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The Application of Pulsed Electromagnetic Fields (PEMFs) for Bone Fracture Repair: Past and Perspective Findings

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Abstract—Bone fractures are one of the most commonly occurring injuries of the musculoskeletal system. A highly complex physiological process, fracture healing has been studied extensively. Data from *in vivo*, *in vitro* and clinical studies, have shown pulsed electromagnetic fields (PEMFs) to be highly influential in the fracture repair process. Whilst the underlying mechanisms acting to either inhibit or advance the physiological processes are yet to be defined conclusively, several non-invasive point of use devices have been developed for the clinical treatment of fractures. With the complexity of the repair process, involving many components acting at different time steps, it has been a challenge to determine which PEMF exposure parameters (i.e., frequency of field, intensity of field and dose) will produce the most optimal repair. In addition, the development of an evidence-backed device comes with challenges of its own, with many elements (including process of exposure, construct materials and tissue densities) being highly influential to the field exposed. The objective of this review is to provide a broad recount of the applications of PEMFs in bone fracture repair and to then demonstrate what is further required for enhanced therapeutic outcomes.

Keywords—Tissue scale, Bone repair, Cell scale, Review, Computational modeling, Clinical devices.

INTRODUCTION

Globally, there are tens of thousands of fractures occurring each week, with treatment costing patients billions of dollars per year.[52,73,107] With a projected significant rise in population, inclusively in the elderly population, the costs of treatment are expected to rise. Despite decades of intensive research in this field, a large proportion of fractures still display delayed healing and complications including non-bony union.[32,110] Additionally, immobilization following fractures can lead to further health conditions through atrophy, including nephrolithiasis, decalcification, hypercalcemia and osteoporosis.[33,81,98]

While pulsed electromagnetic field stimulation has been proven to play an advantageous role in fracture repair, through *in vivo* and *in vitro* studies, and through clinical trials, there exists no set of parameters defined with which an optimal treatment can be applied.[5,26,40,69] The scientific and medical communities still lack the confirmation that different magnetic fields applied to dissimilar tissues can cause varying effects. Despite the fact that there is a significant increase in the numbers of clinical trials and reviews in physiotherapy, including research in electromagnetic modalities, clinicians and practitioners are still unsure of how exactly PEMF treatment works.

As a result of this gap in understanding, exposure parameters have been chosen haphazardly and the corresponding results have not shown quantitatively to what extent each parameter involved (e.g., field stimulation properties, cell medium and fracture gap) plays a role. Extending this, as with many biological systems, the multi-scale effects need to be taken into account. Although a number of studies have shown certain dose characteristics to be beneficial at the cell scale or *in vitro*, the same characteristics have been less influential at the tissue or organ scale.[6,76] Before development of a system to be used clinically, these gaps need to be filled or at least characterized.

In this review, we discuss the research that has been accomplished to date using PEMF to aid fracture repair at all biological scales, and address how to best

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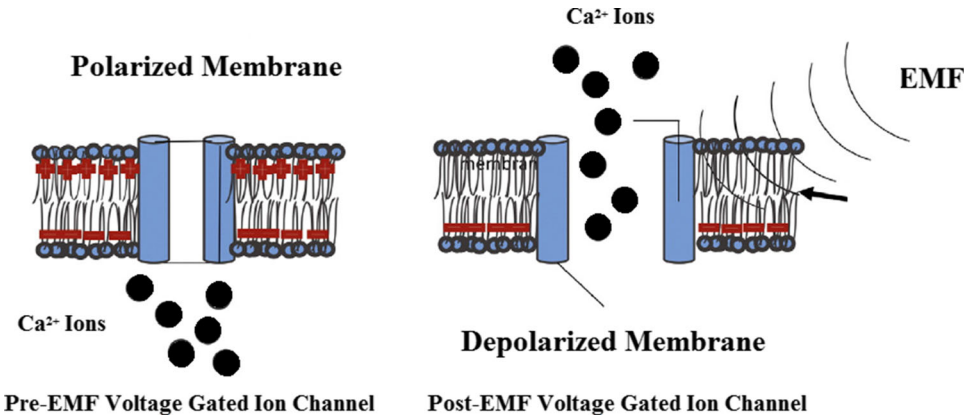

FIGURE 1. Diagram of mechanism of action showing the opening of voltage-gated ion channels due to the charge produced by an EMF, and the subsequent movement of calcium ions, inspired by Ross *et al.*[88]

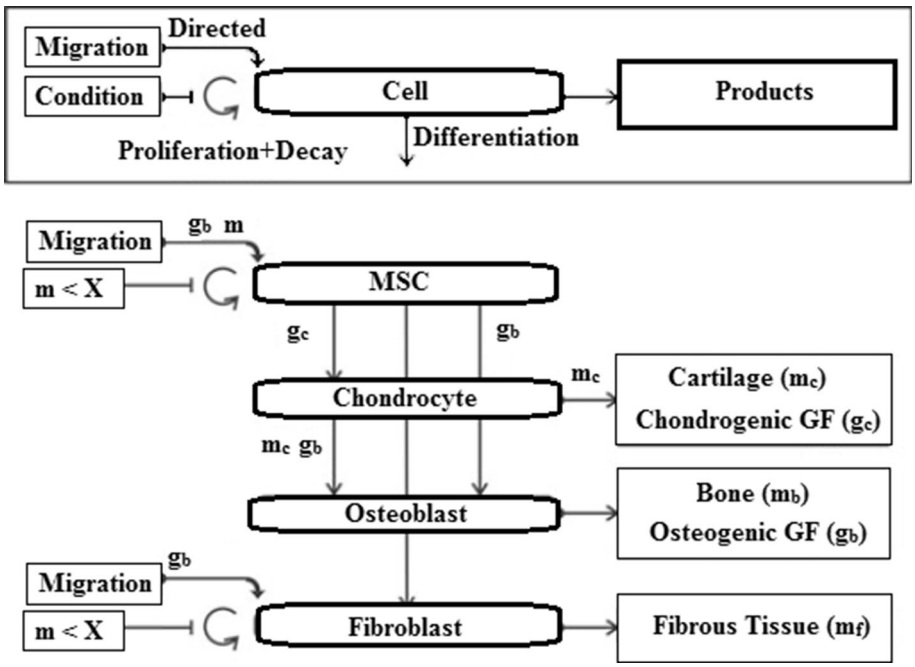

FIGURE 2. Modified computational model schematic presented by Peiffer *et al.*[82]

bridge the knowledge gap through tools such as concise *in vitro* experimentation and computational modeling.

PULSED ELECTROMAGNETIC FIELDS

The use of electric and magnetic forces to treat disease has fascinated the general public and scientists alike since antiquity.[51] Pulsed electromagnetic fields (PEMFs), wherein a time-varying electrical current is passed through a conductor to produce a magnetic field based on Ampere's law,[47] have played a significant role in fracture repair for over 40 years.[12,89] Initially through the pioneering work of Bassett *et al.*, it was thought that PEMFs induced forces through piezoelectricity.[11] In the 1970s it was seen that certain types of time-varying magnetic fields were reported to affect calcium efflux and influx in brain tissue. During the 80s and early 90s a number of cellular and subcellular mechanisms of action were defined when biosystems were exposed to extremely low frequency (ELF) magnetic fields.[13] On superficial examination, many of these field patterns displayed widely disparate energy characteristics, although it appeared that the induced electric field, rather than magnetic field component, exerted the main effect.[67]

As had been detailed by Markov, the movement of electrons (exhibited in excitable cells) will cause ions to move towards the electric fields from external stimu-

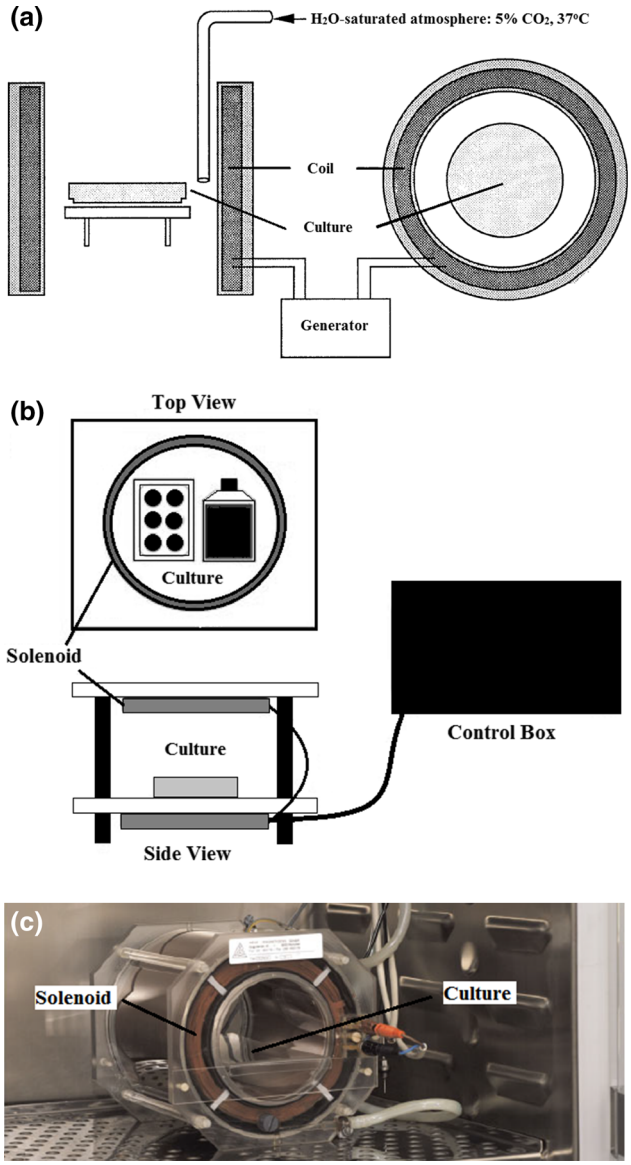

FIGURE 3. ***In vitro*** **experimental setups modified from Heermier *et al.*, Sun *et al.*, and Mayer-Wagner showing (a) schematic of transverse EMF stimulation experimental setup to determine the effects of EMF on collagen and ECM synthesis of human osteoblastic cells[53]; (b) Schematic representation of longitudinal PEMF stimulating device used to study the effect of PEMFs on the proliferation and differentiation potential of human BM-MSCs[100]; and (c) solenoid in incubator setup used by Mayer-Wagner *et al.* to study the effects of chondrogenic differentiation of human MSCs[68].**

lations thereby ostensibly affecting the physiology of the cell, i.e., it has been shown that an electric current can cause a depolarization of excitable cells by the forced movement of ions across a cell membrane.[67] What the electric field and the magnetic field have in common is the forced movement of ions.

Around the early 2000s, Brighton *et al.* followed the findings of Bassett *et al.* by positing that transmembrane channels were involved in the responses to electromagnetic fields.[21] Panagopoulos *et al.* similarly suggested a hypothesis whereby the externally applied EMF caused the ions within a cell to vibrate, forcing the voltage gates within a membrane to either open or close, therefore affecting the physiology of the cell.[80]

In 2007, Markov made the assumption that perhaps EMF may directly alter ion binding and or transport, therefore possibly altering the cascade of biological processes related to tissue growth and repair.[67] This was further concluded by the work of Ross *et al.* (see Fig. 1).[88] In 2008, Funk *et al.* showed that electric fields (EFs) represent forces at the surface of molecules, cell membranes and even the whole body, whereas magnetic fields (MFs) penetrate deeper going inside the cell influencing chemical and biochemical

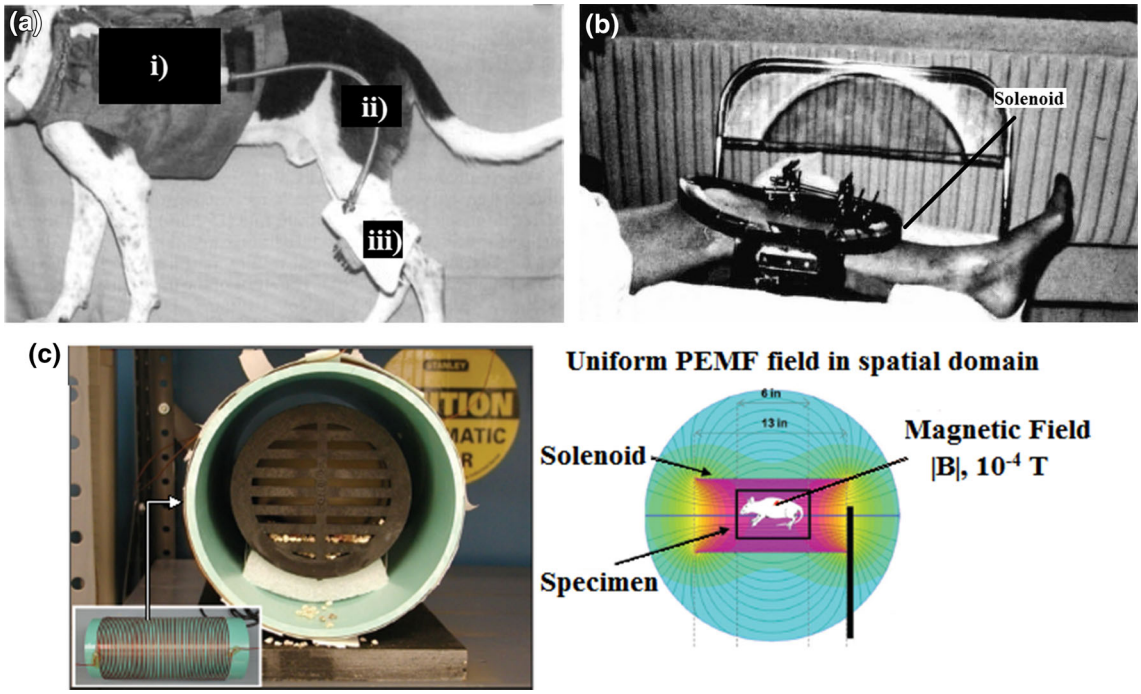

FIGURE 4. Clinical and *in vivo* experimental setups modified from Inoue *et al*, Hisenkamp *et al.* and Androjna *et al.* showing (a) PEMF stimulation system applied to a dog to repair induced osteotomies in canines showing (i) signal generator, (ii) tubing to connect generator to coil and (iii) coil[56]; (b) Double coil setup of the system used to treat fresh tibial fractures in humans[54] and (c) solenoid setup and mapping field for PEMF treatment of osteoporotic fractures in rats[4].

reactions. Their final conclusion was that MFs mainly targeted the cell membrane. Funk *et al.* further explained that outcomes most likely pointed to an MF effect on the rate of ion or ligand binding. They also proposed that the reorientation of molecules during MF exposure resulted in deformation of embedded ion channels, thereby altering their activation kinetics.[40]

To date, despite having a somewhat concrete understanding (discussed later), there exists no conclusively defined mechanism of action and further *in vitro* studies are required to precisely prove how both EFs and MFs affect cells. The main reason for such ambiguity as to how PEMFs act is the highly complex nature of the fracture healing process itself.

BIOLOGY OF BONE FRACTURE HEALING

The bone fracture repair cascade itself is highly complex and consists of a large number of different biological reactions involving various cell types regulated by biochemical and mechanical signals.[62,110] When the fracture site's bony areas are very tight and there is significant stability, direct bony union or primary fracture healing occurs.[110] However, for the majority of bone fractures, treatment involves stabilization in a cast, allowing for small movements and mechanical deformations of cells which enhance fracture repair.[37] This is known as secondary fracture repair and involves inflammation, repair and remodeling at the fracture site. The repair phase of the process can be seen as the most defining moment in the cascade, and consists of the formation of soft callus or cartilage, calcification, cartilage removal, and then development of a hard callus bone, bridging the fracture gap.[110] At the molecular level, this process involves a number of signaling molecules working to induce proliferation and differentiation of mesenchymal stem cells (MSCs) into cartilage, fibrous tissue and bone. Categorized into three groups: (i) pro-inflammatory cytokines (e.g., interleukin-1 and interleukin-6), (ii) transforming growth factor-beta (TGF-β) super family and other growth factors (e.g., bone morphogenic protein 2, insulin-like growth factor and growth differentiation factor), and (iii) angiogenic factors such as angiopoietin and vascular endothelial growth factor. The release of these molecules follows a distinct time line:[36,84,101]

Days 2–5: Proliferation of MSCs and osteoprogenitor cells takes place, and intramembranous ossification is initiated. During intramembranous ossification, stem cells differentiate into osteoblasts at the sub-periosteal fracture callus region, cytokine levels decline and angiogenesis begins.

FIGURE 5. (a) Orthofix Inc., Physio-Stim®; (b) ITO Co., LTD. Osteotron IV LIPUS (c) Ossatec Orthopulse II and (d) IGEA® Clinical Biophisics Biostim® SPT.[20,78,79]

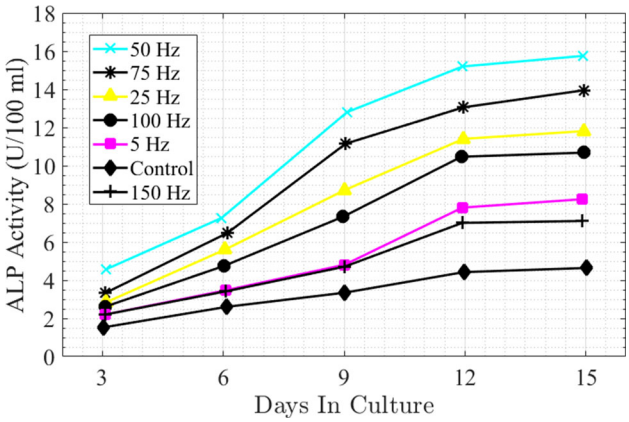

FIGURE 6. Estimated experimental outcome values as derived from data provided by Luo *et al.* varying stimulated field frequency.[66]

Days 5–9: Osteocalcin is expressed in the hard callus, TGF-β expression peaks, soft callus chondrocytes begin to proliferate, chondrogenesis (development of cartilage) begins, followed by endochondral ossification (in which cartilage is used as the model for long bone formation).

Days 9–14: Chondrocytes begin maturation by hypertrophy, a decreased expression of growth factors takes place and cell proliferation ceases whilst osteoblastic activity continues. During this time frame, soft callus is mineralized and woven bone forms, angiogenesis peaks, and vascular invasion takes place releasing calcium and enzymes. After cartilage calcification, the cells undergo programmed cell death (apoptosis), leaving the matrix open for the invasion of blood vessels and consequently osteoclasts and osteoblasts.

Days 14–21: This time frame exhibits the most active osteogenesis (development of bone) until day 21 when remodeling takes place and cellular proliferation stops.

Current evidence of the effect of the aforementioned molecules in accelerating fracture healing in both experimental and clinical studies is promising.[45] This cascade of events and the transport of certain molecules can be modeled in order to investigate the effects of the individual events on the whole process.

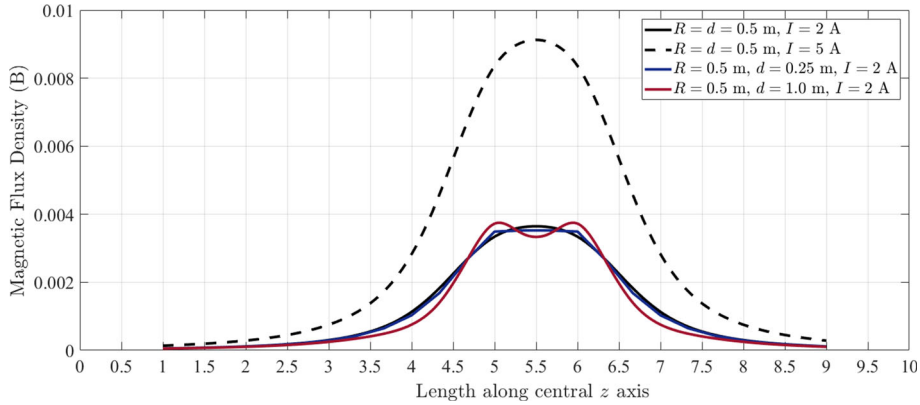

FIGURE 7. Magnetic flux density B distributions along the central *z* (horizontal) axis, from MATLAB (The MathWorks Inc., Natick, MA, USA) simulations showing four different scenarios varying input parameters to Eq. (1), where *d* refers to the distance between the two coils.

COMPUTATIONAL METHODS IN FRACTURE HEALING

Although mathematical and computational modeling of the fracture repair process has only been around for the past few decades, it has proven to be a highly effective tool for providing insight into the repair process. Whilst there are a number of conceptual models defining the secondary, i.e., indirect or non-fixed, repair process,[45,62,65,84] the most commonly used representation of the cascade is that of Claes et al. The model of Claes *et al.* consists of an overlapping four-phase model comprising inflammation, two repair phases, and a remodeling phase.[32,85] From the first single-phase finite element models (FEMs)[2,24,30] and biphasic and adaptive FEMs[7,8] of the early 2000s, to the hybrid, bio-regulatory and mechano-regulatory models that exist today,[44,82] mathematical and computational modeling has been shown to be effective in determining when to apply regulatory factors (e.g., growth factors,[7,8,87] degree of angiogenesis,[27,29,44,71,95,96] and mechanical stimuli such as stress, strain, drag forces and hydrostatic forces[2,44,59,64,86]) and to what degree they impact the repair process. For a further understanding of the role and development of modeling in bone fracture repair, the reader is pointed to the papers of Pivonka and Dunstan, Isaksson, and Geris.[41,57,85] The models discussed have been summarized in Table 1. To date, the groups of Claes and Simon, Peiffer *et al.* and Geris *et al.* have made the most significant advances modeling both tissue differentiation and vascularization in fracture repair. In these models, diffusion type partial differential equations have been developed to map the spatio-temporal variation in density of different variables including mesenchymal stem cells (c_m), osteoblasts (c_b) and osteogenic growth factors (g_b), taking into account species migration, proliferation and differentiation[42,82] (see Fig. 2).

These types of models have been combined with finite element models, resulting in two dimensional and three-dimensional representations of fractures, thereby bridging the gap between multi-scale biologies. Experimental studies have shown that ultrasound also significantly affects bone healing mechanisms by enhancing blood vessel formation due to alterations in the transport of fibroblast growth factor, and vascular endothelial growth factor (VEGF). Van Oosterwyck and Vavva *et al.* have successfully been able to adapt the hybrid bioregulatory model of Peiffer *et al.* to include the external stimulus of ultrasound by inserting the spatiotemporal evolution of ultrasound acoustic pressure into the control of angiogenesis.[102,103]

There are currently no models investigating the effect of PEMF on fracture repair. In parallel with the computational modeling, detailed *in vivo* and *in vitro* experiments are required to calibrate and validate the models.

EFFECTS AT THE MOLECULAR AND CELLULAR SCALES

Through *in vitro* experimentation, using primarily human bone marrow mesenchymal stem cells (BM-MSCs) and adipose-derived stem cells (ASCs), it has been shown that both physical stimuli such as EMF, and biological environment (e.g., presence of transforming growth factors, or culture medium)—can influence and inhibit proliferation and differentiation of certain cell types, although the pathway of action is not yet fully understood.[10,45,83,88] For excellent breakdowns of the entire spectrum of PEMF effects at

TABLE 1. Summary of all fracture repair models to date in chronological order taken from Carlier *et al.*[23]

Model type	Scale	Dimension	Material description	Biophysical stimuli	Healing phase	Authors
PDE	Tissue	2D Axisymmetric	Linear elastic	Principal tensile and hydrostatic stress	Reparative phase	Carter *et al.*[24]
PDE	Tissue	2D Axisymmetric	Linear elastic and hyperelastic	Principal tensile and hydrostatic stress	Reparative phase	Claes and Heigele[31]
PDE, fuzzy logic	Tissue	2D Axisymmetric	Linear elastic	Strain energy density (SED) fuzzy logic	Reparative phase, remodeling phase	Ament and Hofer[2]
PDE	Tissue	2D Axisymmetric	Linear elastic	Deviatoric strain and dilatational strain	Reparative phase	Bailon-Plaza and Meulen[7]
PDE	Tissue	2D Axisymmetric	Linear elastic	Second invariant of the deviatoric strain tensor	Reparative phase, remodeling phase	De Hass *et al.*[50]
PDE, fuzzy logic	Tissue	3D	Linear elastic octahedral	Shear strain, hydrostatic strain	Reparative phase, remodeling phase	Shefelbine *et al.*[93]
PDE	Tissue	2D Axisymmetric	Porelastic	Shear strain and fluid flow	Reparative phase	Andreykiv *et al.*[3]
PDE	Tissue	2D Axisymmetric	Porelastic	Shear strain and fluid flow	Reparative	Isaksson *et al.*[58]
PDE	Tissue	2D Axisymmetric	Poroelastic	Fluid Flow	Reparative	Geris *et al.*[42]
PDE, fuzzy logic	Tissue	2D Axisymmetric	Linear elastic	Dilational, distortional strain	Reparative	Chen *et al.*[29], Simon *et al.*[96]
PDE, fuzzy logic	Tissue	3D	Linear elastic	Volumetric, distortional strain	Reparative	Wehner *et al.*[108]
PDE	Organ	3D	Biphasic poroelastic	Shear strain and fluid flow reparative,	Remodeling	Byrne *et al.*[22]
PDE	Tissue	2D Asymmetric	–	Principal, shear, volumetric, octahedral shear strain	Reparative	Vetter *et al.*[105]
PDE, ABM	Tissue, cell, intracellular	2D Axisymmetric	–	Fluid flow	Reparative	Peiffer *et al.*[82]
PDE	Tissue	3D	Isotropic, poroelastic	Octahedral shear strain, interstitial fluid velocity	Reparative	Nasr *et al.*[74]
PDE	Tissue	3D	Linear elastic	–	Reparative	Moore and Burris[72]

TABLE 2. Summary of the most significant studies to date using PEMF at the molecular and cellular scales, in chronological order.

	EMF parameters				
Model	Intensity	Frequency	Duration	Main results	Authors
BM-MSCs, chondrocytes	35 μT	30 Hz	8 min, 48 h	Impact on cell metabolism and cell matrix structure	Walther *et al.*[106]
BM-MSCs	1.6 mT	15 Hz	8 h/Day, 24 Days	Increase in ALP (alkaline phosphatase) activity and enhancement of stimulatory effect of BMP-2 on Osteoclasts	Schwartz *et al.*[90]
BM-MSCs	1.8 mT	15 Hz	8 h/Day, 3 Days	Enhancement of cell proliferation rate and increase in cell densities	Sun *et al.*[100]
BM-MSCs	1.8 mT	15 Hz	8 h/Day, 7 Days	Significant increase in RUNX2 and ALP expression, enhanced mineralization, and time-dependent alterations of osteogenic marker expression	Sun *et al.*[99]
BM-MSCs	0.1 mT	15 Hz	24 h/Day, 21 Days	Increased BMP2, TGF-Beta2, Osteopontin (OP) and Osteocalcin (OC) expression, but no effect on ALP activity	Jansen *et al.*[60]
BM-MSCs	1.1 mT	5 - 150 Hz	30 min/Day, 21 Days	Enhancement of mineralization, increases in ALP, Osteocalcin, Collagen I and Ca^{2+} expression, and stimulation of osteogenic differentiation	Luo *et al.*[66]
BM-MSCs	2 mT	75 Hz	1 - 8 h/Day	Increase in bone matrix deposition of osteoblasts	Ceccarelli *et al.*[25]
ASCs	2 mT	15 Hz	8 h/Day	Enhancement of chondrogenic gene expression (SOX-9, Collagen 2 and Aggrecan)	Chen *et al.*[28]
BM-MSCs, ASCs	1.6 mT	75 Hz	24 h/Day, 28 Days	Increase in ALP activity, increase in OC expression, and induction of osteogenic differentiation	Ongaro *et al.*[76]
BM-MSCs	2 mT	15 Hz	30 min/Day, 21 Days	Increase in neovascularization, increase in osteogenic differentiation, and increase in ALP concentration	Fu *et al.*[39]
BM-MSCs	2 mT	75 Hz	10 min/Day, 27 Days	Increase in basal level of intracellular Ca^{2+}, increase in ALP concentration, Collagen I and OP	Petecchia *et al.*[83]
BM-MSCs, osteoblasts	0.1 mT	15 Hz	24 h/Day, 1 Day	Increased expression of osteogenic markers (RUNX2, OP, OC and ALP)	Kaivosoja *et al.*[61]

TABLE 3. Summary of *in vitro* and *in vivo* fracture repair experiments using PEMFs showing calculated total exposure.

Experiment type	Calculated total exposure (T × Hz × h)	Duration of treatment	Authors
Cell scale (BM-MSCs, Chondrocytes)	6.72×10^{-5}	8 min/h, 48 h	Walther *et al.*[106]
Cell scale (BM-MSCs)	4.61×10^{-2}	8 h/day, 24 days	Schwartz *et al.*[90]
Cell scale (BM-MSCs)	6.48×10^{-3}	8 h/day, 3 days	Sun *et al.*[100]
Cell scale (BM-MSCs)	1.51×10^{-2}	8 h/day, 7 days	Sun *et al.*[99]
Cell scale (BM-MSCs)	7.56×10^{-3}	24 h/day, 21 days	Jansen *et al.*[60]
Cell scale (BM-MSCs)	8.37×10^{-3}	0.5 h/day, 21 days	Luo *et al.*[66]
Cell scale (BM-MSCs)	1.26×10^{-1}	1–8 h/day	Ceccarelli *et al.*[25]
Cell scale (ASCs)	2.52×10^{-2}	8 h/day	Chen *et al.*[28]
Cell scale (BM-MSCs, ASCs)	8.06×10^{-1}	24 h/day, 28 days	Ongaro *et al.*[76]
Cell scale (BM-MSCs)	3.15×10^{-3}	0.5 h/day, 21 days	Fu *et al.*[39]
Cell scale (BM-MSCs)	6.75×10^{-3}	10 min/day, 27 days	Petecchia *et al.*[83]
Cell scale (BM-MSCs, Osteoblasts)	3.60×10^{-4}	24 h/day, 1 day	Kaivosoja *et al.*[61]
Tissue scale (rabbit)	2.93×10^{-1}	6 h/day, 5 day/week, 4 weeks	De Haas *et al.*[35]
Tissue scale (rat)	4.84×10^{-2}	8 weeks	Grace *et al.*[46]
Tissue scale (canine)	9.66×10^{-3}	1 h/day, 8 weeks	Inoue *et al.*[56]
Tissue scale (rat)	2.10×10^{-2}	10 weeks	Ibiwoye *et al.*[55]
Tissue scale (rat)	7.98	3 h/day, 5 weeks	Midura *et al.*[70]
Tissue scale (rat)	1.32	3 h/day, 5 weeks	Midura *et al.*[70]
Tissue scale (rat)	4.91×10^{-3}	3 h/day	Androjna *et al.*[4]
Tissue scale (rat)	1.35×10^{-1}	6 h/day, 30 days	Atalay *et al.*[6]

the cellular and molecular levels, the reader is directed to reviews by Maziarz *et al.*, Zhang *et al.* and Ross *et al.*[69,88,112] From the vast array of findings from these papers, the most pertinent PEMF-related results are summarized in Table 2. It is clear that PEMFs have a significant influence on osteogenesis and chondrogenesis through enhancement of cellular gene expression, increased bone matrix deposition, increased cellular proliferation and increased differentiation.

In most cases, the degree of osteogenesis is determined by the increase in markers relating to TGF-β. This growth factor is a potent chemotactic stimulator of MSCs that enhances proliferation of MSCs, pre-osteoblasts, chondrocytes and osteoblasts. It also induces the production of extracellular proteins such as collagen, proteoglycans, osteopontin, osteonectin, and most importantly alkaline phosphatase (ALP).[101]

Over the past few years, based on the above information, the mechanisms in which PEMF acts on the cellular level have been tested with promising results. Petecchia *et al.* showed that PEMF resulted in a selective action on Ca^{2+}-related mechanisms, i.e., early enhancement of intracellular calcium concentration. They asserted that chemically induced osteogenesis was due to mechanisms that interfered with some of the calcium-related osteogenic pathways such as permeation and regulation of cytosolic concentration.[83] Ross *et al.* on the other hand reaffirmed that PEMF can promote differentiation *via* ion dynamics and small signaling molecules. They also confirmed that whilst the full effects of PEMF have not yet been defined due to the varying exposure parameters of *in vitro* studies, most results point to an effect on the rate of ion or ligand binding due to a receptor site acting as a modulator of signaling cascades.[88]

Whilst these studies have provided quite concrete evidence of the effect of PEMF, e.g., increase in ALP concentration, enhancement of proliferation rate and increased expression of a variety of markers, there is inconsistency in experimental setup. For testing PEMFs *in vitro* most experiments place a culture of MSCs, within a medium, inside a stimulated PEMF (see Fig. 3). The inconsistency begins with culture medium which varies between standard minimum essential medium (MEM), diamond MEM, and complete osteogenic/chondrogenic mediums.[45] Such changing mediums can include components to different degrees such as fungizone, thymidine, gentamycin and pronase. Measures of calf serum, penicillin/streptomycin and other additions vary from study to study (e.g., fetal calf/bovine serum ranges from 0.1 to 20%). Cell densities and plate well dimensions also differ.

Inconsistency then continues with the type of PEMF stimulated. Studies here involve generation of PEMF by either a single solenoid coil or a Helmholtz coil pair. Whilst both these methods produce a relatively uniform field, position of cell culture, size of coil(s), and even compartment material must be taken into account, as such characteristics can attenuate the electromagnetic field altering the uniformity across the specimens, and therefore varying the exposure dose. Once a uniform field is produced, a set frequency, intensity and duration must be chosen. Tables 2 and 3 illustrate the variability of parameters that have been

TABLE 4. Summary of the most significant studies to date using PEMF *in vivo* models, in chronological order.

	EMF Parameters				
Model	Intensity	Frequency	Duration	Main results	Authors
Rabbit radial osteotomy, restrained	25 mT	0.1–4 Hz	6 Hr/Day, 5 Day/Week, 4 Weeks	Overall better bone growth, at lowest frequency. The side of exposure makes a difference to the treatment. Initial acceleration of healing in first 2 weeks was not maintained. More callus formation after 4 weeks.	De Haas *et al.*[35]
Rat femoral osteotomy, unrestrained	1.2 mT	72 Hz	8 Weeks	Osteogeneis, osteoid trabecular formation and vascular proliferation was advanced with more variation and organised hyaline cartilage. Cartilage comparatively more present after 8 weeks	Grace *et al.*[46]
Canine tibial osteotomy, late phase fixation	0.1–2.4 mT	15 Hz	1 h/Day, 8 Weeks	Torque and torsional stiffness in the treated group were significantly greater. Greater bone formation and higher mechanical strength also	Inoue *et al.*[56]
Rat fibular osteotomy, delayed, non-fixed Physio-Stim®	2 mT	15 Hz	10 Weeks	Reduction in time-dependent bone volume loss and decrease in osteotomy gap. No histological difference after 10 weeks	Ibiwoye *et al.* [55]
Rat fibular osteotomy, Physio-Stim® & Osteo-stim®	2 mT, 0.2 mT	3.8 kHz, 63 kHz	3 h/Day, 5 Weeks	2-fold rate of hard callus formation with a 2-fold increase in callus volume by 20 days post surgery. Quantity of woven bone was significantly better. Apparent modulus of bone was 3 fold greater. No effect on the remodeling phases.	Midura *et al.*[70]
Human femoral fracture, fresh	2 mT	75 Hz	8 h/Day, 90 Days	94% healing compared with 69% non-exposed. Fracture healing accelerated. Pain reduction	Faldini *et al.*[38]
Rat fibular fracture, no fixation	0.52 mT	15 Hz	3 h/Day	Improved hard callus elastic modulus in PEMF treated groups. Improved hard callus bridging. Higher elastic modulus.	Androjna *et al.*[4]
Rat femoral osteotomy	1.5 mT	50 Hz	6 h/Day, 30 Days	No statistical difference between control and stimulated at day 30	Atalay *et al.*[6]

TABLE 5. Summary of the most conclusive studies applying EMF treatment to tibial non-union fractures.

Clinical design	Number of tibial fractures	Duration of treatment	Union rate	Authors
Prospective, non-randomized	17	20 h/Day, 24 Weeks	88%	De Haas *et al.*[50]
Prospective, non-randomized	127	10 h/Day, 5 Months	87%	Bassett *et al.*[14]
Prospective, non-randomized	30	12–16 h/Day, 6 Months	87%	Sharrard *et al.*[92]
Prospective, randomized, double-blind	16	24 Weeks	77%	Barker *et al.*[9]
Prospective, non-randomized	56	–	84%	De Haas *et al.*[34]
Prospective, randomized, double-blind	15	27 Weeks	60%	Scott and King[91]
Prospective, randomized, double-blind	34	6 Months	60%	Simonis *et al.*[97]
Prospective, non-randomized	45	8 Weeks	85%	Gupta *et al.*[48]
Multicenter, randomized, double-blind	259	6 h/Day,	–	Adie *et al.*[1]
Prospective, non-randomized	44	3 h/Day, 29 Weeks	77%	Assiotis *et al.*[5]
Prospective, randomized	58	8 h/Day, 3 Months	77.4%	Shi *et al.*[94]

TABLE 6. Comparison chart of currently available fracture treatment devices.

	Frequency	Intensity	Dose	Price*	Product
Osteo-Stim®	63 kHz	0.2 mT	3 h/Day 90–180 Days	–	Orthofix Inc., McKinney, TX USA
Physio-Stim®	3.8 kHz	2 mT	3 h/Day 90–180 Days	$1010	Orthofix Inc., McKinney, TX USA
Biostim® SPT	75 Hz	3 mT	8 h/Day 90 Days	–	IGEA Medical , Betti *et al.*[19]
Osteotron IV	0.75–1.5 MHz	30– 60 mW cm^{-2}	20 min/Day	$4605	ITO Co., LTD.
Orthopak®	60 kHz	–	24 h/Day 270 Days	–	Biomet® , Beck *et al.*[16], Scott and King[91]
Curatron-2000-XP	–	30 mT	–	$3612	Curatronic LTD.™ , Markov[67]
Orthupulse II	15 Hz	–	8 h/Day	$907	Ossatec , Shi *et al.*[94]

*Prices are estimates based on web searches, indexed to 2016 and given in USD.

used across the board. As is also evident from Tables 2 and 4, PEMFs applied at different time points in the repair process can have different biological effects.

EFFECTS AT THE TISSUE AND ORGAN SCALES

Unfortunately, whilst *in vitro* models have provided vital information and an adequate window of parameter values for further *in vitro* experimentation, upscaling these observations to organ-scale treatments must be taken with precaution.

In vivo studies

As stated by Kirkpatrick *et al.*, *in vitro* studies, *clinical studies* and animal models can yield useful data to understand the phenomenon of fracture repair.[63] Both Kirkpatrick *et al.* and Numamaker et al. detailed the benefits of animal models for studying tissue response and bone fractures, including the easier acquisition of animal tissues, being anatomically similar to that of humans, and being ethically favorable.[63,75] What has further been concluded by these studies is that the animal model chosen will produce different outcomes based on age, fracture type, and size (e.g., small rodents are disadvantageous due to a more primitive bone structure, however, fractures are harder to induce in larger animal species).[75] Figure 4 shows some of the experimental protocols used for animal studies.

Since Bassett and Pawluk first pioneered EMF in animal models in 1974, there have been extensive experiments performed inducing osteotomies in dogs, rats and sheep, using developed PEMF exposure systems.[15] For a distinct time line of the early stages of EMF used in fracture repair, the reader is directed to an earlier review by Bassett.[12] Table 4 shows the most detailed findings from the literature, where duration, intensity and frequency of exposure are all reported. Generally in animal models, the rate of repair is accelerated significantly, however, prolonged exposure (after the repair phase) fails to improve bone healing, and can, in fact, be detrimental to the process.[26,40,51] It has been shown that PEMF induced at different time points during the repair process can either increase or decrease cellular proliferation and differentiation depending on the cell type in question. In most cases observed, treatment in the active proliferation stage accelerated cellular proliferation. In the differentiation stage (based on alkaline phosphatase activity), treatment enhanced cellular differentiation and increased tissue-like formation. In the mineralization stage, there was a decrease in bone tissue like formation, and a

TABLE 7. Field penetration potential comparison of three tissue types of various specimens found in literature, with $\mu = \mu_0$ T *m* A^{-1} and $R = 0.15$ m[47]

	Muscle		Bone		Blood	
Frequency ω (Hz)	σ (m^{-1})	δ (m)	σ (m^{-1})	δ (m)	σ (m)	δ (m)
10×10^0	0.104	390.88	–	–	–	–
10×10^1	0.112	119.06	–	–	0.602	51.40
10×10^2	0.125	35.68	–	–	0.667	15.45
10×10^4	0.500	1.78	–	–	0.680	4.84
10×10^5	0.53	0.55	-	–	0.714	0.47
10×10^8	1.190	0.012	0.050	0.06	1.250	0.01
10×10^9	7.692	0.001	0.770	0.004	9.091	0.001

stoppage of proliferation. From results of *in vivo* and *in vitro* studies, we can see how both scales communicate, i.e., increase in ALP concentration at the cellular scale results in increased osteogenesis at the tissue scale. Similarly to studies at the cellular scale, these experiments show variation in exposure parameters. These variabilities are even observed in the studies using commercially developed stimulating devices.[55,70]

Unfortunately, whilst animal models have been used extensively, there are a number of drawbacks when attempting to match clinical outcomes with *in vivo* outcomes. The problems of species differences can make data interpretation to the clinical situation problematic, for example there are many diseases specific to humans, and each animal species will have its own tolerance to any particular intervention, and its own special response. Even animal models from the same species can conflict based on anatomic, biochemical and gene expression differences. Consensus regarding fracture healing develops from agreement between results of animal models and human clinical studies.[63,75]

Clinical Studies

The main outcomes of most clinical studies is that PEMFs can induce union in fractures exhibiting delayed or non-bony union, as shown in Table 5. Unfortunately, bone healing is affected by other patient-specific factors (initial defect, surgery-related variables, blood flow and circulation). Many major drawbacks in developing outcomes include a poor assessment of PEMF treatment dose, and poor subject compliance.[6] In addition, several different methods have been applied to analyze the bone development, e.g., histological, CT imaging, radiology, X-ray and mechanical methods, i.e., creating more inconsistency in characterization.

Commercial Devices

A number of PEMF stimulating devices have been approved and developed for clinical use, such as the Curatron 2000 System, Biostim® and Physio-Stim®[17,19] (see Table 6). As is evident from studies validating such devices, their operating parameters are not fully scientifically-backed. For example, Midura *et al.* showed that the mean normalized callus volumes for Physio-Stim® treated groups were consistently higher than Osteo-Stim®, and Osteo-Stim® showed no significant difference over the non-stimulated groups, in that specific study. They further showed that the Physio-Stim®-treated specimens contained mostly woven bone and marrow tissues with smaller amounts of hyaline cartilage, while the Osteo-Stim® treated group contained mostly fibro-cartilage tissue with smaller amounts of other types.[70]

For proper optimization of clinical developments, one must take into account not only the physiological characteristics involved, but also the PEMF stimulation parameters, extending frequency, duration and intensity of exposure, to include type of wave propagated, width of the pulse, and fracture gap size. As noted by Atalay *et al.*, selecting the parameters likely to have maximum benefits in PEMF therapy, has been especially complicated, because, as previously mentioned, PEMFs may influence bone healing through a variety of different pathways.[6]

Whilst the stimulating devices shown in Fig. 5 are aesthetically impressive, they lack the scientific backing to prove they provide the most optimal and efficient repair. For the most part, these devices have been commercialized against pain and delayed fracture repair. Despite successful outcomes of developed devices in this instance, no device has been utilized to provide specifically a quicker repair of fresh fractures. In addition, the devices operate under the same properties for each patient, not taking into account the different body types, body part morphologies or fracture location.

From Table 6 it is possible to notice that the frequencies of stimulation are on average significantly higher than those of *in vitro* and *in vivo* studies. Such high frequencies may be dangerously high based on a

number of studies,[18,104,111] even with the attenuation provided by the different tissues surrounding a fracture site (skin, fatty tissue, muscle). Additionally, wearing a device for such long periods of time, such as 3 h/day for 180 days, would become a burden for the patient. The final added burden that stems from the available devices is the cost of purchase.

TOWARDS EVIDENCE-BASED SYSTEMATIC APPROACH: SYNERGIZING *IN SILICO* AND EXPERIMENTAL METHODOLOGIES FOR ENHANCED THERAPEUTIC OUTCOMES

It is clear from the research of the past several decades, there has been excellent progress in utilizing pulsed electromagnetic fields in fracture repair. Despite the discussed setbacks, including unclear translation from bench-based experiments to clinics, limited exposure parameter optimization and inconsistent experimental conditions, with the knowledge already obtained there is potential for advancement.

Consistent Experimental Procedures and Parameter Optimization

It has been made evident from the above sections, that there is no strict set of consistent parameters used in experiments. Not only is there variation in the experimental environment but also in the PEMF field generated. Table 3 shows the span of parameter values and calculated full exposures. From prior sections on *in vitro* and *in vivo* experiments, we note that frequencies range from as low as 0.1 Hertz (Hz) up to 63 kHz, intensities range from 0.000035 to 0.03 Tesla and dose durations range from 15 minutes up to 680 h. As aforementioned, whilst there is a large variance in these values, from this research we have fortunately been provided with a window of values for frequency, dose and intensity. This provides an umbrella under which exposure parameter optimization may take place. Extending this, it is also possible to determine a range of suitable medium concentrations, cell densities and cell lines for *in vitro* experiments. Already a couple of studies have aimed to determine optimal exposure frequencies and intensities, e.g., Luo *et al.* showed with sinusoidal electromagnetic fields that frequencies of 50 Hz and 75 Hz were the most effective at producing ALP activity (see Fig. 6).[66,68,113] For further optimization however, more stringent parameters need to be defined. This process will have to involve numerous time-consuming experiments changing only a single parameter each time. To this end, computational modeling is advantageous.

Computational Modeling of the Magnetic Fields in the Context of Fracture Healing

For optimal representation of experimental conditions, it is a requirement to model both the electromagnetic field itself and the effect of such a field at the cellular and whole tissue scales. Having discussed the requirement for optimized exposure conditions, for consistent experimentation and future device development, it is necessary to ensure the magnetic field **B** and the electric field **E** being produced are completely uniform. For such uniformity, one must simulate the EM field being generated, and then develop a device following the requirements determined from modeling, taking into account the type of coil, the coil radius, the apparatus dimensions and the number of turns of wire. This further extends to considering the surrounding tissue properties in terms of dimension, density, permeability and conductivity. One common tool being used to create a uniform electromagnetic field is a Helmholtz coil pair. A Helmholtz coil consists of two rings or bobbins parallel to one another, with copper wire wound a number of times around each coil. A pulsed current is then passed through the copper wire to produce the desired field. The magnetic flux density **B** between the coils follows Eq. (1) that has been derived from the Biot-Savart law.

$$\mathbf{B} = \frac{4^{3/2}}{5}\frac{\mu_0 \mathbf{nI}}{\mathbf{R}} \tag{1}$$

where μ_0 is the permeability of free space ($4\pi \times \mathrm{T{\cdot}m{\cdot}A^{-1}}$), n the number of turns of copper wire, I the current through the wire and R the radii of the coils. If the coil pair is designed appropriately, i.e., with a radius equal to the distance between the pair, then a uniform field should result. As shown in Fig. 7 with a fixed coil radius and fixed number of turns, varying both current through the coils and the distance between the coils can significantly alter the output magnetic flux density.

When placing a limb (consisting of muscle, bone, fatty tissue, bone marrow and blood) within the imposed EM field, it is important to note that externally applied EMFs can have important consequences due to the electrical fields and currents that they induce within the tissue.[47] The first step in modeling this process is to determine whether or not the EMF actually penetrates the conducting tissue. We can determine the skin depth δ based on the frequency of the EM wave and the material properties, *viz*[47]:

$$\delta = \sqrt{\frac{2}{\omega\mu\sigma}} \tag{2}$$

wherein σ and μ refer to the material's electrical conductivity and magnetic permeability. If the limb radius $R \ll \delta$ then it is reasonable to assume that the imposed field is almost negligibly perturbed by the currents that are induced in the conducting tissue. Table 7 shows the different penetrating skin depths of EMFs of varying frequencies for three separate tissues; muscle, bone and blood. As is clear from the table, the higher the frequency, the more penetrative the field is, and at the lower frequency end the type of tissue makes a substantial difference in penetration depth.

Generally the magnetic flux density in the tissue B_t is not significantly perturbed by the induced current, i.e., $B_t = B$, where B is the stimulating field (e.g., from a Helmholtz coil).[47] Given that we are generally dealing with linear isotropic media, we can define B as $B = \mu H$.[47] Whilst for many non-ferromagnetic substances such as water, bone and other biological tissues, the magnetic permeabilities are often quite close to μ_0,[77] different dielectric constants (ε) and resistivity values $\rho = 1/\sigma$ can still alter the field. With these material properties in mind, we can estimate the induced magnetic field from Ampere's law:

$$\nabla H = J + \frac{\partial \epsilon E}{\partial t} \tag{3}$$

wherein J is the current density (or the electric current per area), ε is the electrical conductivity of the material, E the electric field (equal to the electric charge density divided by the permittivity of free space).

A number of commercial softwares can be used to accurately model these effects including multiphysics software such as Abaqus CAE (ABAQUS Inc., Johnston, RI, USA), ANSYS (ANSYS, Inc., Pittsburgh, PA, USA) and COMSOL Multiphysics (COMSOL, Stockholm, Sweden), specific electromagnetic field simulation tools such as CST Studio (Dassault Systemes®, Velizy-Villacoublay, France), or technical computing softwares such as MATLAB (The MathWorks Inc., Natick, MA, USA) and Mathematica (Wolfram Research, Champaign, Il, USA). This list is non-exhaustive and each of these tools have both limitations and advantages when developing a physical geometry on which to induce a PEMF. In terms of *in silico* modeling, being able to quantify the electromagnetic field exposure allows for the discrete input of variables into a fracture healing model.

As an analogy to the contribution of Van Oosterwyck and Vavva *et al.* to model the ultrasound acoustic pressure, modeling the effects of PEMFs on the cells would be of great benefit to understand the links between cellular-, tissue-, and organ-scale observations. Following experimental results, the preferred path would be through ALP production and TGF-β expression.[101,102] In the context of PEMF modeling, invoking the Maxwell equations and the theory of magnetic flux diffusion, it would be possible to investigate the optimal field parameters to provide the quickest and most effective fracture repair, by varying field frequency and exposure time. In translating the Maxwell equations into spatio-temporal form as with the ultrasound pressure equations, results from *in vitro* experimentations could serve as validation for the computational predictions.

Future Recommendations

In order to expand the use of PEMF devices in clinics, a better understanding of the exposure parameters is necessary. In terms of device development, it begins with ensuring an homogeneous and reproducible electromagnetic field. This should be followed by performing extensive experimental campaigns *in vitro*, aided and rationalized by computational models to screen the effects of PEMFs on different stages of the fracture healing progress. Following optimization of the PEMF exposure at the cell scale, it is then necessary to perform experiments *in vivo* using the determined 'best' exposure parameters. Concurrently, cell scale computational models developed may be up-scaled to represent the full three-dimensional morphology of a fracture. Using these tools will allow for the development of a device, that is known to be evidence-backed, before being tested clinically and commercialized. Additionally, expanding the field may include the combination of PEMFs with further emerging technologies (e.g., biomaterial scaffolds) to enhance fracture repair even further.

CONCLUSION

Bone fractures are commonly occurring injuries that create large burdens for patients. Pulsed electromagnetic fields have been shown to be effective in treating fractures by activating a number of osteogenic markers thereby increasing proliferation and differentiation and therefore osteogenesis. To date there exists numerous studies at several biological scales detailing the effects of PEMF exposure on fractures. Although these studies show significant variation in environmental properties and exposure conditions, from them we have found a window of parameters which can be used to optimize fracture repair. Whilst *in vitro* and *in vivo* experiments add worth to the field, the most efficient tool for advancing this optimization is computational modeling. Although numerous studies have applied computational modeling to stimulate fracture repair,[43,96,109] none have included PEMF and its

parameter window as an additional influence. Following the existing analytical estimates, exposure variables and *in silico* models, there is the potential to narrow down the parameter window. Once such parameters have been defined and validated through further *in vitro* testing alongside extended *in silico* models, a device may be developed that is able to produce the required exposure in a fresh fracture dependent manner. Only following extensive clinical testing and validation, can a device capable of reducing fracture repair time, be commercialized based on scientifically-backed data.

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