Functional Stimulation of Motor and Sensory Axons Via Regenerative Sieve Electrodes

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ABSTRACT

Introduction: The peripheral nervous system (PNS) is a promising biological target for neuroprotheses designed to assist individuals challenged with complex motor deficits. Unfortunately, the development of neuroprotheses capable of interfacing the PNS has been limited by the inability of existing microelectrodes to achieve a stable, chronic, high specificity interface with peripheral nervous tissue *in vivo*. Regenerative macro-sieve electrodes present a unique alternative to such devices, enabling a stable interface to regenerative nerve tissue, yet have not been optimized to facilitate functional electrical stimulation of regenerated motor axons. The present study aimed to design and implement a novel, dual-sided macro-sieve electrode capable of permitting selective stimulation of large numbers of regenerated motor axons and facilitating graded recruitment of distal musculature.

Methods: Single-sided macro-sieve electrodes (8-channel) were fabricated via sacrificial photolithography and fused back-to-back to form dual-sided macro-sieve assemblies (16-channel). Sieve electrode assemblies containing single-sided and dual-side macro-sieve electrodes were implanted in the sciatic nerve of male Lewis rats for a period of 3 months. Post-operatively, functional nerve regeneration through implanted electrodes was assessed *in situ* via nerve conduction studies and evoked muscle force measurement. Peripheral nerve interfacing was assessed *in situ* by stimulating regenerated nerve tissue via implanted macro-sieve electrodes while simultaneously recording initiated action potentials and muscle force production. Selective activation of unidirectional action potentials via dual-side sieve electrodes was additionally examined.

Results: Single-sided and dual-sided macro-sieve electrodes were observed to support robust nerve regeneration, muscle preservation, and peripheral nerve interfacing 3 months post-operatively. *In situ* assessment demonstrated that both single-sided and dual-sided macro-sieve electrodes facilitated functional stimulation of regenerated motor axons, and selective / graded recruitment of distal musculature comparable to gold-standard peripheral nerve interface technologies. Additionally, dual-sided macro-sieve electrodes were tentatively observed to facilitate initiation of unidirectional action potentials in select populations of regenerated axons through the use of multi-polar stimulation paradigms.

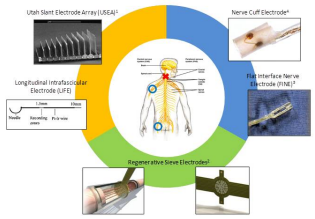
Conclusions: Macro-sieve electrodes represent a significant advance in the design of regenerative microelectrode technologies. Dual-sided macro-sieve electrodes represent an additional improvement, facilitating increased selectivity of activation and initiation of unidirectional action potentials in chronically interfaced peripheral nerve tissue.

INTRODUCTION

Microelectronic Interfaces to the Peripheral Nervous System:

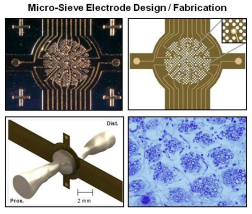
- Numerous devices have been designed to facilitate electrical stimulation of peripheral nervous tissue
- No one device possesses both the selectivity and stability needed for chronic use *in vivo*
- Regenerative sieve electrodes offer a unique approach to the development of a selective, reliable interface to peripheral motor axons

Optimal Approach to Peripheral Nerve Interfacing?



Regenerative Sieve Electrodes Achieve an Intimate Interface with Peripheral Nerves:

Micro-Sieve Electrode Design / Fabrication



Nerve Regeneration through Micro-Sieve Electrodes

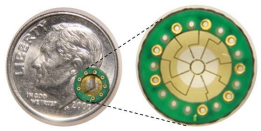
- Regenerative sieve electrodes are flexible thin-film devices capable of interfacing small groups of axons regenerating through via holes in the electrode
- Prior studies demonstrate that axons readily regenerate through the porous region of the electrode forming small "microfascicles" that cross individual holes
- Sieve electrodes enable a stable interface to peripheral axons shown to last >1 year in vivo

INTRODUCTION

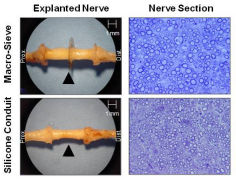
Macro-Sieve Electrodes Enable Stable Interface to Peripheral Nerve Tissue:

- Novel high-porosity sieve electrode with low profile traces
- Support robust axonal regeneration equivalent to empty nerve guidance conduit
- Enables stable FES of regenerated nerve tissue for over 5 months *in vivo*

Macro-Sieve Electrode



Explanted Nerve | **Nerve Section**



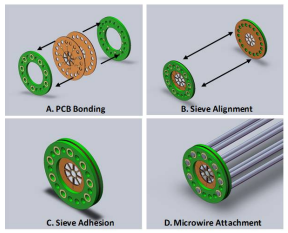
- *Interfacial capabilities of single-sided macro-sieve electrodes are limited*
- Single-sided macro-sieve electrodes posses limited number of channels
- Presence of electrode sites on only one side of wafer results in initiation of action potentials propagating in both anterograde / retrograde directions

HYPOTHESIS: Dual-sided macro-sieve electrodes will support robust axonal regeneration, facilitate selective recruitment of peripheral motor axons, and enable initiation of unidirectional APs

METHODS

Design , Fabrication, and Assembly of Dual-Sided Macro-Sieve Electrodes:

- Custom single-sided macro-sieve electrodes were fabricated via sacrificial photolithography [Specifications: 9 via holes, 600 um hole dia., 8 electrode sites, 85% transparency]
- Single-sided macro-sieve electrode were fused back-to-back to form dual-sided macro-sieve electrodes [Specifications: 9 via holes, 600 um hole dia., 16 electrode sites, 85% transparency]
- Polyimide electrodes were bonded to custom PCBs, and modified with nerve guidance conduits and Pt microwire leads

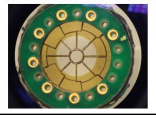


Experimental Design / Surgical Implantation:

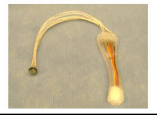
- Macro-sieve electrodes and empty silicone conduits were implanted into the sciatic nerve of 300g male Lewis rats
- Nerve regeneration, functional recovery, and peripheral nerve interfacing were assessed 3 months post-operatively

Group:	I	II	III	IV
Description:	*Healthy Nerve*	*Silicone Conduit*	*Single-Sided Sieve*	*Dual-Sided Sieve*
Conduit:	None	Silicone Conduit	Silicone Conduit	Silicone Conduit
Electrode:	None	None	Macro-Sieve	Macro-Sieve
Dual / Single:	None	None	Single-Sided	Dual-Sided
Image:				

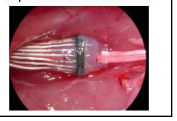
Dual-Sided Macro-Sieve Electrode



Electrode Assembly



Implanted Dual-Sided Electrode

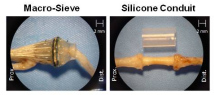


RESULTS: Nerve Regeneration

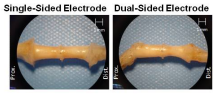
Macroscopic Examination of Explanted Nerve Segments:

- Single-sided and dual-sided macro-sieve electrodes support robust nerve regeneration comparable to empty silicone conduits and superior to previous micro-sieve electrodes

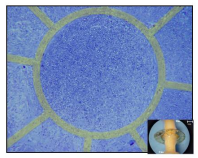
Macro-Sieve | **Silicone Conduit**



Single-Sided Electrode | **Dual-Sided Electrode**



Nerve Regeneration Through Macro-Sieve Electrode

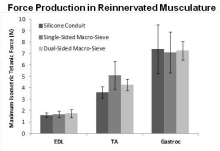


RESULTS: Functional Recovery

Evoked Muscle Force Measurement:

- Single-sided and dual-sided macro-sieve electrodes do not impede functional regeneration and support robust muscle reinnervation post-operatively
- Nerve conduction studies, muscle mass measurements, behavioral assays corroborate observations

Force Production in Reinnervated Musculature



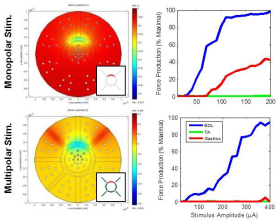
Simulated Response In Model Axons (mV)

RESULTS: Peripheral Nerve Interfacing

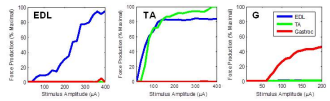
Functional Stimulation and Selective Recruitment of Distal Musculature:

- Dual-sided electrodes supported greater numbers of functional electrode sites, increased number of stimulation paradigms
- Single-sided and dual-sided electrodes demonstrated similar interfacial properties, with stimulus thresholds between 10-40 uA
- Multipolar paradigms ("field steering") facilitate enhanced selectivity of muscle activation

Model Evoked Potential



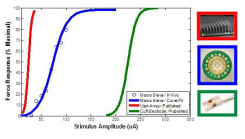
Maximal Inter-Muscle Selectivity:



- Macro-sieve electrodes capable of selectively eliciting >95% maximum force output in individual muscles prior to co-activation of antagonists

Graded Recruitment of Distal Musculature via Macro-Sieve Electrodes:

- Macro-sieve electrodes enable graded recruitment of distal musculature, which is enhanced through implementation of multipolar stimulation paradigms
- Macro-sieve electrodes demonstrate a lower threshold than cuff electrodes and a broader recruitment curve than existing peripheral nerve interface technologies



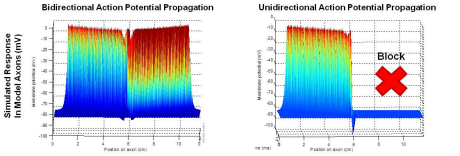
RESULTS: Initiation of "Unidirectional" Action Potentials

Simulation of Dual-Sided Macro-Sieve Electrode Functionality:

- Theoretical models suggest dual-sided macro-sieve electrodes may enable selective blockade of action potential propagation without the use of high-frequency stimuli
- Depolarizing/hyperpolarizing stimuli routed to paired electrode sites on either side of dual-sided macro-sieve electrode enable initiation of "unidirectional" action potentials
- FEM/NEURON simulation of dual-sided macro-sieve electrode confirm ability to control direction of action potential propagation through focal blockade of activated axons

Single-Sided Macro-Sieve Electrode | **Dual-Sided Macro-Sieve Electrode**

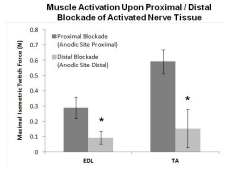
Bidirectional Action Potential Propagation | **Unidirectional Action Potential Propagation**



Initiation of "Unidirectional" Action Potentials *In Vivo*:

- Pairs of electrode sites were identified on implanted dual-sided sieve electrodes
- Muscle activation was recorded upon proximal and distal blockade of similar activated axonal populations (initiation of anterograde / retrograde action potentials)
- Distal blockade was demonstrated to significantly decrease muscle activation, suggesting successful control of the directionality of action potential propagation

Muscle Activation Upon Proximal / Distal Blockade of Activated Nerve Tissue



CONCLUSIONS

1. Dual-sided macro-sieve electrodes support superior axonal regeneration, muscle preservation, and peripheral nerve interfacing similar to single-sided electrodes
2. Dual-sided macro-sieve electrodes enable selective and graded recruitment of distal musculature, comparable to existing gold-standard microelectrodes
3. Dual-sided macro-sieve electrodes may enable selective initiation of uni-directional action potentials without the use of high-frequency blockade
4. Advanced regenerative electrodes represent a viable means of facilitating functional electrical stimulation of peripheral nerve tissue in advanced neuroprosthetic systems aimed at restoring motor/sensory function

ACKNOWLEDGMENTS

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