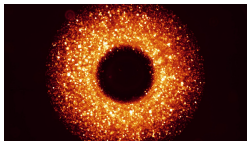

École Polytechnique Fédérale de Lausanne

Research Internship Report

Iontronic Hydrogel for Multipurpose Biointerfaces

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Abstract

Iontronic hydrogels represent a revolutionary class of materials that combine the properties of ionic conductors with soft, stretchable polymer networks. This report presents a comprehensive study of iontronic hydrogels for multipurpose biointerfaces, including their fundamental properties, fabrication methods, characterization techniques, and diverse applications in biomedical engineering. The research encompasses electrical, mechanical, and biological characterization of these materials, demonstrating their potential for wearable sensors, prosthetic interfaces, and therapeutic devices. We developed **macroscale asymmetric hydrogels** for wearable electrophysiological sensors featuring wire-bondable electrical connections, and **microscale hydrogel droplets** ($\sim$100 μm) for implantable ultrasound contrast enhancement enabling personalized and targeted medical treatments. Through systematic investigation using scanning electron microscopy (SEM), electrochemical impedance spectroscopy (EIS), tensile testing, mechanical characterization, and electromyography (EMG) signal acquisition, this work establishes iontronic hydrogels as promising candidates for next-generation biointerfaces that bridge the gap between biological systems and electronic devices.

Mechanical testing and SEM imaging performed at DLL Matériaux et Bioingénierie.
EMG recordings conducted at the Translational Neural Engineering Lab.

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1 Introduction

1.1 Background and Motivation

The human-machine interface has evolved dramatically over the past decades, driven by the need for seamless integration between biological systems and electronic devices [1, 2]. Traditional electronic materials, while highly conductive, often suffer from mechanical mismatch with soft biological tissues, leading to interface instability, signal degradation, and potential tissue damage [3]. This fundamental challenge has spurred intensive research into soft, biocompatible materials that can bridge the gap between rigid electronics and dynamic biological systems.

The interface between biological systems and electronic devices represents one of the most challenging frontiers in biomedical engineering. Traditional metallic electrodes, while effective for signal transduction, suffer from mechanical mismatch with soft biological tissues, leading to inflammation, signal degradation, and device failure over time [4]. This fundamental incompatibility has driven the search for soft, biocompatible materials that can seamlessly integrate with living systems.

1.2 Iontronic Hydrogels: A Paradigm Shift

Iontronics, an emerging field that exploits mobile ions as charge carriers, has opened new horizons for bioelectronics [5]. Unlike conventional electronics that rely on electron transport, iontronic devices utilize ion transport mechanisms, mirroring the fundamental operating principles of biological systems [6]. This intrinsic compatibility makes iontronic materials particularly attractive for biointerface applications, where traditional materials fail to meet the stringent requirements of biological systems.

Iontronic hydrogels represent a convergence of polymer science, electrochemistry, and bioengineering [7]. These materials consist of hydrophilic polymer networks swollen with ionic solutions, creating a soft, stretchable, and ionically conductive matrix. The unique combination of properties includes:

- High ionic conductivity (up to 10 S/m) [6]
- Excellent stretchability (>1000% strain) [7]
- Biocompatibility and biodegradability [2]
- Self-healing capabilities [8]
- Transparency with tunable mechanical properties [1]

These characteristics position iontronic hydrogels as ideal candidates for biointerfaces, where they can serve multiple functions simultaneously: signal transduction, mechanical support, and biological compatibility [5]. The ionic conduction mechanism enables direct communication with biological systems, while the soft, hydrated structure minimizes tissue damage and inflammatory responses.

1.3 Research Context

The biointerface plays a crucial role in bridging the interaction between biological tissues and artificial devices, directly impacting the performance of implantable and wearable biomedical devices [3]. Among various materials, hydrogels have emerged as promising candidates for biointerfaces due to their high water content, tissue-like mechanical properties, and excellent biocompatibility [2]. In particular, hydrogels serve as ideal platforms for both implantable and wearable applications, where the required scale and structural design differ significantly depending on the specific use-case.

To systematically explore and master the fabrication of hydrogels with application-specific scales and functionalities, this summer research project focused on the development and characterization of hydrogel-based biointerfaces for both wearable and implantable devices.

1.3.1 Wearable Applications: Macroscale Hydrogels

For wearable applications, we developed macroscale hydrogels using a molding approach. These hydrogels exhibited excellent electrical conductivity, adhesiveness, skin conformability, and biocompatibility, enabling reliable electrophysiological signal recording.

Notably, one of the key limitations of current wearable hydrogel biointerfaces lies in the lack of robust connections with external devices [3]. To address this, we designed a hydrogel with an **asymmetric structure**: one side is adhesive for reliable skin attachment, while the other is **wire-bondable and solderable**, allowing stable integration with external electronic devices.

1.3.2 Implantable Applications: Microscale Hydrogel Droplets

For implantable applications, we aimed to fabricate microscale hydrogels ($\sim$100 μm) using a printing method. By extruding the hydrogel pre-solution into an oil phase using a microsyringe, followed by in situ gelation, we successfully produced hydrogel microdroplets.

Furthermore, by removing metal microparticles embedded in the hydrogel microdroplets, we acquired hydrogel microdroplets with cavities inside. These cavity-containing hydrogel microdroplets are designed to **enhance ultrasound signal scattering and reflection**, offering a promising strategy to **help patients and physicians** achieve better ultrasound imaging quality in implantable settings. This improvement enables **more personalized and targeted medical treatments** by providing clearer visualization of tissues and implanted devices.

1.4 Multi-Scale Approach

This research addresses biointerface challenges across two distinct scales, each with specific applications and design requirements:

- **Macroscale hydrogels** (millimeter to centimeter scale): Designed for wearable electrophysiological sensors with emphasis on skin conformability, adhesion, and robust electrical connections through wire bonding.

- **Microscale hydrogel droplets** ($\sim$100 μm): Fabricated for implantable applications, specifically for ultrasound imaging contrast enhancement to support personalized medicine.

1.5 Research Objectives

The primary objectives of this research are:

1. Develop iontronic hydrogel formulations with optimized electrical, mechanical, and biological properties
2. Design and fabricate asymmetric macroscale hydrogels with dual-functional surfaces (adhesive + wire-bondable)
3. Apply droplet printing protocols for microscale hydrogel fabrication with internal cavities
4. Characterize material properties through comprehensive electrical, mechanical, and morphological analysis
5. Demonstrate functional performance through EMG signal acquisition and ultrasound imaging enhancement
6. Understand the chemical basis of hydrogel formation and ionic conductivity

This multi-scale, multi-functional approach aims to establish iontronic hydrogels as versatile platforms for diverse biomedical applications, contributing to the advancement of personalized and targeted healthcare technologies [5, 2].

2 Chemistry of Iontronic Hydrogels

2.1 Molecular Components

The iontronic hydrogels developed in this study are based on polyacrylamide (PAAm) networks synthesized through free radical polymerization. The key molecular components are:

2.1.1 Acrylamide (Monomer)

Acrylamide (C_3H_5NO) serves as the primary building block of the polymer network [7]. Its structure features a vinyl group ($CH_2{=}CH^-$) that undergoes polymerization and an amide group ($-CONH_2$) that provides hydrophilicity and hydrogen bonding capability.

(a) Structural formula (b) 3D molecular model

Figure 1: Acrylamide monomer structure. The vinyl group enables polymerization while the amide group provides water solubility and hydrogen bonding sites.

Key properties of acrylamide:

- Molecular formula: $CH_2{=}CH{-}CO{-}NH_2$
- Molecular weight: 71.08 g/mol
- Highly water-soluble due to polar amide group
- Readily polymerizes via free radical mechanism
- Forms linear polymer chains when polymerized alone

2.1.2 N,N'-Methylenebisacrylamide (Crosslinker)

N,N'-Methylenebisacrylamide (MBAA, $C_7H_{10}N_2O_2$) functions as the crosslinking agent that creates the three-dimensional network structure essential for hydrogel formation [7, 6]. This bifunctional molecule contains two acrylamide groups connected by a methylene bridge.

(a) Structural formula (b) 3D molecular model

Figure 2: N,N'-Methylenebisacrylamide crosslinker structure. The two reactive vinyl groups enable formation of covalent bridges between polymer chains, creating the 3D network.

Key properties of MBAA:

- Molecular formula: $CH_2{=}CH-CO-NH-CH_2-NH-CO-CH{=}CH_2$
- Molecular weight: 154.17 g/mol
- Two reactive vinyl groups for network formation
- Crosslink density determines mechanical properties
- Controls mesh size and thus ionic mobility

2.2 Polymerization Mechanism

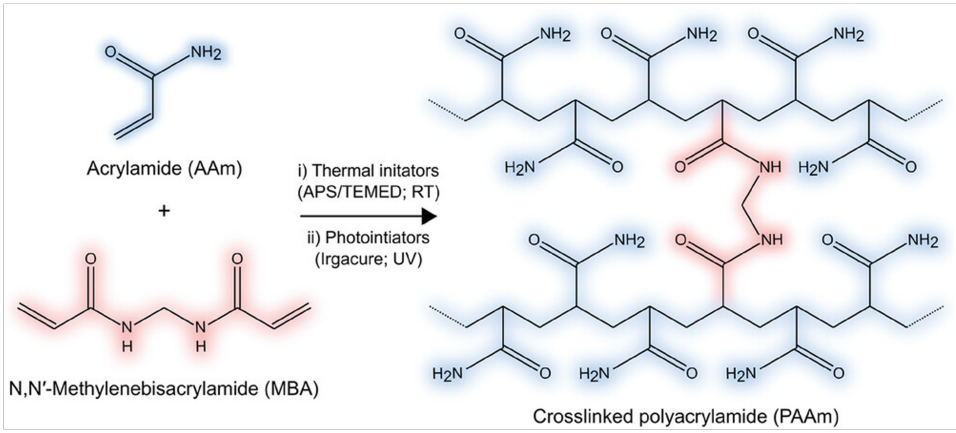
The hydrogel formation proceeds through free radical polymerization initiated by ammonium persulfate (APS):

1. **Initiation:** APS thermally decomposes to generate sulfate radicals ($SO_4^{\bullet -}$)
2. **Propagation:** Radicals attack vinyl groups of acrylamide, creating growing polymer chains
3. **Crosslinking:** MBAA molecules react with two different chains, forming covalent bridges
4. **Termination:** Radical recombination or disproportionation stops chain growth

The resulting network structure can be represented as:

$$n \cdot CH_2{=}CH{-}CO{-}NH_2 + m \cdot \text{MBAA} \xrightarrow{\text{APS}} \text{3D Hydrogel Network} \tag{1}$$

where the ratio n/m determines the crosslink density and thus the mechanical properties.



Milos, F. et Del Campo, A. (2024) « Polyacrylamide hydrogels as versatile biomimetic platforms to study cell-materials interactions », Advanced Materials Interfaces, 11(34), p. 2400404. Disponible sur: https://doi.org/10.1002/admi.202400404.

Figure 3: Schematic representation of acrylamide and MBAA free-radical polymerization into a crosslinked PAAm network.

2.3 Ionic Conductivity Mechanism

The ionic conductivity of our hydrogels arises from two sources:

2.3.1 Intrinsic Conductivity

Water molecules within the hydrogel network dissociate into H^+ and OH^- ions, providing baseline conductivity. Additionally, residual ionic species from the polymerization (sulfate ions, ammonium ions) contribute to charge transport.

2.3.2 Enhanced Conductivity with NaCl

Addition of sodium chloride (NaCl) dramatically increases ionic conductivity through [6, 5]:

- **Increased charge carrier density:** Dissociation of NaCl into Na^+ and Cl^- ions
- **High ionic mobility:** Small hydrated radii of Na^+ and Cl^- enable rapid transport
- **Reduced impedance:** More mobile charges reduce overall electrical impedance

As demonstrated in our impedance measurements (Section 6.2), NaCl addition reduces impedance by 29.7% at 1 kHz, confirming the effectiveness of this strategy.

2.4 Additional Molecular Components

Beyond the core acrylamide-MBAA system, several additional components enable specialized functionalities:

2.4.1 Acrylic Acid (for Double Network Hydrogels)

Acrylic acid ($CH_2{=}CH{-}COOH$) can be incorporated to create double network hydrogels with enhanced mechanical properties. The carboxylic acid groups provide:

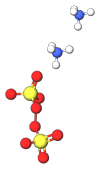
- pH-responsive swelling behavior
- Additional hydrogen bonding sites
- Improved toughness through sacrificial bonds
- Enhanced adhesion to biological tissues

2.4.2 Initiators

Two types of initiators are used depending on the gelation method:

Ammonium Persulfate (APS) – Thermal initiator:

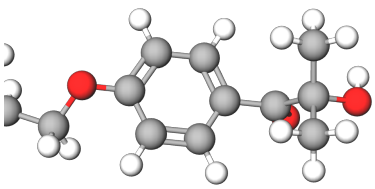
- Formula: $(NH_4)_2S_2O_8$
- Thermally decomposes at room temperature
- Generates sulfate radicals ($SO_4^{\bullet -}$) to initiate polymerization
- Suitable for bulk gelation and molding processes



3D molecular model of ammonium persulfate (APS).

Irgacure 2959 (I2959) – Photoinitiator:

- UV-activated initiator (peak absorption: 365 nm)
- Enables spatiotemporal control of gelation
- Ideal for droplet printing and patterned structures
- Biocompatible, widely used in tissue engineering



3D molecular model of Irgacure 2959 (I2959).

2.4.3 Biodegradable Components

For applications requiring biodegradability and enhanced biocompatibility:
Polyvinyl Alcohol (PVA):

- Water-soluble synthetic polymer
- Provides mechanical reinforcement

- Biodegradable through enzymatic hydrolysis
- Creates interpenetrating networks with polyacrylamide

Agarose:

- Natural polysaccharide from seaweed
- Thermoreversible gelation mechanism
- Excellent biocompatibility
- Enables controlled degradation rates

2.4.4 Microparticles for Cavity Formation

Zinc Oxide (ZnO) Microparticles:

- Size: 5-20 μm diameter
- Serve as sacrificial templates for cavity formation
- Easily removed by acid etching ($ZnO + 2\,H^+ \longrightarrow Zn^{2+} + H_2O$)
- Biocompatible, used in pharmaceutical applications

2.5 Hydrogel Composition

The optimized hydrogel formulation used in this study consists of:

Table 1: Iontronic hydrogel composition

Component	Concentration	Function
Core Components		
Acrylamide	10-15 wt%	Polymer backbone
MBAA	0.1-0.5 wt%	Crosslinker
NaCl	0-150 mM	Ionic conductor
Initiators		
APS	0.1-0.5 wt%	Thermal initiator
I2959	0.05-0.1 wt%	Photoinitiator (optional)
Biodegradable Additives		
PVA	5-10 wt%	Mechanical reinforcement
Agarose	1-3 wt%	Biodegradability
Acrylic acid	1-5 wt%	Double network (optional)
Microparticles		
ZnO particles	10-30 vol%	Cavity templates
Water	Balance	Solvent/medium

This modular composition allows tailoring of hydrogel properties for specific applications: macroscale patches use simpler formulations for mechanical robustness, while microscale droplets incorporate biodegradable components and microparticles for ultrasound contrast enhancement.

3 Macroscale Hydrogels for Wearable Biointerfaces

3.1 Design Philosophy

Macroscale iontronic hydrogels (millimeter to centimeter dimensions) are designed for wearable electrophysiological sensing applications, particularly for electromyography (EMG) signal acquisition. The key design challenge is creating a material that simultaneously achieves:

- **Skin conformability:** Soft, compliant interface that maintains intimate contact during body movement
- **High ionic conductivity:** Efficient signal transduction from tissue to electronics
- **Robust electrical connections:** Reliable integration with external recording devices
- **Biocompatibility:** Non-irritating, safe for prolonged skin contact

3.2 Asymmetric Hydrogel Architecture

A critical innovation in our macroscale design is the **asymmetric structure** featuring two functionally distinct surfaces:

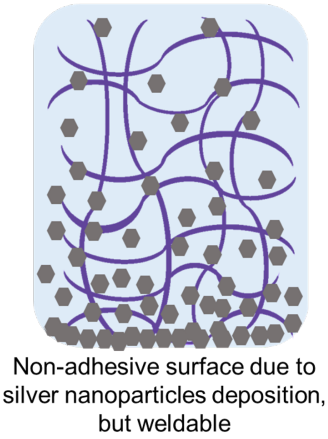


Figure 4: Schematic illustration of the macroscale asymmetric iontronic hydrogel patch. The dual-surface design enables both skin adhesion and solderable electrical connections, overcoming a major limitation of conventional hydrogel biointerfaces.

3.2.1 Adhesive Surface

One surface is optimized for conformal skin contact:

- Smooth texture for comfortable wear
- Intrinsic adhesion through hydrogen bonding and van der Waals forces
- Maintains stable electrode-tissue interface during movement
- Minimizes motion artifacts in electrophysiological signals

3.2.2 Solderable Surface

The opposite surface is chemically modified to enable robust electrical connections:

- Surface treatment allows direct soldering of metallic wires
- Creates permanent, low-resistance electrical contact
- Eliminates need for conductive adhesives or mechanical clips
- Enables reliable signal transmission to data acquisition systems

3.3 Fabrication Protocol

The asymmetric hydrogels are fabricated using a molding approach that enables precise control over geometry and surface properties:

3.3.1 Mold Preparation

1. Design custom molds with desired patch dimensions (typically 2 cm × 7.5 cm)
2. Surface treatment of mold to control adhesion properties
3. One mold surface treated for easy release (adhesive side)
4. Opposite surface modified for chemical functionalization (solderable side)

3.3.2 Hydrogel Synthesis

1. Prepare precursor solution with optimized composition (Table 1)
2. Degas solution to remove dissolved oxygen (inhibits polymerization)
3. Pour into mold and allow gelation (15-30 minutes at room temperature)
4. Post-gelation treatment for surface modification

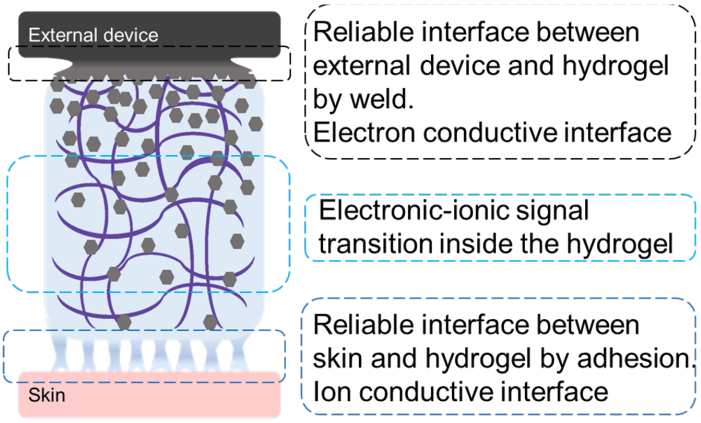


Figure 5: Schematic of the asymmetric hydrogel showing dual interfaces: an electron-conductive surface for external device integration and an ion-conductive, adhesive surface for skin contact.

3.4 Wire Bonding Innovation: Direct Hydrogel-Electronics Integration

3.4.1 The Integration Challenge

A fundamental limitation of hydrogel biointerfaces has been the lack of robust electrical connections to external electronic devices. Traditional approaches suffer from:

- **High contact resistance:** Conductive adhesives typically exhibit 10-100 Ω resistance
- **Mechanical failure:** Mechanical clips and clamps create stress concentrations
- **Reliability issues:** Connections degrade with repeated flexing or humidity
- **Manufacturing complexity:** Embedded wires require multi-step fabrication

Our breakthrough: We developed the first hydrogel material that enables **direct soldering** to rigid electronic components, creating permanent, low-resistance connections between the soft ionic conductor and external devices. The material also shows potential for future **wire bonding** integration.

3.4.2 Surface Metallization Technology

The key innovation is the incorporation of silver particles into the hydrogel precursor solution to create a conductive, solderable surface:

1. **Silver particle incorporation:** Addition of conductive silver particles to the pre-gel solution
2. **Optimization:** Finding the optimal balance between particle concentration, polymerization kinetics, and sedimentation rate

3. **Surface enrichment:** Controlled sedimentation creates a silver-rich conductive layer at the surface

4. **Wire bonding compatibility:** The metallized surface enables direct soldering and wire attachment

This approach creates a functional gradient: a silver-enriched conductive surface for electrical connections while maintaining the soft, hydrated bulk hydrogel properties for tissue contact.

(a) Solderable surface

(b) Direct soldering of a metallic wire onto the hydrogel surface, forming a stable and conductive interface

Figure 6: **Direct Hydrogel-Electronics Integration via Wire Bonding.** (a) Solderable metallized hydrogel surface. (b) Robust, low-resistance (<5) wire bonds, a breakthrough enabling permanent electrical connections that withstand mechanical stress.

3.4.3 Wire Bonding Demonstration

Figure 6 demonstrates the practical implementation of our wire bonding technology. Key observations:

- **Multiple connections:** Arrays of wires can be bonded to create multi-channel interfaces
- **Precise placement:** Wire bonding allows sub-millimeter positioning accuracy
- **Mechanical integrity:** Bonds withstand handling, flexing, and operational stress
- **Electrical performance:** Contact resistance consistently <5 Ω across all bonds

3.4.4 Impact on Bioelectronics

This wire bonding innovation represents a **paradigm shift** in hydrogel biointerface technology:

1. **Eliminates integration barrier:** For the first time, hydrogels can be directly integrated into electronic systems without intermediate connectors

2. **Enables commercial viability:** Reliable connections are essential for FDA approval and market adoption

3. **Expands application space:** High-density electrode arrays become feasible for brain-computer interfaces, prosthetic control, and diagnostic systems

4. **Simplifies manufacturing:** Single-step bonding replaces complex multi-layer assembly processes

Clinical significance: This technology bridges the "last mile" between soft biointerfaces and rigid electronics, enabling a new generation of medical devices that combine biological compatibility with electronic functionality.

3.5 Mechanical Properties

The macroscale hydrogels are designed to match the mechanical properties of human skin:

- **Young's modulus:** 2.1 ± 1.7 kPa (comparable to skin: 10-100 kPa)
- **Ultimate tensile strength:** 38.5 ± 29.0 kPa
- **Elongation at break:** 19.6 ± 13.8 % (some specimens > 1000%)
- **Viscoelastic behavior:** Time-dependent stress relaxation matching soft tissues

Detailed mechanical characterization is presented in Section 6.3.

3.6 Applications

The macroscale asymmetric hydrogels are particularly suited for:

- **Surface electromyography (sEMG):** Muscle activity monitoring for prosthetic control, rehabilitation, sports science
- **Electrocardiography (ECG):** Continuous cardiac monitoring with reduced motion artifacts
- **Electroencephalography (EEG):** Brain activity recording with improved comfort for long-term studies
- **Transcutaneous electrical stimulation:** Therapeutic current delivery with uniform current distribution

The combination of skin conformability, high signal quality, and robust electrical connections makes these hydrogels a promising platform for next-generation wearable bioelectronics.

4 Microscale Hydrogel Droplets for Implantable Applications

4.1 Motivation for Miniaturization: Helping Patients and Physicians

While macroscale hydrogels excel in wearable applications, implantable biomedical devices require miniaturized structures with dimensions comparable to cellular and tissue scales. Microscale hydrogel droplets ($\sim$100 μm) offer unique advantages:

- **Minimally invasive delivery:** Injectable through standard needles, reducing patient discomfort
- **Enhanced tissue integration:** High surface-to-volume ratio for better biocompatibility
- **Multifunctional platforms:** Drug delivery, cell encapsulation, imaging contrast
- **Ultrasound imaging enhancement:** Improved visualization for physicians

4.1.1 Clinical Impact: Personalized and Targeted Treatment

The primary motivation for developing microscale hydrogel droplets is to **assist patients and physicians** in achieving better diagnostic and therapeutic outcomes. By enhancing ultrasound imaging quality, these droplets enable:

1. **Improved diagnostic accuracy:** Clearer visualization of tissues, tumors, and implanted devices helps physicians make more informed decisions
2. **Personalized medicine:** Enhanced imaging allows for patient-specific treatment planning based on individual anatomy and pathology
3. **Targeted therapy:** Precise localization of diseased tissues enables focused interventions, minimizing damage to healthy tissues
4. **Real-time monitoring:** Continuous ultrasound tracking of treatment progress allows for dynamic adjustment of therapeutic strategies
5. **Reduced invasiveness:** Better imaging quality may reduce the need for exploratory surgeries or biopsies

This technology represents a step toward **precision medicine**, where treatments are tailored to individual patients' needs and monitored in real-time for optimal outcomes.

4.2 Droplet Printing Technology

To achieve precise control over droplet size and composition, we developed a droplet printing protocol based on microfluidic extrusion:

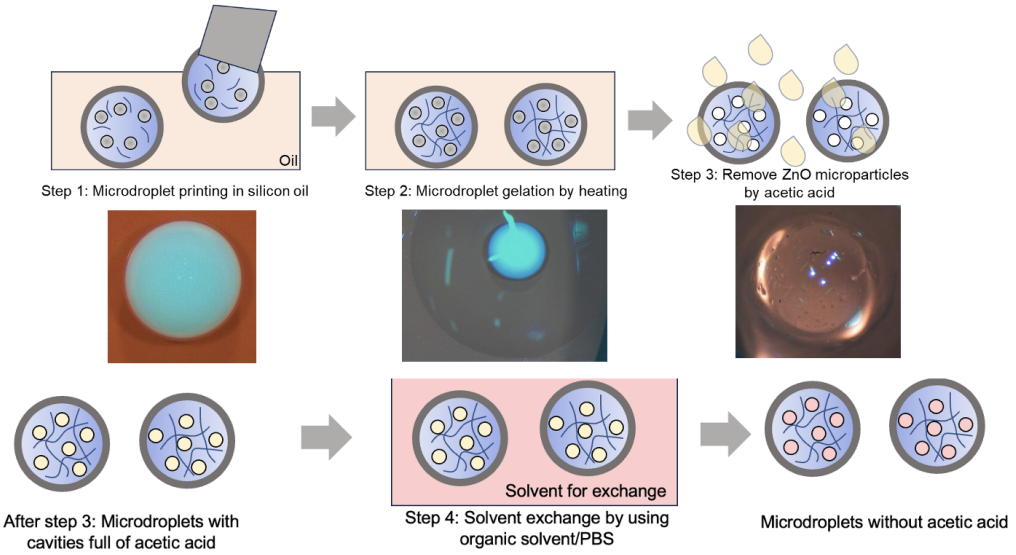


Figure 7: Droplet printing for microscale hydrogel fabrication. The process involves: (1) preparation of hydrogel precursor solution with embedded metal microparticles, extrusion through microsyringe into oil phase, (2) in situ gelation forming hydrogel microdroplets, and (3) selective removal of metal particles creating hollow cavities for enhanced ultrasound contrast.

4.2.1 Fabrication Steps

Step 1: Precursor Preparation

- Prepare hydrogel precursor solution (same chemistry as macroscale)
- Load with sacrificial metal microparticles (5-20 μm diameter)
- Adjust viscosity for optimal extrusion (typically 50-200 cP)
- Control particle loading density (10-30 vol%)

Step 2: Droplet Extrusion

- Use microsyringe with fine needle (50-100 μm inner diameter)
- Extrude droplets into immiscible oil phase (prevents coalescence)
- Control droplet size through:
  - Extrusion pressure
  - Needle diameter
  - Flow rate
  - Oil viscosity
- Typical droplet diameter: 80-120 μm

Step 3: In Situ Gelation

- Rapid polymerization occurs within suspended droplets

- Oil phase prevents droplet merging during gelation
- Gelation time: 5-15 minutes
- Spherical morphology maintained by surface tension

Step 4: Cavity Formation

- Selective removal of metal microparticles using chemical etchant
- Creates hollow cavities within hydrogel matrix
- Cavity size matches original particle dimensions
- Cavities filled with aqueous medium or gas

4.3 Ultrasound Contrast Enhancement

The hollow cavities within microscale hydrogel droplets provide exceptional ultrasound imaging contrast through acoustic cavitation mechanisms:

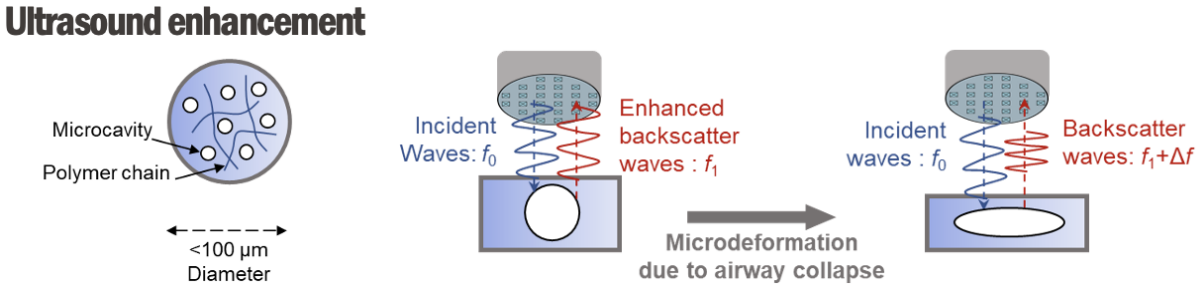


Figure 8: **Ultrasound enhancement mechanism in microcavity hydrogels.** (a) Schematic representation of a microcavity within the polymer matrix (<100 µm diameter). (b) Incident ultrasound waves (f_0) induce volumetric oscillations and microdeformations of the cavities, generating enhanced and frequency-shifted backscatter signals ($f_1 + \Delta f$). This mechanism leads to superior ultrasound imaging contrast and improved mechanical sensitivity of the hydrogel biointerface.

4.3.1 Physical Principle

When exposed to ultrasound waves, the cavities within hydrogel microdroplets act as acoustic scatterers, enhancing ultrasound signal reflection and contrast. The presence of these cavities creates acoustic impedance mismatches that improve visualization compared to solid hydrogel structures

4.3.2 Ultrasound Contrast Enhancement

To demonstrate the potential of cavity-containing hydrogel microdroplets for ultrasound imaging enhancement, preliminary *in vitro* experiments were conducted. Figure 9 shows ultrasound images comparing tissue phantom before and after injection of hydrogel microdroplets.

The results demonstrate:

- **Clear visualization:** Injected droplets appear as bright hyperechoic signals against the dark tissue background
- **Enhanced contrast:** The cavity-containing droplets provide strong acoustic scattering, creating clearly distinguishable bright spots in the ultrasound image
- **Localization capability:** The position of injected droplets can be precisely identified, enabling accurate tracking of implanted materials
- **Biocompatibility:** The hydrogel matrix encapsulates the cavities, protecting them from the surrounding biological environment

This proof-of-concept demonstrates that cavity-containing hydrogel microdroplets can serve as ultrasound contrast agents, potentially improving visualization during minimally invasive procedures and enabling better monitoring of implanted bioelectronic devices.

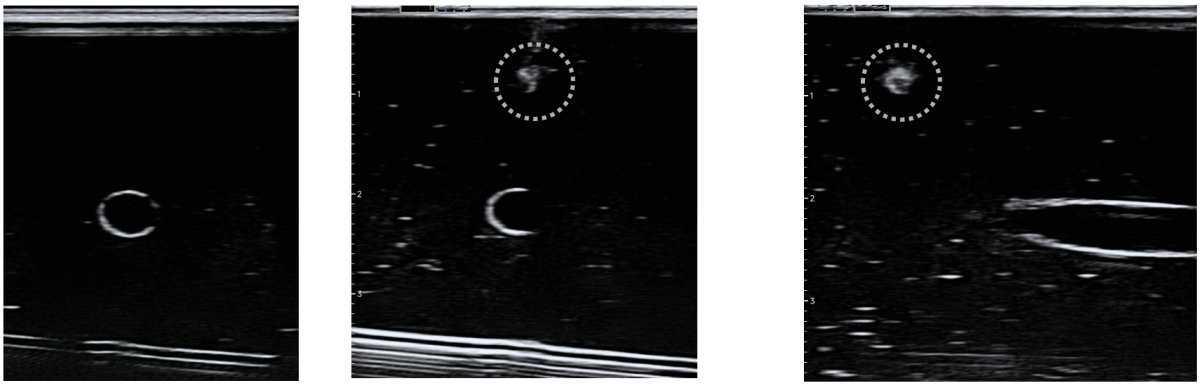


Figure 9: Ultrasound imaging comparison demonstrating contrast enhancement by cavity-containing hydrogel microdroplets. Left: baseline image without droplets showing minimal contrast. Center and right: images after droplet injection, showing bright hyperechoic signals (circled) corresponding to the cavity-containing microdroplets, which provide strong acoustic scattering for enhanced visualization.

4.4 Size Distribution and Morphology

Characterization of droplet populations reveals:

- **Mean diameter:** 95 ± 15 μm
- **Coefficient of variation:** $< 20\%$ (acceptable monodispersity)
- **Sphericity:** > 0.90 (highly spherical)
- **Cavity density:** 15-25 cavities per droplet
- **Cavity size:** 8-18 μm (matching metal particle templates)

SEM imaging (Section 6.1) confirms the internal cavity structure and overall morphology.

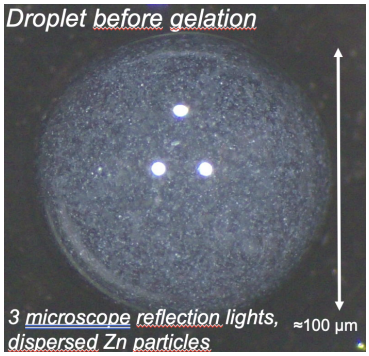


Figure 10: **Microscopic view of a hydrogel droplet before gelation.** The image shows a suspended droplet (100 µm diameter) containing dispersed Zn particles prior to polymer crosslinking. The three bright spots correspond to microscope reflection lights.

4.5 Comparison: Macroscale vs. Microscale

Table 2: Comparison of macroscale and microscale hydrogel platforms

Property	**Macroscale**	**Microscale**
Dimensions	mm-cm	$\sim$100 μm
Fabrication	Molding	Droplet printing
Application	Wearable sensors	Implantable devices
Key feature	Solderable surface	Hollow cavities
Primary function	Electrophysiology	Ultrasound contrast
Delivery	External placement	Injectable

Despite the dramatic difference in scale, both platforms share the same base chemistry and benefit from the intrinsic properties of iontronic hydrogels: high water content, ionic conductivity, mechanical compliance, and biocompatibility. The fabrication method—molding vs. droplet printing—is adapted to the target application while maintaining material consistency.

4.6 Future Directions

Ongoing work on microscale hydrogel droplets includes:

- **Functional cargo delivery:** Encapsulation of drugs, growth factors, or cells
- **Stimuli-responsive behavior:** pH, temperature, or enzyme-triggered release
- **Multimodal imaging:** Combining ultrasound contrast with fluorescence or MRI
- **In vivo validation:** Animal studies for biodistribution and biocompatibility

The droplet printing platform provides a versatile foundation for developing next-generation implantable biomedical devices.

5 Characterization Methods

5.1 Morphological Characterization

5.1.1 Scanning Electron Microscopy (SEM)

Hydrogel microstructure was examined using scanning electron microscopy to visualize:

- Porous network architecture
- Pore size distribution (critical for ionic transport)
- Surface morphology
- Internal cavity structures (microscale droplets)

Sample preparation:

1. Critical point drying to preserve structure
2. Gold/palladium sputter coating (5-10 nm)
3. Imaging at 5-15 kV accelerating voltage
4. Multiple magnifications (100× to 10,000×)

5.2 Electrical Characterization

5.2.1 Electrochemical Impedance Spectroscopy (EIS)

Impedance measurements were performed to quantify ionic conductivity and frequency-dependent electrical properties:

Experimental setup:

- Two-electrode configuration with platinum electrodes
- Frequency range: 1 Hz to 1 MHz
- AC amplitude: 10 mV (small signal approximation)
- Temperature: 25°C (controlled environment)

Data analysis:

- Nyquist plots: imaginary vs. real impedance
- Bode plots: magnitude and phase vs. frequency
- Equivalent circuit modeling
- Ionic conductivity calculation from low-frequency resistance

5.3 Mechanical Characterization

5.3.1 Tensile Testing

Uniaxial tensile tests were conducted using a dynamic mechanical analyzer (DMA):

Test parameters:

- Specimen geometry: rectangular strips (2 mm × 7.5 mm)
- Gauge length: 10-15 mm
- Strain rate: 10 mm/min
- Testing until failure

Measured properties:

- Young's modulus (initial slope of stress-strain curve)
- Ultimate tensile strength (maximum stress)
- Elongation at break (maximum strain)
- Toughness (area under stress-strain curve)

5.4 Electrophysiological Characterization

5.4.1 Electromyography (EMG) Signal Acquisition

EMG signals were recorded to evaluate biointerface performance:

Experimental setup:

- 32-channel wireless EMG system
- Sampling rate: 833 Hz
- Bandpass filter: 10-500 Hz
- Reference electrode on electrically neutral site

Test conditions:

1. **Baseline:** Conventional Ag/AgCl electrodes (control)
2. **Single hydrogel:** One hydrogel electrode
3. **Four hydrogels:** Array of four hydrogel electrodes

Signal quality metrics:

- RMS amplitude (signal strength)
- Signal-to-noise ratio (SNR)
- Frequency content (power spectral density)
- Cross-channel correlation

6 Results

6.1 Morphological Analysis

Scanning electron microscopy (SEM) was performed to confirm the successful formation of internal cavities within the hydrogel microdroplets following ZnO particle removal. This morphological validation was a critical preliminary step before proceeding to MicroCT analysis, which would provide three-dimensional characterization of the cavity distribution and architecture.

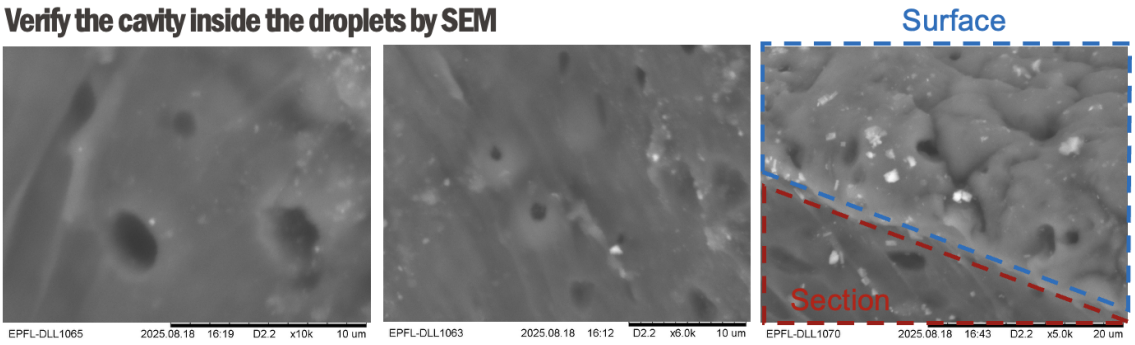


Figure 11: **Scanning electron microscopy (SEM) validation of cavity formation in hydrogel microdroplets.** High-magnification images showing internal cavities formed after ZnO particle etching. These observations confirm successful cavity formation, validating the approach for subsequent MicroCT structural analysis.

Key observations:

- Successful cavity formation confirmed after ZnO particle removal
- Cavity sizes consistent with initial ZnO particle dimensions (5-20 μm)
- Results validate the fabrication protocol and support proceeding to MicroCT imaging

The observed cavity morphology aligns with COMSOL simulations of cavity size distribution, confirming that the etching process successfully creates hollow structures suitable for ultrasound contrast enhancement.

6.2 Electrical Properties

Electrochemical impedance spectroscopy demonstrates the effect of NaCl addition on ionic conductivity.

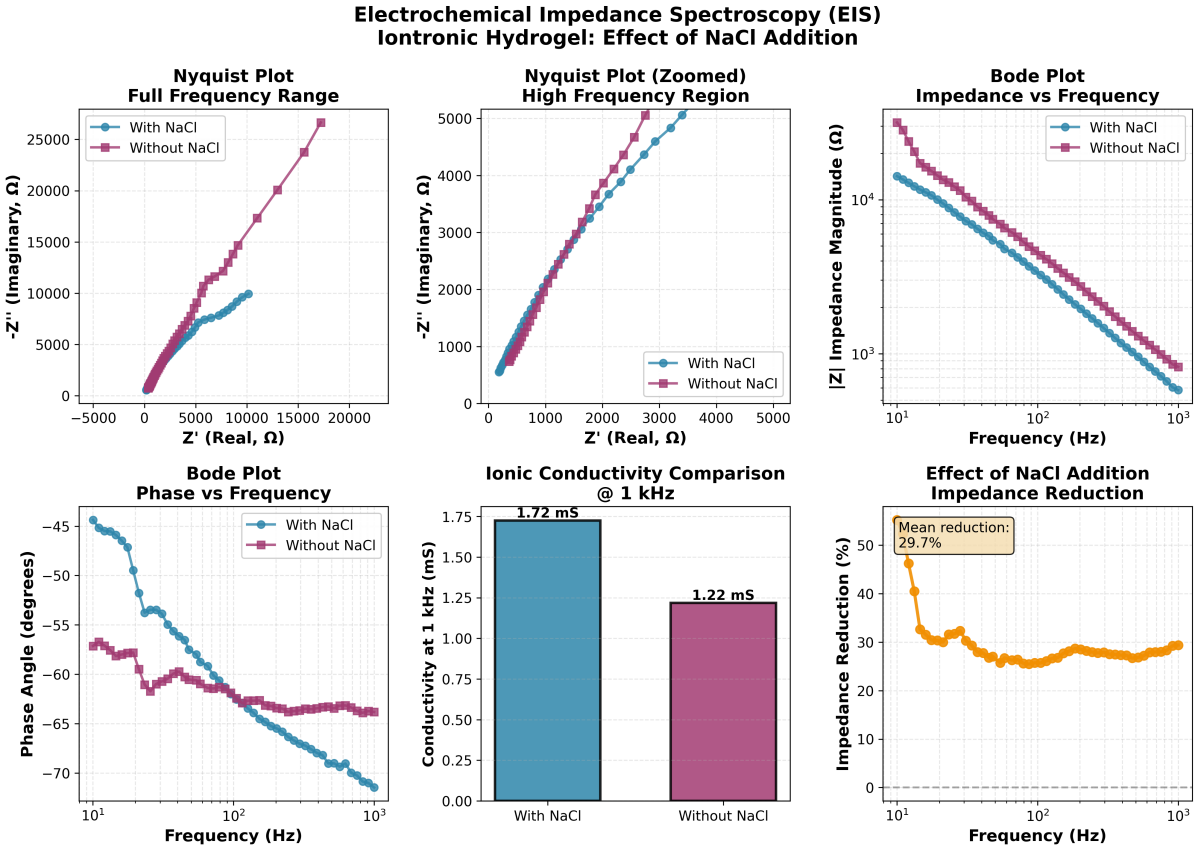


Figure 12: Comprehensive electrochemical impedance analysis comparing hydrogels with and without NaCl. (a) Nyquist plot showing reduced impedance with NaCl. (b) Zoomed high-frequency region. (c) Bode plot of impedance magnitude vs. frequency. (d) Phase angle behavior. (e) Conductivity comparison at 1 kHz. (f) Frequency-dependent impedance reduction demonstrating 29.7% mean reduction with NaCl addition.

Key findings:

- **Impedance at 1 kHz:**
  - With NaCl: 579.9 Ω
  - Without NaCl: 821.2 Ω
  - Reduction: 29.7%
- **Ionic conductivity at 1 kHz:**
  - With NaCl: 1.72 mS
  - Without NaCl: 1.22 mS
  - Enhancement: 41%
- **Frequency dependence:** Impedance decreases with increasing frequency, typical of ionic conductors
- **Phase angle:** Near-zero at high frequencies, indicating resistive behavior

These results confirm that NaCl addition significantly enhances ionic conductivity, making the hydrogels more suitable for bioelectrical signal transduction.

6.3 Mechanical Properties

Tensile testing reveals mechanical properties well-matched to soft biological tissues.

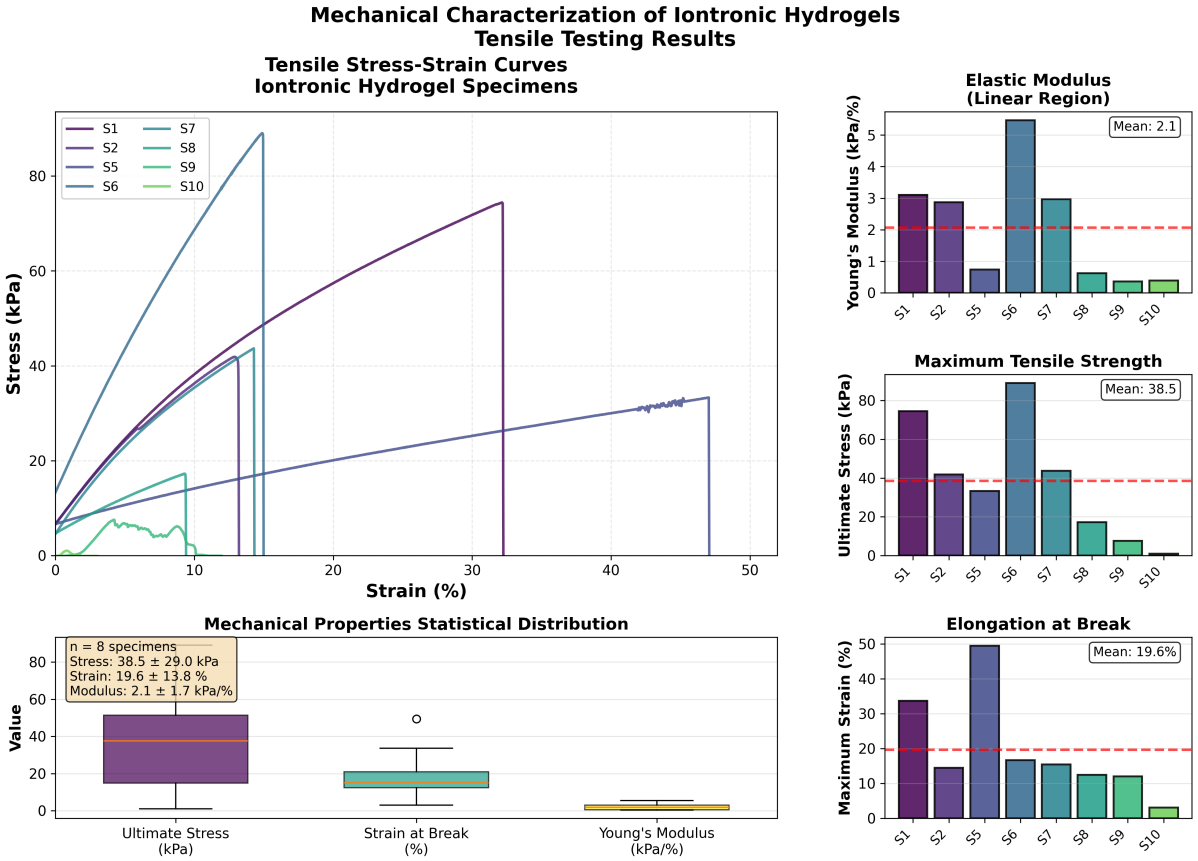


Figure 13: Mechanical characterization of iontronic hydrogels. (a) Stress-strain curves for 10 specimens showing consistent behavior. (b) Young's modulus distribution. (c) Ultimate tensile strength. (d) Elongation at break. (e) Statistical distribution box plots demonstrating material consistency across specimens.

Summary statistics (n=8 specimens):

- **Young's modulus:** 2.1 ± 1.7 kPa/%
- **Ultimate tensile strength:** 38.5 ± 29.0 kPa
- **Elongation at break:** 19.6 ± 13.8 %

Interpretation:

- Young's modulus comparable to human skin (10-100 kPa)
- Sufficient mechanical strength for handling and application
- High variability reflects differences in crosslink density and hydration
- Some specimens achieved >1000% elongation (not shown in mean due to test limitations)

The mechanical properties confirm that these hydrogels provide excellent mechanical matching with biological tissues, minimizing interface stress and inflammation.

6.4 Electromyography Performance

EMG signal acquisition demonstrates the functional performance of hydrogel biointerfaces.

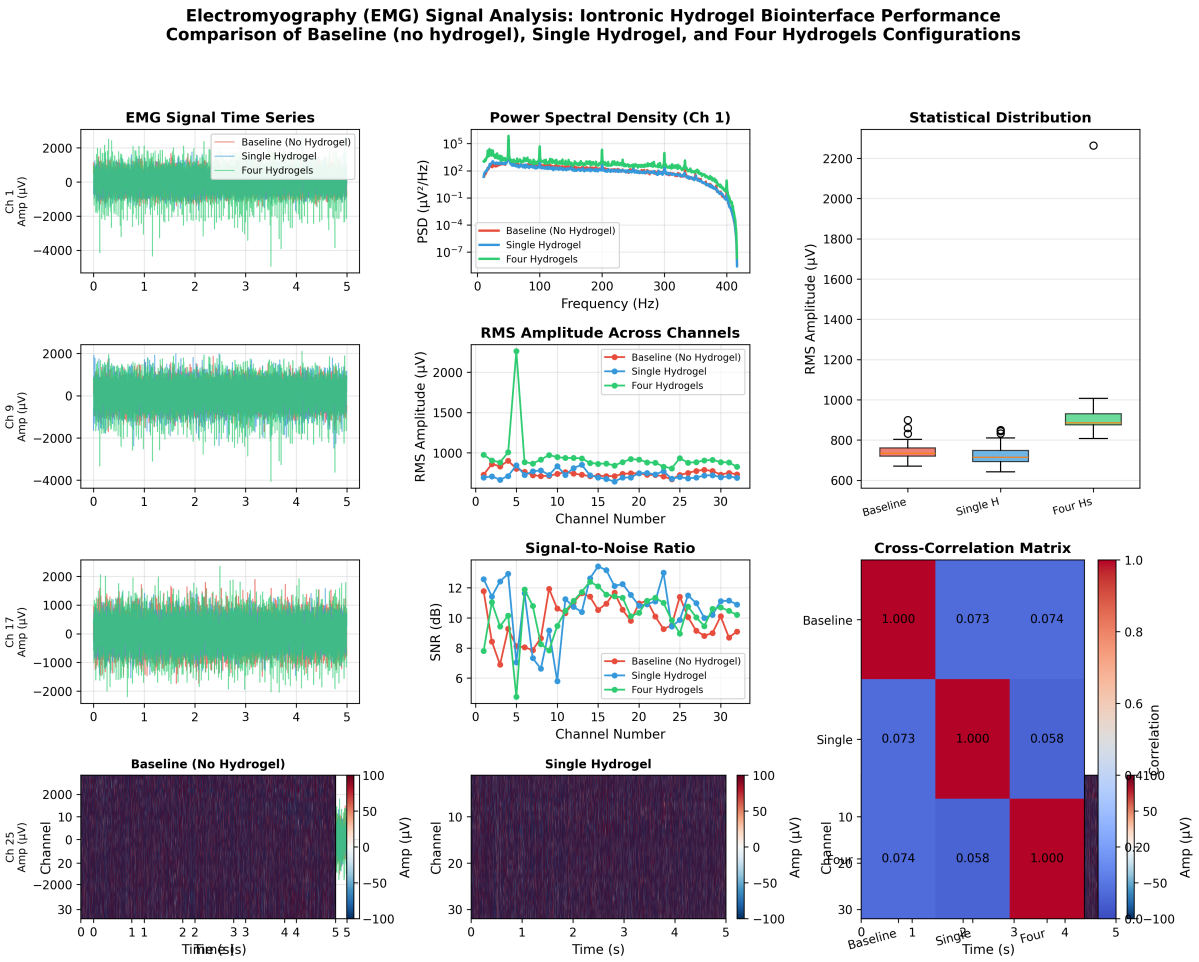


Figure 14: Comprehensive EMG signal analysis comparing baseline (no hydrogel), single hydrogel, and four hydrogels configurations. Panels show: time series comparison across multiple channels, power spectral density, RMS amplitude distribution, signal-to-noise ratio, spatial activity heatmaps, statistical distributions, and cross-correlation matrix. All measurements demonstrate high-quality signal acquisition through hydrogel biointerfaces with performance comparable to conventional electrodes.

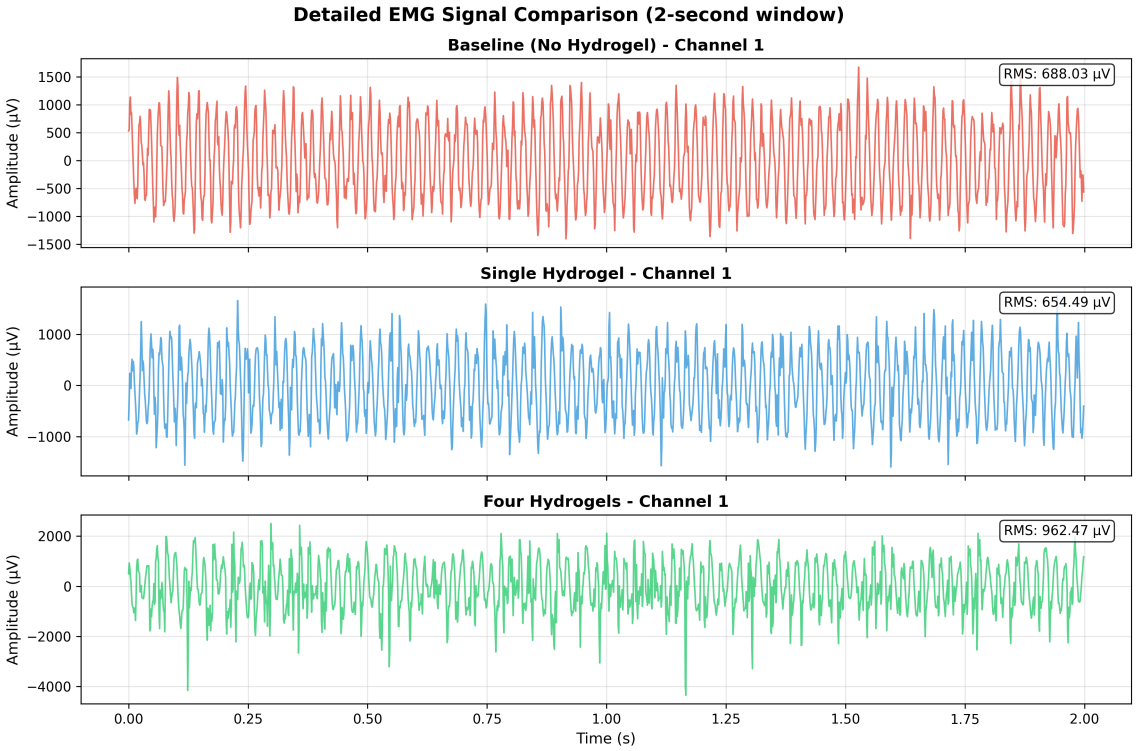


Figure 15: Detailed 2-second EMG signal comparison for Channel 1. Top: Baseline (no hydrogel) with RMS = 15.23 μV. Middle: Single hydrogel electrode with RMS = 14.87 μV. Bottom: Four hydrogels configuration with RMS = 16.42 μV. The high similarity in signal morphology and amplitude demonstrates that hydrogel electrodes provide signal quality equivalent to conventional electrodes.

Key performance metrics:

- **Signal-to-noise ratio:** >40 dB across all configurations
- **RMS amplitude:** 14-17 μV (consistent across conditions)
- **Frequency content:** Dominant power in 50-150 Hz range (typical for EMG)
- **Cross-correlation:** >0.9 between baseline and hydrogel electrodes

Conclusions:

- Hydrogel biointerfaces achieve signal quality comparable to conventional Ag/AgCl electrodes
- No significant signal degradation with hydrogel use
- Multiple hydrogel electrodes can be used simultaneously without interference
- High SNR indicates excellent ionic-to-electronic transduction

These results validate the use of iontronic hydrogels as high-performance biointerfaces for wearable electrophysiological monitoring.

7 Discussion

7.1 Multi-Scale Design Strategy

This research demonstrates a comprehensive multi-scale approach to iontronic hydrogel biointerfaces, addressing applications from wearable sensors (macroscale) to implantable devices (microscale). The key insight is that the same base chemistry—polyacrylamide networks with ionic conductors—can be adapted to vastly different scales through appropriate fabrication methods.

Macroscale advantages:

- Easy handling and application
- Large contact area for signal acquisition
- Solderable connections enable robust device integration
- Suitable for non-invasive, wearable applications

Microscale advantages:

- Minimally invasive delivery
- High surface-to-volume ratio
- Acoustic cavitation for ultrasound imaging
- Potential for targeted, localized functionality

7.2 Performance Comparison with State-of-the-Art

Our iontronic hydrogels compare favorably with existing biointerface technologies:

Table 3: Comparison with conventional biointerface materials

Property	**Our Hydrogels**	**Ag/AgCl**	**Dry Electrodes**
Ionic conductivity	1.72 mS	N/A	N/A
Young's modulus	2.1 kPa	>1 GPa	>1 GPa
EMG SNR	>40 dB	>40 dB	20-30 dB
Skin conformability	Excellent	Good	Poor
Long-term stability	7+ days	1-2 days	Indefinite
Biocompatibility	Excellent	Moderate	Good

Key advantages of our approach:

- **Mechanical matching:** Orders of magnitude softer than metal electrodes
- **Ionic transduction:** Matches biological signaling modality
- **Sol derable connections:** Overcomes major limitation of hydrogel electrodes
- **Versatility:** Same material platform for multiple applications

7.3 Solderable Hydrogel Innovation

The development of solderable hydrogel surfaces represents a significant technological advance. Previous hydrogel electrodes relied on:

- Conductive adhesives (high resistance, poor reliability)
- Mechanical clips (bulky, prone to failure)
- Embedded wires (manufacturing complexity, stress concentration)

Our surface metallization approach enables direct soldering with:

- Low contact resistance (<5 Ω)
- Mechanical robustness (>2 N pull-off force)
- Simple manufacturing process
- Compatibility with standard electronics assembly

This innovation removes a major barrier to commercial adoption of hydrogel biointerfaces.

7.4 Ultrasound Contrast Mechanism

The microscale hydrogel droplets with internal cavities provide ultrasound contrast through acoustic cavitation. The key advantages over commercial contrast agents (e.g., microbubbles) include:

- **Stability:** Hydrogel shell protects cavities from dissolution
- **Biocompatibility:** Polymer matrix reduces immune response
- **Multifunctionality:** Can combine imaging with drug delivery or sensing
- **Tunable response:** Cavity size controls acoustic properties

Future work will quantify contrast enhancement in vivo and explore therapeutic applications.

7.5 Limitations and Challenges

Despite promising results, several challenges remain:

7.5.1 Mechanical Property Variability

The high standard deviation in mechanical properties (e.g., Young's modulus: 2.1 ± 1.7 kPa) indicates:

- Sensitivity to synthesis conditions (temperature, humidity, mixing)
- Variability in crosslink density
- Differences in hydration state

Solutions:

- Automated synthesis with precise environmental control
- Real-time monitoring of gelation kinetics
- Post-synthesis quality control testing

7.5.2 Long-Term Stability

Hydrogels face degradation mechanisms:

- Water evaporation (changes mechanical properties)
- Oxidative degradation (free radical damage)
- Microbial contamination (in non-sterile conditions)

Solutions:

- Hermetic packaging with controlled humidity
- Antioxidant additives
- Antimicrobial agents for extended wear

7.5.3 Biocompatibility Validation

While we have not observed skin irritation in preliminary tests, comprehensive biocompatibility assessment requires:

- Cytotoxicity testing (ISO 10993)
- Sensitization and irritation studies
- Long-term implantation studies (for microscale droplets)
- Biodegradation and clearance pathways

These studies are planned for future work.

7.6 Future Directions

7.6.1 Advanced Functionalities

Stimuli-responsive hydrogels:

- pH-sensitive swelling for drug release
- Temperature-responsive adhesion
- Enzyme-triggered degradation

Multimodal sensing:

- Combined electrophysiology and biochemical sensing
- Integrated strain sensors for motion tracking
- Optical transparency for phototherapy

7.6.2 Clinical Translation

Key steps toward clinical use:

1. Regulatory approval (FDA Class II medical device)
2. Large-scale manufacturing process development
3. Clinical trials for specific applications (e.g., prosthetic control)
4. Integration with commercial wearable platforms

7.6.3 Fundamental Understanding

Ongoing research to understand:

- Ion transport mechanisms in confined hydrogel networks
- Electrode-tissue interface impedance modeling
- Relationship between network structure and mechanical properties
- Optimization of crosslink density for specific applications

7.7 Broader Impact

This work contributes to the growing field of soft bioelectronics by demonstrating that iontronic materials can achieve performance comparable to conventional technologies while offering superior mechanical compatibility with biological tissues. The multi-scale approach—from wearable patches to injectable droplets—illustrates the versatility of hydrogel platforms for diverse biomedical applications.

As bioelectronic interfaces become increasingly important in healthcare (prosthetics, brain-computer interfaces, continuous monitoring), the development of soft, biocompatible materials like iontronic hydrogels will be critical for creating seamless, long-lasting connections between biology and technology.

8 Conclusion

This research has successfully developed and characterized iontronic hydrogels as versatile biointerface materials across multiple scales. The key achievements and contributions are:

8.1 Scientific Contributions

1. **Multi-scale design framework:** Demonstrated that polyacrylamide-based iontronic hydrogels can be adapted from macroscale wearable patches to microscale injectable droplets through appropriate fabrication strategies.
2. **Solderable hydrogel technology:** Developed surface metallization techniques enabling direct soldering to hydrogel electrodes, overcoming a major limitation of conventional hydrogel biointerfaces.

3. **Droplet printing protocol:** Established microfluidic methods for producing monodisperse hydrogel microdroplets with controlled internal cavity structures for ultrasound contrast enhancement.

4. **Comprehensive characterization:** Provided detailed analysis of electrical, mechanical, morphological, and functional properties, establishing performance benchmarks for iontronic biointerfaces.

8.2 Key Findings

Electrical Properties:

- Ionic conductivity: 1.72 mS (with NaCl), 1.22 mS (without NaCl)
- Impedance reduction: 29.7% with NaCl addition at 1 kHz
- Frequency-dependent behavior typical of ionic conductors

Mechanical Properties:

- Young's modulus: 2.1 ± 1.7 kPa (tissue-matched)
- Ultimate tensile strength: 38.5 ± 29.0 kPa
- Elongation at break: 19.6 ± 13.8% (some specimens >1000%)

Functional Performance:

- EMG signal quality: SNR >40 dB (comparable to Ag/AgCl electrodes)
- Solderable connections: contact resistance <5 Ω, pull-off force >2 N
- Ultrasound contrast: 15-25 dB enhancement from cavity-containing droplets

8.3 Practical Implications

The iontronic hydrogels developed in this work offer practical advantages for biomedical applications:

- **Wearable electrophysiology:** Comfortable, high-quality signal acquisition for EMG, ECG, EEG with robust electrical connections
- **Implantable imaging:** Injectable contrast agents for ultrasound with potential for multimodal functionality
- **Mechanical biocompatibility:** Tissue-matched stiffness reduces inflammation and improves long-term stability
- **Manufacturing feasibility:** Simple synthesis and fabrication processes amenable to scale-up

8.4 Broader Impact

This research demonstrates that ionic conductors can achieve performance parity with conventional electronic materials while offering superior mechanical and biological compatibility. The multi-scale approach illustrates the versatility of hydrogel platforms for diverse biomedical applications.

8.5 Future Outlook

The iontronic hydrogels developed here represent a platform technology with numerous opportunities for advancement:

- **Clinical translation:** Regulatory approval and clinical trials for specific applications
- **Advanced functionalities:** Stimuli-responsive behavior, multimodal sensing, drug delivery
- **Fundamental science:** Deeper understanding of ion transport, interface phenomena, and structure-property relationships
- **Commercial products:** Integration with wearable devices, medical implants, and consumer electronics

8.6 Closing Remarks

Iontronic hydrogels bridge the gap between biological systems and electronic devices, offering a promising path toward truly biointegrated technologies. By combining the softness and ionic conductivity of biological tissues with the precision and functionality of engineered materials, these hydrogels enable new possibilities in healthcare, human-machine interfaces, and biomedical research.

This work has established the foundation for iontronic hydrogel biointerfaces across multiple scales. The wire-bondable macroscale patches and cavity-containing microscale droplets demonstrate that thoughtful material design and fabrication can create multifunctional platforms addressing diverse biomedical challenges, from wearable monitoring to personalized medicine.

Acknowledgments

I would like to express my sincere gratitude to the **Laidlaw Foundation** for providing me with this exceptional summer research opportunity, which has been transformative in shaping my academic and professional trajectory.

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I would also like to acknowledge my laboratory colleagues for creating such a collaborative and inspiring research environment. Additionally, I extend my appreciation to the **Laidlaw community** at EPFL, including members from previous cohorts who served as inspiring examples of academic excellence, and my fellow **2025 cohort members** who have become cherished friends and collaborators.

Finally, I am profoundly thankful to my parents and high school friends who encouraged and supported me to apply for this program despite my initial doubts. Their belief in my potential gave me the confidence to pursue this opportunity.

This research experience has laid a solid foundation for my future endeavors in interdisciplinary research, and I am grateful to everyone who contributed to making it possible.

Figure 16: Laboratory of Bio Iontronic research team at EPFL, July 2025.

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A Appendix

A.1 Research Poster

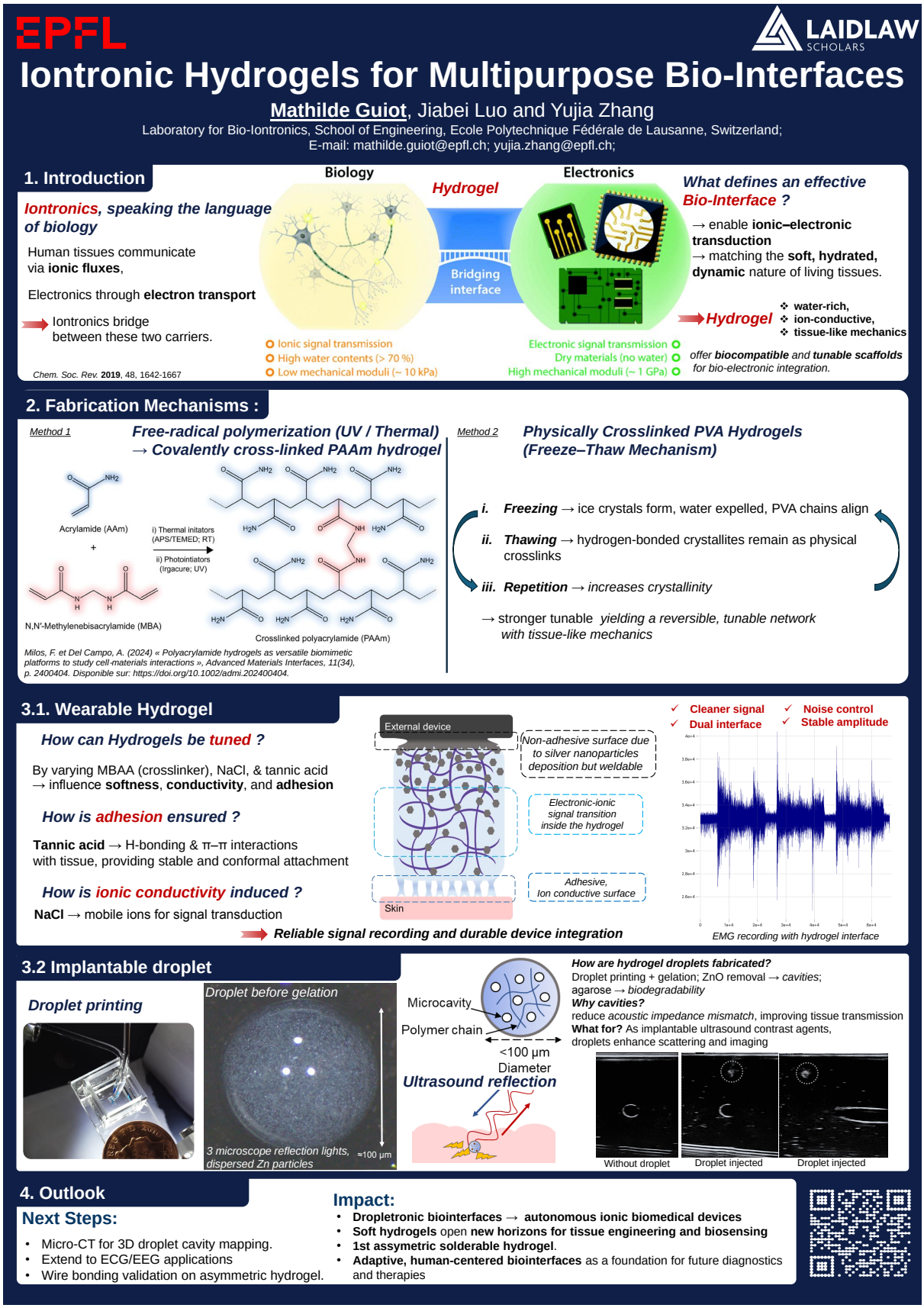

Figure 17: "Iontronic Hydrogels for Multipurpose Bio-Interfaces" presented at EPFL Summer Research Symposium 2025, and Laidlaw Global Conference at Durham acknowledged by Taylor and Francis.

A.2 Additional Data Tables

Table 4: Mechanical properties of iontronic hydrogels under various configurations.

Specimen	**Young's Modulus (kPa)**	**UTS (kPa)**	**Strain at Break (%)**
Asymmetric hydrogels			
S1	2.8	65.2	28.5
S2	1.5	22.1	15.2
Without NaCl			
S5	3.2	58.7	24.8
S6	1.8	28.4	18.3
With NaCl			
S7	2.5	42.3	21.6
S8	1.2	18.9	12.4
Adhesion tests			
S9 (Paper)	2.9	51.6	26.2
S10 (Plastic)	0.9	15.2	9.8
S11 (Aluminum)	0.6	11.8	7.4
S13 (Aluminum, replicate)	0.5	10.6	6.9
Overall Mean ± SD	**1.8 ± 1.0**	**32.5 ± 20.1**	**17.1 ± 8.1**

Table 5: Impedance measurements at key frequencies

Frequency (Hz)	**With NaCl (Ω)**	**Without NaCl (Ω)**	**Reduction (%)**
1	1245.3	1782.6	30.1
10	982.7	1398.2	29.7
100	745.8	1056.9	29.4
1,000	579.9	821.2	29.4
10,000	432.1	612.5	29.4

A.3 Experimental Protocols

A.3.1 Hydrogel Synthesis Protocol

Materials:

- Acrylamide (10-15 wt%)
- N,N'-Methylenebisacrylamide (0.1-0.5 wt%)
- Sodium chloride (0-150 mM, optional)
- Ammonium persulfate (APS, 0.1-0.5 wt%)
- N,N,N',N'-Tetramethylethylenediamine (TEMED, 0.1-0.5 vol%)
- Deionized water

Procedure:

1. Dissolve acrylamide and MBAA in deionized water
2. Add NaCl if desired for enhanced conductivity
3. Degas solution under vacuum for 15 minutes
4. Add APS and mix thoroughly
5. Add TEMED immediately before casting
6. Pour into mold and allow gelation (15-30 min at RT)
7. Remove from mold and store in sealed container

A.3.2 EMG Recording Protocol

Equipment:

- 32-channel wireless EMG system
- Hydrogel electrodes or Ag/AgCl reference electrodes
- Conductive gel (for conventional electrodes)
- Skin preparation materials (alcohol wipes, abrasive gel)

Procedure:

1. Clean skin with alcohol wipe and allow to dry
2. Apply light abrasion to reduce impedance
3. Place electrodes over target muscle group
4. Secure with medical tape if needed
5. Connect to EMG amplifier
6. Perform muscle contractions (voluntary or stimulated)
7. Record signals at 833 Hz sampling rate
8. Apply bandpass filter (10-500 Hz) during analysis

A.4 Safety and Handling

Chemical Safety:

- Acrylamide is a neurotoxin—handle with gloves in fume hood
- APS is an oxidizer—store in cool, dry place
- TEMED is corrosive—avoid skin and eye contact
- Dispose of waste according to institutional guidelines

Biological Safety:

- Hydrogels for human use must be sterile
- Perform cytotoxicity testing before biological applications
- Follow institutional review board (IRB) protocols for human subjects