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Electroactive Scaffolds for Controlled Tissue Regeneration: Crosslinking Kinetics and Bioelectronic Feedback Loops

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Title of Article

Electroactive Scaffolds for Controlled Tissue Regeneration: Crosslinking Kinetics and Bioelectronic Feedback Loops

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Abstract

Electroactive scaffolds offer a promising platform for controlled tissue regeneration through the synergistic integration of conductive materials, crosslinking dynamics, and real-time bioelectronic feedback. This study presents a comparative analysis of crosslinking kinetics and electrochemical properties in composite hydrogels and polymeric matrices incorporating materials such as gelatin methacryloyl, carbon nanotubes (CNTs), and poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS). Electrochemical impedance spectroscopy and cyclic voltammetry were employed to quantify scaffold conductivity and charge storage capacity under varied crosslinking regimes. Cellular response was assessed through alignment, proliferation, and gene expression in mesenchymal stem cells subjected to controlled electrical stimulation. Real-time feedback loops were embedded within scaffold environments using low-voltage circuits to modulate signal amplitude based on cellular input parameters. The results demonstrate that scaffold crosslinking rate directly influences conductivity, interface capacitance, and biological outcomes. These findings suggest a robust platform for electro-mediated regenerative architectures, enabling dynamic control of cell behavior through tunable bioelectronic interfaces.

Keywords

Electroactive scaffolds, Crosslinking kinetics, Conductive hydrogels, PEDOT:PSS, Carbon nanotube composites, Bioelectronic feedback loops, Electrochemical impedance spectroscopy (EIS), Cyclic voltammetry, Mesenchymal stem cells, Electrical stimulation in tissue engineering

1. Introduction

The development of electroactive scaffolds represents a significant advancement in tissue engineering, enabling dynamic modulation of cellular behavior through controlled electrical stimuli. Traditional biomaterial platforms—while supportive in static environments—often fail to replicate the bioelectrical microenvironment essential for tissue morphogenesis, repair, and function. Electrically conductive matrices, especially those incorporating conjugated polymers and carbon-based nanomaterials, offer a mechanism to bridge this gap by facilitating signal transduction between synthetic substrates and biological systems.

Electroactive materials such as poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS), polypyrrole, and carbon nanotube-enhanced hydrogels provide tunable conductivity, flexibility, and biocompatibility. Their integration into scaffold architectures allows for the delivery of spatially controlled electrical cues, promoting cellular alignment, proliferation, and lineage-specific differentiation. Central to scaffold performance is the crosslinking kinetics of the host matrix, which influences ionic transport, impedance behavior, and mechanical stability under physiological conditions.

Recent efforts have explored the incorporation of closed-loop feedback systems within scaffold environments, enabling real-time adjustment of stimulation parameters in response to biological input signals such as cellular impedance shifts, local pH changes, or electrochemical activity. This feedback-controlled approach offers an avenue for adaptive tissue regeneration, where scaffold conductivity and bioelectronic responsiveness are precisely synchronized with regenerative trajectories.

This manuscript investigates the relationship between crosslinking rate, electrochemical properties, and feedback loop performance in electroactive scaffolds engineered for tissue regeneration. By coupling material characterization with biological response profiling, the study aims to establish a reproducible framework for scaffold optimization across electrically sensitive tissue types.

2. Methods

Electroactive scaffolds were fabricated using composite hydrogels composed of gelatin methacryloyl (GelMA), poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS), and multiwalled carbon nanotubes (MWCNTs). GelMA was synthesized via methacrylation of Type A porcine gelatin, followed by purification and lyophilization. Scaffold formulations varied in GelMA concentration (5–15 wt%) and included 0.3–1.2 wt% PEDOT:PSS and 0.1–0.5 wt% MWCNTs. The components were dispersed in phosphate-buffered saline (PBS), photoinitiated with Irgacure 2959 (0.5 wt%), and crosslinked under UV exposure (365 nm) for 30–120 seconds to study temporal crosslinking dynamics.

Electrochemical properties of the scaffolds were characterized using electrochemical impedance spectroscopy (EIS), cyclic voltammetry (CV), and chronopotentiometry. EIS was performed in a three-electrode setup over the frequency range of 0.1 Hz to 100 kHz to extract bulk impedance and phase angles. CV analysis was conducted between −0.8 V and +0.8 V at 100 mV/s to assess redox stability and charge storage capacity. Measurements were repeated for scaffolds crosslinked at varying intervals to evaluate the effect of gelation rate on electroactivity.

Rheological behavior was evaluated using oscillatory shear measurements on a rotational rheometer to determine storage (G′) and loss (G″) moduli. Crosslinking kinetics were quantified via time-dependent moduli changes during photopolymerization. Scaffold porosity and microstructure were examined using scanning electron microscopy (SEM) post-freeze drying.

Human mesenchymal stem cells (hMSCs) were seeded at 1×10^5 cells/cm² onto pre-hydrated scaffolds and cultured for up to 10 days under standard conditions. Electrical stimulation protocols were applied using biphasic pulses (±0.5 V, 1 Hz, 2 ms duration) administered via embedded platinum electrodes. Cell viability was assessed by live/dead staining, while alignment and cytoskeletal organization were analyzed using immunofluorescent markers for F-actin and vinculin. Quantitative PCR (qPCR) was performed to evaluate expression of regeneration-associated genes (e.g., VEGFA, ACTN4, COL1A1) in response to electrical cues.

To establish feedback loop functionality, a low-voltage circuit incorporating operational amplifiers and analog-to-digital converters was designed to interface with scaffold impedance readings. Signal outputs were modulated based on dynamic impedance shifts, creating closed-loop control over stimulation amplitude and timing. Response fidelity and lag times were benchmarked against open-loop stimulation protocols.

3. Results

3.1 Crosslinking Dynamics and Rheological Evolution

Photopolymerization of GelMA-based scaffolds revealed distinct temporal moduli profiles. Storage modulus (G′) increased from ~120 Pa to ~890 Pa across 30–120 seconds of UV exposure, with faster gelation rates observed in formulations containing ≥1.0 wt% PEDOT:PSS. Modulus plateau onset occurred earlier in scaffolds containing MWCNTs, suggesting enhanced network stabilization. Loss modulus (G″) trajectories remained below 30% of G′ values, confirming elastic dominance post-

crosslinking. Time-resolved gelation curves enabled the mapping of scaffold stiffness windows suitable for cellular attachment (~250–500 Pa).

3.2 Electrochemical Performance and Impedance Profiles

Scaffolds displayed capacitive and resistive behavior modulated by conductive filler concentrations. EIS measurements showed a marked decrease in bulk impedance with increasing PEDOT:PSS from 0.3 to 1.2 wt% (from ~9.4 kΩ to ~2.6 kΩ at 1 kHz). MWCNT inclusion further reduced impedance and narrowed phase angles toward 0°, indicating enhanced electron mobility. CV curves exhibited quasi-rectangular profiles with increasing current density proportional to conductive filler loading. Charge storage capacity peaked at 1.2 wt% PEDOT:PSS (~1.7 mC/cm²), revealing optimal redox response at intermediate crosslinking durations (60–90 seconds).

3.3 Microstructure and Porosity Control

SEM imaging unveiled interconnected porosity with pore diameters ranging from 40–120 µm, varying inversely with GelMA concentration. Inclusion of PEDOT:PSS and MWCNTs resulted in localized nanofibrillar features within pore walls, correlating with improved electrochemical interface area. Freeze-dried morphology analysis indicated that scaffolds crosslinked beyond 90 seconds began to exhibit pore wall densification, reducing effective diffusion paths for nutrients and signaling molecules.

3.4 Cellular Responses to Electroactive Cues

Live/dead staining confirmed >90% hMSC viability across all scaffold variants. Electrically stimulated cultures showed enhanced cellular alignment along field vectors and increased expression of regeneration-associated markers. qPCR data revealed 2.3-fold upregulation of VEGFA and 1.7-fold upregulation of COL1A1 in biphasically stimulated scaffolds relative to static controls. Immunostaining showed elongated F-actin filaments and polarized vinculin localization, supporting cytoskeletal engagement and mechanoelectrical coupling.

3.5 Bioelectronic Feedback Loop Functionality

Closed-loop control systems successfully modulated stimulation parameters in response to scaffold impedance dynamics. Impedance drops ≥5% triggered amplitude adjustment within 30 ms, maintaining cellular stimulation fidelity. Comparative benchmarking indicated 25% reduction in stimulation latency and 18% improvement in gene expression stability versus open-loop controls. Signal processing fidelity exceeded 90% for 1 Hz modulation frequencies, confirming loop responsiveness within biologically relevant temporal domains.

4. Discussion

The modular integration of conductive fillers and photo-crosslinked GelMA matrices produced scaffolds with tunable rheological and electrochemical properties tailored for bioelectronic tissue interfaces. Temporal mapping of crosslinking kinetics revealed stiffness windows conducive to early cell adhesion (~250–500 Pa), while reinforcing agents like PEDOT:PSS and MWCNTs expedited gelation and stabilized network architecture. These findings align with prior reports on thiol-based hydrogels and nanofiller-assisted polymerization, though the present system demonstrates superior impedance attenuation under physiological frequencies.

Electrochemical analyses confirmed the efficacy of composite scaffolds in sustaining capacitive behavior and enhancing redox response. The nonlinear charge storage performance and phase angle convergence reflect multiscale electron mobility pathways contributed by filler dispersion. Benchmark comparisons with polyaniline- and graphene-based analogs indicate that PEDOT:PSS–MWCNT synergy achieves comparable conductivity with improved cytocompatibility and polymerization control.

Porosity profiling through SEM emphasized the role of GelMA concentration in defining scaffold microarchitecture. The emergence of nanofibrillar domains upon filler inclusion suggests localized phase separation and conductive zone formation—potentially enhancing electrochemical field

uniformity during stimulation. While pore wall densification post-90 seconds crosslinking introduces diffusion constraints, it may also reduce scaffold degradation rate and bolster mechanical integrity for long-term implantation.

Cellular assays affirmed the electroactive scaffold's capacity to modulate stem cell behavior in response to low-voltage cues. Upregulation of angiogenic and structural genes under biphasic stimulation corroborates prior literature on mechanoelectrical transduction. Importantly, closed-loop feedback architecture enabled real-time modulation of stimulation amplitude based on impedance shifts, bridging material conductivity with digital responsiveness.

This bioelectronic loop introduces a paradigm for adaptive stimulation, particularly in tissue niches where electrical thresholds fluctuate over regeneration phases. The 25% latency reduction and 18% gene expression stability improvement over open-loop controls underscore the utility of impedance-guided feedback. Future iterations may explore integration with stretchable sensors and wireless interfaces to enable untethered, chronically adaptive platforms.

5. Conclusion

Electroactive scaffolds fabricated through the synergistic integration of GelMA, PEDOT:PSS, and MWCNTs demonstrated tunable mechanical and electrochemical profiles conducive to stem cell viability and functional gene expression. The defined crosslinking kinetics enabled precise rheological control, while conductive filler dispersion enhanced redox activity and impedance modulation. Microarchitectural tailoring through porosity and nanofibrillar domain formation established favorable electrochemical interfaces for bio-stimulation.

The closed-loop bioelectronic framework introduced here showcases a responsive material platform capable of real-time feedback-driven stimulation, achieving latency and gene expression gains over traditional open-loop paradigms. This integrative approach—merging scaffold design with signal-processing logic—lays the foundation for chronically adaptive tissue interfaces suited for regenerative medicine applications.

Future work may explore scaffold miniaturization, stretchable circuit integration, and multimodal sensing to enable autonomous biofeedback across diverse tissue systems. The convergence of programmable electroactivity and biologically adaptive control systems offers a scalable framework for next-generation therapeutic platforms.

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