail: asdzhurk@ucalgary.ca).

A. J. Arriagada is with the Department of Electrical and Computer Engineering, University of Calgary, Calgary, AB T2N 1N4 Canada (phone: 403-220-2298; e-mail: ajarriag@ucalgary.ca).

M. P. Mintchev is with the Department of Electrical and Computer Engineering, University of Calgary, Calgary, AB T2N 1N4 Canada (phone: 403-220-5309; fax: 403-282-6855; e-mail: mintchev@ucalgary.ca).

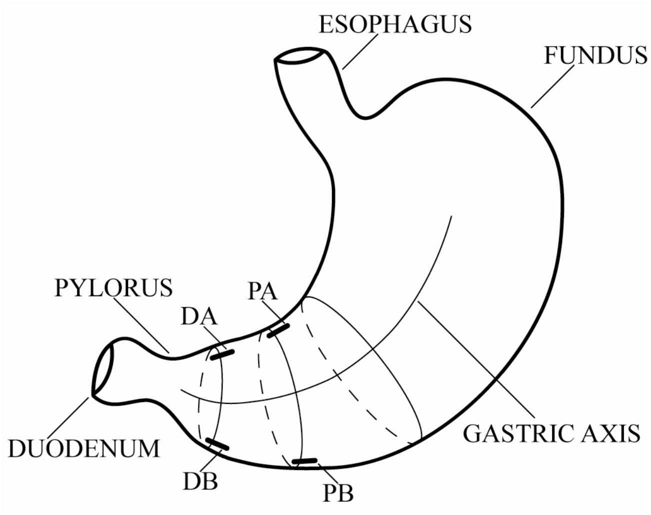

Fig.2. Electrode placement on the stomach for two-channel NGES: DA – active distal electrode, DB – reference distal electrode, PA – active proximal electrode, PB – reference proximal electrode.

NGES stimulating patterns consists of 2-channel, controlled, charge-balanced bipolar rectangular voltage waveforms with 20–500 Hz frequency, 2–10 s on-time, 0–100 % overlap, 2–20 V_{pp} amplitude, and off-time of 8 s to 1 hour (Fig. 3).

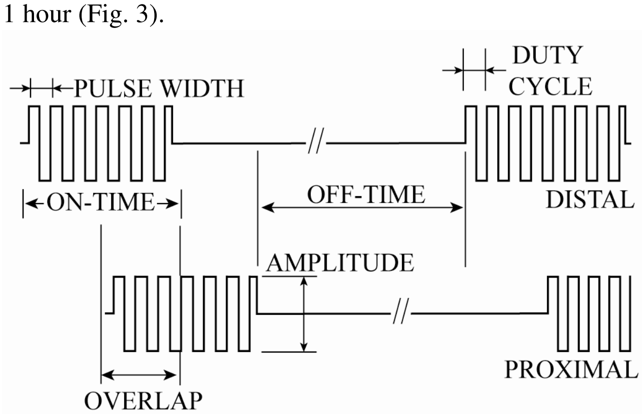

Fig.3. Two-channel stimulation pattern for NGES

By sequentially activating the channels, the direction of propagation of the invoked contractions could be controlled. In an implantable neurostimulator, synchronization and adjustability over the stimulating pattern parameters is easily achievable via a microcontroller. Several such microcontroller-based implantable neurostimulators have already been designed and built. Their performance has been evaluated in acute and chronic tests. Overview of the design of an implantable neurostimulator is discussed below.

II. METHODS

A. Implantable Neurostimulator Design Overview

The utilized implantable stimulator consists of five major blocks: (1) microcontroller; (2) wireless transceiver; (3) DC-DC converter; (4) transistor-based level-shifter; and (5) analog electronic switches [16]. Fig. 4 depicts the block diagram of this implantable stimulator system.

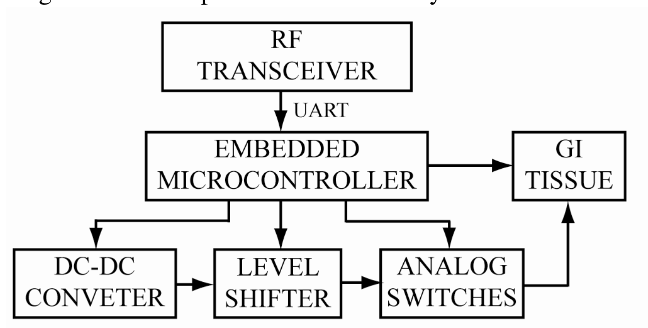

Fig.4. Block diagram of the implantable stimulator system

The embedded microcontroller is the decision-making block of the implant. It receives the stimulation parameters from the wireless transceiver via serial communication. Prior to the onset of a stimulation session, the embedded microcontroller sets the output voltage level of the DC-DC converter. This output voltage is set to the desired amplitude of the stimulating waveform. The embedded microcontroller produces digital pulse trains with frequency and duty cycle specified in the stimulation parameters. The transistor-based level shifter stage converts these digital waveforms into a bipolar analog waveform with amplitude equal to the output level of the DC-DC converter. The analog switches, whose timing is controlled by the microcontroller, distribute the stimulating waveform to the different channels. The implant requires to be powered by 3–3.6 V for a nominal operation.

B. RF Programming and Control

The implant can execute various stimulation protocols with pre-programmed parameters. In addition, any arbitrary stimulation pattern within the acceptable range of parameters can be downloaded from a personal computer (PC) to an external controller. These parameters are then relayed to the implant via wireless telemetry. The wireless link is also utilized by the implant to transmit status update information back to the external controller, which can in turn display the received information to the operator on a PC. The block diagram of the complete electrical stimulation system is shown in Fig.5.

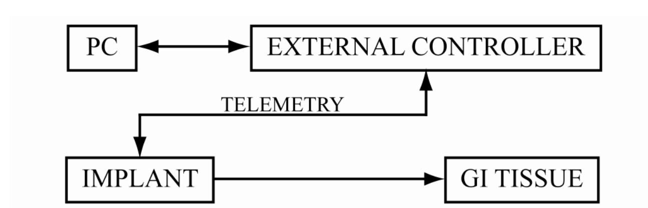

Fig.5. Block diagram of the complete stimulation system [16]

C. Power Consumption

Previous study [17] indicates that a possible application of the implantable neurostimulator for the treatment of obesity may consist of the following stimulation parameters: 12Vpp; 5 s stimulating waveform duration (on-time); and 60 % duty cycle. This stimulation pattern would repeat every 60 s for 24 h/day. The energy requirements for a single stimulation session would be 0.109 J, resulting in a daily energy consumption of 1329 J. Using a 3V, 2.3 Ah battery (SVO8830, Wilson Greatbatch, Clarence, NY) with an estimated effective voltage and capacity of 2.6 V and 1.2 Ah, the device life is calculated to be 77.5 days.

D. Packaging

The implantable stimulator was fabricated using surface-mount devices (SMD) on a small 4-layer printed circuit board (PCB) [16]. The final size of the implantable stimulator was 5.8 cm x 2.8 cm x 2 cm, with a mass of 52.2 g. A special housing case was designed for the implant using polyoxymethylene. The decision to use polyoxymethylene to house the implant was based on its merits as a non-toxic, inexpensive, readily available and easily machined material.

III. TESTING

A. Acute Stomach Testing On Animals

Extensive acute animal testing of the NGES technique has been performed over the past several years as an alternative treatment for gastroparesis, obesity and related diseases. The first tests on two dogs were aimed at validating a computational model of the method [14]. Voltage amplitudes of 10 to 20 V with 50 Hz frequency were found to be optimal to produce strong, circumferential, non-propagated contractions. After this initial success, multi-channel stimulation was tested to produce controlled sequential contractions for liquid (water) movement and emptying [8]. Eight dogs underwent implantation of four sets of bipolar stainless steel electrodes in an acute setup. Liquid emptying was achieved by producing sequential contractions with 50 Hz, 14-V (peak to peak) pulse trains. Further studies expanded the applicability of the method by confirming the possibility of solid content movement [7]. Solid food was mixed with plastic pellets and fed to nine anesthetized dogs. Stimulation voltage pulse trains were applied to 4 electrode sets with distally diminishing voltage amplitudes from 12 to 6 V (peak to peak) in steps of 2 V. The duration of the stimulus were also distally diminished from 16 to 4 seconds in steps of 4 seconds. The amount of pellets evacuated using the method was higher ($p<0.01$) than the number of pellets evacuated by spontaneous contractions.

The possibility of applying NGES for obesity treatment was explored as well [9]. In this case stimulation is controlled so that proximal contractions are generated and full lumen occlusion occurs. Eight dogs had 2 circumferential electrode sets implanted at approximately 3 and 7 cm from the pylorus.

The latest development of the NGES method, the implantable stimulator, was tested on 9 dogs [16]. Gastric emptying studies using 14-V (peak to peak), 50 Hz pulse trains with duration of 6 seconds showed that the implantable stimulator delayed gastric emptying on all cases, hence opening an avenue for chronic obesity treatment.

B. Acute Colon Testing On Animals

The first NGES attempt at colonic stimulation was to validate a three-dimensional parametric modeling of colonic contractions [20]. A pair of stainless steel electrodes were implanted longitudinally in the descending colon 20 to 25 cm proximally to the rectum of an anesthesized dog. In a second dog, a second set of electrodes was added 15 cm proximally to the first set. Voltage amplitudes of 10 to 24 V (peak to peak) at 50 Hz were utilized to produce strong circumferential contractions. Further refinement of the method was tested to provide information on the overlap patterns of the phasic contractions and the synchronization patterns for the applied stimuli applied to the implanted electrodes [21]. Movement of solid colonic content was verified on six dogs [22]. In this study, 50 Hz, 20V (peak to peak), 18-second stimulation patterns were applied to four sets of subserosal electrodes implanted at 3 cm intervals. The method can be indistinctively applied for orad or aboral artificial colon movement for potential alternative treatment for ostomy cases or chronic constipation.

C. Acute Tests on Humans

The first acute test of the NGES method on a human patient showed the feasibility of producing circumferential contractions on a gastroparetic stomach [8]. The same stimulation parameters used in the canine models were applied and it was observed that contractions occurred albeit no test was performed to induce gastric content movement. A more recent study has compared the effectiveness of high frequency (including NGES) vs. low frequency gastric stimulation in post operative gastroparetic patients [15]. Gastric retention in patients being administered high-frequency stimulation was comparatively much lower ($p<0.05$) than in patients administered low-frequency stimulation. The study concluded that high-frequency methods are more effective than and as safe as low-frequency gastric stimulation techniques.

D. Chronic Tests on Experimental Animals

Recently, a chronic study has been carried out to test the effectiveness of the NGES method for the treatment of obesity [18]. In one testing protocol, 4 dogs exhibited significant reduction in food intake and weight. However, this first chronic gastric study also evidenced tissue accommodation where the effectiveness of the method was affected when using fixed voltage stimulation amplitudes. This limitation was overcome by changing the stimulation voltage amplitude in 1 V (peak to peak) steps.

The need for including a feedback mechanism to address battery power consumption of the implantable device and tissue accommodation has also been explored [19]. This feature is necessary for detecting spontaneous gastric contractions and, therefore, to impose retrograde stimulation in order to oppose them and thus delay gastric emptying.

NGES was successfully tested in a chronic study of nine dogs [23]. A custom built stimulator was used for this study [24]. 6 second bipolar rectangular pulses of 50 Hz were used on 4 channels and were applied to the colon tissue to produce sequential movement. It was observed that sequential contractions in the colon accelerated content movement in a canine model of delayed colonic transit. This result improves the possibility of using an NGES implantable device in patients suffering from chronic constipation.

IV. Discussion

The present review paper describes NGES as the most promising technique for externally-controlled recreation of impaired gastrointestinal motility compared to other GES methods. However, this technique is energy-demanding, and if utilized in an open-loop setup could pose difficult, if not impossible long-term requirements for a multi-channel programmable implant. Moreover, recent chronic studies on experimental animals [18] indicated that although the method was effective in inducing retrograde peristalsis, frequently invoked contractions in an open-loop system may lead to tissue accommodation resulting in NGES losing its ability to invoke contractility using the same amplitude of the stimulating voltage. Therefore, optimization of the invoked contractile patterns using feedback control is an important avenue to increase the effectiveness and the applicability of NGES by decreasing the energy demands for the stimulator and preventing gastric muscle fatigue due to over-stimulation.

A study on feedback neural electrical stimulation demonstrates that an impedance-based feedback is the preferred feedback modality in order to keep the surgical procedures minimally invasive and to reduce the technological requirements for the stimulator [19]. Such feedback employs the same electrodes utilized for stimulation, and therefore is technologically quite beneficial.

V. Conclusion

NGES is a promising new technique for manipulating gastrointestinal motility.

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