Advances in Non-Invasive Neuromodulation: Closed-Loop Vagus Nerve Stimulation

Subjects: Engineering, Biomedical | Health Care Sciences & Services | Computer Science, Hardware & Architecture
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Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation therapy that eliminates the need for internal device implantation, presenting as a favorable therapeutic option. This method relies on electrical surface stimulation, bypassing the need for surgical procedures.

Keywords: neuromodulation ; tVNS ; closed-loop ; Node-RED

1. Introduction

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation therapy that eliminates the need for internal device implantation, presenting as a favorable therapeutic option. This method relies on electrical surface stimulation, bypassing the need for surgical procedures [1]. In the context of evaluating autonomic state regulation, heart rate variability (HRV) calculation stands as a commonly employed method, allowing for the assessment of sympathetic or parasympathetic system activation [2]. Consequently, evidence suggests that taVNS effectively modulates the auricular vagus nerve's parasympathetic pathway, with studies proposing its systemic effects [3]. Non-invasive stimulation of auricular afferent receptors is achieved by employing surface electrodes on the outer ear, utilizing an electronic device to produce pulses at specific stimulation frequencies [4][5]. Despite the increased application of transcutaneous stimulation techniques, commercial devices currently operate as open-loop approaches, lacking adaptive adjustments based on the user's physiological variables.

2. Closed-Loop Stimulation

In recent years, there has been an increasing focus on enhancing therapy by synchronizing stimulation parameters with a patient's physiological response. This has led to the proposal of closed-loop models aiming to optimize treatment outcomes [6].

Differing from the traditional approach, closed-loop VNS allows for adjusting stimulation to the patient's physiological conditions in real time. In this system, stimulation is automatically adjusted based on the detection of specific physiological signals or biomarkers, providing a personalized and effective intervention. In therapies for stroke rehabilitation, for instance, closed-loop VNS enables precise control over when stimulation is delivered to the patient, ensuring it occurs during appropriate moments [7], maximizing functional recovery and enhancing rehabilitation efficacy [8]. Stimulation can be synchronized with specific cardiac parameters, such as heart rate or blood pressure, to aid in the treatment of cardiovascular diseases like hypertension and myocardial ischemia [9].

Decoding techniques enabling the identification and classification of patterns assist in determining the precise timing of VNS application in cardiovascular treatments, based on the evaluation of neural activity [10]. As vagal neural activity synchronizes with respiratory and cardiac cycles, these physiological signals provide an avenue for external modulation to enhance stimulation efficacy. Furthermore, indirect and non-invasive measures like heart rate variability, baroreflex sensitivity, and respiratory sinus arrhythmia can serve as indicators of cardiac vagal nerve activity, allowing for adjustment of parameters in the stimulating device [11]. Pulmonary respiratory reflexes, facilitated by mechanical lung-stretch receptors, convey information regarding the solitary tract nucleus, thereby influencing cardiac and autonomic rhythms. In this context, by synchronizing the pulse train of stimulation with the respiratory rhythm, especially during the expiration phase, the intended neuromodulation may have a more significant physiological impact. Moreover, the acquisition and analysis of various physiological signals in response to taVNS usage can complete the therapeutic cycle, allowing for real-time assessment of the therapy, thereby facilitating more efficient optimization [3].

Advancements in wearable sensor technologies and real-time signal processing methodologies collectively form the foundation for research involving closed-loop taVNS. Not only does this approach offer innovative and personalized treatment options for the patient, but it also enables the tailoring of stimulation dosage according to the measured outcomes during stimulation, potentially reducing side effects and enhancing the overall quality of life for patients.

3. Sensors for Signal Acquisition

Advancements in sensor technology have enabled the precise and continuous collection of physiological data, such as heart rate, blood pressure, stress levels, and even brain activity, in an unobtrusive and real-time manner. These data are crucial for evaluating the effects of therapy and tailoring treatments to meet the specific needs of each patient. Commercial devices, such as smartwatches, are commonly used by athletes to track daily vital signs and performance during activities throughout the day. They are also employed for the continuous monitoring of patients, especially the elderly, in a discreet and comfortable manner, without exposing that the individual is under care. More sophisticated devices, like biosensors and wearable sensors [6], allow for the recording of variables used to monitor blood glucose levels, oxygen saturation, heart rate, and blood pressure [12].

4. Methodologies for Signal Processing and Real-Time Variable Detection

Methods for extracting physiological data using real-time signal processing are currently utilized in both research and medical devices to support remote treatment [13]. Although tools for categorizing time-varying signals are widely adopted in diverse research areas, the majority of these solutions depend on algorithms crafted for high computational intensity. This poses challenges when implementing them in small embedded systems that have limited resources [14].

In stimulation therapies, the assessment of heartbeats can assist in the safe practice of therapy. Through real-time signal processing methodologies, instantaneous detection of a drop in heart rate to critical levels, due to vagal stimulation, can indicate to the user to adjust or interrupt the session. In the context of autonomic assessment, heart rate variability (HRV) is widely used to evaluate these systems' activation [2]. Among the challenges associated with this metric, the need for wider time windows for frequency domain analysis stands out, as well as the requirement for high-sampling-rate sensors to detect pulse intervals and the capacity of the processing unit remotely.

Quantitatively, changes in heart rhythm patterns can be obtained with beat recognition algorithms, such as QRS complex detection. Temporal domain analyses can be performed using calculations involving "mean RR, SDNN, rMSSD, pNN50". In turn, signal transformation methods are employed to analyze HRV indices in the frequency domain, such as fast Fourier transform (FFT), discrete Fourier transform (DFT), wavelet transform, or auto-regressive (AR) modeling [15]. Developed in collaboration between the European Society of Cardiology and the North American Society for Pacing and Electrophysiology, these methodologies delineate protocols and clarify correlations among physiological assessment parameters [16].

While frequency domain methods are effective for assessing biological variables not observable in the time domain, they necessitate a longer signal window—typically at least two minutes—to extract the LF, HF, and VLF bands. Obtaining other parameters may require even lengthier measurements [17]. This requirement could limit their utility in short sampling periods, particularly in real-time event identification.

Conversely, methods for processing respiratory signals are commonly observed in respiratory performance tests and polysomnography examinations. Some studies have proposed algorithms that utilize tools like discrete wavelet transform (DWT) and FFT for sleep respiration detection [18]. The accurate detection of the end of inspiration and the start of expiration has been investigated by other researchers as well [14][19]. The online processing steps applied to the recorded respiratory signal highlight the complexity of managing signal variations and irregular patterns [20].

5. Remote Therapies

The implementation of advanced signal processing techniques enables precise and controlled delivery of therapies in conjunction with a parallel assessment of effects. Therefore, stimulation devices can be combined with monitoring systems to evaluate patient responses to electrical stimuli. This integration allows for better control of therapeutic interventions and the ability to adjust stimulation settings based on the specific needs of the patient [21].

The advancement of remote technologies has made it possible to offer remote therapies, surpassing geographical barriers and granting access to specialized treatments, even for patients in remote areas. Telemedicine and digital health platforms facilitate remote patient monitoring, treatment adjustments, and real-time interactions with healthcare professionals. This fosters a more convenient and flexible approach while enhancing treatment adherence [13]. These advancements suggest a reconfiguration of healthcare management, aiming to prioritize preventive care and well-being, shifting away from the traditional focus solely on crisis management and disease treatment in conventional healthcare systems. The advancement of continuous and remote monitoring is achieved through the application of real-time data processing, transmission, and integration with cloud-connected sensors and devices [22][23]. The process involves the segmentation of data into transmission packets, wherein each packet contains identifiable information that is utilized for subsequent processing, aiming to accurately extract parameters.

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