Development of Conductive Stimuli-Responsive Fibrous Hydrogels for Neural Interfaces

Seyed Shahrooz Zargarian, Chiara Rinoldi, Yasamin Ziai, Mohammad Ali Haghighat Bayan, Paweł Nakielski, and Filippo Pierini

Institute of Fundamental Technological Research Polish Academy of Sciences, 02-106 Warsaw, Poland.

shzargar@ippt.pan.pl

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Introduction

Conductive hydrogels in neuroscience

- ✓ Tissue-like softness and sufficient electrical conductivity
- ✓ Promising for neural electrode soft interfaces
- ✓ Neural tissue mechanical properties match
- ✓ Lower tissue irritation and scarring
- ✓ Poly(N-isopropylacrylamide) (PNIPAAm) as a thermal-stimulus responsive material.
- ✓ Volume phase transition (VPT) of PNIPAAm, depending on the temperature

a) b)

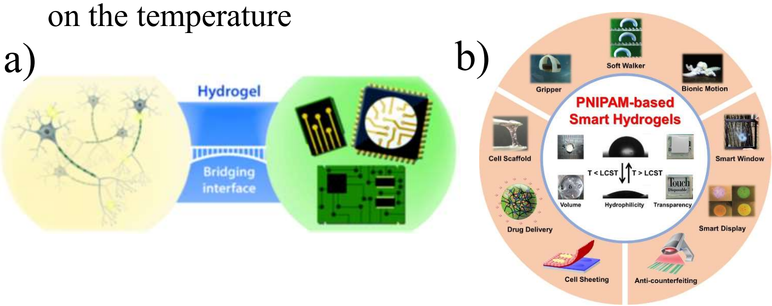

Figure 1. a) Conductive hydrogels at the interface between biology and electronics. b) Thermo-responsive properties and applications of PNIPAM-based smart hydrogels. (https://doi.org/10.1039/C8CS00595H) (https://doi.org/10.1016/j.pmatsci.2020.100702)

Shortcomings of isotropic hydrogels

- Slow stimuli responsivity of the ordinary isotropic hydrogels
- Poor adhesion of hydrogels to metallic electrodes
- Low specific capacitance

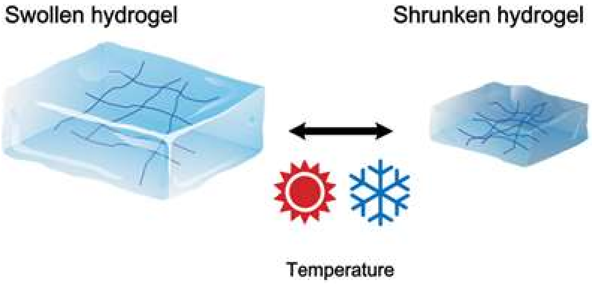

Figure 2. An example of anisotropic fibrous hydrogels with reversible swelling/shrinking behaviours in response to temperature. (https://doi.org/10.1038/s41427-019-0165-3)

Demand for anisotropic responsive conductive hydrogels

Producing anisotropic hydrogel by electrospinning

- ✓ High porosity and specific surface area
- ✓ Low thickness
- ✓ Good match of mechanical properties
- ✓ Easy adjustment of the hydrogel properties
- ✓ Fast hydration/dehydration response
- ✓ Fast stimuli responsivity
- ✓ Low electrical impedance
- ✓ Better recording/stimulating

Synthesis of cross-linkable NIPAAm copolymers

Co-polymerization Kinetic of P(NIPAAm-*co*-GMA) (NG)

A free-radical copolymerization yielded high Mw and a low PDI copolymers

- High dependency of kinetic on the GMA content

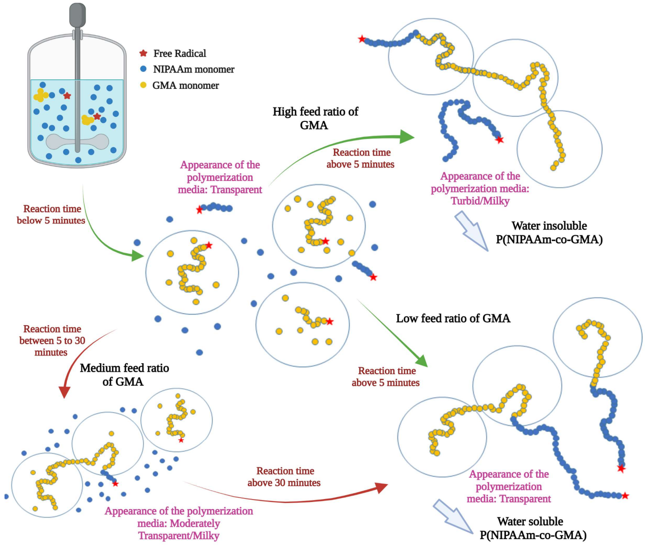

Figure 3. Depiction of polymerization kinetic: high dependency of copolymer water solubility on initial monomer feed ratio.

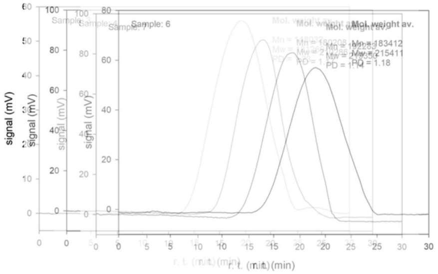

Figure 4. GPC results of the synthesized copolymers, having:

- High molecular weight (118000<Mw<230000)
- Narrow molecular weight distribution (1.14<PDI<1.23)

A hydrophilic copolymer with pendant epoxy groups

- Proof of GMA presence in the copolymer backbone
- NG copolymer is water soluble for GMA<7% (feed ratio)
- A good balance of hydrophilicity and GMA content for NG95

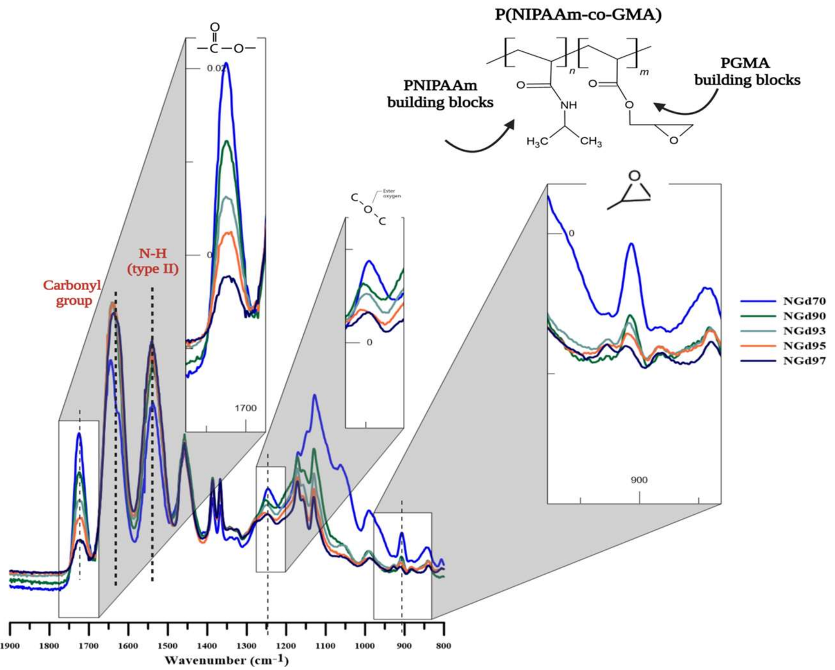

Figure 5. FTIR spectra of the synthesized crosslinkable P(NIPAAm-co-GMA) polymers.

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NG95 hydrogel

A thermogelling NG95 and a hydrophilic dendrimer

- Thermogelling properties of NG95
- When Combined with a chemical crosslink: dual hardening properties
- Crosslinking of NG95 with a cytocompatible and degradable dendrimer: Poly(amidoamine) (PAMAM)
- Switches on injectability

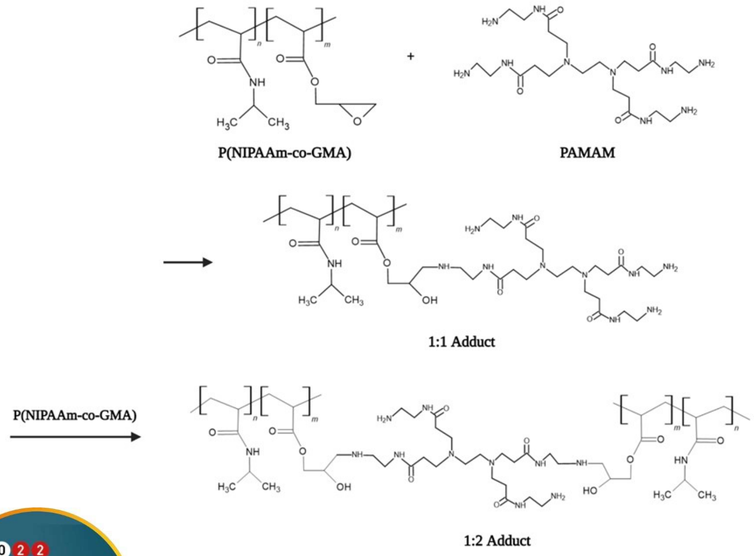

Figure 7. Crosslinking mechanism between the NG and PAMAM

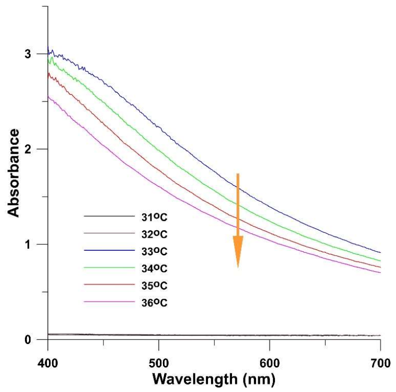

Figure 6. Determining the LCST of NG95 by UV–vis spectroscopy. Absorbance spectra of sample heated at 1 °C/min.

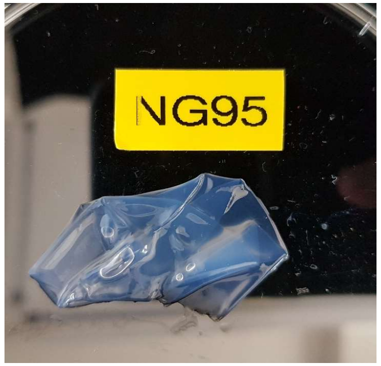

Figure 8. Bulk hydrogel of NG95 crosslinked with PAMAM

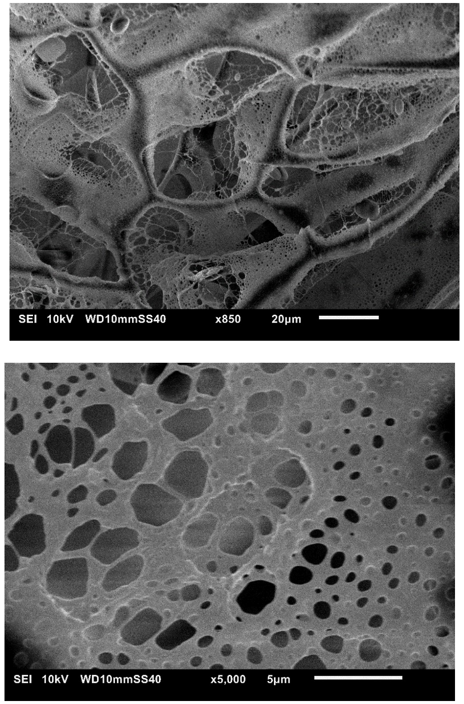

Figure 9. SEM images of lyophilized NG95 bulk hydrogel with two different levels of magnification

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Fabrication of anisotropic conductive fibrous semi-IPN hydrogels

Properties of the crosslinked fibrous membrane

- Tolerance for several hydration/dehydration cycles
- Higher porosity while in hydrogel state
- NG95 soak up water more than 30 times of its original weight

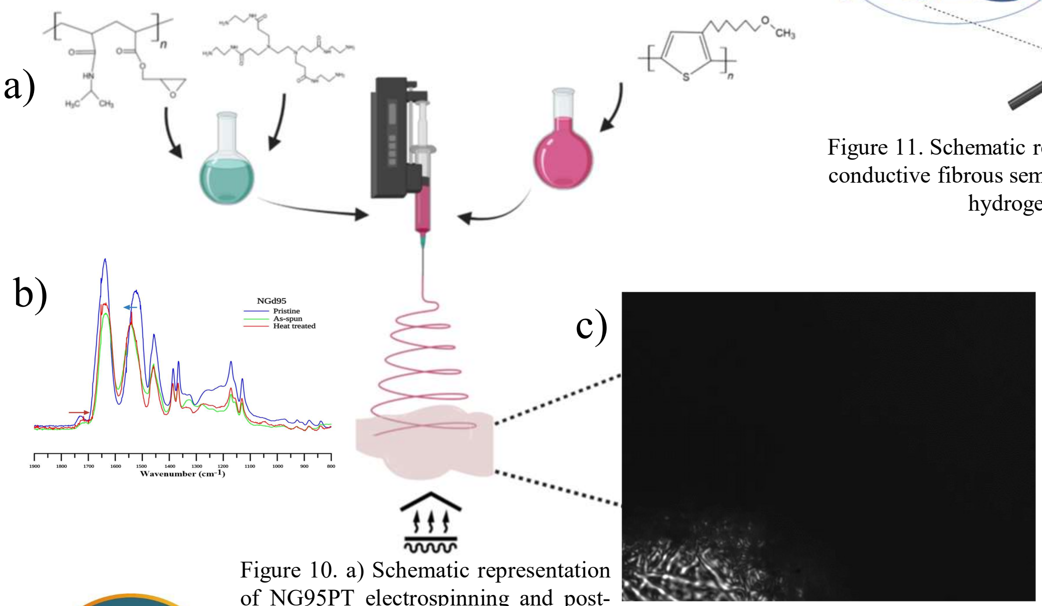

Figure 10. a) Schematic representation of NG95PT electrospinning and post-heat treatment, b) FTIR spectra of the pristine, as-spun, and heat treated NG95, c) time evolution of crosslinked fibrous membrane into its hydrogel state recorded by light microscope.

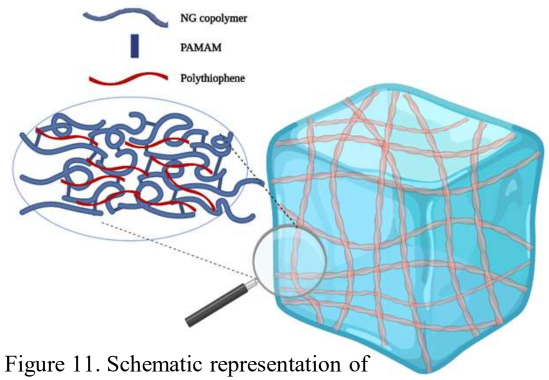

Figure 11. Schematic representation of conductive fibrous semi-IPN NG95PT hydrogel

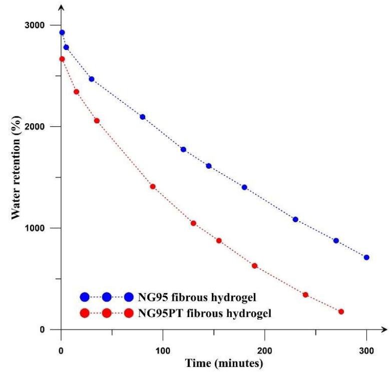

Figure 12. Water retention of NG95 and NG95PT

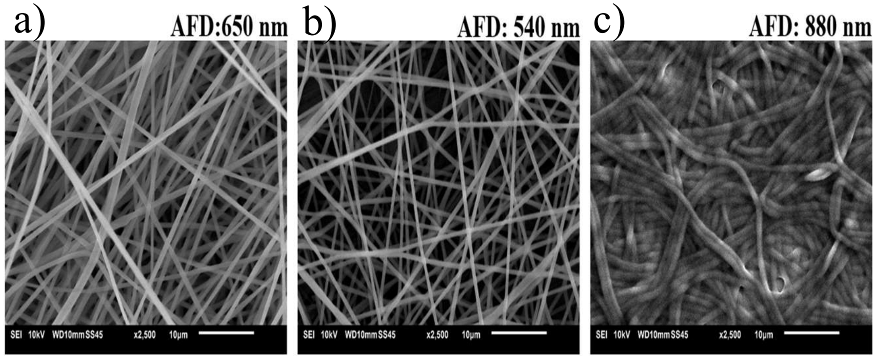

Figure 13. SEM images of nanofibrous semi-IPN network: (a) as-spun, (b) heat-treated, and (c) swelled in water and then dried.

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Conductive NG95 fibrous hydrogel for neural probe coating

Cell studies

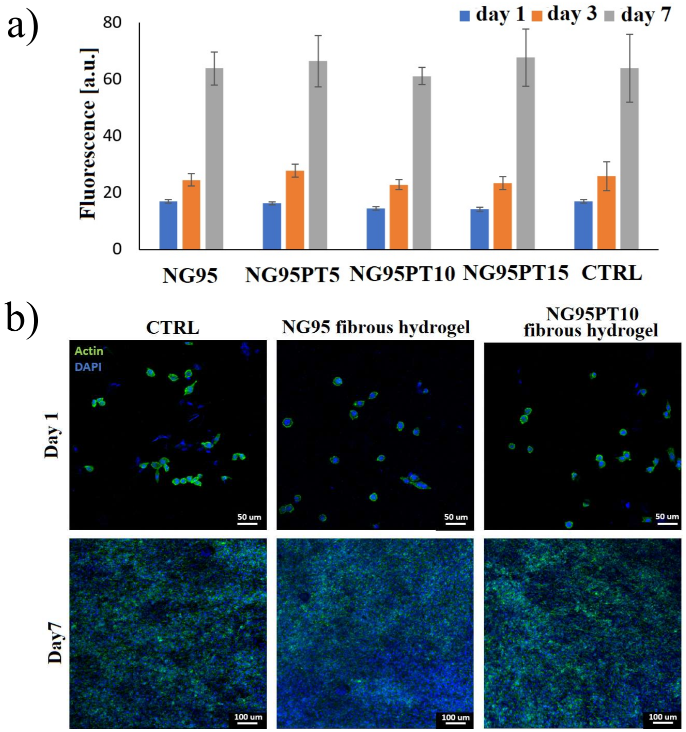

Figure 14. Cell studies on fibrous NG95 and its conductive variants (a) direct contact cytotoxicity assay and (b) confocal images of fibroblast cells cultured on the fibrous hydrogels.

Electrical properties

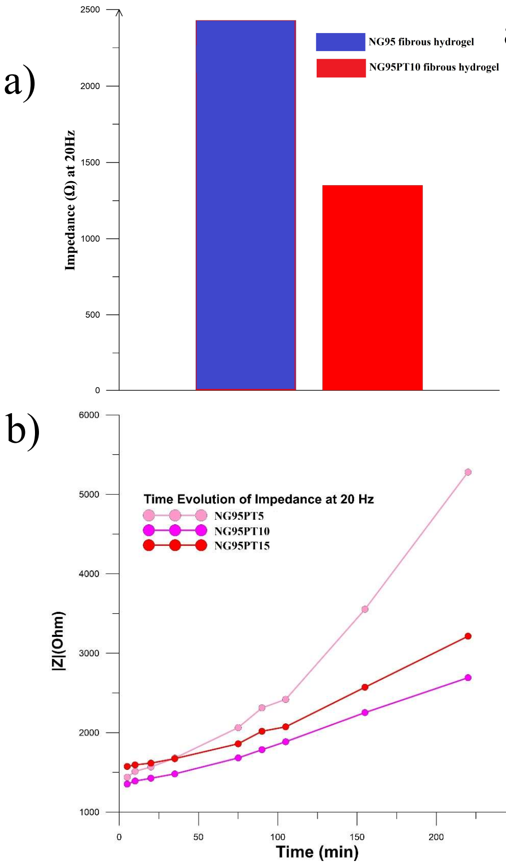

Figure 15. Impedance values at biomedically significant frequencies a) of NG95 fibrous hydrogel and its conductive variants, and b) their relevant time dependency of impedance

Coating on a neural probe

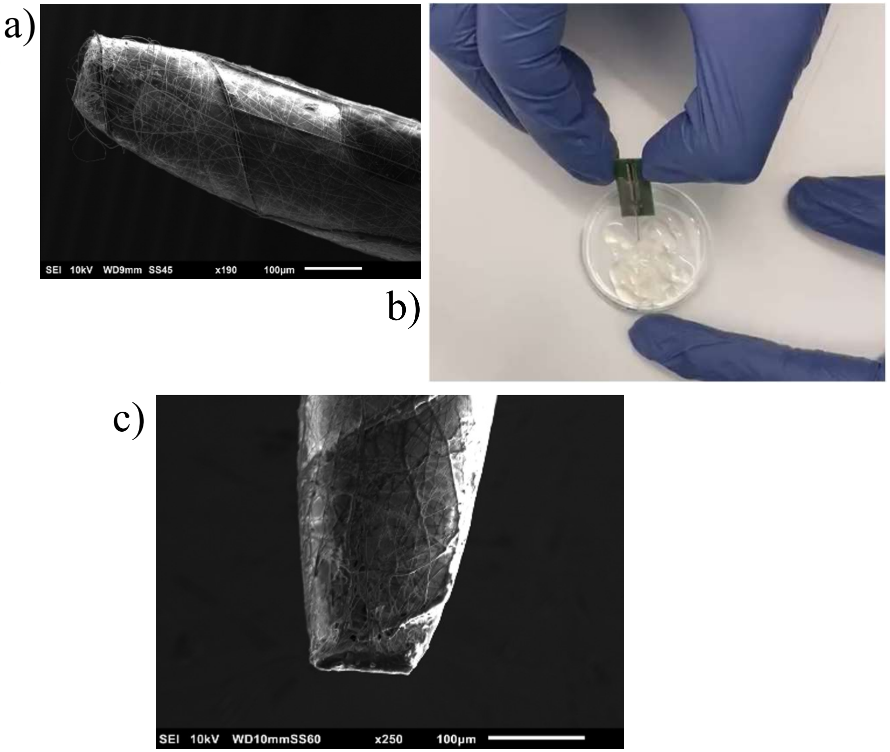

Figure 16. SEM and camera video of fibrous NG95PT10 coated on a neural probe a) heat-treated, b) inserted in and pulled out from sodium alginate bulk hydrogel, and c) dried afterwards.

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Applications of NG95, extended

Thermogelling ink

Fast shape recovery

Photo-thermal responsivity

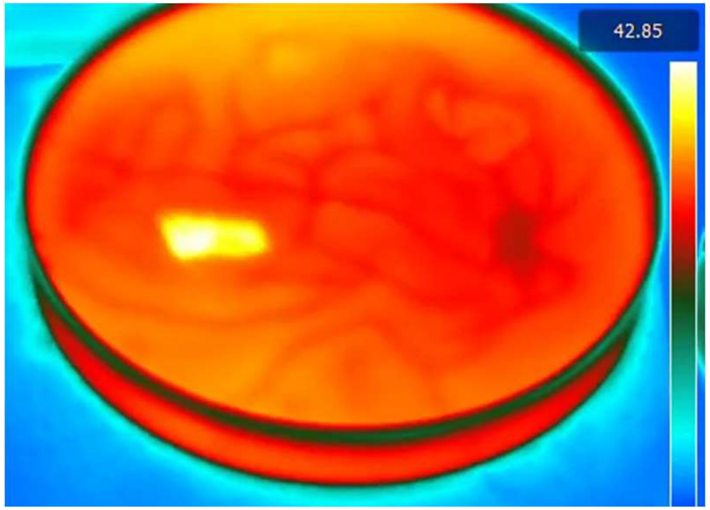

Figure 17. Camera video of a) NG95PT solution injection in water bath at 37^{o}C b) the fibrous NG95 fast shape recovery and c) the fast thermal actuation of this fibrous structure when filled with photo-responsive materials.

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Conclusions

An innovative method for fabricating fibrous hydrogels derived from P(NIPAAm-*co*-GMA) copolymers has been demonstrated in this work. The post electrospinning heat treatment led to the formation of highly crosslinked nanofibers. The fabricated membrane can tolerate several hydration/dehydration cycles. The results of this work can open the doors for these smart nanostructure hydrogels in applications such as neural interfaces, bio 3D printing and soft robotics.

ACKNOWLEDGMENTS

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