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Research report

Bioelectronics for mapping gut activity

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ABSTRACT

Gastric peristalsis is initiated and coordinated by an underlying bioelectrical activity, termed slow waves. High-resolution (HR) mapping of the slow waves has become a fundamental tool for accurately defining electrophysiological properties in gastroenterology, including dysrhythmias in gastric disorders such as gastroparesis and functional dyspepsia. Currently, HR mapping is achieved via acquisition of slow waves taken directly from the serosa of fasted subjects undergoing invasive abdominal surgery. Recently, a minimally invasive retractable catheter and electrode has been developed for HR mapping that can only be used in short-term studies in subjects undergoing laparoscopy. Noninvasive mapping has also emerged from multichannel cutaneous electrogastrography; however, it lacks sufficient resolution and is prone to artifacts.

Bioelectronics that can map slow waves in conscious subjects, postprandially and long-term, are in high demand. Due to the low signal-to-noise ratio of cutaneous electrogastrography, electrodes for HR mapping of gut activity have to acquire slow waves directly from the gut; hence, development of novel device implantation methods has inevitably accompanied development of the devices themselves. Initial efforts that have paved the way toward achieving these goals have included development of miniature wireless systems with a limited number of acquisition channels using commercially available off-the-shelf electronic components, flexible HR electrodes, and endoscopic methods for minimally invasive device implantation. To further increase the spatial resolution of HR mapping, and to minimize the size and power consumption of the implant for long-term studies, application-specific integrated circuitry, wireless power transfer, and stretchable electronics technologies have had to be integrated into a single system.

1. Gastrointestinal electrophysiology and slow wave origin

Orchestrated movements of the gastrointestinal (GI) tract facilitate digestion and absorption of nutrients (Sanders et al., 2006). Enteric neurons, interstitial cells of Cajal (ICC) and smooth muscle cells are the main elements that produce the motor behaviors of the GI tract. GI motility is initiated and coordinated by an underlying bioelectrical activity caused by ICC, termed slow waves (Huizinga and Lammers, 2009). ICC were discovered by Santigo Ramon y Cajal (Cajal, 1911), and their loss and injury can result in a number of functional GI motility disorders (Farrugia, 2008) such as gastroparesis (Grover et al., 2011), slow transit constipation (Wedel et al., 2002) and intestinal pseudo-obstruction (Feldstein et al., 2003). Cannon and Moser (1898) were the first to use X-ray and ingestible contrasts to obtain motility information of the GI tract to understand swallowing mechanisms (Cannon and Moser, 1898). Later on, more advanced techniques such as scintigraphy (Feinle et al., 1999), advanced X-ray imaging and magnetic resonance imaging provided a plethora of new information about the motor function and motility of the GI tract (Camilleri and Linden, 2016). Due to the electrophysiological nature of slow waves, the aforementioned imaging techniques were not well-suited for capturing the detailed underlying sources of GI motility patterns (Cheng, 2015).

2. Apparatus to acquire slow waves and electrogastrography

The first recordings of electrical slow waves from mammals (dogs, cats and rabbits) and humans were carried out by Walter Alvarez (Szurszewski, 1998). He introduced a practical apparatus (see Fig. 1a) as early as 1922 (Alvarez and Mahoney, 1922), and used it to acquire slow waves from the serosa through a laparotomy procedure, and noninvasively from abdominal skin. Alvarez recorded a cutaneous electrogastrogram from a "little old woman whose abdominal wall was so thin that her gastric peristalsis was easily visible" (Alvarez, 1922). Davis et al. (1957) rediscovered

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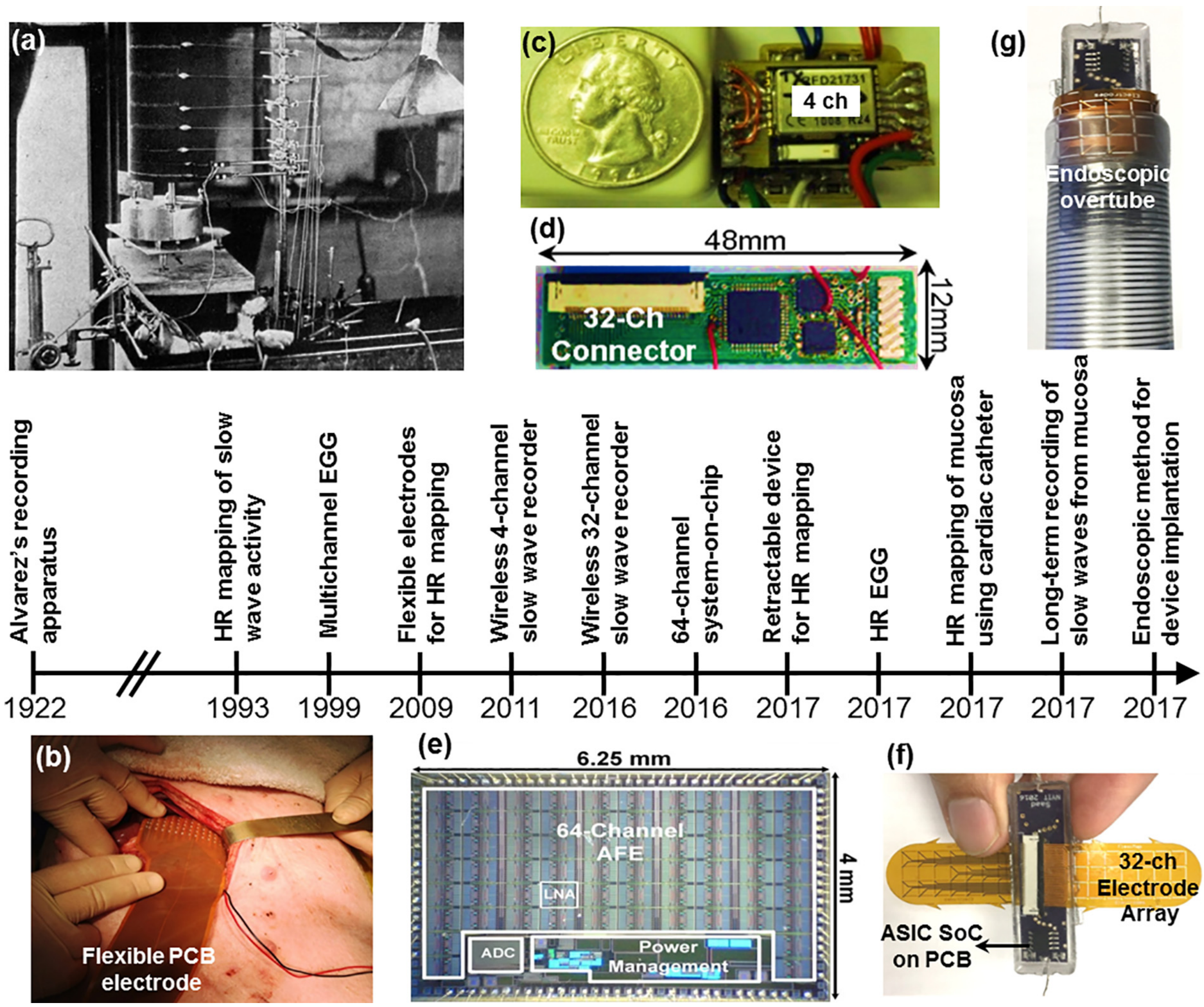

Fig. 1. Timeline of selected major milestones in gut bioelectronics. Illustrated above is a timeline of selected major milestones in the development of devices to acquire gastric slow waves. (a) The apparatus used by Alvarez, (b) flexible electrodes fabricated on printed circuit board (PCB), (c) the first wireless device for signal acquisition with 4 channels, (d) the 32-channel wireless device with flexible printed circuit connector, (e) the first system-on-chip (SoC) for high resolution mapping of slow waves, fabricated using application-specific integrated circuit (ASIC) technology, and including 64-channel low-noise amplifiers (LNA), an analog-to-digital converter (ADC), and a power management unit, (f) an implantable concept system that includes the SoC and two custom-made 32-channel flexible electrode arrays, and (g) the electrodes of the system depicted in (f), wrapped around the implant and fitted in an endoscopic overtube.

electrogastrography (EGG) in 1957; however, research in EGG received relatively little attention from the scientific community until the late 1980s (Abell and Malagelada, 1988) and early 1990s (Chen and McCallum, 1994; Yin and Chen, 2013). Fig. 1 depicts selected major milestones over the past century in the development of devices for acquiring slow waves from the gut.

Using EGG, researchers have found that the normal frequency of the gastric slow wave, which is species-dependent, in humans is about 2–4 cycles per minute (cpm). Lower (0.5–2 cpm) and higher (4–9 cpm) frequency ranges, measured using EGG, have been categorized as bradygastria and tachygastria, respectively. The absence of rhythmic slow waves, observed using EGG, has been referred to as arrhythmia (Yin and Chen, 2013). Because the frequency of the 'classic' EGG reflects the summation –and not patterns– of slow waves, it fails to accurately reflect dysrhythmia. In fact, various dysrhythmias can occur in the normal frequency range (Angeli et al., 2015).

The amplitude of an EGG recording is usually weak (50–500 μV) and depends on the thickness of the subject's abdominal wall. Thus the body mass index criterion is often used in EGG studies to exclude overweight subjects (Simonian et al., 2004). The clinical meaning of EGG amplitude is not well understood, and although a plethora of evidence suggests that EGG has bioelectrical origin (Smout et al., 1980; O'Grady, 2012), some researchers have claimed that the EGG is not truly an electrical activity, but the result of motion artifacts (Rhee et al., 2011; Sanders et al., 2016). Most EGG has been acquired from a single or a limited number of channels (Chen et al., 1999), and thus no information on the regional activity of the stomach can be deduced (Krusiec-Świdergoł and Jonderko, 2008).

3. High-Resolution mapping of slow waves and current mapping technologies

Inspired by studies in cardiac electrophysiology, high-resolution (HR) mapping of the GI tract was introduced in 1993 (Lammers et al., 1993). In this investigation, 240 silver wire microelectrodes arranged in a rectangular array with an inter-electrode spacing of 1 mm were gently placed on the serosal surface of duodenum tissue *in vitro*, using a micromanipulator, and extracellular HR mapping of GI smooth muscle was demonstrated. Utilizing flexible printed-circuit board technology, Du et al. developed a flexible electrode array which conforms to the surface of the GI tract and can be used in HR mapping (see Fig. 1b) (Du et al., 2009). The head