Abstract

The present dissertation is based on pioneering studies aimed at investing means and procedures for the development of a next generation type of therapeutic devices named “bioelectronic medicines”. The author of this dissertation performed those studies in collaboration with PhD students, postdoctoral fellows and senior researchers that he coordinated at Aalborg University, Denmark. In addition, some earlier studies performed by the author at Babeş-Bolyai University, Romania, were also included in this dissertation as the results of those studies could also contribute to the development of bioelectronic medicines.

The bioelectronic medicines are envisioned as implantable smart electronic systems meant to deliver closed-loop controlled electrical impulses to neural circuits that regulate impaired body functions in order to take control over those functions, drive them in a desired direction and thus achieve therapeutic effects. By doing so, such devices would act as artificial neural centers, which mimic, interfere with, and modulate the natural neural centers that regulate the physiological mechanisms supporting the targeted impaired functions. According to visionaries of such technologies, the bioelectronic medicines could one day be used to treat “an array of conditions”, from a diversity of diseases caused by autonomic dysfunctions, such as obesity, diabetes and hypertension, to inflammatory diseases, paralysis and epilepsy.

However, implementation of such devices as large scale applications requires further advances in several fields of research, such as biomaterials, embedded systems, implantable sensors, neural signal decoding and modulation, and neural interfacing technologies. In this vast area of interdisciplinary research, our attention was focused for more than a decade on neural signal decoding and modulation, and neural interfacing modalities. The studies that we performed in those directions led to defining concepts, procedures and device models with possible applicability in bioelectronic therapies. The results of those studies were published in several journals and conference proceedings and included in three patent applications and two patents. The present dissertation is a review of those results.

As stated above, in order to become applicable in clinics, the bioelectronic therapies require the development of implantable hardware and software components able to monitor the function to be treated and generate appropriate stimulation paradigms when a malfunction is detected. Meanwhile, those stimulation paradigms should be in real time adaptable to the actual needs of

the patient, which change continuously, including in response to the therapeutic action of the system. Last but not least, being implantable, such bioelectronic systems must be minimally invasive in order to be accepted by patients and clinicians.

In those regards, as we have shown in several publications, the best modality to provide a bioelectronic therapy is through devices that interface peripheral nerves which mediate the regulation of the affected function. Indeed, a nerve which mediates the regulation of a function conducts neural signals which encode the information concerning the performance and/or control of that function. Consequently, such nerves could serve not only as a target for the modulatory action of such a bioelectronic system, but also as a source of information regarding the affected function and thus of closed-loop variables (or function markers) as necessary for the adaptation of the therapeutic action of that system to the actual needs of the patient. Since both of those operations (i.e. marker extraction and neural stimulation to modulate the targeted function) can be performed using just one neural electrode (or interface), such a technology would not be only elegant, but also effective concerning its closed-loop capabilities, and minimally invasive.

As we have also shown in several publications, an ideal nerve for being interfaced with such procedures is the left vagus nerve and two diseases that could be treated by such means are epilepsy and hypertension as both of those conditions are influenced by, and/or influence the left vagus nerve activity. The present dissertation is based on the results of our studies aimed at developing means and procedures addressing the left vagus nerve for treating those diseases through bioelectronic therapies. In line with those objectives and with the author's view on the research activity, those studies also aimed at understanding the physiological support of those procedures, which is a crucial condition for the development of such novel therapies.

The dissertation consists of eight chapters which are divided in several sub-chapters. The first chapter provides a chronological perspective on the progression of bioelectronic ideas and methods in general. The following two chapters of the thesis analyze the need and possibilities of using bioelectronic therapies for treating patients with epilepsy and hypertension, and, in relation with such possibilities, the physiological characteristics which defines the left vagus nerve as an ideal nerve for being interfaced with such procedures. The fourth chapter of the thesis presents the author's vision concerning the concept and principles of interfacing the left vagus nerve with bioelectronic therapies for treatment of epilepsy and hypertension, and the last four chapters review the results obtained in those two directions. Last but not least, the contribution of our studies to future developments in the addressed medical field and to a better understanding the related physiological mechanisms is also discussed in those four chapters of the thesis.