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Accelerating peripheral nerve regeneration using electrical stimulation of selected power spectral densities

Wei-Ming Yu, Madelyn A. McCullen, Vincent C.-F. Chen*

Peripheral nerve injuries are common consequences of extremity trauma or chronic compression with a prevalence of 43.8 per 1 million people (on average) reported in the United States annually, accompanied by a yearly increase in cost of care. Patients suffering from these injuries require surgical procedures and rehabilitative strategies to reinforce their extensive recovery. Several studies have found that the application of electrical stimulation can accelerate peripheral nerve regeneration, thus shortening the time of peripheral nerve growth and reducing the cost of care (Willand et al., 2016). The electrical stimulation paradigms that effectively enhanced functional recovery in most studies employed signals of sinusoidal waves delivered at higher frequencies (50–100 Hz) or pulsed waves delivered at lower frequencies (< 20 Hz). As it would be impractical to try to pinpoint the exact stimulation parameter (i.e., frequency or waveform) that will enhance the healing procedure, our task at hand is to conduct a series of experiments with the objective of identifying an optimal arrangement of stimulation parameters for clinical applications. Indeed, the goal of our research is to identify an improved stimulation strategy by precisely determining the contribution of different stimulation parameters and factoring in the possible contribution of these parameters to the response of peripheral glial cells.

Typical electrical stimulation patterns are trains of periodic pulses that are applied at stimulation rates between 20 and 100 Hz. The reported stimulation parameters in these clinical studies include only intensity, frequency, or pulse duration. We assume the stimulation pulses in most of these studies

are rectangular, which invites the question: could other waveforms be more effective? The main difference between rectangular pulses and other waveforms is the distribution of power over the frequency domain, which can be derived by Fourier transform as the power spectral density. Studies of the impact of electric fields on synaptic plasticity suggest that the power spectral density of the stimulation train is likely to account for the majority of the impact on neural plasticity. Modeling indicates that the most probable direct effect of electrical stimulation is modulation of N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Figure 1). Although both of these channels are ligand-gated, they also have voltage and frequency dependent characteristics (Castellani et al., 2001). The equivalent circuit models of these ion channel receptors indicate that higher frequencies will induce a shunting current while lower frequencies will store transmembrane energy. We previously showed that voltage and frequency are inversely related due to the reactance of membrane capacitance (Chen et al., 2012). The significance of the power spectral density and the reactance of membrane capacitance indicate every aspect of the electrical stimulation parameters, including waveform, influence NMDA and AMPA ion channel receptor dynamics. As NMDA and AMPA receptors are present in peripheral glial cells, how is this relevant to electrical stimulation-promoted peripheral nerve regrowth?

The frequency explained here is exactly how an input signal is being defined in signal processing, which is different from the

stimulation frequency typically recited in clinical studies. This could be due to the fact that electrical stimulations are output signals that are rarely analyzed via a signal processing approach. In most clinical studies, reference was made to stimulation rate (how many pulses were generated per second) without identifying the power spectrum concept. Because the unconstrained increase of stimulation intensity or frequency may be nociceptive, dangerous and ineffective, we have attempted to shift the current research and clinical practice paradigm. This is accomplished by generating electrical stimulation trains based on power spectral densities instead of providing controlled intensity (voltage or current amplitude) or frequency (rate) to enhance the effects of peripheral nerve regeneration. The existence of glutamatergic signaling and NMDA and AMPA ion channels in peripheral nerve recommends basing electrical stimulation strategy on power spectral density considerations (Chen and Kukley, 2020). It has been indicated that electrical stimulation elevates neuronal cyclic adenosine monophosphate and upregulates neurotrophic factor and neurotrophic factor receptor expression not only in neurons but in Schwann cells of injured peripheral nerves (Willand et al., 2016). Thus, Schwann cells may play an important role in assisting nerve growth of injured neurons. Since different power spectral densities will differentially impact ion channels in Schwann cells, optimization of this component will likely have therapeutic benefit and may deepen our understanding of how electrical stimulation affects cells and cellular communication. Additional considerations are discussed below.

Both direct and alternating currents increased nerve growth factor production from Schwann cells (Huang et al., 2010), so it is important to address whether these seemingly contradictory approaches operate through any common mechanisms. To this end, we first examined the effects of different frequency components of electrical stimulation on muscle force or electromyography induced by the power spectral densities extracted from a standard 20 Hz stimulation train. Customized electrical stimulation circuitry can split the stimulation power at 40 Hz and 200 Hz (0–40 Hz, 40–200 Hz, or 200 Hz and above) and be utilized to compare the effects of power spectral densities. These can include or exclude the bandwidth corresponding to the fundamental frequencies of conventional low (20 Hz) and high (100 Hz) stimulation frequencies (Kesar et al., 2008) as well as the reciprocal of the absolute refractory period of neural firings (1000 Hz). Since a regular 20 Hz stimulation train of rectangular pulses includes harmonic frequencies (40 Hz, 60 Hz, 80 Hz, ...) superimposed on the fundamental stimulation rate (20 Hz), high frequency components are present in these low frequency stimulation trains. Our earlier studies showed that a correlation exists between the extent of the corticospinal contribution to muscle force and the response of the muscle to higher order harmonics of the stimulation train (Chen et al., 2017). We now plan to focus on the impact of power spectral densities by factoring in the amount of high frequency components of rectangular pulses and the wideband/narrowband power distributions. Low-frequency pulses are superimposed with

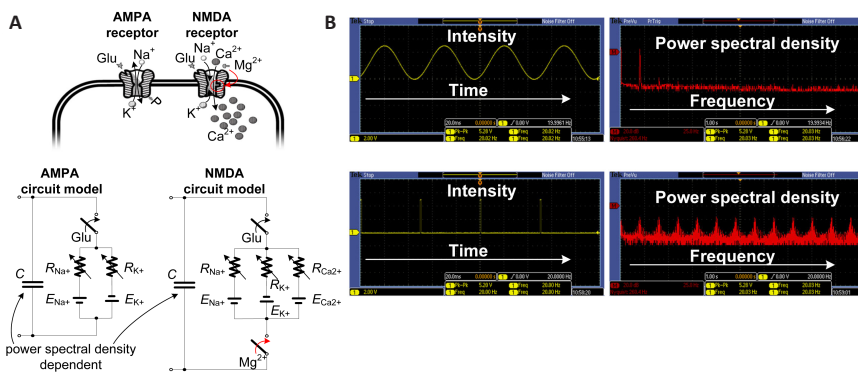


Figure 1 | Circuit models and stimulation waveforms. (A) Modified Hodgkin-Huxley circuit models for α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) ion channels showing induction of long-term potentiation, wherein the capacitance C is power spectral density dependent. (B) 20 Hz sinusoidal and pulsed stimulation trains (yellow) with their corresponding power spectral densities (red). Note that the power spectral densities include frequency components other than their respective fundamental frequencies.

harmonics that are identical or similar to the harmonics of high-frequency pulses. This novel approach will change the current definition of low vs. high frequency stimulation. Further, it accounts for the results observed in trials of random noise stimulation where a large range of stimulation frequencies are included in a random noise power spectrum.

Since afferent axons will also be activated during electrical stimulation (Chen et al., 2016), the contribution of the central nervous system on neural regeneration should be carefully evaluated. By learning how afferent fibers could be selectively activated by a composition of harmonics (or sinusoidal stimulations), we could potentially replicate quasi-voluntary contractions and induce the necessary neuroplasticity to assist the recovery of peripheral nerve injuries. Nonetheless, the nonlinear function derived from the stimulation pulses and the peripheral nerves raises the possibility of a more complex relationship between the stimulation intensity or frequency and alterations of the nervous system (Chen et al., 2012). This leads us to explore the effects of electrode-tissue interfaces during electrical stimulation, which is an important topic for both invasive and noninvasive applications. The electrode-tissue impedance model suggests that human tissues act as a complex analog filter that can attenuate the power spectral density of certain frequency bandwidths. This was demonstrated through the analyses of electrode-tissue impedance generated from current-controlled and voltage-controlled stimulation circuits (Chen et al., 2012). Based on fundamental circuit analysis, the voltage difference between the terminals of the capacitor element in the electrode-tissue impedance model (a function of frequency) fluctuates due to the power spectral densities. It is difficult to assess the attenuation of power spectral density within specific frequency bandwidths when applied to human subjects. This warrants further investigation by determining force and electromyography profiles generated in animal models using the application of both transcutaneous (noninvasive) and percutaneous (minimally invasive) stimulation pulses. Such studies will help establish the optimal intensity, frequency, power, and geometric location for noninvasive applications of peripheral nerve stimulation.

A number of studies of the application of electrical stimulation to promote peripheral nerve regeneration have been conducted in mammalian model systems. Rodent models of peripheral nerve injuries are the most widely used (Gordon and Borschel, 2017). Rodents are easy to keep at low costs for long duration, have a high reproduction rate and short generation time, and an accelerated lifespan. The benefits of using rodent models also include the opportunity to conduct well-established behavioral assays to evaluate their functional recovery (Anand et al., 2011). Compared to mice, peripheral nerves in rats are larger in diameter and easier to perform surgical interventions to manipulate, repair, or apply electrical stimulation. Despite these advantages with the rat model, there is a widespread availability of different genetically modified mouse strains. These mouse models thus have the advantage of addressing

questions at the molecular level and allowing the use of genetic approaches to image cellular responses of interest. Middle sized animal models such as rabbits and cats have also been used to study electrical stimulation on peripheral nerve regeneration. They have larger and thicker peripheral nerves, and the regenerative capacity of their peripheral nerves is more similar to that of humans. However, the high costs, the intensive maintenance efforts required, opposition to their use by animal rights groups and the public, and the longer operating time limit their use as models to study electrical stimulation on peripheral nerve regeneration.

The hindlimb nerves are most frequently used in the study of peripheral nerve regeneration. These include the sciatic nerve, the common peroneal nerve, the tibial nerve, and the femoral nerve. Of the hindlimb nerves, the sciatic nerve is the most commonly used. In all of the aforementioned mammals, the sciatic nerve is the largest and thickest nerve in the body. It is easy to locate and introduce injuries to by crush or transection even in small mammals like rodents. However, the sciatic nerve forms several branches and innervates multiple muscles. Because each branch may show different regenerative capacities and re-innervate muscle targets to various extents, it is more difficult to evaluate functional and behavior outcomes consistently across experiments. Branches of the sciatic nerve, such as the common peroneal nerve, were chosen based on the advantage of their more selective innervation. In addition to allowing more accurate outcome measurements, the common peroneal nerve can also be used to study peripheral nerve regeneration in chronic conditions such as chronic axotomy, chronic Schwann cell denervation, or chronic muscle denervation. Peripheral nerve regeneration studies surrounding these conditions involve cross-suturing the peroneal nerve to the tibial nerve (another branch of the sciatic nerve) in delayed nerve repair after both nerves are cut (Gordon et al., 2011). The femoral nerve model was introduced in order to study how motoneurons regenerate their axons preferentially into the motor branch but not the sensory branch. This model also demonstrates that electrical stimulation can promote this preferential reinnervation (Al-Majed et al., 2000). The forelimb nerves and the head and neck nerves were less frequently used for studying peripheral nerve regeneration because they are more difficult to access and manipulate, thus it is more difficult to evaluate the functional outcomes after regeneration. Lastly, data collected from both of the hindlimbs of the animal subjects provides the opportunity to compare bilateral functional recovery of peripheral nerve injuries with the least possible bias.

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