

Smart Scaffolds in Tissue Engineering: Stimuli-Responsive Platforms for Dynamic Tissue Regeneration

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Received: 17 Aug. 2026, Revised: 31 Sep. 2026, Accepted: 5 Oct. 2026

Abstract

Traditional scaffolds in tissue engineering are static structural supports and cannot cope with the changing physiological state of the wound or tissue formation. Smart scaffolds are able to adapt the physical or chemical form of a scaffold in response to the internal or external triggers. The design principles, material classes, and mechanisms of stimuli-responsive frameworks are discussed in this review. We analyze scaffolds responsive to pH, temperature, enzymes, reactive oxygen species, glucose, magnetic fields, electrical cues, mechanical force, and light. We also discuss multi-stimuli-responsive systems and 4D printing technologies. We also discuss translational barriers such as biocompatibility, long-term stability, scale-up, and regulatory complexity. The review ends with future aspirations for immuno-smart and sensor-integrated scaffolds. With the dynamic nature of biological processes, smart scaffolds allow the drug release, mechanical properties, and cell behavior to be controlled with precision.

Keywords: Smart scaffolds; stimuli-responsive biomaterials; tissue engineering; 4D bioprinting; dynamic regeneration; piezoelectric scaffolds

Literature Search Strategy

This narrative review has been developed by purposive searches on PubMed, Scopus, and Web of Science. Some of the key keywords were "stimuli-responsive scaffolds," "smart biomaterials," "4D printing tissue engineering," "piezoelectric scaffolds," and "immune-responsive biomaterials." We have also tracked the key reviews published between 2018 and 2026 and selected studies that have demonstrated mechanistic insight, design innovation, and translational focus. We have also preserved historical research for historical context.

1. Introduction: From Conventional Scaffolds to Smart Tissue Regeneration

Tissue engineering relies on scaffolds to provide a physical framework for cell attachment and proliferation [1]. Conventional scaffolds maintain a fixed shape and chemical composition after implantation [2]. While these materials support basic tissue growth, they cannot adapt to the

changing physiological conditions of a healing wound or developing tissue [3]. Native tissue regeneration is a dynamic process [4]. The biochemical and mechanical demands of a defect site change over time [5]. A tissue defect moves from an inflammatory state to a proliferative state and finally to a remodeling phase [6]. Static scaffolds cannot respond to these changes [7]. This inability to adapt restricts their effectiveness in complex injuries where temporal control over drug release or mechanical stiffness is necessary [8].

Smart scaffolds alter their physical or chemical properties in response to specific internal or external triggers [1]. The triggers include changes in pH, temperature, enzyme activity, or reactive oxygen species [9]. External triggers include magnetic fields, electrical currents, light, and mechanical stress [10]. By responding to these signals, smart scaffolds release drugs on demand [11]. They can alter their mechanical stiffness or change their shape to better fit a defect [12].

Ahadian and Khademhosseini (2018) describe this transition as a shift from passive to active biomaterials [13]. These

active platforms interact with the cellular environment [14]. Khan and Tanaka (2017) note that smart biomaterials mimic the dynamic nature of the extracellular matrix [1]. This mimicry is necessary for directing cell fate and tissue formation [15]. The extracellular matrix constantly remodels in response to cellular activity [16]. Smart scaffolds replicate this behavior by degrading or altering their properties in sync with tissue repair [17-19].

This review aims to elucidate how dynamic scaffolds function and actively participate in tissue healing by providing precise biochemical and physical cues throughout the regenerative cascade. To this end, we systematically outline design principles, responsive mechanisms (encompassing pH, temperature, enzymes, reactive oxygen species, glucose, magnetic fields, electrical cues, mechanical forces, and light), and emerging manufacturing paradigms such as 4D bioprinting. Furthermore, we critically evaluate translational barriers including immunogenicity, long-term stability, and regulatory hurdles and highlight future directions toward immuno-smart and sensor-integrated platforms.

2. Design Principles and Fabrication Strategies of Smart Scaffolds

Smart scaffolds are built from several material classes [1]. Natural polymers like collagen, alginate, and hyaluronic acid offer high biocompatibility and specific cell-recognition sites [20-22]. They interact well with biological systems but often lack mechanical strength [16]. Varaprasad and Jayaramudu (2025) review smart alginate-based biomaterials and note that alginate requires chemical modification to achieve stable mechanical properties for tissue engineering [23]. Synthetic polymers such as polyethylene glycol, polycaprolactone, and poly (lactic-co-glycolic acid) have tunable mechanical properties and predictable degradation rates [3]. Hydrogels are widely used because their high water content mimics soft tissues [24]. Composite materials combine polymers with inorganic particles to add functionality such as electrical conductivity or magnetic susceptibility [16]. Table 1 summarizes the material platforms used for smart scaffolds.

Table 1. Material platforms for smart scaffolds

Material Class	Examples	Key Properties	Responsiveness Mechanism	References
Natural Polymers	Collagen, Alginate, Hyaluronic acid	High biocompatibility, specific cell-recognition sites	Enzyme-cleavable sequences, pH-sensitive linkers	[6, 16, 23]
Synthetic Polymers	Polyethylene glycol (PEG), ¹ Polycaprolactone (PCL), ² Poly(lactic-co-glycolic acid) (PLGA) ³	Tunable mechanics, predictable degradation	Thermoresponsive phase transitions, hydrolysis	[3, 24]
Hydrogels	PEG-based, Alginate-based	High water content, soft tissue mimicry	Volume phase transitions, swelling/deswelling	[4, 9]
Composite Materials	Polymer/ceramic, Polymer/carbon	Electrical conductivity, magnetic susceptibility	Piezoelectricity, magnetic responsiveness	[16, 25-30]

Materials can contain labile bonds that break in the presence of specific enzymes or at certain pH levels [36]. Other materials undergo volume phase transitions, where thermoresponsive polymers change from hydrophilic to

hydrophobic at a specific temperature [31, 38, 40]. This causes the scaffold to shrink or swell and release trapped drugs [4]. Figure 1 shows a schematic of internal and external stimuli-responsive mechanisms in smart scaffolds.

¹ PEG: Polyethylene glycol

² PCL: Polycaprolactone

³ PLGA: Poly(lactic-co-glycolic acid)

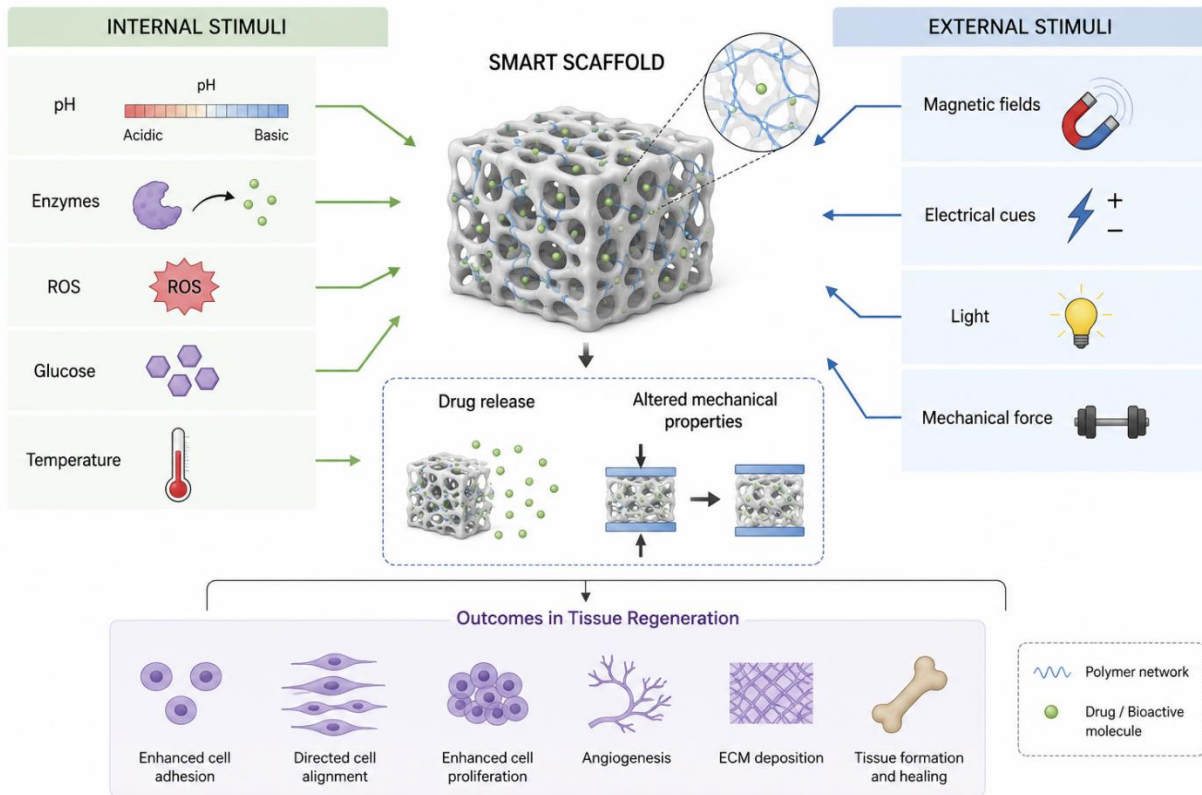


Figure 1. Schematic of internal and external stimuli-responsive mechanisms in smart scaffolds. The diagram illustrates how internal triggers (pH, enzymes, ROS, glucose, temperature) and external triggers (magnetic fields, electrical cues, light, mechanical force) interact with the polymer network to release drugs or alter mechanical properties.

Fabrication strategies determine the architecture of the scaffold [8]. Conventional methods like electrospinning and freeze-drying create porous networks [2]. Newer techniques use 3D printing to build custom geometries layer by layer [26]. Afzali et al. (2024) discuss how bioreactor-assisted bioprinting improves the fabrication of stimuli-responsive materials by controlling the printing environment [8]. This control is necessary for materials that require specific crosslinking conditions during the printing process [27].

As an advanced fabrication paradigm, four-dimensional (4D) printing utilizes 3D printing methodologies to generate dynamic constructs capable of altering their morphology or functional properties over time in response to external stimuli [19, 28]. The shape-memory effect allows a scaffold to be compressed for minimally invasive delivery and then expand to fill a defect upon reaching body temperature [12]. Sadraei and Naghib (2024) review 4D printing of physical stimuli-responsive hydrogels for localized drug delivery [28]. They say that these structures can be programmed to release drugs in particular locations [28]. Khan et al. (2025) explain that hybrid scaffolds combine various materials to create complex programmable responses [29]. These fabrication methods allow for precise control over the spatial distribution of stimuli-responsive elements in the scaffold [30].

By combining different materials, engineers can create single structures with multiple responsive mechanisms, a strategy that Neumann et al. (2023) highlight as requiring a deep understanding of polymer chemistry and cell biology [24, 56]. El-Husseiny et al. (2021) say that smart hydrogels need to be responsive and also safe [9]. If a scaffold reacts too strongly to a stimulus, it might lose its mechanical support function before the tissue heals [5]. Municoy et al. (2020) stress that choosing the right material class depends on the target tissue [6]. Hard tissues (bone) require stiff composites while soft tissues (skin) need flexible hydrogels [31]. As indicated by Pérez et al. (2013), synthetic and natural smart composite biomaterials must integrate with the host tissue [16]. And, Stratton et al. (2016) note that bioactive polymeric scaffolds have to support cell bonding and cell proliferation and remain responsive [2]. Turnbull et al. (2017) discuss 3D bioactive composite scaffolds for bone tissue engineering and how to keep structure stable during degradation [32].

3. Stimuli-Responsive Scaffolds for Dynamic Tissue Regeneration

3.1 Chemical and Biochemical Stimuli

While healthy tissues maintain a physiological pH of approximately 7.4, pathological microenvironments such as

sites of inflammation, infection, or tumor growth exhibit local acidosis [6, 33–35]. pH-responsive scaffolds exploit these environmental gradients via protonation-driven swelling or bond hydrolysis, enabling targeted drug release and tailored scaffold degradation directly within compromised tissues [6, 9, 33, 34]. Zarur et al. (2023) review the *in vivo* performance of pH-responsive scaffolds for tissue regeneration [33]. They note that acidic environments protonate specific functional groups in the polymer network [33]. This reaction causes the scaffold to swell or dissolve [6]. The swelling increases the pore size, allowing trapped therapeutic agents to diffuse out of the matrix [4]. This targeted release minimizes systemic side effects and concentrates the drug where the injury is most severe [11]. Rodríguez-González et al. (2024) developed silica 3D-printed scaffolds as pH-responsive drug release platforms. In these systems, the silica matrix protects the drug at physiological pH. When the local pH drops due to inflammation or bacterial infection, the silica bonds hydrolyze [34]. The drug releases directly into the acidic zone [34]. This mechanism is useful for treating bone defects, where inflammation creates localized acidic zones [55]. The scaffold delivers anti-inflammatory drugs or growth factors only when the environment demands it [11]. pH-responsive systems provide a self-regulating treatment approach [6]. As the inflammation subsides and the pH returns to normal, the release rate decreases [33]. This automatic regulation prevents overexposure to the drug and supports the transition to the proliferative phase of healing [34].

Exploiting the distinct enzymatic profiles overexpressed in diseased or remodeling tissues, enzyme-responsive scaffolds incorporate cleavable peptide linkers such as matrix metalloproteinase substrates that degrade specifically in response to localized cellular activity [5, 6, 36, 37]. Pi et al. (2025) review enzyme-responsive biomaterials for biomedical applications [36]. They focus on how matrix metalloproteinases degrade the extracellular matrix during tissue remodeling [36]. Scaffolds designed with matrix metalloproteinase-cleavable sequences degrade in sync with cellular invasion [5]. As cells secrete these enzymes, the scaffold opens up [37]. This opening allows further cell migration and matrix deposition [5]. Qu et al. (2020) examine the stimuli-responsive delivery of growth factors for tissue engineering [11]. They note that enzyme-responsive release prevents growth factor depletion [11]. The growth factor remains bound to the scaffold until the relevant enzyme is present [11]. This localized release improves tissue formation efficiency and prevents abnormal cell growth [11]. Han et al. (2013) describe dynamic tissue engineering scaffolds with stimuli-responsive macroporosity formation [5]. They use

enzyme-responsive polymers that degrade when cells invade the area [5]. This creates a scaffold that opens its pores exactly when cells need space to grow [5]. Enzyme-responsive scaffolds are useful for regenerating complex tissues like cartilage and bone [31]. These tissues require specific spatial and temporal cues during formation [30]. The scaffold degrades exactly where new tissue is forming [17]. This process removes the physical barrier to growth while releasing factors that stimulate local cells [11]. The material adapts to the pace of the tissue repair process [37].

Reactive oxygen species accumulate at injury sites due to inflammation and ischemia [35]. Low levels of reactive oxygen species aid cell signaling [22]. High levels cause oxidative stress and cell damage [9]. ROS-responsive scaffolds scavenge excess radicals and release protective drugs. Wei et al. (2022) review smart stimuli-responsive biomaterials for bone therapeutics. They describe polymers with oxidation-sensitive linkers, such as thioketals or polysulfides. When reactive oxygen species levels rise, these linkers oxidize and break. The scaffold releases antioxidants or anti-inflammatory agents directly into the oxidative stress zone [35]. Zhang et al. (2025) conceptualize smart biomaterials as active immune modulators to shape pro-regenerative microenvironments. ROS-responsive scaffolds can move macrophage polarization away from a pro-inflammatory state to an anti-inflammatory state. This scaffold reduces local oxidative stress and promotes tissue repair rather than destruction [22]. El-Husseiny et al. (2021) note that hydrogels responsive to reactive oxygen species protect transplanted cells from the harsh conditions of the injury site. The scaffold consumes the damaging radicals before they can harm the embedded cells. This protection improves cell survival rates and enhances the overall success of the regenerative therapy [9]. Municoy et al. (2020) add that ROS-responsive materials can be designed to release their payload only when oxidative stress reaches a dangerous threshold. This prevents unnecessary drug release and preserves the scaffold structure during normal healing phases [6].

Glucose-responsive materials are mainly designed for diabetes-related applications, e.g., chronic diabetic wounds [6]. These scaffolds sense elevated glucose levels and release insulin or other drugs [9]. Municoy et al. (2020) review stimuli-responsive materials for tissue engineering and drug delivery. They discuss polymers with glucose-binding molecules, such as phenylboronic acid. When glucose binds to these molecules, it creates a conformational change in the polymer network. This change swells the hydrogel and releases insulin [6]. El-Husseiny et al. (2021) show how glucose-responsive hydrogels maintain normal glucose levels

in the wound environment. High glucose inhibits wound healing by damaging blood vessels and reducing immune function. A scaffold that releases insulin in response to high glucose levels helps restore normal healing processes in diabetic patients [9].

3.2 Physical Stimuli

Temperature changes occur naturally in the body during inflammation [38]. They can also be applied externally [40]. Thermo-responsive scaffolds use polymers that exhibit a lower critical solution temperature [38]. Below this temperature, the polymer is hydrophilic and swelled with water [39]. Above this temperature, it becomes hydrophobic and collapses [4]. Yadav et al. (2025) discuss the molecular engineering of thermo-responsive smart hydrogels. They explain that dynamic cross-linking strategies allow these hydrogels to switch between liquid and gel states [38]. This property makes them injectable [9]. A polymer solution loaded with cells or drugs can be injected into a defect in a liquid state [4]. Once it reaches body temperature, it forms a solid gel that fills the irregular shape of the wound [21]. Castillo-Henríquez et al. (2021) explore thermo-responsive polymers for drug delivery in wound healing. The scaffold releases growth factors as the local temperature rises due to the inflammatory response [40]. Vejjasilpa et al. (2022) describe adjustable thermo-responsive tissue engineering scaffolds. These scaffolds stimulate cells through periodic changes in culture temperature. By cycling the temperature, researchers can control cell adhesion and proliferation. Cells detach from the scaffold when the temperature drops below the lower critical solution temperature. This feature allows the harvest of cell sheets for transplantation without using enzymatic digestion [41]. Amirthalingam et al. (2023) review stimuli-responsive dynamic hydrogels and note that temperature changes can trigger conformational changes in the polymer backbone. These changes alter the mechanical properties of the scaffold [4]. Thermo-responsive materials offer a non-invasive way to control scaffold behavior [38]. They require no external power source inside the body [40]. Their function depends solely on the thermal properties of the polymer and the temperature of the surrounding tissue [39].

Magnetic nanoparticles, such as iron oxide, are embedded in polymer matrices to form magnetically responsive scaffolds. These scaffolds respond to external magnetic fields by generating heat, moving, or altering mechanical stress. Chernozem et al. (2026) review magnetoelectric 3D microenvironments for tissue engineering. They explain that magnetic fields can induce electrical signals in magnetoelectric composites. These electrical signals

stimulate cell growth and direct tissue formation without the need for implanted electrodes. Because external magnetic fields can penetrate deep into tissue to actuate scaffolds non-invasively, magnetically responsive constructs can effectively guide cellular alignment and spatial organization. When a magnetic field is applied, the embedded particles align in chains. This alignment creates topographical cues that direct cells to form organized structures, like muscle fibers or nerve bundles. The heat generated by alternating magnetic fields can be used for localized hyperthermia treatment. This heat kills tumor cells while sparing healthy tissue. Magnetically responsive scaffolds offer a way to control cell behavior remotely. They provide both physical and thermal cues that can be turned on and off as needed during the healing process [42].

Electrically conductive scaffolds send electrical signals to cells. They are useful for regenerating excitable tissues like nerve, muscle, and bone [25]. These scaffolds integrate a structural polymer with a conductive material like graphene or polyaniline [27]. Liu et al. (2021) describe electroactive biomaterials and systems for cell fate determination. They find that electrical stimulation promotes neurite outgrowth and myoblast differentiation [25]. Bellet et al. (2021) highlighted graphene-based scaffolds, which establish conductive networks throughout the matrix while providing superior mechanical strength for regenerative applications [27]. Halvaeikhanekahdani et al. (2026) review nanoparticle integrated electrostimulation responsive biomaterials. They explain that electroactive polymers change their shape or volume when an electric field is applied. This movement can physically stimulate cells. It directs tissue alignment [43]. Peidavosi et al. (2022) developed a piezoelectric conductive electrospun nanocomposite scaffold using polyaniline and barium titanate. This scaffold combines the benefits of electrical conductivity and piezoelectricity. It provides continuous electrical cues to cells as they grow [44]. The conductive properties ensure that an externally applied electrical signal reaches all cells evenly. This uniform stimulation is necessary for forming functional muscle or nerve tissues [25]. Mohamed et al. (2019) discuss stimuli-responsive hydrogels for the manipulation of the cell microenvironment. They note that conductive hydrogels can deliver localized electrical cues to guide stem cell differentiation [14].

Piezoelectric materials generate an electrical charge when mechanically deformed [10]. In the body, natural movements like walking, breathing, or heartbeats provide continuous mechanical stress [12]. Piezoelectric scaffolds convert this stress into electrical signals that stimulate tissue repair. Jacob

et al. (2018) review piezoelectric smart biomaterials for bone and cartilage tissue engineering. They explain that bone is naturally piezoelectric. Synthetic piezoelectric scaffolds mimic this property. They promote bone formation through internal electrical cues generated by the patient's own movement [45]. Zaszczynska et al. (2020, 2024) detail the use of piezoelectric polymers like polyvinylidene fluoride for neural and bone tissue engineering [46, 47]. These scaffolds generate surface charges under mechanical load [46]. The charges attract calcium ions and accelerate mineral deposition [47]. Alvarez Lorenzo et al. (2023) review physical stimuli-emitting scaffolds and the role of piezoelectricity. They note that these scaffolds emit electrical signals without external power sources [10]. Joo et al. (2024) show that piezoelectrically and

topographically engineered scaffolds accelerate bone regeneration. They combine electrical cues with structural guidance [39]. Bagherzadeh et al. (2023) demonstrate that polycaprolactone and polyvinylidene fluoride fibrous scaffolds provide the mechanical support and piezoelectric stimulation necessary for bone defect repair. The mechanical force from daily activity acts as the trigger [48]. This creates a self-sustaining system that promotes healing without patient intervention [47]. Zhang et al. (2018) review advanced smart biomaterials for hard tissue engineering and regeneration. They highlight piezoelectric ceramics and polymers as primary materials for generating internal electrical cues [49]. Figure 2 shows how the electrically conductive and piezoelectric scaffolds act in tissue regeneration.

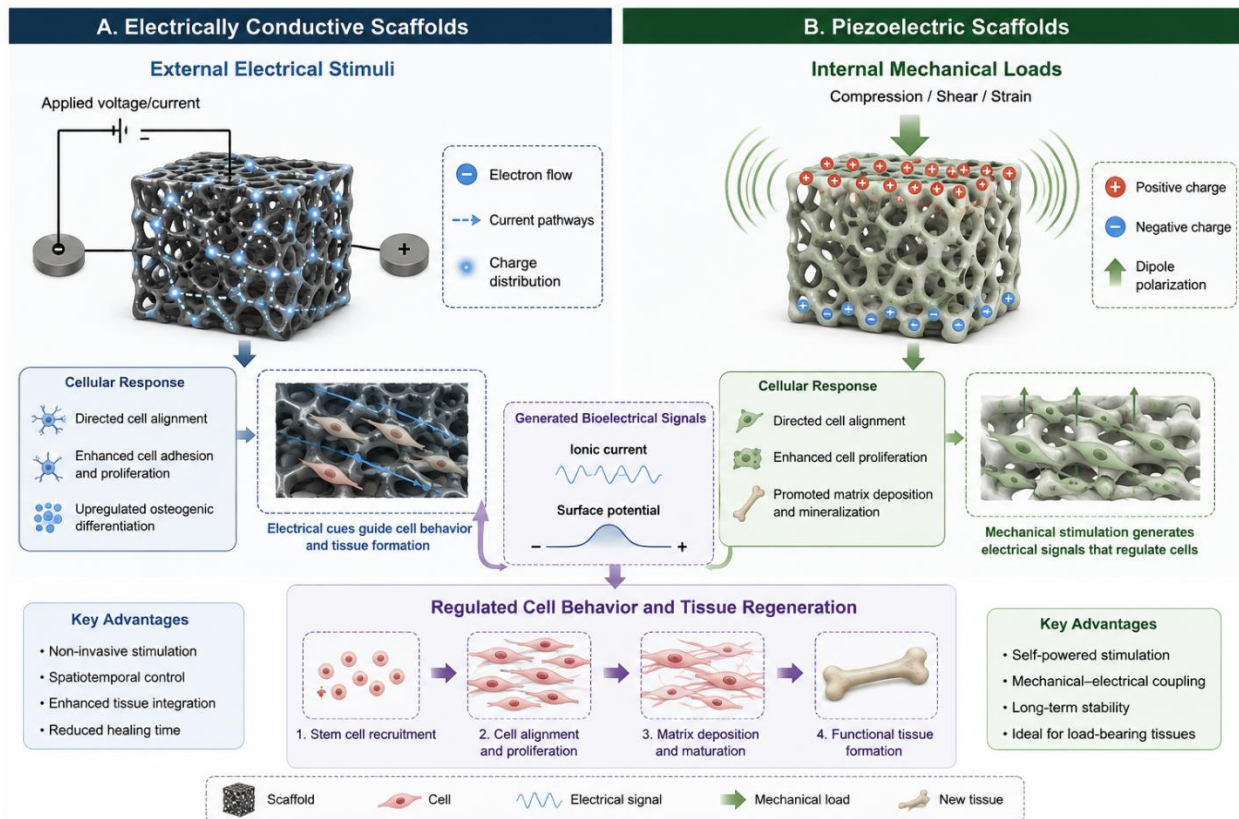


Figure 2. Mechanisms of electrically conductive and piezoelectric scaffolds in tissue regeneration. Figure shows how external electrical stimuli and internal mechanical loads generate charges or currents in the scaffold, directing cell alignment and tissue formation.

Light-responsive scaffolds react to specific wavelengths of light [50]. Near-infrared light is commonly used because it is able to penetrate deep into tissues without damage [51]. Light-responsive materials frequently include photothermal agents that convert light into heat. Wang et al. (2025) designed a near-infrared-programmable 3D-printed shape-memory scaffold. The scaffold uses a dual-thermal responsive mechanism for bone regeneration processes and bone tumor management. Upon near-infrared light exposure, the localized photothermal rise simultaneously triggers the shape-memory effect enabling the scaffold to expand and

precisely fill the bone defect while eradicating residual tumor cells [50]. Zhang et al. (2021) created a 3D-printed near-infrared-responsive shape memory polyurethane and magnesium scaffold. The shape-memory effect ensures tight contact between the scaffold and the surrounding bone. The magnesium ions released during degradation promote bone growth [52]. Zhang et al. (2023) report that bioinspired mild photothermal effects in multifunctional fiber scaffolds promote bone regeneration. The mild heat improves local blood flow. It does not damage surrounding cells [51]. Four-dimensional printing expands on these concepts by creating structures

that change shape over time [19]. Liu and Ding (2025) review 4D printing of alginate hydrogels for tissue regeneration. Alginate hydrogels swell or shrink in response to environmental changes. They adapt to the defect site [53]. Sadraei and Naghib (2024) detail how 4D printing creates physical stimuli-responsive hydrogels that release drugs only when exposed to a specific light trigger [28]. Yuan et al. (2024) review recent advances in 3D printing of smart scaffolds. They highlight how multi-material printing creates complex structures that respond to light dynamically [26]. Acharya et al. (2025) discuss physical stimuli-responsive DNA hydrogels. These hydrogels change their structure when exposed to light, offering a highly biocompatible platform for targeted drug delivery [54]. Pfau and Grunlan (2021) review shape memory polymers in tissue engineering. They explain how these polymers are programmed to return to their original shape

after being deformed, allowing for minimally invasive surgical delivery [12]. Vickram et al. (2026) review bioinspired and stimuli-responsive hydrogels for regenerative medicine, noting that light-triggered systems offer high spatial and temporal control [21].

3.3 Multi-Stimuli-Responsive Platforms

Biological tissues respond to multiple cues simultaneously [15]. Single-stimuli-responsive scaffolds often cannot fully replicate this complexity [55]. Multi-stimuli-responsive scaffolds combine two or more responsive mechanisms [29]. This combination creates more precise control over drug release and material behavior [17]. Table 2 provides a summary of internal and external stimuli-responsive scaffolds.

Table 2. Summary of internal and external stimuli-responsive scaffolds

Stimulus	Type	Biological/External Trigger	Mechanism of Action	Primary Application	References
pH	Internal	Acidic microenvironment (inflammation, infection)	Protonation of functional groups causes swelling or bond hydrolysis	Bone defects, infected wounds	[6, 34, 33]
Enzyme	Internal	Matrix metalloproteinases (MMPs)	Cleavage of specific peptide crosslinkers	Cartilage repair, complex tissue regeneration	[5, 37, 36, 11]
ROS	Internal	Oxidative stress, ischemia	Oxidation of thioketal or polysulfide linkers	Inflammation control, cell protection	[9, 6, 35, 22]
Glucose	Internal	Hyperglycemia	Glucose binding to phenylboronic acid causes swelling	Diabetic wound healing, insulin delivery	[9, 6]
Temperature	Internal/External	Body heat, inflammatory fever, external heating	Hydrophilic/hydrophobic phase transition causes gelation or collapse	Injectable scaffolds, cell sheet harvest	[4, 40, 41, 38]
Magnetic	External	External magnetic field	Magnetic particle alignment, hyperthermia	Cell alignment, tumor ablation	[42]
Electrical	External	Applied electric field	Conductive network transmits signals	Nerve, muscle, bone regeneration	[27, 43, 25, 14, 44]
Piezoelectric	Internal/External	Mechanical load/stress	Generation of internal electrical charges	Bone and cartilage repair	[10, 48, 45, 39, 46, 47, 49]
Light	External	Near-infrared light	Photothermal conversion, shape-memory trigger	Bone regeneration, tumor management	[54, 53, 12, 28, 21, 50, 26, 52, 51]

Percival et al. (2024) review recent advancements in bone tissue engineering. They integrate smart scaffold technologies and bio-responsive systems. They note that combining pH and enzyme responsiveness allows a scaffold to react to both the chemical environment and cellular activity. This dual response ensures that drugs are released only when both inflammation is present and remodeling enzymes

are active [55]. Ansari et al. (2023) discuss engineered stimuli-responsive smart grafts for bone regeneration. They describe grafts that respond to both mechanical stress and temperature. The mechanical stress generates electrical signals through piezoelectric components. The temperature sensitivity enables the graft to adapt to become stiff as the tissue heals [17]. Hasan et al. (2026) review smart

nanocomposite scaffolds for bone regeneration. They focus on mechanobiological regulation. The scaffolds combine magnetic nanoparticles for external control with enzymatic degradable polymers for biological integration [30]. Liang et al. (2026) investigate smart biomaterials for skeletal aging repair. Aging tissues are complex environments with altered pH, reduced blood flow, and lower enzyme levels. A multi-stimuli scaffold addresses these interconnected issues simultaneously [37]. Xing et al. (2023) underscored that multi-responsive polymeric scaffolds dynamically accommodate the evolving biochemical demands of the bone healing cascade, substantially minimizing the need for secondary surgical interventions [56]. Khan et al. (2025) describe smart hybrid scaffolds as a strategic approach for regenerative clinical applications. They combine natural and synthetic components to achieve multi-stimuli responsiveness. This balances biocompatibility with functional control [29]. Ooi et al. (2017) review hydrogels that listen to cells. They propose that multi-stimuli systems can be designed to respond directly to cell-secreted signals, creating a continuous feedback loop between the scaffold and the tissue [15]. Naranda et al. (2025) review smart hydrogel-based materials in cartilage tissue engineering. They highlight that cartilage repair requires scaffolds that respond to both mechanical load and enzymatic degradation [31].

4. Biomedical Applications, Current Challenges, and Translational Barriers

Smart scaffolds are applied across multiple tissue engineering disciplines. For bone and cartilage regeneration, piezoelectric and mechanically responsive materials provide the electrical and physical cues necessary to drive mineral deposition and chondrogenesis [17, 30, 58, 31, 55, 49]. Neural tissue regeneration relies heavily on electroactive scaffolds to bridge gaps and direct neurite outgrowth [25, 46]. Cardiac tissue engineering benefits from electrically conductive and mechanically compliant scaffolds that synchronize muscle contraction [27]. Skin and wound healing applications utilize thermo-responsive and pH-responsive materials to adapt to the changing wound bed and prevent infection [40]. Controlled drug and growth-factor delivery

remains a primary application across all tissues, allowing localized and temporal release of therapeutics [8, 11].

Despite these capabilities, several barriers prevent widespread clinical use [7]. Biocompatibility remains a primary concern; recognition of complex synthetic constructs by the host immune system often induces a robust foreign body response, leading to fibrous encapsulation that physically isolates the scaffold and hinders tissue integration [3, 20]. Long-term stability is another issue [24]. The properties of smart materials can degrade over time [9]. pH-responsive bonds might break down prematurely in the presence of normal metabolic byproducts [6]. Photo-responsive agents might lose their sensitivity after repeated exposure to light [50]. Scale-up and manufacturing pose significant challenges [8]. Many smart scaffolds are produced in small batches in laboratory settings [27]. Afzali et al. (2024) note that taking bioreactor-assisted bioprinting to an industrial scale requires overcoming technical hurdles in maintaining material uniformity and cell viability [8]. Sterilization is also difficult. Standard methods like autoclaving or gamma irradiation can damage the sensitive chemical structures that give smart materials their responsive properties [3]. Regulatory considerations add another layer of complexity. Regulatory agencies have established pathways for simple medical devices and drugs [7]. Smart scaffolds often fall into the category of combination products. They require approval for both the device and the drug components. The dynamic nature of these materials makes it difficult to establish standard testing protocols [18]. Eldeeb et al. (2022) review biomaterials for tissue engineering applications. They highlight the gap between in vitro success and in vivo performance. A scaffold that responds perfectly in a controlled laboratory environment might behave unpredictably in the variable conditions of a living body [3]. Williams (2019) stresses that sustainable tissue engineering requires designing materials that are practical to manufacture, sterilize, and regulate [7]. It is in this spirit that materials scientists, engineers, and clinicians must be working together to resolve the issues [18]. Table 3 outlines these translational barriers and potential mitigation strategies.

Table 3. *Translational barriers and mitigation strategies for smart scaffolds*

Barrier Category	Specific Challenge	Potential Mitigation	References
Biocompatibility	Toxicity of conductive particles or crosslinkers	Use of highly purified composites, surface coating	[3, 20]
Immune Response	Foreign body reaction, fibrous encapsulation	Immuno-modulatory surface design, controlled degradation	[20, 22]
Stability	Premature bond breakage, loss of sensitivity	Rigorous in vivo testing, material reinforcement	[9, 6, 50]
Manufacturing	Small batch production, scale-up issues	Automated bioreactor printing, standardization	[8, 27]
Sterilization	Damage to sensitive smart polymers	Low-temperature plasma, supercritical CO ₂	[3]
Regulatory	Combination product classification, dynamic testing	Clear guidelines for smart materials, functional assays	[3, 18, 7]

5. Future Perspectives and Conclusions

The field of smart scaffolds is moving toward greater integration with biological systems [21]. Future directions include developing scaffolds that can actively communicate with cells rather than just reacting to them [15]. Hui et al. (2026) demonstrated that engineered immuno-smart scaffolds functionalized with pro-regenerative surface ligands can directly instruct macrophage polarization toward a healing

phenotype, actively orchestrating tissue repair rather than functioning as passive substrates [57]. Zhang et al. (2025) expand on this idea. They view smart biomaterials as active immune modulators. Future scaffolds will shape the pro-regenerative microenvironment by releasing cytokines in response to cellular signals. This creates a continuous feedback loop between the material and the tissue [22]. Figure 3 depicts the concept of 4D printing and shape-memory scaffolds for minimally invasive delivery and defect filling.

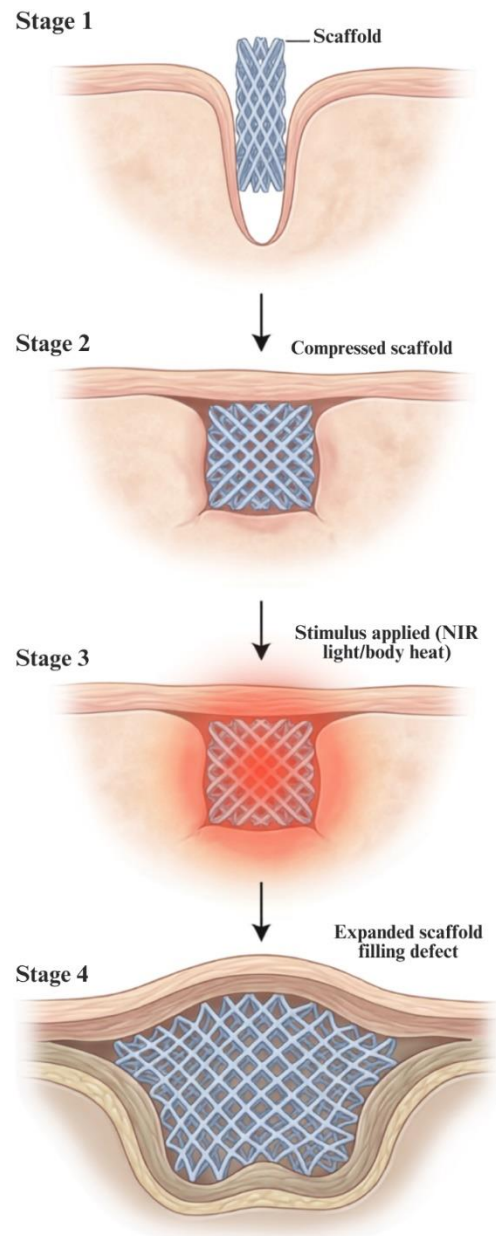


Figure 3. 4D printing and shape-memory scaffold concept for minimally invasive delivery and defect filling. The figure shows a compressed scaffold delivered through an incision. Upon exposure to a specific stimulus (e.g. near-infrared light or body heat), the scaffold expands to fill in the irregular tissue defect.

Karunakar et al. (2025) explore how stimuli-responsive smart materials bridge the gap between biotechnology and regenerative medicine. They point to the development of biohybrid scaffolds. These biohybrids combine living cells with synthetic responsive elements. They can adapt to physiological changes more naturally than fully synthetic materials [18]. Kumar et al. (2025) review next-generation biomaterials for load-bearing tissue interfaces. They describe sensor-integrated scaffolds. These scaffolds contain embedded sensors that monitor mechanical strain and tissue growth. The data collected from these sensors could be used to adjust rehabilitation protocols in real time [58]. Mechanoadaptive constructs that change their structure based on the load they experience will improve the

regeneration of joints and tendons. These emerging directions point toward scaffolds that are active participants in the healing process [57].

Smart scaffolds represent a shift in tissue engineering from static supports to dynamic platforms [13]. By responding to internal and external stimuli, these materials provide precise control over drug release, mechanical properties, and cell behavior [1]. pH, temperature, enzymes, light, and mechanical force all offer distinct ways to trigger therapeutic functions [6]. The development of multi-stimuli-responsive systems and 4D printing techniques allows scaffolds to adapt to the complex environment of a healing tissue [19]. These technologies address the limitations of conventional

biomaterials by matching the dynamic nature of biological processes [4]. Clinical translation remains challenging [7]. The issues of biocompatibility, long-term stability, manufacturing scale-up, and regulatory approval must be resolved before smart scaffolds achieve broad clinical adoption [3]. The gap between laboratory success and in vivo performance needs to be carefully considered in terms of how these materials interact with the immune system and the varying conditions of the human body [20]. Future research will focus on immuno-smart scaffolds and sensor-integrated systems that provide continuous feedback [57]. By bridging biotechnology and material science, smart scaffolds offer a path toward regenerative medicine that restores full tissue function [18].

Acknowledgments

The author would like to express their sincere gratitude to Karabuk University, Department of Biomedical Engineering, for providing the institutional support and academic environment that facilitated this comprehensive review. This review article did not involve direct experimental research with human or animal subjects; therefore, no ethics committee approval was required.

The author would also like to thank the editors and reviewers for their constructive feedback, which significantly improved the quality of this manuscript. Finally, the author acknowledges the broader scientific community whose foundational research in biomaterials, wound healing, and regenerative medicine made this work possible.

Conflict of Interest

The author declares no conflicts of interest.

Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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