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Optimization of the cell microenvironment in a dual magnetic-pH-sensitive hydrogel-based scaffold by multiphysics modeling

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ABSTRACT:

A dual magnetic-pH-sensitive hydrogel-based scaffold was studied for optimization of a cell microenvironment by scaffold mechanical deformation and its biochemical response. In particular, the positions of the seeding cells and the concentration of potassium (K^+) within the scaffold were optimized by a multieffect-coupling magnetic-pH-stimuli (MECmpH) model based on (i) the threshold of the mechanical force required for a mechanotransduction effect at the cellular level, and (ii) the common biological requirement for cell growth. In this model, the physicochemical mechanisms of a magnetic hydrogel were characterized using magneto-chemo-electro-mechanical coupled effects, including hydrogel magnetization, diffusion of the solvent and ions, ionic polarization, and nonlinear deformation. After validation of the model with experimental data, it was found that a higher pH and current intensity at the electromagnet and a shorter hydrogel-magnet distance contribute to larger scaffold deformation and thus a stronger mechanical force on the cells. Moreover, the cell seeding positions within the magnetic scaffold were optimized for improved cell culture through controlled current intensity in the electromagnet. Furthermore, the physiological concentration of K^+ was also optimized by the initial fixed charge density within the scaffold. We concluded that

this optimized magnetic scaffold via the MECmpH model may provide an appropriate microenvironment for efficient cell growth.

Keywords:

Dual magnetic-pH-sensitive hydrogel; Cell microenvironment; Multiphysics model

1. Introduction

One of the ultimate goals in tissue engineering for regenerative medicine is to provide appropriate microenvironments for cells. This not only provides structural support for cells to reside in but also delivers numerous biophysical and biochemical cues to regulate cell behaviors [1]. As a key physiological stimulus, mechanical force plays a crucial role in tissue development, remodeling and regeneration, and maintaining body homeostasis [1-4]. For example, lack of a mechanical load may lead to detrimental effects, including a significant loss of bone mass, higher incidence of cardiovascular disease, and accelerated biological aging [2]. Sufficient physical stimulus, on the contrary, exhibits positive effects, such as improvements to cell survival and viability, decreases in apoptotic molecules, and acceleration of chondrogenic differentiation for bone regeneration [5].

To maintain the physiological mechanical condition, various stimulation strategies have been employed to regulate cell behavior, including ultrasound, electricity, capacitive coupling, and magnetism, where the magnetic actuation exhibits superior merits over other types of stimuli, such as fast responsiveness, noninvasive and noncontact controllability, and a high penetrating capability [2, 6]. Therefore, a great attempt was made to develop magnetic material-based scaffolds for clinical treatment of bone fracture, avascular necrosis, and osteoarthritis [3] by means of integrating magnetic

particles, including magneto-rheological fluid and magnetic hydrogel, into the nonmagnetic medium. Usually, the former suffers from sedimentation, environmental contamination, and performance degradation [7]. As such, magnetic hydrogel has alternatively been used as a scaffold to cultivate the biological objects in tissue engineering via providing a suitable mechanical microenvironment in addition to the required biochemical cues. Subject to an external magnetic field, the magnetic particles are magnetized and move towards the region of the higher magnetic field together with the polymeric matrix, due to tight attachment of the particles onto the polymeric chain. Consequently, the scaffold deforms to generate physical forces transferable to cells that are adherent to the scaffold wall [8]. The remarkable features of the magnetic scaffold enables cell mechanical stimulation in a remote and noninvasive manner, which may also be of potential interest for its application *in vivo* [4].

It is clear from published literature that the physiological processes including cell metabolism, mass transfer, and tissue growth are highly dependent on the synergistic effects of biophysical (e.g., mechanical force) and biochemical factors (e.g., ionic concentration) [3]. Thereby, the magnetic scaffold in biological tissue is often synthesized using pH-sensitive hydrogels. Furthermore, most researchers have opted for the hydrogen bonding [9], coordination bonds [10], or covalent attachment [11] to incorporate the magnetic particles onto the polymeric chain for fabrication of the dual magnetic- and pH-sensitive hydrogel.

Recently, magnetic scaffolds have attracted considerable attention in tissue engineering, whereas a comprehensive understanding of the scaffold is still preliminary.

Particularly most reported works were experiment-based, which are time-consuming and can be inadequate for exploring all of the effects on the scaffold behavior. For example, under an extremely low magnetic field, the induced relatively small deformation of the scaffold was not accurately measured by the existing experimental setup [12]. Furthermore, the cells within the scaffold were assumed to experience an equivalent force in other words, the scaffold underwent homogeneous deformation [12]. However, a localized magnetic field gradient exists in a nonuniform magnetic field and can induce inhomogeneous deformation, such that cells seeded at different regions may undergo unequal mechanical stimulation. Therefore, the positions of the seeding cells are required to be optimized for better promotion of cellular organization for tissue generation, and it is thus worthwhile to elucidate the responsive mechanism of the hydrogel-based scaffold by a multiphysics model.

A further literature survey reveals that no effort has previously been made into theoretical modeling of a magnetic-pH-sensitive hydrogel. From the open literature, it is clear that almost all of the relevant models concentrated on a magneto-active elastomer that works in the surrounding air, with the assumption of an incompressible elastomer with a constant volume [13]. Nevertheless, the multiphysics model formulated in the present work emphasizes a deformable hydrogel immersed in a bath solution with mobile ions, where the hydrogel magnetization is characterized by a magnetic field, the diffusion of the solvent and ions characterized by a chemical field, the ionic polarization described by an electric field, and the remarkable volume variation of the hydrogel described by a mechanical field.

In this work, a magnetic-pH-sensitive hydrogel-based scaffold was investigated by a multieffect-coupling magnetic-pH-stimuli (MECmpH) model for optimization of the physiological microenvironment of the cell. In the model, the responsive mechanisms of the magnetic hydrogel are considered, including hydrogel magnetization, ionic polarization, diffusion of the solvent and ions, and nonlinear large deformations when subjected to various physical (i.e., magnetic field) and chemical (i.e., solution pH) stimuli. To examine the present MECmpH model, two comparisons were made between the numerical simulation and experimental results [14, 15] for the magnetic hydrogel subject to the pH and nonuniform magnetic stimuli respectively, in which satisfactory agreements were reached. Hence, the MECmpH model enables good prediction of the performance of the dual magnetic-pH-sensitive hydrogel-based scaffold. Furthermore, the model is employed for two optimum designs: (i) the positions of the seeding cells within the scaffold based on the threshold of mechanical force for a mechanotransduction effect at the cellular-size level, and (ii) the concentration of potassium (K^+) within the scaffold based on the common biological requirement for cell growth.

2. Theory

In this section, the responsive mechanisms of the magnetic-pH-sensitive hydrogel are characterized by the mathematic description of the hydrogel magnetization, ionic polarization, solvent and ions diffusions, and the large hydrogel deformation.

As shown in Schematic 1, the magnetic-pH-sensitive hydrogel is a combination of an anionic hydrogel embedded with micro- or nanosized magnetic particles, such as $\gamma - Fe_2O_3$, Fe_3O_4 , and $CoFe_2O_3$, which can simultaneously respond to external magnetic

fields and changes of solution pH [16]. The surrounding solution is comprised of four species, solvent molecules (i.e., water), hydrogen ions, co-ions that have the same charge as the fixed charge (i.e., chloride ions), and their counterions that have the opposite charge to the fixed charge (i.e., potassium ions). If the hydrogel is submerged in the bath solution, some functional groups in the polymeric chain dissociate, leading to the formation of mobile ions and fixed charges attached to the polymeric chain. Owing to the fixed charges, the ionic concentration within the interior hydrogel differs from that in the exterior solution. Thereby, an osmotic pressure is generated and it contributes to the swelling or deswelling of the hydrogel. Concurrently, if an external magnetic field is employed, two distinct interactions may occur, particle-particle and field-particle interactions, due to the magnetization of the magnetic particles and the magnetic field gradients respectively [17]. Since the particles are tightly anchored into the flexible chain, the movement of the particles further drives the hydrogel deformation, which in turn redistributes the magnetic field, mobile ions, and fixed charge density. Therefore, it is a full-loop magneto-chemo-electro-mechanical coupled system.

In general, the theoretical models for hydrogels are formulated in two coordinate systems. One is the Eulerian coordinate for the spatial description and the other is the Lagrangian coordinate for the material description. The two coordinate systems can be transformed by the method of the Piola transform, and the detailed transformation processes can easily be found in the published works [18-20]. As is well known, the model formulated in the Eulerian coordinate requires a moving mesh due to the deformation of the hydrogel [20]. Therefore, unless otherwise stated, the equations in the present model are formulated in the Lagrangian coordinate.

2.1. Governing equations

In the absence of a free current, the distributive magnetic field is governed by [21]

$$\nabla \times \mathbf{H} = 0, \quad \nabla \cdot \mathbf{B} = 0 \quad (1)$$

where $\nabla \times (\bullet)$ and $\nabla \cdot (\bullet)$ are the material curl and divergence operators respectively, $\mathbf{B}$ and $\mathbf{H}$ are the magnetic induction and intensity, respectively, and they are associated by [21]

$$\mathbf{B} = \mu_0 J \mathbf{C}^{-1} (\mathbf{H} + \mathbf{M}) \quad (2)$$

where $\mathbf{M}$ is the magnetization, μ_0 the vacuum magnetic permeability, $\mathbf{F}$ the deformation gradient with the determinant $J = \det(\mathbf{F})$, and $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ the right Cauchy-Green tensor. Over the interface between the magnetic hydrogel and the environmental solution, the magnetic variables $\mathbf{B}$ and $\mathbf{H}$ are needed to meet the conditions below [21],

$$\mathbf{N} \cdot [[\mathbf{B}]] = 0, \quad \mathbf{N} \times [[\mathbf{H}]] = 0 \quad (3)$$

where $\mathbf{N}$ is the Lagrangian unit outward normal, and the double square bracket represents a quantity jump across the surface from the inside to the outside of the material.

By Gauss's theorem [22], the electric displacement $\mathbf{D}$ in the hydrogel and surrounding solution satisfies the equation below,

$$\nabla \cdot \mathbf{D} = F_r (z_f C_f + \sum_k z_k C_k) \quad (4)$$

where z_f and C_f are the valence and the molar concentration of the fixed charges, z_k and C_k are the valence and the molar concentrations of the mobile ions, and F_r is the Faraday's constant.

By the conservation of mass [23], the chemical field with respect to the solvent diffusion is written in the local form of

$$\dot{C}_s = -\nabla \cdot \mathbf{J}_s + R_s \quad (5)$$

where $C_s(\mathbf{X}, t)$ denotes the molar concentration of solvent, $\mathbf{J}_s$ the solvent flux, and R_s the rate of solvent generation by the chemical reaction.

Similarly, the chemical field with respect to the ionic diffusion is expressed as [24]

$$\dot{C}_k = -\nabla \cdot \mathbf{J}_k + R_k \quad (6)$$

where $\mathbf{J}_k$ and R_k are the molar flux and generation of the k th mobile species respectively.

For incorporation of the mechanical effect into the hydrogel response, the mechanical equilibrium with nonlinear large deformation is employed as [17]

$$\rho_0 \dot{\mathbf{V}}_h = \nabla \cdot \mathbf{P} + \mathbf{f}_b \quad (7)$$

where ρ_0 denotes the mass density of the polymer network, $\mathbf{V}_h$ the deformation velocity, $\mathbf{P}$ the nominal stress tensor, and $\mathbf{f}_b$ the external force density.

2.2. Constitutive equations

To formulate the equations of state for the present hydrogel system with a large deformation at the isothermal condition, the inequality of free energy imbalance is employed via [18]

$$\frac{d}{dt} \left\{ \int_{V_0} \left(\Omega + \frac{1}{2} \rho_0 |\mathbf{V}_h|^2 \right) dv \right\} \leq \dot{W} + \dot{C} + \dot{E} + \dot{M} \quad (8)$$

where Ω is the Helmholtz free energy density and $\dot{W}$ the mechanical power given by [18]

$$\dot{W} = \int_{S_0} \mathbf{PN} \cdot \mathbf{V}_h ds + \int_{V_0} \mathbf{f}_b \cdot \mathbf{V}_h dv \quad (9)$$

The chemical power $\dot{C}$ may change due to two contributions, (i) the diffusion of the solvent and ions, and (ii) the mass generation of R_s and R_k by chemical reaction. Hence, the power $\dot{C}$ is written as [25]

$$\dot{C} = - \int_{S_0} \mu_s \mathbf{J}_s \cdot \mathbf{N} ds + \int_{V_0} \mu_s R_s dv - \sum_k \left(\int_{S_0} \mu_k \mathbf{J}_k \cdot \mathbf{N} ds - \int_{V_0} \mu_k R_k dv \right) \quad (10)$$

where μ_s and μ_k are the chemical potentials of the solvent and mobile ions, respectively.

The rate of work $\dot{E}$ done by the electric field is given by [26, 27]

$$\dot{E} = \int_{V_0} (\mathbf{E} \cdot \dot{\mathbf{D}} - F_r \phi \sum_k z_k \dot{C}_k) dv \quad (11)$$

where $\mathbf{E}$ and ϕ are the electric field strength and the electric potential, respectively.

In general, the magnetic power $\dot{M}$ is mainly contributed by two components, one related to the magnetization of the magnetic hydrogel [28] and the other associated with the magnetic migration effect on the mobile ions. Consequently, we have

$$\dot{M} = \int_{V_0} (\mathbf{H} \cdot \dot{\mathbf{B}} - F_r L \sum_k z_k \dot{C}_k) dv \quad (12)$$

where L is a function that satisfies the relationship $\mathbf{v} \times \mathbf{B} = -\nabla L$ [29] (here, $\mathbf{v}$ is the fluid velocity).

By the sum of Equations (9) to (12), and with the aid of the mass and mechanical balance Equations (5)-(7) and the divergence theorem, the local form of the inequality (8) is rewritten as

$$\begin{aligned} \dot{\Omega} \leq & \mathbf{P} : \dot{\mathbf{F}} + \mu_s \dot{C}_s + \sum_k \mu_k \dot{C}_k - \mathbf{J}_s \cdot \nabla \mu_s - \sum_k (\mathbf{J}_k \cdot \nabla \mu_k) \\ & + \mathbf{H} \cdot \dot{\mathbf{B}} - F_r L \sum_k z_k \dot{C}_k + \mathbf{E} \cdot \dot{\mathbf{D}} - F_r \phi \sum_k z_k C_k \end{aligned} \quad (13)$$

where the double dot symbol ‘:’ is used for double tensor contraction, i.e., for any second-order tensors $\mathbf{S}$ and $\mathbf{T}$, $\mathbf{S} : \mathbf{T} = S_{ij} T_{ij}$.

If the free energy density Ω is specified as a function of the five independent variables, namely, the magnetic induction $\mathbf{B}$, the electric displacement $\mathbf{D}$, the molar concentrations of solvent C_s and ions C_k , as well as the deformation gradient $\mathbf{F}$, we have

$$\begin{aligned}
 & \left(\frac{\partial \Omega}{\partial \mathbf{F}} - \mathbf{P} \right) : \dot{\mathbf{F}} + \left(\frac{\partial \Omega}{\partial \mathbf{B}} - \mathbf{H} \right) \cdot \dot{\mathbf{B}} + \left(\frac{\partial \Omega}{\partial \mathbf{D}} - \mathbf{E} \right) \cdot \dot{\mathbf{D}} + \left(\frac{\partial \Omega}{\partial C_s} - \mu_s \right) \cdot \dot{C}_s \\
 & + \sum_k \left[\frac{\partial \Omega}{\partial C_k} - \mu_k + F_r(\phi + L)z_k \right] \dot{C}_k + \mathbf{J}_s \cdot \nabla \mu_s + \sum_k \mathbf{J}_k \cdot \nabla \mu_k \leq 0
 \end{aligned} \tag{14}$$

The coefficient in any bracket vanishes as a result of the arbitrariness of the variables, such that the constitutive equations are given below

$$\mathbf{P} = \frac{\partial \Omega}{\partial \mathbf{F}}, \quad \mathbf{H} = \frac{\partial \Omega}{\partial \mathbf{B}}, \quad \mathbf{E} = \frac{\partial \Omega}{\partial \mathbf{D}}, \quad \mu_s = \frac{\partial \Omega}{\partial C_s}, \quad \mu_k = \frac{\partial \Omega}{\partial C_k} + F_r(\phi + L)z_k \tag{15}$$

To ensure the inequality held, the solvent flux $\mathbf{J}_s$ and the ionic flux $\mathbf{J}_k$ are associated with the chemical potential gradients $\nabla \mu_s$ and $\nabla \mu_k$, respectively, via [30]

$$\mathbf{J}_s = -\frac{C_s D_s \mathbf{C}^{-1}}{k_B T} \nabla \mu_s, \quad \mathbf{J}_k = -\frac{C_k D_k \mathbf{C}^{-1}}{k_B T} \nabla \mu_k \tag{16}$$

where $k_B T$ is the temperature in the unit of energy and D_s and D_k are the diffusion coefficients of the solvent and ions respectively.

2.3. Free energy function

For characterization of the performance of the magnetic hydrogel, a specific free energy density Ω is required. In many hydrogels, the density of the crosslinks is so low that the effect of crosslinks on mixing may be neglected [31]. Furthermore, if the magnetic hydrogel exhibits a liquid-like polarization or magnetization behavior [28, 31, 32], the free energy of the hydrogel system is assumed to be separated into contributions from stretching of the polymer networks Ω_{ela} , the mixing of the polymers and solvent Ω_{sol} ,

the mixing of the solvent and ions Ω_{ion} , the magnetization Ω_{mag} , and the polarization Ω_{ele} . Based on the Flory-Rehner theory, the free energy densities Ω_{ela} and Ω_{sol} with the effect of the volume fraction of the magnetic particles ξ_p are given respectively by [17, 33, 34]

$$\Omega_{ela} = \frac{1}{2} G \{ \text{tr}(\mathbf{F}^T \mathbf{F}) - 3 - 2 \ln[\det(\mathbf{F})] \} \quad (17)$$

$$\Omega_{sol} = \frac{k_B T}{v_s} \left[v_s C_s \ln \left(\frac{v_s C_s + \xi_p}{\det(\mathbf{F})} \right) + \chi_H v_s C_s \frac{1 - \xi_p}{\det(\mathbf{F})} \right] \quad (18)$$

where G denotes the hydrogel shear modulus, v_s denotes the volume per mole of the solvent species, and χ_H is the Flory-Huggins parameter.

The free energy density due to the mixing of the solvent with mobile ions is expressed as [26, 27]

$$\Omega_{ion} = k_B T \sum_k C_k (\ln C_k - \ln C_s - 1) \quad (19)$$

The free energy densities of magnetization Ω_{mag} and polarization Ω_{ele} for an ideal hydrogel in reference configuration are generally given in the form of [35]

$$\Omega_{mag} = \frac{\mathbf{B} \cdot \mathbf{CB}}{2\mu_0\mu_r J}, \quad \Omega_{ele} = \frac{\mathbf{D} \cdot \mathbf{CD}}{2\varepsilon_0\varepsilon_r J} \quad (20)$$

where ε_0 is the dielectric permittivity in a vacuum and ε_r and μ_r are the relative dielectric permittivity and magnetic permeability, respectively.

If the concentrations of the ions are assumed to be much lower than that of the solvent, such that the ion contributions to the volume of the hydrogel are negligible, the solvent molecules contribute the most to the swelling of the hydrogel. By the sum of Equations (17) to (20), and accounting for the condition of incompressibility of the polymers and solvent $1 + v_s C_s = \det(\mathbf{F})$ [26, 30, 36], the free energy density Ω is expressed as

$$\begin{aligned} \Omega = & \frac{1}{2} G \{ \text{tr}(\mathbf{F}^T \mathbf{F}) - 3 - 2 \ln[\det(\mathbf{F})] \} + \frac{k_B T}{v_s} [v_s C_s \ln(\frac{v_s C_s + \xi_p}{1 + v_s C_s}) + \chi_H v_s C_s \frac{1 - \xi_p}{1 + v_s C_s}] \\ & + \frac{\mathbf{D} \cdot \mathbf{CD}}{2 \varepsilon_0 \varepsilon_r J} + \frac{\mathbf{B} \cdot \mathbf{CB}}{2 \mu_0 \mu_r J} + k_B T \sum_k C_k (\ln C_k - \ln C_s - 1) + \Pi [1 + v_s C_s - \det(\mathbf{F})] \end{aligned} \quad (21)$$

where Π is the Lagrange multiplier [30].

From the free energy equation (21) and the constitutive equation (15), the magnetic intensity $\mathbf{H}$, the electric intensity $\mathbf{E}$, the chemical potential μ_k and μ_s , and the stress $\mathbf{P}$ are expressed respectively as

$$\mathbf{H} = \mathbf{CB} / (\mu_0 \mu_r J) \quad (22)$$

$$\mathbf{E} = \mathbf{CD} / (\varepsilon_0 \varepsilon_r J) \quad (23)$$

$$\mu_k = k_B T \ln \frac{C_k}{C_s} + F_r (\phi + L) z_k \quad (24)$$

$$\mu_s = k_B T \left[\ln \left(\frac{v C_s + \xi_p}{1 + v C_s} \right) + \frac{1 - \xi_p}{1 + v C_s} + \chi_H \left(\frac{1 - \xi_p}{1 + v C_s} \right)^2 \right] - k_B T \sum_k C_k / C_s + \Pi v_s \quad (25)$$

$$\mathbf{P} = G(\mathbf{F} - \mathbf{F}^{-T}) - \Pi \mathbf{F}^{-T} + \frac{(\mathbf{F}\mathbf{D}) \otimes \mathbf{D}}{\varepsilon_0 \varepsilon_r J} - \frac{\mathbf{D} \cdot \mathbf{C}\mathbf{D}}{2\varepsilon_0 \varepsilon_r J} \mathbf{F}^{-T} + \frac{(\mathbf{F}\mathbf{B}) \otimes \mathbf{B}}{\mu_0 \mu_r J} - \frac{\mathbf{B} \cdot \mathbf{C}\mathbf{B}}{2\mu_0 \mu_r J} \mathbf{F}^{-T} \quad (26)$$

where $\mathbf{F}^{-T}$ in Equation (26) is used for the transpose of the inverse of the deformation gradient $\mathbf{F}$.

Based on Faraday's law, the magnetic intensity $\mathbf{H}$ is associated with the magnetic scalar potential ψ by $\mathbf{H} = -\nabla\psi$, and the electric intensity $\mathbf{E}$ relates to the electric potential ϕ via $\mathbf{E} = -\nabla\phi$. By Equations (1) and (22), the magnetic potentials ψ in both the magnetic hydrogel and the exterior solution are rewritten as

$$\nabla \cdot (J\mu_0\mu_r \mathbf{C}^{-1} \nabla \psi) = 0 \quad (27)$$

and by Equations (4) and (23), the electric potentials ϕ in both the magnetic hydrogel and the exterior solvent are rewritten as

$$\nabla \cdot (J\varepsilon_0\varepsilon_r \mathbf{C}^{-1} \nabla \phi) = -F_r(z_f C_f + \sum_k z_k C_k) \quad (28)$$

where the fixed charge density of the anionic hydrogel C_f is given by [37]

$$C_f = \frac{\phi_s^0 C_f^0 J K_d}{J K_d + C_{H^+}} \quad (29)$$

where K_d is the dissociation constant, ϕ_s^0 the volume fraction of the polymeric network at the reference state, C_f^0 the molar concentration of the fixed charges in the dry state, and C_{H^+} the molar concentration of the hydrogen ion.

2.4. Model at equilibrium state

Based on Equations (6), (16) and (24), and without any chemical reaction, the ion transport in the equilibrium state is given by

$$\nabla \cdot \left[D_k \mathbf{C}^{-1} \left(\nabla C_k + \frac{z_k C_k F_r}{k_B T} (\nabla \phi - \mathbf{v} \times \mathbf{B}) \right) \right] = 0 \quad (30)$$

where the diffusion of the mobile ions is dependent on three driving forces, namely, the ion concentration gradient, electric force, and magnetic effect. In addition, the diffusion equation developed by the present model is consistent with the theoretical work [38] for magnetohydrodynamic flow in a microfluidic device subject to the electric and magnetic fields. If the hydrogel is immersed in an unstirred solution, the ionic diffusion contributed by convection can be neglected [24], such that the induction term $\mathbf{v} \times \mathbf{B}$ is not considered in the subsequent analysis.

For the mechanical equilibrium of the hydrogel system, Equation (7) is rewritten as

$$\nabla \cdot \mathbf{P} = 0 \quad (31)$$

if the external body force $\mathbf{f}_b$ is neglected and only the equilibrium state is considered.

Under equilibrium conditions, the chemical potentials of the solvent and ions in the hydrogel coincide with those in the bath solution, namely

$$\mu_s = \bar{\mu}_s, \mu_{H^+} = \bar{\mu}_{H^+}, \mu_+ = \bar{\mu}_+, \mu_- = \bar{\mu}_- \quad (32)$$

where the overbar denotes the parameters in the solution. After insertion of Equation (25) into (32), the osmotic pressure Π is obtained as

$$\begin{aligned} \Pi = & -\frac{k_B T}{v_s} \left(\ln\left(\frac{vC_s + \xi_p}{1 + vC_s}\right) + \frac{1 - \xi_p}{1 + vC_s} + \chi_H \left(\frac{1 - \xi_p}{1 + vC_s}\right)^2 \right) \\ & + \frac{k_B T}{v_s} \left(\frac{C_{H^+} + C_+ + C_-}{C_s} - \frac{\bar{C}_{H^+} + \bar{C}_+ + \bar{C}_-}{\bar{C}_s} \right) \end{aligned} \quad (33)$$

where the first term arises due to the mixing of the hydrogel and solvent, and the second one due to the imbalanced distribution of the ionic concentration between the interior hydrogel and the exterior solution.

In this paper, a two-dimensional (2D) simulation is conducted in the equilibrium state with the MECmpH model for the performance of a cylindrical magnetic hydrogel placed in an unstirred bath solution, as shown in Schematic 2. The hydrogel bottom is mechanically constrained along the Z-axis direction. Due to the axisymmetry of the present problem, the Neumann electrochemical boundary conditions are utilized at the hydrogel center, namely

$$\frac{\partial C_k}{\partial R} = 0, \quad \frac{\partial \phi}{\partial R} = 0, \quad \frac{\partial \psi}{\partial R} = 0 \quad \text{at } R = 0 \quad (34)$$

and the Dirichlet boundary conditions at the edge of the solution domain ∂S_0

$$C_{H^+} = \bar{C}_{H^+}, \quad C_+ = \bar{C}_+, \quad C_- = \bar{C}_-, \quad \phi = 0, \quad \psi = \psi(R, Z) \quad \text{at } \partial S_0 \quad (35)$$

where the magnetic boundary condition $\psi = \psi(R, Z)$ is constructed from the measured magnetic field along the axial direction by Equation (27).

At the hydrogel-solution interface $\partial\beta_0$, we have the following mechanical boundary condition,

$$\mathbf{P} \cdot \mathbf{N} = \mathbf{T}_m + \mathbf{T}_e \quad \text{at } \partial\beta_0 \quad (36)$$

where $\mathbf{T}_m$ and $\mathbf{T}_e$ are the magnetic and electric tractions acting on the boundary $\partial\beta_0$.

So far, the MECmpH model has been completed theoretically for the magnetic-sensitive hydrogel placed in an ionic solution subjected to magneto-chemo-electro-mechanical coupled fields. At the equilibrium state, the governing equations are comprised of the magnetostatic equation (27), the electrostatic equation (28), the ionic diffusion equation (30), and the mechanical equilibrium equation (31). Furthermore, the free energy density is given by Equation (21) and the constitutive relations are given by Equations (22) to (26). For simulation and analysis of the hydrogel response in the equilibrium state, the finite element package COMSOL MULTIPHYSICS 5.3 was employed as a result of its ability to solve the coupled nonlinear equations with high efficiency and the desired accuracy.

3. Results and discussion

3.1. Model validation

For validation of the MECmpH model, a comparison was carried out, and the experimental result [14] was that a hydrogel was synthesized by homogeneous copolymers of acrylic acid and hydroxyl-ethyl-methacrylate acid (HEMA) with a diacrylate crosslinker. The axial displacement of the cylindrical hydrogel was constrained by the cover glasses positioned at the two ends, such that the hydrogel with a radius R_0

of 250 μm only swelled in the radial direction. In the present simulation, it is reasonable to employ the 2D MECmpH model to characterize the hydrogel response in the equilibrium state, where it is placed in a bath solution with an ionic strength of 300 mM. The input parameters are tabulated in Table 1. It is noted that the experimental shear modulus G varies in a trilinear form [14]. At low $\text{pH} < 5.5$, the shear modulus almost remains constant $G = 101.4 \text{ kPa}$, whereas it decreases to another constant $G = 80.4 \text{ kPa}$ when $\text{pH} > 7.5$. In the intermediate pH range from 5.5 to 7.5, the linear decrease of shear modulus G is obtained.

Figure 1 is plotted for comparison between the present simulation and the published experimental result for the deformation of the HEMA hydrogel placed in the bath solution at various pH levels. As seen from the figure, the solution pH has a pronounced effect on variations of the hydrogel deformation. The diameters of the HEMA hydrogel remain approximately 570 and 1100 μm when $\text{pH} < 4$ and $\text{pH} > 7$, respectively, whereas the hydrogel undergoes an abrupt change in a pH level ranging from 4 to 7. The pH-induced hydrogel swelling may be attributed to acid pendant groups on the backbone of the network. The acidic group is marginally ionized if the solution pH is far below the pKa value of the HEMA hydrogel ($\text{pKa} = 4.7$), resulting in minimal swelling of the hydrogel. However, when the environmental pH increases and approaches the hydrogel pKa, the acidic functional group may be remarkably ionized, resulting in a sharp increase in the fixed charge density C_f . It is commonly known that an increase of fixed charge density C_f in the acidic hydrogel contributes to the diffusion of mobile ions with positive charges [39], and the associated increase of the ionic concentration inside the

hydrogel generates a large osmotic pressure to stimulate an observable increase in swelling. When the ionization degree of the hydrogel reaches its saturation point at about $\text{pH}=7$, no noticeable change is found in the swelling of the HEMA hydrogel if the solution pH increases further. Furthermore, the simulation results coincide well with the experimental data, such that the present model enables prediction of the hydrogel behavior with the desired accuracy.

For further validation, the simulated magnetic hydrogel deformation in the equilibrium state was compared with the published experimental results [15] in which a cylindrical magnetic hydrogel was prepared via a chemically crosslinked polyvinyl alcohol polymer and magnetic particles (i.e., Fe_3O_4), and it was immersed in water and then subjected to a nonuniform magnetic field. To describe the hydrogel performance, the boundary condition on the magnetic scalar potential $\psi = \psi(R, Z)$ is required at the exterior solution edge ∂S_0 . In this validation, it is reconstructed from the experimental measurement [15] on the magnetic induction along the axial direction divided by the current intensity of the electromagnet $B(0, Z)/I$. Before inserting the magnetic hydrogel in water, $B(0, Z)/I$ was experimentally measured as a function of the distance Z from the top surface of the electromagnet, which is fitted by a fifth-degree polynomial, $B/I = 60.4934 Z^5 - 4.8576 Z^4 - 9.6825 Z^3 + 2.9074 Z^2 - 0.3136 Z + 0.0124$, as shown in Figure 2(a). It is noted that the maximum magnetic field $H_{\max}$ on the top surface of the electromagnet is related to the current intensity of the electromagnet I by $H_{\max} = 9946.8I \text{ Am}^{-1}$. According to the relation $\mathbf{H} = -\nabla\psi$, the magnetic scalar potential ψ is written as a sixth-degree polynomial $\psi(0, Z) = p_6(Z)$. Moreover, the distribution

of the magnetic scalar potential ψ in the bath solution satisfies the Laplace's equation $\nabla^2\psi = 0$ (27). Therefore, the analytical solution of the magnetic potential ψ is given by $\psi(R, Z) = p_6(Z) - R^2 p_6^{(2)}(Z)/4 + R^4 p_6^{(4)}(Z)/64 - R^6 p_6^{(6)}(Z)/2304$ [40], which is imposed on the solution boundary ∂S_0 . The input parameters for the validation include: $L_R = 80$ mm, $L_H = 200$ mm, $r_0 = 7$ mm, $h_0 = 122.1$ mm, $z_0 = 24.2$ mm, and $\mu_{mr} = 1.14$. Since the value for the shear modulus G is not given explicitly in the reference, we performed fitting to obtain the value using $G = 10^3$ Pa. Other input parameters are cited from the experimental work [15]. Figure 2(b) illustrates the comparison of the present numerical simulation with the experimental data [15] for the magnetic field-induced hydrogel length change Δh . The deformation Δh increases with the increase of the current intensity of the electromagnet I due to the stronger magneto-elastic effect. Furthermore, the simulated results agree well with the experimental findings, which further support the validity of the present MECmpH model, such that it is reasonable to utilize the model to undertake the studies below.

3.2. Mechanical behavior of the magnetic scaffold

To understand the mechanical stimulation of the cells by the scaffold deformation in response to the magnetic and pH coupled stimuli, it is essential to capture the distributive magnetic field and the coupled field-induced deformation. To the extent of our knowledge, no literature exists that reports the study of the magneto-chemo-electro-mechanical behavior of magnetic hydrogel. Thereby, the validated MECmpH model is utilized for the first time to investigate the mechanical response of the magnetic scaffold. In general, the magnetic field distributions in both the hydrogel and solution domains are

associated with the hydrogel-magnet distance z_0 [15, 41] and the maximum magnetic field due to the current intensity of the electromagnet I applied to the electromagnet [15], such that these two key factors are considered in the present study to investigate the mechanical behavior of the magnetic scaffold. It is known that the physiological pH of the human body approximates 7.4 and exhibits pronounced differences among certain organs, such as the bladder with urine (e.g., pH 4.6~8), and the tumor tissue (e.g., pH 4.5~6) [42]. Herein, the anionic magnetic hydrogel-based scaffold works in a bath solution with a pH ranging from 4 to 8 and with the concentrations of ions of Na^+ , H^+ , Cl^- , and OH^- at physiological conditions [43]. To predict the magnitude of the mechanical force developed in the present scaffold due to the scaffold deformation, that was potentially acting on cells within the scaffold, the stimulation force F was estimated by Hooke's law: $F = EA_0\Delta h/h_0$ [12], where E is the cell Young's modulus and A_0 is the original cross-sectional area. The original nonuniform magnetic field generated by the external electromagnet follows that in Figure 2(a). The inputs required by the model include: $C_f^0 = 100 \text{ mM}$, $\bar{C}_{\text{Na}^+} = \bar{C}_{\text{Cl}^-} = 150 \text{ mM}$, $r_0 = 4 \text{ mm}$, $h_0 = 4 \text{ mm}$, $E = 7 \text{ kPa}$, $A_0 = 10^{-10} \text{ m}^2$, $G = 100 \text{ kPa}$, and $\xi_p = 0.15$, and the other inputs are obtained from Table 1. The input parameters were obtained from the open literature [12, 43-45] for the hydrogel under a human physiological condition, such that the *in vivo* performance of the magnetic scaffold can be characterized by the MECmpH model.

Figure 3(a) and (b) show the influence of the environmental pH level on the variation of the mechanical force F acting on the cells inside the scaffold very close to the scaffold surface against the current intensity of the electromagnet I , when subjected to a varying

hydrogel-magnet distance z_0 , 2 and 8mm, respectively. The mechanical force F increases with the increasing current intensity I and it further increases with the increase in the solution pH. This is because the acidic functional groups are ionized more with an increasing pH, which results in a larger osmotic pressure and thus drives the larger scaffold deformation. It is also found from Figure 3(a) that the mechanical force F acting on cells is approximately 4.6 pN when the current intensity $I = 0.14$ A and pH =4, whereas the force F decreases by approximately 1.4 times accordingly, as demonstrated in Figure 3(b). This is because the magnetic field decays away from the electromagnet, so the magnetic field-induced scaffold deformation decreases with increasing hydrogel-magnet distance z_0 . Thereby, it is worthwhile to quantify the magnetic field distribution for optimization of the magnetic hydrogel-based scaffold.

Figure 4 presents the distribution of the nondimensional magnetic field $H/H_{\max}$ along the coordinate $R=0$ in the presence of the magnetic hydrogel at distances z_0 of 2, 4, 6, and 8 mm. It is seen that the nondimensional magnetic field $H/H_{\max}$ decreases with increasing nondimensional coordinate Z/L_H , and then it increases to a maximum at the hydrogel-solution interface, where the field $H/H_{\max}$ follows a step function with a drastic decrease at the interface within a small range of the normalized coordinate Z/L_H . Subsequently, it rises to another maximum and then decreases until it reaches the interface again, where it increases drastically. Moreover, it is found that the magnetic field $H/H_{\max}$ is discontinuous across the hydrogel-solution interface. We may understand the phenomena above by the following two reasons: (i) the different magnetic permeabilities between the hydrogel and the bath solution, and (ii) the magnetic boundary

condition (3) at the interface between the hydrogel and solution, demonstrating tangential component of the magnetic intensity $\mathbf{H}$ and the normal component of magnetic induction $\mathbf{B}$ are continuous across the material boundary [17]. Furthermore, as is seen from the inset in the figure, the nondimensional magnetic field strength $H/H_{\max}$ at the coordinate $Z/L_H = 0$ increases greatly from 1.005 to 1.114 if the distance z_0 decreases from 8 to 2 mm. The original magnetic field applied is distorted via inserting the magnetic hydrogel and the distortion becomes more obvious when the hydrogel approaches the electromagnet. This phenomenon is referred to as an edge effect [46], which is crucial in the design and optimization of magnetic material-based devices [47].

In general, the magnetic scaffold undergoes an inhomogeneous deformation due to the local gradient field by a nonuniform magnetic stimulus [28]. As the cells are tightly attached to the scaffold, the inhomogeneous scaffold deformation may induce the varying mechanical forces on the cells at different seeding positions. It has been reported in the literature that a mechanical force of 0.2 pN was required to activate the TREK-1 channel [48], while 2 pN may break the molecular slip bond between fibronectin and the cytoskeleton [49]. In addition, the range of 0.2~2 pN was used as the threshold of mechanical force for a mechanotransduction effect at a cellular-size level, under which the mechanosensitive receptors were activated, initiating biochemical pathways to produce the mature tissue [12, 41]. Therefore, the range of 0.2~2 pN is adopted here in the present optimization of the cell mechanical microenvironment. Figure 5 demonstrates the influence of the current intensity of the electromagnet I on the distribution of the mechanical force F exerted on the cells, where the solution pH = 6 and $z_0 = 6$ mm. As

observed from Figure 5(a), the force F is less than 0.2 pN if the current intensity $I = 0.024$ A, where the weak stimulation force may be insufficient to activate the mechanosensitive ion channels in the cells. If the current intensity I increases from 0.024 to 0.028 A, the force F is still less than 0.2 pN if the cells are seeded at the upper region of the scaffold, while it is larger than 0.2 pN if the cells are seeded at the lower region of the scaffold, as illustrated in Figure 5(b). It is seen that the upper and lower regions in the contour are separated by a black curve for the force $F = 0.2$ pN. It is also found that the force increases with an increasing coordinate R when the axial coordinate is fixed (i.e. $Z = 0.012$ m). The nonuniform magnetic field-induced deformation at the centerline of the scaffold (i.e., $R = 0$) is the smallest, which is qualitatively in line with corresponding experimental findings [50]. This is because the magnitude of the magnetic force F_m is associated with a local magnetic field via $F_m = \mu_0(\mu_r - 1)(H_t^2 + \mu_r H_n^2)/2$ [51], where H_n and H_t are the normal and tangential components of the magnetic fields over the hydrogel-solution interface, respectively. Although the normal magnetic field H_n decreases with the increasing coordinate R , the tangential one H_t increases gradually. Consequently, the magnetic force and the force-induced deformation at the larger coordinate R may exceed that at the center. Regarding the case of the current intensity $I = 0.076$ A, the cells may be seeded on any region of the scaffold since the force F is distributed in the optimized range of 0.2 ~ 2 pN, as illustrated in Figure 5(c). However, if the current intensity I increases further from 0.076 to 0.084 A, the cell structure may be broken [12], since the force F is larger than 2 pN if the cells are seeded at the lower region of the scaffold, as illustrated in Figure 5(d). Therefore, the positions of the seeding

cells are effectively predicted and optimized by the multiphysics model, and it is thus confirmed that the present magnetic scaffold can provide a suitable cell mechanical microenvironment for tissue generation.

3.3. Biochemical behavior of the magnetic scaffold

It is commonly known that biochemical cues such as growth factor, pH, and ion concentration may play critical roles in biological systems [3, 52]. For example, the depletion of potassium (K^+) is associated with an impaired carbohydrate and protein metabolism, neuromuscular and cardiac toxicity, and abnormal renal function [53]. As such, the synergistic effects of the biophysical (e.g., mechanical forces) and biochemical cues are required to be fully considered in the design of a bioreactor in order to provide appropriate culture conditions [3]. Therefore, the molar concentration C_{K^+} of the monovalent cation K^+ within the magnetic scaffold has been predicted and optimized via the validated multiphysics model when subjected to the varying material parameters such as initial fixed charge densities C_f^0 . Typically, the concentration of the K^+ ion is approximately 140 mM in regular cell growth medium [52, 54], and herein this critical value was adopted as the optimal concentration. In this study, the environmental solution contains the ions of K^+ , H^+ , Cl^- , and OH^- with a pH of 7.4. The ion concentrations at the solution are $\bar{C}_{K^+} = \bar{C}_{Cl^-} = 120$ mM, the hydrogel-magnet distance $z_0 = 6$ mm, the current intensity of the electromagnet $I = 0.05$ A, and the remaining inputs are provided as given in Section 3.2.

Figure 6 is a plot showing the effect of the initial fixed charge density C_f^0 on the variation of the concentration C_{K^+} along the vertical line located at coordinate $R = 0$ across the domains covering both the hydrogel and its surrounding solution. It is observed that the initial fixed charge density C_f^0 has a pronounced impact on the distribution of the concentration C_{K^+} . The concentration of the K^+ ion remains almost unchanged within the environmental solution, while a sharp increase or decrease is found at the hydrogel-solution interface, and the concentration C_{K^+} within the hydrogel is higher than that in the solution. This is because the fixed charged groups merely exist in the anionic hydrogel and they attract numerous counterions from the bath solution to the hydrogel, achieving an electroneutrality state. This phenomenon results in an imbalance of ionic concentration between the interior hydrogel and exterior solution. As the valence of the fixed charge group is negative, the mobile ions with the same sign of the fixed charge groups are repulsed from entering the interior hydrogel, while the mobile ions with a positive sign (e.g., K^+) are attracted into the hydrogel. Therefore, the concentration of the K^+ ion is higher within the interior of the hydrogel than that in the exterior solution. It is also seen from the figure that the concentration C_{K^+} reaches approximately 140 mM when the fixed charge density $C_f^0 = 38 \text{ mM}$. Therefore, the present magnetic scaffold enables us to provide the desired biochemical cues in addition to biophysical cues such as mechanical stimulation for the cell culture in tissue engineering by optimization of the fixed charge groups in the hydrogel.

4. Conclusions

A magnetic-pH-sensitive hydrogel-based scaffold has been investigated for optimization of the cell biophysical and biochemical microenvironment when subjected to the magneto-chemo-electro-mechanical coupled effects. In particular, the positions of the seeding cells and the concentration of potassium (K^+) within the scaffold have been suggested by a multieffect-coupling magnetic-pH-stimuli (MECmpH) model based on the threshold of the mechanical force for a mechanotransduction effect at the cellular-size level and the requirements for the regular cell growth medium. In the developed MECmpH model, the responsive mechanisms are considered, such as transport of solvent and ions, hydrogel magnetization, ionic polarization, and large hydrogel deformation. To examine the MECmpH model, two comparisons were made between the simulation results and the published experimental data [14, 15] for the magnetic hydrogel under pH and nonuniform magnetic effects, and satisfactory agreements were achieved. Subsequently, the performance of the magnetic scaffold was studied in detail under various pH levels and magnetic stimuli. The results show that a higher pH level and magnetic intensity due to the current intensity and a shorter hydrogel-magnet distance contribute to the larger deformation of the magnetic scaffold and thus a stronger mechanical force acting on the cells. Furthermore, the cell seeding position on the magnetic scaffold was optimized quantitatively by the multiphysics model. Apart from that, the physiological concentration of K^+ within the scaffold was also optimized by the controllable initial fixed charge density of the scaffold. Therefore, the MECmpH model can easily capture and characterize the response of the dual magnetic-pH-sensitive hydrogel and the presently optimized magnetic hydrogel-based scaffold may provide the

right stimulatory conditions, such as biophysical and biochemical cues for an appropriate cell microenvironment.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Schematic 1. Cylindrical magnetic-pH-sensitive hydrogel immersed in a bath solution and subjected to a nonuniform magnetic field generated by an electromagnet. 34

Schematic 2. Boundary conditions for the MECmpH model in the equilibrium state. ... 35

- Figure 1.** Comparison of the present simulation (line) and a published experiment (square) for deformation of the HEMA hydrogel with the solution pH ranging from 2 to 12, where the hydrogel radius $R_0 = 250 \mu\text{m}$ 36
- Figure 2.** (a) Fitting curve (line) of the experimental measurement (square) of a magnetic induction distribution along the axial direction by a fifth-degree polynomial, namely

$$B/I = 60.4934 Z^5 - 4.8576 Z^4 - 9.6825 Z^3 + 2.9074 Z^2 - 0.3136 Z + 0.0124$$
 .
 (b) Comparison of the present theoretical simulation (line) and the experiment (square) for the magnetic field-dependent deformation of the magnetic hydrogel. 37
- Figure 3.** Variations of the mechanical force on cells close to the top surface of the scaffold against the current intensity of the electromagnet I at the solution pH of 4 (black solid line), 6 (blue dashed line), and 8 (red dotted line) when subjected to different hydrogel-magnet distance $z_0 = 2 \text{ mm}$ (a) and 8 mm (b). 38
- Figure 4.** Variations of the nondimensional magnetic field distribution $H/H_{\max}$ along the vertical line located at $R = 0$ when subjected to different hydrogel-magnet distance $z_0 = 2 \text{ mm}$ (purple dot-dashed line), 4 mm (red dotted line), 6 mm (blue dashed line), and 8 mm (black solid line). The green dashed line represents the original magnetic field applied. 39
- Figure 5.** Influence of the current intensity I on variations of the distribution of the mechanical force F on cells adhesive to the magnetic scaffold, where pH = 6, $z_0 = 6 \text{ mm}$, and $I = 0.024 \text{ A}$ (a), 0.028 A (b), 0.076 A (c), and 0.084 A (d). 40
- Figure 6.** Variations of the ion concentration C_{K^+} along the coordinate $R = 0$ at the initial fixed charge density C_f^0 of 34 mM (black solid line), 38 mM (blue dashed line), 42 mM (red dotted line), and 46 mM (purple dot-dashed line). 41

Table 1. Input parameters for validation of the MECmpH model.

Parameters	Symbol	Value
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Initial fixed charge density	C_f^0	1800 mM [14]
External concentration of Na^+	$\bar{C}_{\text{Na}^+}$	300 mM [14]
External concentration of Cl^-	$\bar{C}_{\text{Cl}^-}$	300 mM [14]
External concentration of H^+	$\bar{C}_{\text{H}^+}$	$10^{(3-\text{pH})}$ mM
Diffusion coefficient of Na^+	D_{Na^+}	$1.3 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ [55]
Diffusion coefficient of Cl^-	D_{Cl^-}	$2.032 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ [55]
Diffusion coefficient of H^+	D_{H^+}	$9.31 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ [55]
Dissociation constant	K_d	0.01 mM [14]
Faraday's constant	F	$1.603 \times 10^{-19} \text{ C}$
Dielectric permittivity in vacuum	ϵ_0	$8.8542 \times 10^{-12} \text{ F m}^{-1}$
Relative dielectric permittivity	ϵ_r	80 [56]

Schematic 1. Cylindrical magnetic-pH-sensitive hydrogel immersed in a bath solution and subjected to a nonuniform magnetic field generated by an electromagnet.

Schematic 2. Boundary conditions for the MECmpH model in the equilibrium state.

Figure 1. Comparison of the present simulation (line) and a published experiment (square) for deformation of the HEMA hydrogel with the solution pH ranging from 2 to 12, where the hydrogel radius $R_0 = 250\mu\text{m}$.

Figure 2. (a) Fitting curve (line) of the experimental measurement (square) of a magnetic induction distribution along the axial direction by a fifth-degree polynomial, namely $B/I = 60.4934 Z^5 - 4.8576 Z^4 - 9.6825 Z^3 + 2.9074 Z^2 - 0.3136 Z + 0.0124$. (b) Comparison of the present theoretical simulation (line) and the experiment (square) for the magnetic field-dependent deformation of the magnetic hydrogel.

Figure 3. Variations of the mechanical force on cells close to the top surface of the scaffold against the current intensity of the electromagnet I at the solution pH of 4 (black solid line), 6 (blue dashed line), and 8 (red dotted line) when subjected to different hydrogel-magnet distance $z_0 = 2$ mm (a) and 8 mm (b).

Figure 4. Variations of the nondimensional magnetic field distribution $H/H_{\max}$ along the vertical line located at $R=0$ when subjected to different hydrogel-magnet distance $z_0 = 2$ mm (purple dot-dashed line), 4 mm (red dotted line), 6 mm (blue dashed line), and 8 mm (black solid line). The green dashed line represents the original magnetic field applied.

Figure 5. Influence of the current intensity I on variations of the distribution of the mechanical force F on cells adhesive to the magnetic scaffold, where $\text{pH} = 6$, $z_0 = 6$ mm, and $I = 0.024\text{A}$ (a), 0.028A (b), 0.076A (c), and 0.084A (d).

Figure 6. Variations of the ion concentration C_{K^+} along the coordinate $R = 0$ at the initial fixed charge density C_f^0 of 34 mM (black solid line), 38 mM (blue dashed line), 42 mM (red dotted line), and 46 mM (purple dot-dashed line).

Graphic abstract

Highlights:

- A magnetic-pH-sensitive hydrogel-based scaffold was studied by a validated model
- Cell seeding position and concentration of K^+ within scaffold were optimized
- Responsive mechanism was characterized with magneto-chemo-electro-mechanical effect