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In Vivo Evaluation of Fractal Microelectrodes Towards a More Targeted and Energy-Efficient Vagus Nerve Stimulation

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Vagus nerve stimulation (VNS) is a moderately effective treatment option for intractable epilepsy, depression, and pain, with promising applications in the treatment of gastrointestinal motility disorders like gastroparesis. The wide-ranging potential indications of VNS suggest an opportunity for a better understanding of underlying neural circuits that can be targeted using microscale electrodes. However, microscale Platinum (Pt) electrodes often have limited charge injection capacity due to their high impedance. Recently, we experimentally demonstrated that microscale Pt electrodes with Vicsek fractal geometry can facilitate electrochemical charge transfer more efficiently with 57% higher cathodic charge storage capacity than conventional circular microelectrodes [1]. Here we are investigating whether the fractal electrode may be more effective in eliciting small fibers in the vagus nerve with less energy consumption due to its enhanced charge injection capability. To evaluate the *in vivo* performance of these novel microelectrode designs and to determine whether these electrodes are capable of stimulating small, unmyelinated C fibers that supply the stomach, we designed a cuff electrode with an array with four pairs of fractal and circular microelectrode to explore the possibility of radial selective stimulation of vagus nerve. We determined the dimension of the cuff to be 760 μm in diameter to wrap around a rat's vagus nerve so that it can withstand the swelling of the nerve from chronic implantation. We patterned fractal microelectrode to have a geometrical surface area equivalent to that of a circle with 100 μm of diameter. Using a rat model, we have stimulated the right cervical vagus nerve with fractal/circular electrode and recorded the compound action potential (CAP) distal from the stimulation site with 5-7 mm of conduction distance or the dorsal trunk of the abdominal vagus (conduction distance: 70 mm). We used an autonomous neural control (ANC) system [2], which can stimulate and record from the nerve with randomized stimulus parameter combinations (pulse amplitude: 0-0.4 mA, pulse width: 0.02-1 ms). We adapted a cathode-first, alternating monophasic stimulation for the reliable suppression of stimulus artifact (pulse repetition frequency: 5 Hz) [2]. Results from right cervical VNS experiments in anesthetized rats showed that both the fractal and the circular electrodes can recruit small, myelinated Aδ and B fibers to a similar degree (pulse amplitude: 0-0.4 mA, pulse width: 0.1 ms) (Figure 1.), but fractal electrodes produce a more uniform and consistent fiber recruitment profile (Figure 2.). We observed volleys within the slow conduction velocity range (< 3 m/s), which we suspect to be signals from the C-fibers. Our next

plan is to obtain more experimental data to statistically identify the efficiency of various electrode designs in stimulating small fibers and to investigate the electrical potential profile of these electrodes in a biophysical model.

[1] H. Park, P. Takmakov, and H. Lee. (2018). "Electrochemical Evaluations of Fractal Microelectrodes for Energy Efficient Neurostimulation" *Sci Rep*, 8(1), pp. 4375.
[2] M. P. Ward, K. Y. Qing, K. J. Otto, R. M. Worth, S. W. John, and P. P. Irazoqui. (2015). "A flexible platform for biofeedback-driven control and personalization of electrical nerve stimulation therapy" *IEEE transactions on neural systems and rehabilitation engineering*, 23(3), pp. 475-484.

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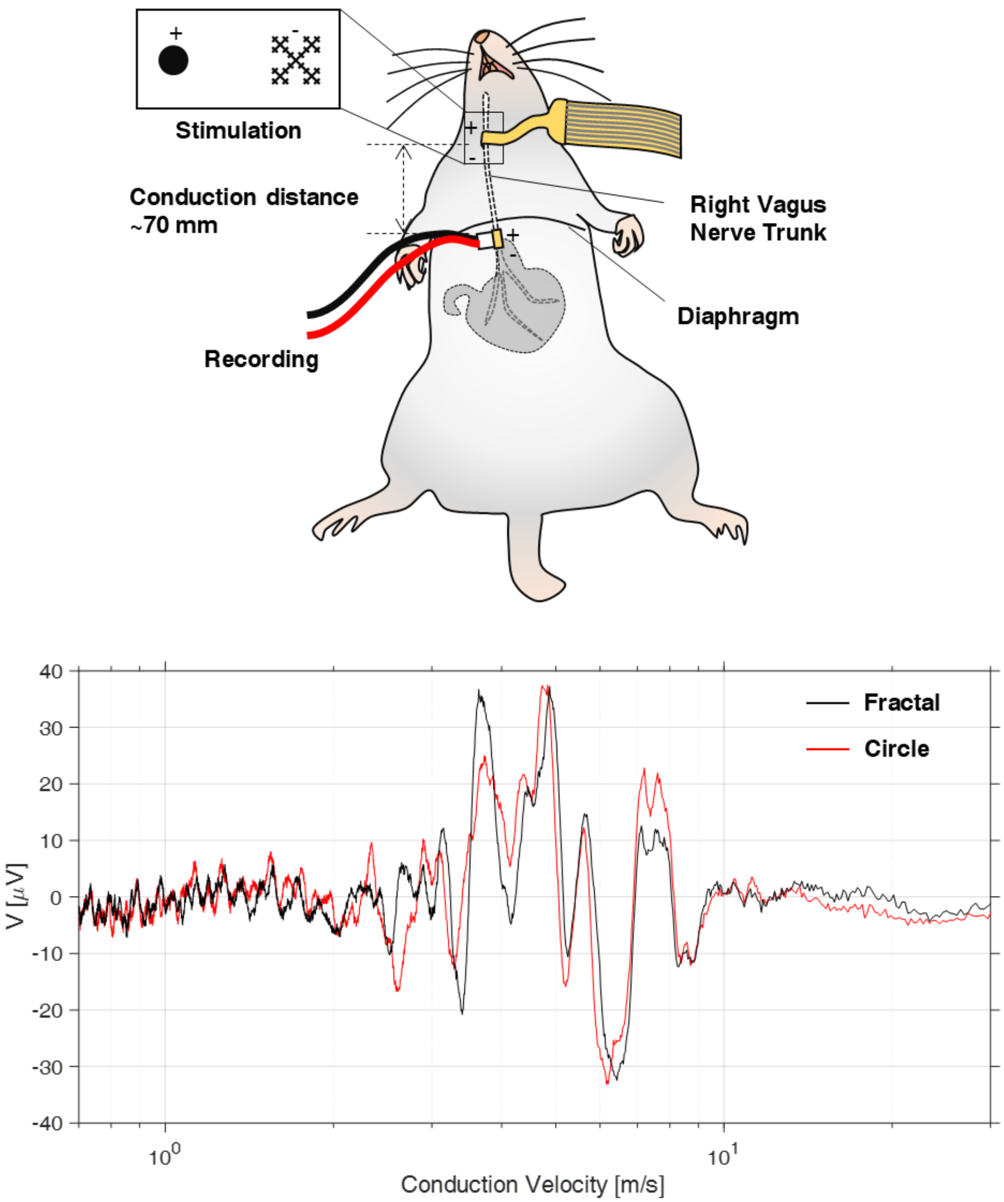

Figure 1. Representative compound action potentials elicited by stimulating the right cervical vagus nerve with fractal/circle microelectrodes (pulse amplitude: 0.4 mA, pulse width: 0.1 ms), and measured from the dorsal abdominal vagal trunk. We observed clear volleys in the conduction velocity range for small myelinated fibers (Aδ and B, 15-3 m/s) as well as highly dispersed volleys in the conduction velocity range for unmyelinated fibers (C, > 3 m/s) for both fractal and circle electrodes.

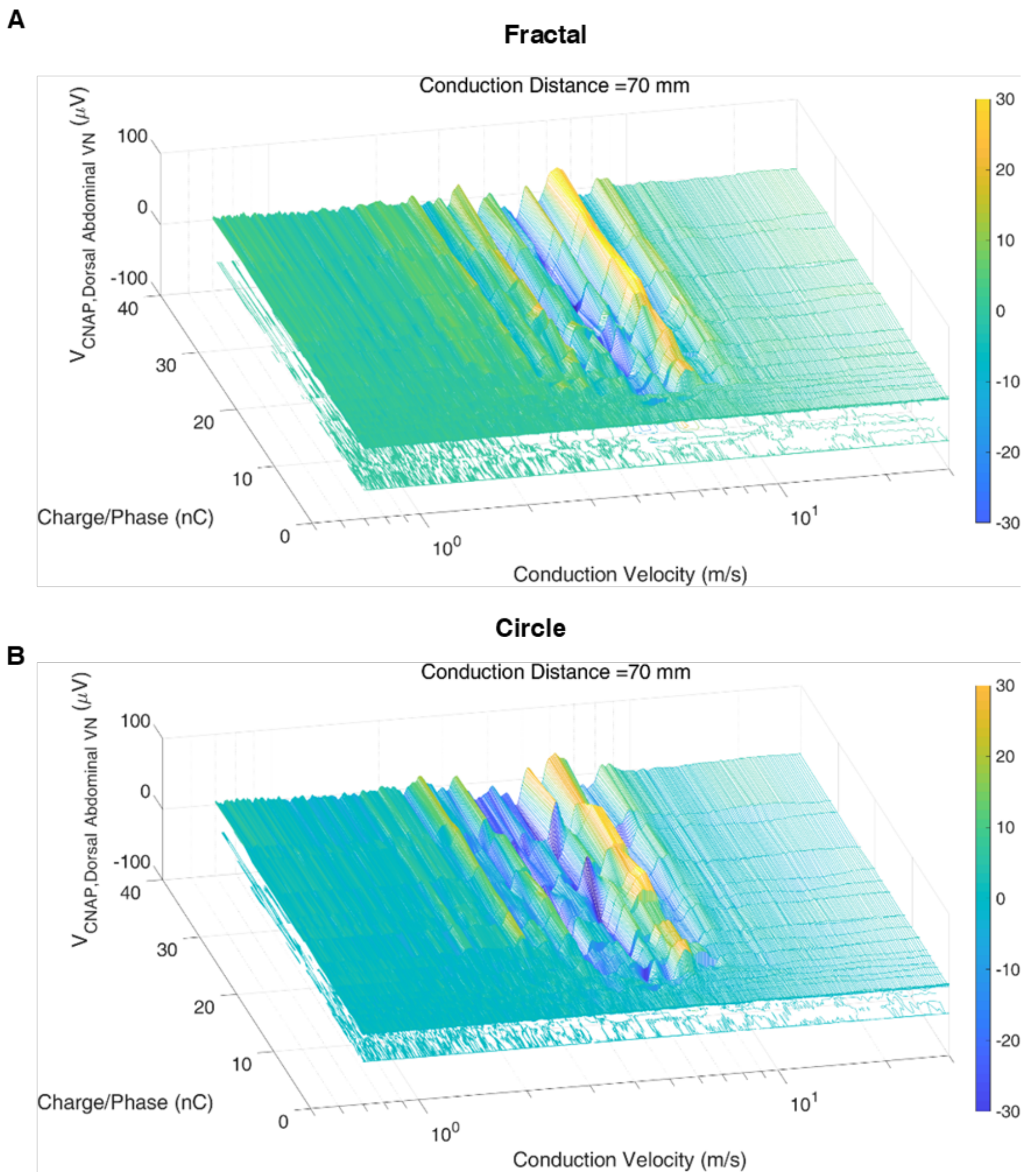

Figure 2. Results from parameter sweep using the autonomous neural control (ANC) system. Mesh plots of the resultant CAPs with respect to the conduction velocity and the charge per phase from the fractal electrode (A) and the circle electrode (B).