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MATHEMATICAL MODELING OF MAGNETIC SCAFFOLDS FOR TARGETED DRUG DELIVERY AND BONE REPAIR

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Abstract Magnetic bone substitutes are multifunctional nanocomposite biomaterials designed to serve as an in situ attraction platform for magnetic carriers of growth factors. The morphological and functional properties of these biomaterials were characterized so far, but very little is known on the treatment dynamics, and the latter cannot be designed from an engineering point of view. For the first time, this work deals with the mathematical modeling of the use of magnetic scaffolds and functionalized nanoparticles to evaluate the enhancement of osteogenesis and bone repair. The non-linear magnetization of the scaffolds is considered to simulate the attraction and transport of magnetic nanoparticles. Different biomaterials and drug carriers from the literature are analyzed. The drug release via RF-heating is modeled considering the multiphysics nature of the phenomena. The physiological process of bone healing is reproduced using nine non-linear equations. The influence of the delivered growth factor on osteogenesis is assessed and quantified in silico, while compared to numerical simulations of intravenous injection of growth factor and to its release from the biomaterial. The exploitation of magnetic carriers of biomolecules with magnetic scaffolds allows to produce a more homogeneous and uniform distribution of mature bone, overcoming the limitation of traditional drug delivery techniques.

Keywords — Biomagnetics, magnetic scaffolds, magnetic particles, tissue engineering, targeted drug delivery

I. INTRODUCTION

THE goal of bone tissue engineering is the development of tools capable of favoring and selectively elicit the physiological process of bone healing to repair or regenerate an injured area [1], [2]. Such tools are called scaffolds and are polymeric or ceramic objects to be implanted in a damaged tissue [1]. Bone scaffolds use exogenous and/or extrinsic factors to induce a therapeutic action to facilitate the healing process [3], [4]. Their first function is structural: they withstand the injured tissue during its healing [5]. However, scaffolds should be designed to establish conditions to favor the mesenchymal stem cells (MSCs) migration, adhesion, and differentiation [4]-[6]. Many research efforts have been spent to turn bone scaffolds into functional objects capable of minimizing tissue rejection and the inflammatory response. This allows a better, faster integration of the prosthetic implants by eliciting specific physical or biological processes fundamental for bone repair and regeneration [1]-[6]. Scaffolds with an optimized nanostructured surface topography as a vehicle for mechanobiological stimulation

to the intracellular structures are thoroughly investigated [7], [8]. Other researchers manufactured implants which provided external cues to bone regeneration by embedding ionic species (e.g., Ca^{2+} , Ag^+ , Cu^+) or growth factors (GFs) [9]. Hence the scaffold itself may constitutes a local drug delivery system. However, traditional drug-loaded scaffolds are associated with burst release, scarce spatial control and impossibility of reloading [6]. These limitations have led to the investigation of the bone scaffold functionalized with magnetic nanoparticles (MNPs) to obtain a remotely controlled functional device [10]-[14]. A so-called magnetic scaffold (MagS) is a nanocomposite material with strong saturation magnetization ($2.5\text{-}100\text{ kAm}^{-1}$), implanted in the injured bone and can be exploited as an in situ magnet able to control and enhance the magnetic drug delivery (MDD) of growth factors to the defect site [12]-[14].

MDD systems triggered by thermal release are studied [15], [16]. Recently, Monsalve et al. manufactured a poly(ethylene glycol)-coated iron oxide nanoparticles with Transforming Growth Factor- β (TGF- β), which is released in its active form through an external radio-frequency (RF) magnetic field (58 mT, 359 kHz) [17]. The heating favors the thermal degradation of the Sulfo-SMCC complex and frees the bioactive molecule [17]. Similarly, the group of Meikle et al. used thermoresponsive poly(epsilon-lysine) dendrons to tether Vascular Endothelial Growth Factor (VEGF) to magnetite MNPs [18]. Under the action of a 30 mT magnetic field, working at 293 kHz, this latter MDD

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Fig. 1. Magnetic scaffolds (MagS) are biomaterial functionalized with magnetic nanoparticles (MNPs). They can be implanted to enhance bone healing. During normal healing, the proteins adsorb on the biomaterial, recalling the platelets, which release growth factors (GFs). The mesenchymal stem cells (MSCs) are attracted by GFs, then migrate, adhere to the MagS, proliferate and differentiate in osteoblasts (OBs). During this process, MNPs carrying GFs can be injected intravenously and attracted to the scaffold surface using a static magnetic field (DC MF). Then a radiofrequency (RF) field is applied to heat the system up to 42°C and release the GFs, which has the effect of fastening and enhancing the bone repair process.

system was heated from 20°C to 45°C in deionized water, for 300 s. The 18% of ϵ loaded VEGF was released [18]. The choice of the GFs for the bio-conjugation is strategic for bone tissue engineering [2], [19]. VEGF is a biomolecule relevant for endochondral bone formation, since it recruits osteoprogenitor cells and has the ability of forming new blood vessels [19]. The TGF- β stimulate bone formation by recruiting MSCs and increasing their proliferation, while affecting inflammation and angiogenesis [19]. However, the timing, dose and distribution affects VEGF and TGF-beta activity. Therefore, the therapeutic window should be carefully chosen to obtain high level of bone formation. Moreover, the amount of GF released must lie in the range 0.1-50 $\mu\text{g}\cdot\text{ml}^{-1}$, since higher concentrations can lead to tumor formation [3], [17].

Magnetic scaffolds were characterized in term of their morphological and functional properties [20]-[22], and were studied in a simplified way to investigate their potential in drug delivery applications [23], [24]. This work deals, for the first time, with the mathematical modeling of the combined use of magnetic scaffolds and MNPs carrying GFs to favor bone regeneration process. We aim to model the administration and drug transport of the MDD system to the MagS in a way controlled by an external static magnetic field, as presented in Fig. 1. The magnetic drug carriers are intravenously injected and attracted to the MNPs-loaded implant by using a static magnetic field. The drug is released after heating the system to 42°C. The GF is then free to exert its specific biological action. The release of the GFs via RF-heating is investigated considering the multiphysics aspects involved in the process. Finally, the biological effect of the GFs is studied to evaluate if the proposed delivery strategy can favor the bone healing process and hence be of interest for regenerative medicine.

II. THE MATHEMATICAL FRAMEWORK

The case of a scaffold implanted in a long bone after surgery is considered. A transverse section of bone ($r_b = 17.5$ mm, domain Ω_3) with a 2 mm fracture gap (r_f , domain

Fig. 2. 2D axial-symmetric analysis domain representing an implanted scaffold, in gray ($r_s = 5.5$ mm), surrounded by a fracture gap, depicted in red, ($r_f = 2$ mm) and the host bone, shown in yellow ($r_b = 10$ mm).

	Impregnated HA	MHA	FeHA-PCL	Unit
M_s	414.45	310.8	336.7	kAm^{-1}
r_{mnp}	50	10	14	nm
ϕ	12.5-25	1.6	9.18	%
M_{sat}	2.6-100.36	0.94	6.15	kAm^{-1}

Ω_2) and the scaffold ($r_s = 5.5$ mm, domain Ω_1) is considered, as shown in Fig. 2. Assuming a spherical scaffold geometry or considering the cross-section of a cylindrical implant, the problem is reduced to a 2D axial-symmetric formulation in spherical coordinates.

A. The Non-Linear Magnetostatic Problem

In presence of a static magnetic flux density field ($\vec{B}_0$), applied on the z -direction, the magnetic nanoparticles dispersed in the scaffold (Ω_1 : $0 < r < r_s$) give rise to a uniform magnetization vector according to the following non-linear law [20], [25]:

$$\vec{M}(\vec{B}_0, \phi, T) = M_s \phi L \left(\frac{|\vec{B}_0| \mu_{\text{mnp}}}{k_B T} \right) \quad (1)$$

where k_B is the Boltzmann's constant, T is the temperature of the system, M_s is the saturation magnetization of the single nanoparticle in Am^{-1} . The function $L(x)$ is the Langevin function [24]. The magnetic moment of the MNP is μ_{mnp} in JT^{-1} and ϕ is the volumetric fraction of nanoparticles in the biomaterial matrix. For each scaffold the MNPs are assumed to be monodisperse in size and to be homogeneously distributed in the prosthetic implant [24], [26]. The MagS of interest are reported in Tab. I. We considered a ferrofluid impregnated hydroxyapatite-collagen scaffold (Impregnated HA) [20], an implant made of hydroxyapatite chemically doped with iron ions (MHA) [21] and a 3D printed poly-caprolactone (PCL) scaffold loaded with intrinsic magnetic hydroxyapatite (FeHA-PCL) [22]. Depending on MNPs characteristics and the manufacturing process, the saturation magnetization varies from low (2.5 kAm^{-1}) to very high values (100 kAm^{-1}) [20], [27]. It is very crucial to investigate how the material parameters can influence the proposed magnetically targeted drug delivery strategy sketched in Fig. 1.

In presence of the static external magnetic fields, strong field gradients arise between the scaffold and the surrounding diamagnetic tissues (creating a force field in the domain Ω_2 and Ω_3). Therefore, the magnetic carriers in the system will experience an attractive force toward the scaffold. Previous works which dealt with the numerical study of using magnetic scaffolds as a part of a magnetic drug delivery system solved the magnetostatic problem and inferred the possibility of attracting MNPs or magnetized cells by assuming that a magnetic field gradient higher than 1.3 Tm^{-1} could be sufficient to determine a force capable of attracting MNPs to the scaffold [14], [16], [20], [23]. However, this is a limited view of the problem [24].

In this work, relying on a continuum-based approach, we refined the modeling of the magnetic attraction of MNPs to the scaffold by explicitly addressing the problem of the coupling between magnetostatic and mass transport phenomena. To this aim, the magnetic force exerted on the MNPs can be computed as [28]:

$$\overline{F_m} = \frac{M_{s,mnp2} V_{mnp2}}{6k_B T} \nabla |\overline{B}|^2 \quad (2)$$

where $M_{s,mnp2}$ is the saturation magnetization of the magnetic carrier to attract, whilst V_{mnp2} is the volume of the magnetic nanoparticle core. For the process sketched in Fig. 1, it is of pivotal interest to maximize Eq. (2). In this framework, from Eq. (2), we can already infer that it is possible to act on the magnetic field gradient (i.e., on the strength of the external magnetic field or on the properties of the implanted magnetic scaffold). However, the magnetic drug delivery can be fostered by designing and manufacture magnetic carriers of growth factor with high saturation magnetization. However, recalling biocompatibility issues and hemodynamic problems, the volume of the MNPs to

attract should be controlled [28]. From a material science point of view, the contemporary satisfaction of these criteria is a non-trivial task.

Under the action of the magnetic force in Eq. (2), the drug shuttles are set in motion with a velocity v_m defined as [24], [28], [29]:

$$\overline{v_m} = \frac{\overline{F_m}}{6\eta r_{m-d}} \nabla |\overline{B}|^2 \quad (3)$$

where r_{m-d} is the hydrodynamic radius of the MNPs plus the bioconjugated GF molecules and η is the viscosity of the medium in $\text{Pa}\cdot\text{s}$. A value of $450 \text{ Pa}\cdot\text{s}$ was used to mimic the drag the MNPs would experience in the fibrin extracellular matrix [29]. The Comsol AC/DC module is used for solving the non-linear magnetostatic problem.

B. Tissue-scale Modeling of Mass Transport and attraction of Magnetic Nanoparticles

Given the knowledge of the magnetic field, force and the velocity, we face the coupling to the mass transport at the tissue-scale. The goal is to derive a framework which can predict the spatial distribution of the MNPs to attract.

The population of MNPs is subject to the magnetic force due to the scaffold presence and is drifted to the implant, against the action of a random dispersal flux [30]. To investigate the pattern of C_{mnp} in the injured area, a diffusion-advection equation holds [24], [30], [31]:

$$\frac{\partial C_{mnp}}{\partial t} = D_{mnp} \nabla^2 C_{mnp} - \overline{v_m} \nabla C_{mnp} - k_c C_{mnp} \quad (4)$$

where D_{mnp} is the diffusivity of the nanoscale drug delivery system, in m^2s^{-1} . The influence of the scaffold on MNPs administration in the bone cavity is expressed by the term $\overline{v_m}$ from Eq. (3). The degradation term $k_c C_{mnp}$ accounts for the capture and elimination of the nanoparticles from the endoplasmic reticulum [32]. In this work, k_c was set to $4.85 \cdot 10^{-7} \text{ d}^{-1}$ for the size of the MNPs from Tab. II [32].

To solve Eq. (4), for simulate the magnetic drug delivery process from Fig. 1, it is necessary to constrain the concentration to a fixed value at the interface between bone and fracture (between domain Ω_2 and Ω_3). We assume here, differently from [23], [24], that the magnetic carriers are intravenously injected [30]. The concentration of MNPs at the host bone boundary is assumed to depend on particles characteristics and, for the first time, from the local, microvasculature tissue properties, so that [30], [31]:

$$C_{mnp}^0 \Big|_{\text{bone}} = C_{mnp,\text{inj}}^0 \frac{L_p s (1-\theta) (P_e - P_i)}{e^{P_{e_{mv}} - 1}} \quad (5)$$

where $C_{mnp,\text{inj}}^0$ is the concentration of the injected MNPs in $\text{mg}\cdot\text{ml}^{-1}$. In Eq. (5), L_p is the hydraulic conductivity of the vascular tissue, i.e. [31]:

TABLE II
PARAMETERS FOR DESCRIBING THE INTRAVENOUS INJECTION OF MNPS

Parameter Name	Value	Units
$D_{mnp,b}$	25	mm^2d^{-1}
s	0.0018	mm^{-1}
v_c	0.1	cm s^{-1}
l_c	25	μm
ψ	0.001	Adim.
r_c	0.1	μm
η_b	3	cP
t_m	0.5	μm

$$L_p = \frac{\psi r_c^2}{8\eta_b t_m \sqrt{\psi}} \quad (6)$$

where ψ is the porosity of the capillaries, whilst r_c is the average radius of the capillaries μm , η_b is the blood viscosity, and t_m is the thickness of capillary membranes in μm , which are reported in Tab. II [31]. The symbol s is the surface area of capillaries per volumetric unit of tissue, as reported in Tab. II.

In Eq. (5) θ indicates the sieving coefficient, which depends on the ratio between the size of the carrier ($v = r_{mnp} / r_c$) and the pore of:

$$\theta = (1-v)^2 \left[2 - (1-v)^2 \right] \left[1 - \frac{2}{3}v^2 - 0.136v^3 \right] \quad (7)$$

The sieving (i.e., $1-\theta$) is almost total (i.e., around 99%) for both the MNPs [17], [18], considered in this work.

The terms P_e and P_i are the Sterling's and interstitial pressure, 25 mmHg and -3 mmHg respectively, and P_{mv} is the Peclet number of the micro-vascular system [31]:

$$P_{mv} = \frac{v_c l_c}{D_{mnp,b}} \quad (8)$$

where l_c is the average capillary length in μm . These parameters are related to the microvasculature and blood flow properties. It should be noticed that the diffusion coefficient of MNPs in blood ($D_{mnp,b}$) is calculated considering blood viscosity, and it is therefore different from the value the magnetic carriers experiences in the extracellular matrix, during the attraction to the magnetic scaffold. Given this difference, The Peclet number magnitude is relatively high, since the average velocity of blood in capillaries is moderate but the nanoparticles are very small-sized object and are subject to high drift in the blood vessels. This causes the velocity of filtration in Eq. (4), i.e., $L_p(P_e - P_i)$, to be equal to circa 0.4 - 0.5 mms^{-1} .

To respect symmetry, two Neumann-line zero-flux boundary conditions were applied to the r- and z-axes.

TABLE III
FEATURES OF THE MAGNETIC DRUG CARRIERS

	VEGF+MNPs [18]	TGF- β + MNPs [17]	Unit
$M_{s,mnp2}$	60.0	80.0	$\text{emu}\cdot\text{g}^{-1}$
V_{mnp2}	53.0	4188.8	nm^3
r_{m-d}	16.7	53.0	nm
D_{mnp}	0.1	0.3	mm^2d^{-1}
k_{rel}	0.8	12.0	h^{-1}
$C_{mnp,inj}^0$	40.0	6.7	$\text{mg}\cdot\text{ml}^{-1}$
C_{GF}^0	19	40.0	$\mu\text{g}\cdot\text{ml}^{-1}$
B_0	30	58	mT
f	293	350	kHz
SAR	13.9	186.0	$\text{W}\cdot\text{g}^{-1}$

Typically, in the literature, the works which cope with the mathematical modeling of MNPs attraction and biodistribution neglect this contribution to the final solution [24], [28], [30]. This approach could be of interest for other tissues and magnetic drug delivery systems.

To solve Eq. (4), the concentration of MNPs is assumed to be zero at the initial time, whilst zero flux boundary condition is considered at the scaffold surface (see Fig. 2).

The attraction of the nano-carriers from Tab. III [17], [18], is assessed for the three scaffolds from Tab. I under different magnetic field strengths. From this analysis, the most effective MagS is selected. The Transport of Dilute Species interface from Comsol is used to solve the mass transport problem [Eq.s (4)-(8) using the solution of Eq. (2)].

C. Drug Release via RF-Heating

As described in Sect. I and showed in Fig. 1, after the injection and the following attraction of the magnetic carriers to the scaffold, the static magnetic field is turned off and a time-varying magnetic field is applied [6], [17], [18] to heat the magnetic carriers and reach an average macroscopic temperature of 42°C , to destroy the linkers and freeing the biomolecules [18]. We assume that the release temperature does not alter the GFs activity. Furthermore, the time required to reach 42°C is considered so low that the biological system is not damaged.

The RF-heating was carefully modeled solving the Pennes' bioheat equation in the analysis domain ($\Omega_1\Omega_3$) of Fig. 2 [26], [33]:

$$\rho C_p \frac{\partial T}{\partial t} = k \nabla^2 T - \rho_b C_{p,b} \omega_b \Delta T + Q + Q_M \quad (9)$$

where ρ is tissue density in $\text{kg}\cdot\text{m}^{-3}$, C_p is the specific heat in $\text{Jkg}^{-1}\text{K}^{-1}$. The terms ρ_b , $C_{p,b}$ indicates the thermal blood properties, with ω_b being the tissue perfusion and Q_M the metabolic heat.

TABLE IV
THERMAL PROPERTIES OF MAGNETIC SCAFFOLDS AND TISSUES AT 37°C

	k ($\text{Wm}^{-1}\text{K}^{-1}$)	C_p ($\text{J kg}^{-1}\text{K}^{-1}$)	Q_M (Wm^{-3})	ω_B (s^{-1})
Ha	1.3	700	/	/
PCL	1.75	1300	/	/
Fracture (inflamed)	0.558	2450	5262.5	6.95e-3
Fracture (ischemic)	0.1	2450	342.1	0.262e-3
Bone	0.32	1313	286.2	0.175e-3

TABLE V
ELECTROMAGNETIC PROPERTIES OF MAGNETIC SCAFFOLDS AND TISSUES
AT 37°C

	ϵ (293 kHz)	σ (293 kHz) Sm^{-1}	ϵ (350 kHz)	σ (350 kHz) Sm^{-1}
Ha	12.5	$2.1 \cdot 10^{-3}$	12.01	$2.3 \cdot 10^{-3}$
PCL	2.2	10^{-5}	2.17	$0.68 \cdot 10^{-4}$
Fracture (inflamed)	3580	0.545	3420	0.551
Fracture (ischemic)	1321.5	0.196	1293.25	0.199
Bone	192	0.0214	187.2	$2.14 \cdot 10^{-2}$

In this framework, the problem is assumed in this work to be non-linear and multiphysics. During the RF-heating, the system temperature increases and the electric, magnetic and thermal properties of the materials and tissues modifies, thus changing the dissipated power and the heat transfer during the exposure. These aspects must be taken into account for properly studying the magnetic drug delivery process shown in Fig. 1.

The electromagnetic problem is solved in the frequency domain for the geometry of Fig. 2 by employing the Comsol RF module. A uniform and homogeneous distribution is considered as background field. The spatial distribution of the magnetic field is computed considering the magnetic scaffold in Tab. I.

The electromagnetic problem is bi-directionally coupled to the bioheat transfer problem, which is solved in the time domain using the Bioheat Transfer module from Comsol.

As explained in [33], the resolution is carried out considering that the electromagnetic and thermal field have very different time scales, thus considering the calculation of electric and magnetic field as a stationary problem. Then, starting from the initial temperature distribution at time $t = 0$, the power losses can be evaluated and used to solve Eq. (9). Given the new temperature distribution at time $t + \Delta t$, the Maxwell's equations and the deposited power can be computed again to re-evaluate Eq. (9). This scheme implemented using a frequency-transient solver [33].

The thermal properties are assumed to linearly increase with a 1°C increase of 0.5% for the thermal conductivities, whilst a 1°C increase of 0.33% is assumed for the specific heat [33]. The heat capacity of blood has been assumed linear with a $1\% \cdot ^\circ\text{C}^{-1}$ in the temperature range from 37°C to 70°C. The blood tissue perfusion (ω_b) is a non-linear function of temperature [33].

Differently from the interstitial hyperthermia treatment of bone tumors [26], [33], the exposure time is not of tens of minutes, but of the order of few to tens of seconds, because the threshold temperature of 42°C must be reached in the proximity of the implant and three different heat sources are present. The total electromagnetic power per unit volume deposited during the heating is:

$$Q = Q_{sc} + Q_{mnp} + Q_t \quad (10)$$

The heat dissipated by the magnetic scaffolds is [33]:

$$Q_{sc} = \pi f |H|^2 \chi''(T) \quad (11)$$

where f is the working frequency, in Hz, H is the magnetic field vector in Am^{-1} and $\chi''(T)$ is the imaginary susceptibility of the magnetic scaffolds. In Eq. (11), we explicitly consider the temperature dependence in the Cole-Cole susceptibility spectra of magnetic scaffolds [33], which is a non-linear function of temperature, as described in [26], [33]. The heat dissipated by the biological tissues is:

$$Q_t = \frac{1}{2} |E|^2 \sigma \quad (12)$$

where σ is the electrical conductivity of biological tissues, in Sm^{-1} , and E is the induced electric field, in Vm^{-1} . The dielectric properties, reported in Table V at 37°C, are assumed to linearly increase with temperature, with a variation of $3\% \cdot ^\circ\text{C}^{-1}$ [33]. The scaffolds and tissues thermal and electromagnetic properties are taken from [24], [26], [33] and reported in Tab. IV and V.

The heat dissipated by the concentration of injected MNPs is evaluated as $Q_{mnp} = \text{SAR} \cdot C_{mnp}$ [34]. The MNPs distribution is recovered from the solution of Eq. (4), implying that $Q_{mnp}(r, z, t)$, i.e. it is a function of position and time. The Specific Absorption Rate (SAR) of the MNPs reported in Tab. II was retrieved by the initial slope method [34] from the experimental data of [17], [18].

Eq. (9) is solved assuming open boundary at the outer bone interface (Ω_3) and imposing an initial temperature of 37°C for all tissues. The thermal insulation condition is applied for symmetry along the r - and z -axis.

III. BONE REPAIR PROCESS: PHYSIOLOGY AND MATHEMATICAL MODELING

A. Physiological Process & Biomathematics

The aim of this work is the modeling and investigation of how magnetic scaffold, after their implantation, could be used as the core of a magnetically targeted drug delivery system for magnetic nanoparticles functionalized with biomolecules. To this aim, it is crucial to include the bone healing process, summarized in Fig. 1, in our model [35]-[45]. Then, this model must be modified to account for the drug delivery guided by magnetic attraction and triggered

by RF-heating (see Fig. 1).

In this work, the bone healing process (Fig. 1) is described using the model work of Moreo et al. [36], [37]. This model was already analyzed in the literature in terms of sensitivity, stability, existence of the solution and the a-priori error estimate [36]-[38]. Therefore, the set of nine non-linear reaction-diffusion coupled equations developed to account for the early stages of bone healing is slightly modified and used for simulating the physiological process shown in Fig. 1. Considering a moderate mechanical stimulation, a continuum-based approach is used to describe the spatio-temporal dynamics of the biological elements depicted in Fig. 1.

In presence of a biomaterial, the bone healing process initiates with a surgical or accidental fracture and with blood vessel injury [36], [39]. The bone cavity is immediately filled with blood [35]. Plasma, platelets and proteins invade the injured area. As depicted in Fig. 1 in the manuscript, firstly proteins (e.g., plasmin, albumin) adsorb onto biomaterial surface (within μs) [40], [41]. Therefore proteins (p , $\mu\text{g}\cdot\text{mm}^{-2}$) adhesion onto the rough biomaterial surface ($p_0 = 0.5 \mu\text{g}\cdot\text{mm}^{-2}$) is assumed to be a steady-state process [20], [36]:

$$D_p \nabla^2 p - \gamma_p p = 0 \quad (13)$$

where D_p is protein diffusion coefficient and γ_p is the linear decay rate. The value of both D_p and γ_p are chosen to get a characteristic diffusion length ($l_{diff} = \sqrt{D_p/\gamma_p}$) of about 0.1 mm. Subsequently the coagulation process begins with platelets (c , $\text{cells}\cdot\text{ml}^{-1}$) activation, migration to the biomaterial and the following release of several GFs, such as VEGF or TGF- β [19]. The platelets dynamic obeys the following random dispersal motion and taxis [36]:

$$\frac{\partial c}{\partial t} = \nabla \cdot [D_c \nabla c - H_c \nabla p] - A_c c \quad (14)$$

where H_c is a chemotaxis coefficient and A_c is a linear decay rate.

As platelets start diffusing and moving down protein chemotactic gradient, they release an angiogenic GFs, whose concentration is $s_1(r, z, t)$ (Fig. 1). This molecule is able to recruit osteo-progenitor cells, exactly as VEGF or TGF- β [17]-[19]. Since the proposed magnetic drug delivery strategy, shown in Fig. 1, aims to introduce more growth factors and boost the cellular response it is of great relevance to model the dynamics of the growth factor s_1 . In physiological conditions (without drug delivery), the mass balance equation for the biomolecule s_1 is [36]:

$$\begin{aligned} \frac{\partial s_1}{\partial t} = & \nabla \cdot [D_{s1} \nabla s_1] + \\ & + \left(\frac{\alpha_{c1} p}{\beta_{c1} + p} + \frac{\alpha_{c2} s_1}{\beta_{c2} + s_1} \right) c - A_{s1} s_1 \end{aligned} \quad (15)$$

where the kinetic terms in parentheses represent GFs secretion by platelets (p) and model their degree of activation. The linear decay rate, A_{s1} , accounts for the low bio-availability of GFs in vivo [36].

During the release of the angiogenic growth factor by platelets, the fibrin network assemblies in an ischemic environment [42]. Then hematoma forms, locally necrosis takes place and the inflammatory phase establishes [35]. Around 2-10 days, while MSCs migrate from the host bone following the chemotactic gradient of GFs, the angiogenesis process starts to build new vessels [19]. At about 14 days, the osteoprogenitor cells differentiate in Osteoblasts (OBs) and initiate to deposit the mineral bone matrix [39]. The main biological actors of bone healing, MSCs, migrate from the host bone towards biomaterial surface along gradients of both the angiogenic, i.e., s_1 , and the osteogenic GFs, i.e., s_2 . The influence of the GF s_1 is twofold, since it also favors the differentiation of MSCs into the osteoblastic phenotype. In mathematical terms the patterns of osteogenic cells, $m(r, z, t)$, can be obtained by the following equation [36]:

$$\begin{aligned} \frac{\partial m}{\partial t} = & \nabla \cdot [D_m \nabla m - m(B_{m1} \nabla s_1 + B_{m2} \nabla s_2)] + \\ & + \left(\alpha_{m0} + \frac{\alpha_m s_1}{\beta_m + s_1} + \frac{\alpha_m s_2}{\beta_m + s_2} \right) m \left(1 - \frac{m}{N} \right) + \\ & - \left(\frac{\alpha_{mb} s_1}{\beta_{mb} + s_1} + A_m \right) m \end{aligned} \quad (16)$$

where the parameters are listed and explained in Tab. VI [36]. With respect to the model of Moreo et al. [36], the taxis coefficients B_{m1} , B_{m2} are assumed herein to be not constant, but limited to a maximum velocity value [43], [44], i.e.:

$$\begin{aligned} B_{m1} &= \frac{\sigma_1 B_{m10}}{1 + \eta_1 s_1} \\ B_{m2} &= \frac{\sigma_2 B_{m20}}{1 + \eta_2 s_2} \end{aligned} \quad (17)$$

where σ_1 is 0.05, η_1 is 0.033 ml ng^{-1} , σ_2 and η_2 are 0.01 and $0.050 \text{ ml}\cdot\text{ng}^{-1}$, respectively. In this way, the chemotaxis coefficients are written in the form of a density-dependent sensitivity model and an upper bound for the chemotaxis velocity exists when the concentration of the chemical agent is elevated [43], [44]. This modification allows to avoid the blow-up of the solutions, while maintaining a meaningful and physical representation of cells concentration in the analysis domain.

As regards the osteogenic growth factor s_2 (e.g., BMP) the analytical balance is the following [36]:

$$\frac{\partial s_2}{\partial t} = \nabla \cdot [D_{s_2} \nabla s_2] + \left(\frac{\alpha_{m2}s_2}{\beta_{m2} + s_2} m + \frac{\alpha_{b2}s_2}{\beta_{b2} + s_2} b \right) - A_{s_2} s_2 \quad (18)$$

The availability of both growth factors causes the MSCs to differentiate into osteoblasts, which then produce the new bone in the fracture gap [36]. The dynamics of osteoblasts obeys the following equation [36]:

$$\frac{\partial b}{\partial t} = \frac{\alpha_{mb}s_1}{\beta_{mb} + s_1} - A_b b \quad (19)$$

After the differentiation, the creation of new and non-mature bone starts with the degradation of the temporary extracellular fibrin assembly produced by the platelets (Fig. 1). Therefore, the fraction of fibrin matrix (v_f) can be investigated by solving the following equation [36]:

$$\frac{\partial v_f}{\partial t} = -\frac{\alpha_w s_2}{\beta_w + s_2} b v_f (1 - v_w) \quad (20)$$

Then the periostium can undergo bone formation and intramembraneous ossifications, which determine woven bone production and the callus presence [35], [39]-[42]. In mathematical terms:

$$\frac{\partial v_w}{\partial t} = \frac{\alpha_w s_2}{\beta_w + s_2} b v_f (1 - v_w) - \gamma v_w (1 - v_l) \quad (21)$$

Finally, bone remodelling process works to form the mature lamellar bone [39], [45], whose spatial and temporal distribution can be computed by solving [36]:

$$\frac{\partial v_l}{\partial t} = \gamma v_w (1 - v_l) \quad (22)$$

Essentially, to summarize, the implant of the MagS initiates a cascade of biological events: protein adsorption [35], [40], [41], which determines platelets migration [36], [39], leading to the release of osteogenic (e.g., BMP-2) and angiogenic growth factors (i.e., VEGF or TGF- β) [19]. As a result, the stem cells are recruited by the growth factors signaling, then migrate to the scaffold, where they proliferate and differentiate into osteoblast, which, finally, secrete the bone matrix.

With the model (Eq. (13)-(22), solved on Ω_2 in Fig. 2) is possible to evaluate the distribution of osteoblasts and then the production of lamellar bone (v_l). The external and additional contribution of the MDD acts directly on Eq. (15) and indirectly on osteoblasts.

Zero flux condition applies to all boundaries (host bone, implant surface and symmetry axes in Fig. 3 in the

manuscript) for p , c , s_1 , s_2 , m , b , v_f , v_w , v_l .

A time-dependent Dirichlet boundary condition applies for the osteogenic cells at the host bone surface [36]. In fact, as derived from physiology, the cell density value is set to $2 \cdot 10^5$ cells·ml⁻¹ for the first 14 days. This non-linearity is implemented defining a step function continuous in its second derivative and applying it to host bone boundary.

As regards the initial conditions, the platelets are assumed to have an initial concentration of $2.5 \cdot 10^8$ cells ml⁻¹, whereas m and b have a starting concentration of 10^3 cells·ml⁻¹. Regarding the growth factors, both s_1 and s_2 are assumed to be poorly concentrated at time $t=0$, hence their initial value is set to 1 ng·ml⁻¹ [36].

The bone healing process shown in Fig. 1 was simulated for a period of 365 days, with a 1 day step, in presence of the magnetic scaffolds and in absence of external field and drug stimulation. The Comsol Mathematics interface is used. Since the several model variables have a strong mutual interdependence, it is worth to explain the relationship between the aforementioned physical quantities. The protein mass balance is first solved. Then, the spatial distribution of p is employed to evaluate the platelets dynamic, while solving for the growth factors s_1 and s_2 , together with the MSCs (m) and the osteoblasts (b). Then, in sequence, v_f is computed, then v_w and, finally v_l .

B. Bone Healing Outcomes

Currently available MagS demonstrated the capability to increase MSCs adhesion, proliferation and differentiation thanks to a rough surface microtopography [46], [47]. The bone integration was experimentally observed in absence of drug delivery. However, we hypothesize that the bone-healing process can be further enhanced with magnetically targeted drug delivery of MNPs carriers of GFs [6]-[9], [15]-[18].

TABLE VI
PARAMETERS FOR THE BONE HEALING SIMULATIONS

Parameter	VEGF	TGF- β	Unit
p_0	0.5	0.5	$\mu\text{g mm}^{-2}$
D_p	0.001	0.001	$\text{mm}^2 \text{day}^{-1}$
γ_p	0.01	0.01	day^{-1}
D_c	1.365 10^{-2}	1.365 10^{-2}	$\text{mm}^2 \text{day}^{-1}$
A_c	0.067	0.067	day^{-1}
H_c	0.333	0.333	$\text{mm}^4 (\text{day } \mu\text{g})^{-1}$
D_m	0.133	0.133	$\text{mm}^2 \text{day}^{-1}$
B_{m10}	0.2	0.667	$\text{mm}^2 \text{day}^{-1} (\text{ng/ml})^{-1}$
B_{m20}	0.167	0.167	$\text{mm}^2 \text{day}^{-1} (\text{ng/ml})^{-1}$
α_{m0}, α_m	0.25	0.25	day^{-1}
N	10^6	10^6	cells ml^{-1}
A_m	$2 \cdot 10^{-3}$	$2 \cdot 10^{-3}$	day^{-1}

α_{mb}	0.5	0.5	day ⁻¹
β_m, β_{mb}	10	10	ng ml ⁻¹
A_b	$6.67 \cdot 10^{-3}$	$6.67 \cdot 10^{-3}$	day ⁻¹
D_{s1}	0.3	0.85	mm ² day ⁻¹
D_{s2}	0.1	0.1	mm ² day ⁻¹
A_{s1}, A_{s2}	10	10	day ⁻¹
α_{c1}	$6.67 \cdot 10^{-5}$	$6.67 \cdot 10^{-5}$	ng ml ⁻¹ day ⁻¹ (cells/ml) ⁻¹
α_{c2}	10^{-5}	10^{-5}	ng ml ⁻¹ day ⁻¹ (cells/ml) ⁻¹
α_{m2}	$6.67 \cdot 10^{-5}$	$6.67 \cdot 10^{-5}$	ng ml ⁻¹ day ⁻¹ (cells/ml) ⁻¹
α_{b2}	$2.5 \cdot 10^{-5}$	$2.5 \cdot 10^{-5}$	ng ml ⁻¹ day ⁻¹ (cells/ml) ⁻¹
β_{c1}	0.1	0.1	$\mu\text{g mm}^2$
$\beta_{c2}, \beta_{m2}, \beta_{b2}$	10	10	ng ml ⁻¹
α_w	10^{-7}	10^{-7}	day ⁻¹ (cells/ml) ⁻¹
β_w	10	10	ng ml ⁻¹
γ	20	20	a.u.

Therefore, we consider the physiological osteogenesis in presence of a biomaterial as the reference situation. We aim to evaluate, for the first time, if the combination of MagS and magnetic drug delivery can alter and favor the osteogenesis. To this aim, under physiological conditions, the homogeneity (ξ) of the lamellar bone fraction (v_l) in the fracture gap is considered as biological outcome. This quantity is evaluated as the ratio of the mean value of v_l to its standard deviation. In mathematical terms:

$$\xi = \frac{v_{l,mean}}{v_{l,std}} \quad (23)$$

If the mean value of the mature bone fraction is high and its standard deviation is low, the resulting bone is of high quality and the damage can be considered as repaired [39], [35]. The homogeneity of bone determines the mechanical properties. Hence, the Young modulus (E, in GPa) of new bone is evaluated as a function of lamellar bone [48]:

$$\begin{aligned} E(v_l) = & 8.83 \cdot 10^5 (1-v_l)^6 + \\ & -2.99 \cdot 10^6 (1-v_l)^5 + 3.99 \cdot 10^6 (1-v_l)^4 + \\ & -2.64 \cdot 10^6 (1-v_l)^3 + 9.08 \cdot 10^5 (1-v_l)^2 + \\ & -1.68 \cdot 10^5 (1-v_l) + 2.37 \cdot 10^4 \end{aligned} \quad (24)$$

C. Effects of Magnetic Drug Delivery

In the case of VEGF or TGF- β release from the MNPs attracted to the scaffold site, MSCs distribution and their

Fig. 3. Release profiles of intravenous injection (IV) and release from scaffold (ScR) of growth factors (GFs). The IV profile is taken from [49]. The ScR profile is derived from the experimental data from [55]-[57].

differentiation rate into a higher OBs augments due to an increase in s_1 concentration. To model the further availability of s_1 due to the RF-heating release, the following generation term $R_{m,s1}$ is added to the r.h.s. of Eq. (15):

$$R_{m,s1} = k_{rel} \frac{C_{GF}^0}{C_{mnp,inj}} C_{mnp} e^{\frac{T-T_{th}}{2v^2}} \Pi\left(\frac{t}{T_d}\right) \quad (25)$$

where $\Pi(t)$ is a rectangular unit window of duration T_d . This function permits to simulate the injection of the MDD system and the GFs release for any given time of the healing process (1 d, 14 d, 28 d, 60 d). T_d is 1 day and C_{GF}^0 ($\mu\text{g}\cdot\text{ml}^{-1}$) is the dose of growth factor linked to the MNPs surface. This quantity is assumed to be a constant for each carrier, e.g., 0.194 μg of VEGF for mg of nanoparticle [18], as reported in Tab. II. The MNPs concentration, C_{mnp} , is the solution of Eq. (4) at the final time. As explained in Sect. I, the GFs are bound to the MNPs using proteic or aminoacidic linkers which degrade if heated at the threshold temperature $T_{th} = 42^\circ\text{C}$ for several minutes [17], [18]. The term v is equal to 0.3°C , to account for the narrow release temperature range observed experimentally [17], [18].

D. Comparison with Traditional Drug Delivery Strategies

The combined use of MagS and MDD is numerically validated against the traditional and established drug delivery methodologies of GFs direct injection [3], [49].

The direct injection of VEGF or TGF- β is simulated by adding the following time-dependent Dirichlet boundary condition for solving Eq. (15) for s_l on the boundary between domains Ω_2 and Ω_3 [30], [50]-[52]:

$$\begin{aligned} R_{inj} = & C_{GF}^0 \frac{L_p s(1-\theta)(P_e - P_l)}{e^{Pe_{mv}} - 1} F_1(t) \\ F_1(t) = & \begin{cases} 0 & 0 < t < 1 \\ 0.4 & 1 < t < 5 \\ 0.5 & 5 < t < 10 \\ 0.6 & 10 < t < 15 \\ 0.7 & 15 < t < 20 \\ 0.8 & 20 < t < 28 \\ 0 & t > 28 \end{cases} \end{aligned} \quad (26)$$

The spatio-temporal release ($F_I(t)$ - IV) is assumed equal to the experimental results from [53], [54], as shown in Fig. 3. It should be noted that the release is quite high after 1 day (i.e., about the 40% of the loaded GF) and then is maximum after 28 days, implying that the release is incomplete. The microvascular parameters for the first of Eq. (26) are evaluated for the VEGF or the TGF- β .

Furthermore, the GFs release from the scaffold was simulated. A drug-loaded implant with similar chemical and physical features was retrieved in the literature [55]. A time-dependent BC for s_1 is imposed on the scaffold boundary to simulate the concentration profiles of [56], [57]:

$$R_{sc} = C_{GF}^0 e^{-\frac{\sqrt{r^2+z^2}}{\kappa}} F_2(t) \quad (27)$$

$$F_2(t) = \begin{cases} 0.7 & 0 < t < 1 \\ 0.28 & 1 < t < 16 \\ 0 & 16 < t < 365 \end{cases}$$

The concentration of GFs released from the scaffold is assumed to exponentially decrease with the distance, being ineffective after distance $\kappa = 0.1$ mm, and with the cumulative release trend from [55]-[57], which is shown in Fig. 3.

The homogeneity of lamellar bone density for the cases of the novel MDD are compared to normal osteogenesis and to the direct injection and the direct release from the scaffold are compared through the bone homogeneity parameter and elastic modulus.

IV. RESULTS

The three different type of MagS reported in Tab. I are tested as potential candidates for the magnetic drug delivery strategy for bone healing shown in Fig. 1. The three magnetic scaffolds were analyzed in silico for strengths of the external static magnetic flux density field $\vec{B}_0$ ranging from 0.1 T to 1 T. Moreover, the attraction of the magnetic carriers [17], [18] is investigated.

The magnetic field distribution in the entire analysis domain (Ω_1 - Ω_3 in Fig. 1) resembles the pattern of a uniformly magnetized sphere [20], [24]. The higher the saturation magnetization of the MagS, the higher the maximum amplitude of the magnetic field on the scaffold surface and hence, the magnetic field gradient in the

Fig. 4. a) Force exerted from the MagS in Tab. II on the two MDD systems. b) Velocity (ms^{-1}) on the MNPs+VEGF [18]. c) Velocity (ms^{-1}). d) Dissipated power during the RF-heating step (Q_{sc} for the MagS in Tab. II, Q_{mnp} for the MDD of [17] and [18], and Q_t for biological tissues).

Fig. 5. a) 2D distribution of the magnitude of magnetic force (F_m) in the fracture gap and bone. The external magnetic flux density is 0.5 T, the magnetic scaffold is the MHA and the MNPs carrying VEGF are considered. b) Concentration profile (C_{mnp}) of MNPs+VEGF [18] in the gap, ($t = 24$ h, $B_0 = 1$ T). c) Temperature distribution (T) in the gap after 5 s for Impregnated HA, MNPs+VEGF [18] exposed to a 30 mT and 293 kHz magnetic field. d) Pattern of the GF released (R_{mst}) in the gap from the magnetic drug delivery system.

system. By solving Eq. (2), the resulting magnetic force magnitude in the fracture gap is shown in Fig. 5.a. The average intensity of the magnetic force $\vec{F}_m$ in the bone and fracture gap is significantly different across the magnetic scaffolds (Fig. 4.a). The higher the magnetization of the scaffold, the stronger the force. Indeed, the ferrofluid impregnated scaffold is the best MagS to be used as attraction platform for MDD [17], [18]. This finding poses an interesting challenge to material science, i.e., the search for a manufacturing method for deriving scaffolds loaded with a high amount of nanoparticles or synthesizing a

magnetic material with high saturation magnetization. From the physical properties of the MNPs (Tab. II), the nanoparticles carrying the TGF- β are bigger and experience a two orders of magnitude higher magnetic force, i.e., hundreds of pN compared to tens of pN for the MNPs plus VEGF (Fig. 4.a).

In the viscous fibrin matrix, the velocity impressed to the magnetic carriers is maximum at a magnetic flux density of 1 T and in the case of impregnated HA (Fig. 4.b and 4.c). Hence, for the modeling of MNPs administration and attraction, the applied magnetic field was set to 1 T. MagS allows to drive the drug transport by the external magnetic field and distributes it according to a controlled gradient [18], [20]. The solutions of Eq.s (4) and (5) presented in Fig. 5.b show that the MNPs concentration in the bone cavity follows the force distribution of Fig. 5.a. Indeed, along the equator of the system ($r, 0$), it is possible to notice a small depletion region where the magnetic force is minimum. The results for the MDD system with TGF- β are qualitatively similar and are not shown. The time of attraction is the same as that measured in similar experimental conditions (i.e., field strength, MNPs size) [58], [59], thus corroborating our numerical findings.

According to Fig. 1, after the attraction, the static field is turned off and the RF magnetic field is applied to the system. After calculating C_{mnp} it is possible to evaluate the spatio-temporal evolution of Q_{mnp} . Therefore, the overall dissipated power Q can be estimated (see Fig. 4.d) and the temperature pattern can be computed using the approach from [26], [33]. The three magnetic scaffolds considered in this study present a different heat dissipation dynamic due to the very different type of MNPs embedded in them and due to the volume fraction of the magnetic phase. Using our previous non-linear model [33], we investigate the temporal evolution of power dissipation. From Fig. 4.d, it is possible to notice that the impregnated scaffold has a deposited power which is slightly lower than the other scaffolds. Even if the Impregnated HA scaffolds has a higher content of MNPs, the MHA and Fe-PCL scaffolds contains superparamagnetic nanoparticles which were synthesized to maximize the hyperthermia effect. This step is crucial, since an accurate planning of the time required to reach the release temperature for the GFs would fasten the treatment, while avoiding tissues overheating. With a homogeneous and radial temperature pattern, as shown in Fig. 5.c, the value of T_{th} is reached within 0.2 mm from the scaffold surface after 2-5 s, depending on the MDD system. This allows to release the growth factor nearby the biomaterial, as presented in Fig. 5.d, and accelerates the contact osteogenesis.

Having implemented the system of equations for simulating the process in Fig. 1, the analysis is devoted to find suitable values of the dose of the GFs and the proper time of delivery. For an initial dose of $40 \text{ ng}\cdot\text{ml}^{-1}$, the MDD release of growth factors is simulated for different stages of

Fig. 6. a) Resulting bone fraction for different administration times. b) Time evolution of the lamellar bone fraction in the fracture gap for different doses of TGF- β .

Fig. 7. a) Pattern of the lamellar bone fraction (v_l) at $t = 365$ d in the normal healing case. b) The spatial distribution of v_l at $t = 365$ d following the magnetic drug delivery treatment using TGF- β . c) The spatial distribution of v_l at $t = 365$ d when the growth factors are administered by intravenous injection. d) The spatial distribution of v_l at $t = 365$ d when the growth factors are released from the scaffold surface.

TABLE VIII
COMPARISON OF DIFFERENT METHODS OF DRUG DELIVERY OF TGF- β AND VEGF.

	$V_{l,mean}$	$V_{l,std}$	ξ	E_s GPa
Normal healing	0.9315	0.0446	20.8856	15.95
MagS+TGF- β [17]	0.9447	0.0012	787.250	16.78
MagS+VEGF [18]	0.9436	0.0058	162.689	16.68
Direct TGF- β injection	0.9030	0.1627	5.5512	13.70
Direct VEGF injection	0.9015	0.1631	5.501	13.78
TGF- β from scaffold	0.8169	0.1541	5.3011	11.04
VEGF from scaffold	0.8356	0.1502	5.5612	11.45

the healing process (Fig. 1). From Fig. 6.a, it can be noticed that there is scarce difference (below 1%) between the administration of MDD at day 1 or 14 day, since the highest bone fraction are obtained. On the other hand, feed the GFs after 14 days, results in a lower fraction of newly formed bone. Therefore, relying on the physiology of bone healing

process, best time to perform the treatment is within the first 14 days, during the early stage of bone healing (see Fig. 6.a), since the density of MSCs is still high and the differentiation into osteoblastic phenotype is occurring. Hence, simulating an intravenous injection of MNPs at 13 days, different doses of GFs are tested to evaluate the treatment effectiveness. Concentrations of VEGF and TGF- β from $0.194 \mu\text{g}\cdot\text{ml}^{-1}$ to $5 \mu\text{g}\cdot\text{ml}^{-1}$ are considered. On average, the higher the dose, the higher the final amount of lamellar bone produced in the cavity, as shown in Fig. 6.b. Similar findings holds for the VEGF (data not shown). The maximum difference with the physiological case is more than 5%. The findings from Fig. 6.b allows us to infer that the proposed mathematical model can be useful for computing the dose and time of administration of GFs through magnetic drug delivery.

The distribution of v_i is rather homogeneous when comparing the MagS+MDD case with the normal healing as in Fig. 7.a and Fig. 7.b. From Fig. 7.c., it can be noticed that the intravenous injection allows to reach high value of bone density in the cavity, but there is a thin layer annulus of ~ 0.1 mm which present very low value of lamellar bone fraction, in accordance with the experimental findings from [53], [54]. This drawback is due to the burst release of the GF. On the other hand, the drug release from the scaffold ensures the apposition of bone layers from the biomaterial surface. However, far from the implant, as shown in Fig. 7.d, due to the limited spatial influence of the drug release, the new bone density is lower, resulting in poor mechanical properties (see Tab. VII), as found in [55]-[57]. The combined use of magnetic scaffolds and MDD allows to overcome these limitations.

Results from Tab. VIII stress that the treatment using MDD and MagS allows the best bone homogeneity and the highest quality of mechanical properties. The MDD with TGF- β is the most effective since tends to $E_{\max} = 18$ GPa [60]. In terms of ξ , the direct injection of GFs is comparable to the drug release from the scaffold, but the direct injection ensures better mechanical stability of the newly formed bone.

V. CONCLUSIONS

This work dealt, for the first time, with the mathematical modeling of magnetic drug delivery of growth factors bone healing and repair. The concept is to implant a magnetic prosthesis and use it as an in situ attraction platform for magnetic nanoparticles carrying bioactive molecules using static magnetic field. Then, the growth factors can be release by increasing the system temperature above a threshold temperature of 42°C through radio-frequency heating. The growth factors can then exert a direct action on the adhesion, proliferation and differentiation of osteo-progenitor cells. As a result, the bone repair process can be enhanced. This magnetic drug delivery procedure is a rather non-linear and multiphysic process which call for a specific, innovative mathematical model to study the

feasibility and gain, for the first time, an in-depth knowledge about the crucial parameters involved in this tissue engineering strategy.

To this aim, we solved a non-linear magnetostatic problem for computing the field distribution during the exposure to the static magnetic field. Then, the magnetic force exerted on the magnetic carriers is computed. This is already a refinement of the modeling of magnetic scaffolds and this kind of targeted drug delivery [14], [16], [20], [23], [24]. We found that scaffolds with higher saturation magnetization (around 400 kAm^{-1}) are interesting candidates to be used. Furthermore, we found that the volume and saturation magnetization of the magnetic carriers are also crucial parameters. These findings can indicate and provide useful feedbacks to material scientists.

Then, we investigated the coupling between the magnetostatic problem and the mass transport of the magnetic carriers, in order to predict the spatio-temporal distribution after intravenous injection. Furthermore, we included in the model the microvasculature parameters of the tissue. We found that the concentration profile of MNPs+GFs is strictly connected to the magnetic force profile. We forecast that, if the loading of magnetic scaffolds is not uniform, then relevant limitation to the attraction process or great enhancement could be obtained. This aspect could be of interest for further studies.

The proposed model accounted for the bi-directional coupling between electromagnetic and thermal phenomena during the radio-frequency heating step for the drug release. With our framework, we were able to determine that the presence of the magnetic scaffolds greatly enhances the dissipated power and lower considerably the time required to reach the threshold temperature. The pattern of the releases additional bioactive molecule cannot be easily predicted. Therefore, our model can be regarded as a valuable, unique platform for this case. It can be of interested for researchers working in the field of magnetic fluid hyperthermia with multi-therapeutic nanoparticles.

Finally, slightly modifying a biomathematics model for bone healing [36], we were able to quantify and investigate the direct effects of the magnetic drug delivery strategy for the first time. In this regard, we found that, if performed within the first 14 days of healing and suitable dose, the magnetic drug delivery, compared to physiological healing, to the intravenous injection of growth factors and to the release of biomolecules from the biomaterial (which are traditional drug delivery strategies), stands out in terms of quality of newly formed bone both in homogeneity and mechanical properties.

Therefore, with our numerical experiments we demonstrated that the combined use of magnetic scaffolds and magnetic drug delivery systems for bone repair can be effective. The proposed model may also help in setup validation experiments, under controlled condition, or, even, planning this innovative treatment modality with great advantages for regenerative medicine. Our

mathematical framework could be used as tool for investigating new type of magnetic carriers and magnetic scaffolds to enhance this therapeutic process, since, from an electromagnetic engineering perspective, it could help in bridging the gap between nanotechnology and biomedicine. Future works must deal with the problem of modeling the angiogenesis using continuum, discrete [61] or multiphase heterogeneous model [62], [63].

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