Closed-loop Neuromodulation in Epilepsy and Depression

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VAGUS nerve stimulation (VNS) is an effective treatment alternative for many epileptic and depressed patients whose symptoms are not well managed with pharmaceutical therapy. Approximately 2-weeks after device implantation, a physician programs the pacemaker-like device to deliver intermittent pulses of current to the left cervical vagus nerve. The highest efficacy is typically observed after 1 year, but only after several minimally informed stimulus parameter adjustments [1, 2].

Stimulus parameters are poor predictors of therapeutic efficacy, as each patient and nerve will uniquely respond to the same strength of stimulation [3]. With this in mind, the stimulus parameter-based dosing system in use today helps to explain why the therapeutic mechanisms are not well understood despite decades of investigation [1], and perhaps why better efficacy is not observed on a shorter timescale [2]. It has impeded the development of an objective, informed dosing system and limited the full therapeutic potential of this highly promising technology. A selective, biofeedback-driven and responsive form of VNS is needed to improve the overall efficacy and to further reduce the number and severity of side effects.

We present Autonomous Neural Control (ANC), a nerve activation control system designed to eliminate patient response variability and the detrimental effects of the foreign-body response at the device-tissue interface (Fig. 1). In rats, ANC rapidly learns how to most efficiently activate any proportion of vagal A, B, and/or C fibers over time. It provides a new dosing mechanism based on neural activation – the biological conduit of the therapy – rather than the strength of a stimulus, which has variable effect across patients. In real time, evoked compound nerve action potential (CAP) responses are systematically decoded and used to construct a patient-specific Nerve Activation Profile (NAP), which describes how each neuron population in the nerve will respond to any strength of stimulation. As VNS therapy is provided, ANC continuously refines the NAP to improve its prediction accuracy and adapt to circadian, drug-induced, or immune-mediated changes at the device-tissue interface [3].

For investigators, ANC can be used to design and perform experiments that systematically delineate the therapeutic and non-therapeutic mechanisms of VNS. Furthermore, suspected or known biological markers of treatment response can be measured and classified with respect to the NAP, simplifying the development of fully-personalized, closed-loop control systems for epilepsy and depression. *For physicians*, ANC will 1) establish an objective, standardized dosing system based on the level of nerve/neuron activation (expressed as a % of maximal nerve/neuron activation), 2) eliminate the complicated, time-consuming stimulus parameter tuning process, 3) provide a simple mechanism to adjust the relative ratios of A, B and C fiber activation, and 4) ensure that therapeutic nerve/neuron activation is maintained over time. *For patients*, ANC will 1) enhance the overall quality of VNS therapy, 2) reduce the number of doctor visits, and 3) help extend device lifetime by reducing energy waste from excessive stimulation [3].

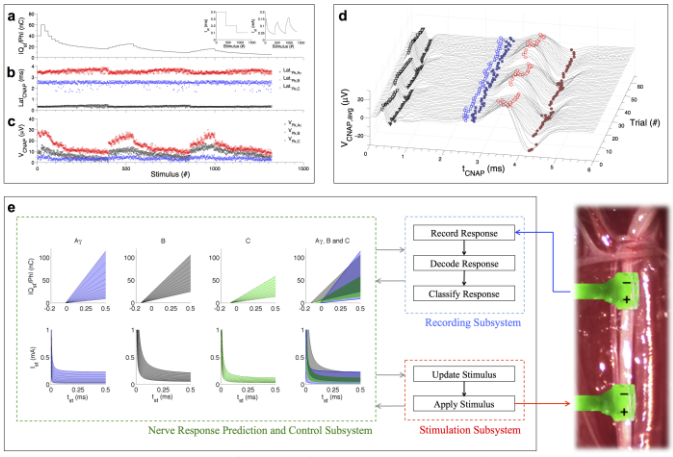

Fig. 1. Autonomous Neural Control (ANC). **a-c**) Stimulus response data from the left cervical vagus nerve of rat (PRF = 20 Hz; d_{cond} = 8.0 mm). **d**) Mean compound nerve action potential response waveforms (N = 20 responses/trial). **e**) ANC-generated NAP from data in *a-d* with predicted charge-duration and strength-duration curves for [0, 10, …, 100%] activation.

REFERENCES

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