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Pain Relief and Tissue Healing Using PEMF Therapy: A Review of Stimulation Waveform Effects

Abstract

Over the past seventy years, pulsed electromagnetic field (PEMF) therapy has been revealed as an effective means of reducing pain and inflammation in a wide variety of conditions while often promoting healing (Rohde et al. 2009; Hedén & Arthur a Pilla 2008; C. A. L. Bassett, R. J. Pawluk, et al. 1974; C. a Bassett, R. J. Pawluk, et al. 1974; C. a Bassett et al. 1977; Strauch et al. 2007; Strauch et al. 2011; Strauch et al. 2006). Observations and mathematical models suggest that one of the primary anti-inflammatory mechanisms

of PEMF is via the Calcium-Calmodulin (Ca2+/CaM) dependent nitric-oxide synthase pathway (M. Markov & A Pilla 1997; a Pilla et al. 1997; David J Muehsam & Arthur a Pilla 2009b; David J Muehsam & Arthur a Pilla 2009a; A A Pilla et al. 1999; Robert J Fitzsimmons et al. 2008; a a Pilla 1974; Arthur a Pilla 2002; Diniz, Shomura, et al. 2002; Diniz, Soejima, et al. 2002). Specifically, it is hypothesized that electromagnetic pulses of appropriate parameters will preferentially induce calcium binding to CaM (A A Pilla et al. 1999). Of utmost importance are the waveform parameters—with the most effective parameters falling within a range producing induced electrical fields on the order of 1 V/cm (W. Pawluk 2003; A A Pilla et al. 1999).

Unfortunately, the majority of the PEMF literature fails the basic scientific requirement of repeatability. By our accounting, more than 90% of all published reports fail to include adequate waveform parameters to fully define the dosimitry of the applied treatment. This shortcoming in the literature is very unfortunate as it tends to drive reputable clinicians and scientists away from the scientific study and clinical acceptance of PEMF, even though there is strong evidence to suggest that PEMF, when properly applied, is safe and can be very effective at reducing inflammation and pain while also accelerating healing of otherwise refractory injuries.

Herein we seek to review past and current technologies, effective waveform parameters, and propose a summary of the current theories regarding the mechanism of PEMF. Our goal is to establish clearly those experiments which are properly executed and have well-described stimulation parameters, and show that PEMF is an effective treatment for pain and inflammation given the appropriate stimulation waveforms.

Introduction

Electromagnetic therapies have been in use for many years. Electrical stimulation of tissues has been studied since Galvani's experiments using electricity and frog legs (Galvani 1954). The systematic study of the effects of electrical and magnetic fields on living and dead tissues began with Galvani in the late 18th century, whose research led to the discovery that one of the primary methods of information transfer within nerve and muscle tissues is via electrical pathways. In the middle of the 20th century, it was discovered that bone is piezoelectric in nature, and therefore was hypothesized to also transfer information electrically (Fukada & Yasuda 1957; Yasuda 1954). Soon thereafter, many experiments demonstrated that directly-applied electrical currents can be employed to induce bone formation and remodeling (Duriez & A. Bassett 1980; C. A. L. Bassett, R. J. Pawluk, et al. 1974; C. a Bassett, R. J. Pawluk, et al. 1974; C. a Bassett et al. 1977). One problem with these early methods of direct electrical stimulation of bone tissue was that they required the implantation of electrodes into and around the bones to be stimulated. The deeply invasive nature of direct electrical stimulation of bone led to the development of non-invasive methods, such as the use of induced electrical fields. These inductive methods employ magnetic fields from external magnets or solenoids that change over time to induce the desired electrical fields within the tissues, based on the well-understood Faraday's Law of Induction (Halliday et al. 2000). Electrical fields induced in this non-invasive manner were subsequently shown to be effective in eliciting accelerated bone formation and healing (C. A. L. Bassett, R. J. Pawluk, et al. 1974). With the advent of inductive stimulation methods came the study of the effects of non-depolarizing electromagnetic fields on tissues other than bone. Non-depolarizing electric fields are those which are too low to induce overt depolarization of the cell membrane as in the case of an action potential, but strong enough to presumably have other effects on molecular mechanisms within cells and in the extracellular space. Nerve regeneration became a topic of interest as it was shown that non-depolarizing electromagnetic pulses could improve nerve lesion healing. Further studies showed that inflammatory factors could be reduced in tissue inflammation in humans post operatively (Rohde et al. 2009; Hedén & Arthur a Pilla 2008). Pilla et al. developed a theory of interaction between pulsed radio frequency (PRF) waves and tissues which makes use of the frequency response of tissues and places lower bounds on waveform parameters based on the thermal noise threshold (David J Muehsam & Arthur a Pilla 2009a; A A Pilla et al. 1999; a a Pilla 1974; David J Muehsam & Arthur a Pilla 2009b; D J Muehsam & a a Pilla 1999; McLeod & AA Pilla 1983; M. Markov & A Pilla 1997; a Pilla et al. 1997; M. S. Markov et al. 1993). More recently, PEMF has been studied in terms of behavioural modulations—specifically the effects of PEMF on bipolar disorder, autism spectral disorder (ASD), Alzheimer's, and Parkinson's disease (R Sandyk 1998b; R Sandyk 1997; R Sandyk 1999a; R Sandyk 1999c; R Sandyk 1998c; R Sandyk 1998a; R Sandyk 1999d; R Sandyk 1999b; R Sandyk 1998d; Rohan et al. 2004). Prior to discussing the effects of PEMFs on cells, tissues and systems, it is necessary to discuss the important parameters which govern how tissues will respond to electromagnetic radiation.

Waveform parameters

There are three key levels of signals that need to be specified in order to properly define the waveform parameters that are to be used when inductively stimulating:

1. Current flowing into the coils from the stimulation unit. This is the original driving signal that is produced by the electronic circuit within the PEMF device to drive the coil that will then produce the magnetic field.
2. The time-varying magnetic flux in and around the coils resulting from the electrical current driving the wire coils.
3. The induced electric field in the tissue volume resulting from the time-varying magnetic flux generated by the coils.

Based on our detailed review of the literature, we have determined that in most cases investigators report only a partial description of the original driving signal emanating from the electronic circuit (#1 above), but do not measure, calculate, report, or estimate the resulting magnetic field vs. time (#2 above) or the electrical fields that are ultimately induced within the target tissues (#3 above). For the most part, the second level signal—magnetic flux—is the most relevant signal to specify because it is prone to deviate from theoretical values when calculated based upon the presumed driver circuit performance, it is readily measured using modern analog signal Hall effect sensors, and when measured accurately yields good estimates of the induced field within the tissues. It should be noted that it is the final signal—the electric field induced within the tissues—which is the hypothesized mediator of the responses seen in vivo and in vitro, but that it is difficult to directly measure these induced fields within tissue.

Current Flowing into the Coils (Primary or First-Level Signal)

In time-varying magnetic field stimulators it is the primary signal from the electronic device that drives the coil(s) to produce the magnetic field. For the purposes of this discussion, we will not consider "static" magnetic devices such as permanent magnets or solenoids driven by steady DC current. In these cases the magnetic fields are largely steady and non-varying over time, so their ability to induce electrical fields is essentially zero because the first time derivative of the magnetic flux in steady magnetic fields is by definition equal to zero. That is not to say that such devices would have no biological effects, because they certainly may have effects through such mechanisms as the Hall Effect, in which charged particles (ions) ubiquitous in biological systems would be influenced as they move through the steady magnetic field. The induction of electrical fields within tissues requires magnetic fields that vary in time, and typically this is accomplished using a computer or a microcontroller-based platform to drive current waveforms through solenoid coils. To induce the desired electrical fields it is essential to control the slew-rate (rate of change or first time derivative of the magnetic flux) of the signal. Thus, it is of utmost importance that the primary driving electronics have adequate dynamic performance. However, since most investigators do not measure or report the second- or third-level signals (above) they generally cannot guarantee that the primary driver electronics had adequate dynamic performance to achieve the desired biological effect. The primary signal also allows one to determine the

upper limit of the overall stimulus signal power. Basically the maximum power into the system can be calculated by knowing the maximum current flowing into the coils and the impedance of the coils (though empirically, the power transfer to the body is much lower because of inefficiency). Because the undesirable effects of non-ionizing radio frequency (RF) energy generally are regarded to arise from thermal effects within the tissue, it is conservative and correct to consider the total PEMF system power when determining the upper limit of potential harmfulness of any PEMF or RF stimulation system, and the power consumption of the primary driving electronics provide a direct and convenient opportunity to measure and determine the upper boundary for power for the entire system.

Magnetic Flux Produced by Coils (Secondary or Second-Level Signal)

Because there are electrical (Ohmic and reactive) energy losses in driving the primary signal through the coils, it is most accurate to directly measure the dynamic magnetic flux produced by the current flowing into the coils. From these measures one can disregard the need to correct for dynamic limitations of the primary driver circuit, and the induced electric field within the tissues can be accurately estimated. Faraday's law of induction shows that the induced circular electric field in a conducting surface is proportional to the inverse of the rate of change of the magnetic flux (defined as the magnetic field strength times the area through which it is passing). The key parameters involved with the induced electric field are the rate of change of the magnetic field (i.e. dB/dt, which is the first time derivative of the magnetic flux B) and the radius around which one examines the field of interest. Specifically, the larger the rate of change of the magnetic field, the larger the possible induced electric field. Maxwell's relationship explains why the driving electronics must have good dynamic performance: to provide adequate magnetic flux slew rate to induce the desired electric field in the tissue. For a given magnetic flux change, the larger the radius of interest (up to the inner radius of the stimulating coil), the larger the induced field; and the smaller the radius, the smaller the induced field. The induced electric field for a Helmholtz coil (i.e. separation distance of the coils approximately the same as the radius of the coils) decays linearly to zero within the boundaries of the coils and falls off as the inverse of the distance from the outer edge of the coil outside of the boundaries of the coils (Figure 1). The internal surface of the graph in figure 1 is a cone, representing the induced electrical field strength between the coils where the induced electric field decreases toward zero linearly as the radius of curvature of the induced field drops to zero in the x-y plane. The inner conical surface is perhaps most relevant because it is the volume of tissue between or within the coils that generally is intended to undergo treatment with PEMF.

Induced Electric Field within Tissues (Tertiary or Third-level signal)

Finally, it is necessary to briefly discuss the induced electric field—specifically with regard to the tissue volumes of interest. For example, if one considers a stimulation volume on the order of 10 μm (average cell diameter), then with a magnetic flux slew rate of 1,400,000 Gauss/second (=140 Tesla/second), the magnetic pulse will induce a peak electric field of approximately 3.5 x 10-4 V/m around the perimeter of a typical cell. If one considers thermal noise averaging and cellular response, then the predicted threshold induced field for a measureable response is on the order of 10-3 – 10-5 V/m (Weaver & Astumian 1990). However, if one considers a conduction pathway on the order of the radius 35 mm (ex: the outer edge of a 6-well plate well), then the peak electric field produced by the same magnetic pulse is on the order of 1.23 V/m. We would like to point out that in fact, the model being used to explain the induction of electric fields within a tissue volume is identical to the model of eddy currents (Halliday et al. 2000). In the case of eddy currents within a tissue, one can consider the conducting pathways to be represented by the fluid in the pericellular space, just outside the cell membrane and between cells and thus, circular pathways around cells are those of interest. Since there are many cells in a tissue mass, there are various conducting pathways, some circular, but most are not. Considering that the field strength in a plane varies with respect to the radius of interest, one can determine that if cells meet in locations where the cross sectional radii are not identical, then the currents where the cells meet will not cancel, and there will be a net flow of current around the larger radius of interest. However, if two cells meet at a location such that their cross-sectional areas are approximately the same (and they are both relatively circular cross sections) then circular currents flow around each cell, and should approximately cancel where the cells meet—producing a conducting path around both cells (Figure 2). Because of these geometric effects, it is possible that amplification effects might be seen for signals that fall below stimulation thresholds. Such circumstances may dominate the geometry in tissues with relatively high cellular density such as muscle and skin in which the cells occupy well over 50% of the volume in any representative sample of tissue. In the case where cells are separated by relatively larger distances, the induced electric fields in the pericellular fluid spaces surrounding each individual cell may not interact as shown, each cell being subjected to an induced electric field. If all cells in the target tissue have approximately the same geometry, then each individual cell in the target tissue would be stimulated very nearly uniformly throughout the tissue within the coils. This geometry could dominate in tissues with relatively lower cellular density with widely distributed (not clumped) cellular arrangement, such as bone, tendon, all types of cartilage, ligament and crucially, the interfaces where these tissues meet (Nordin & Frankel 2001).

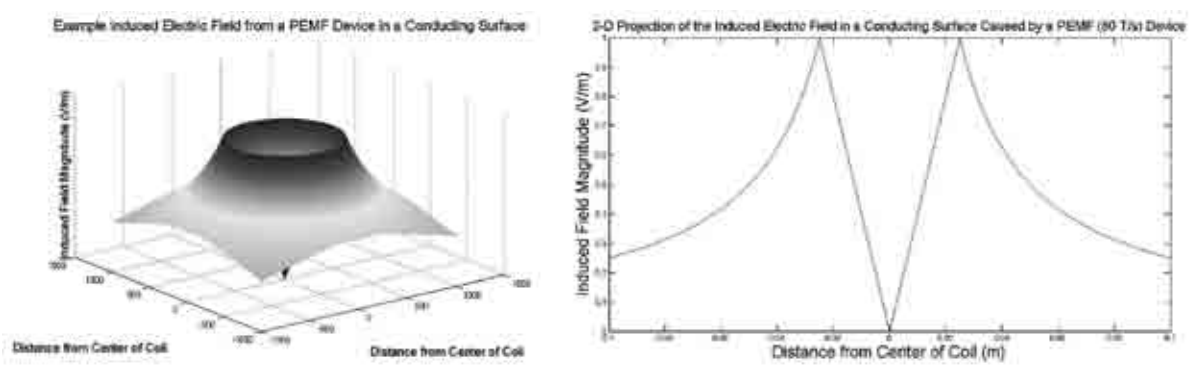

Figure 1. (Left) Representative plot of induced (tertiary or third level) electric field strengths within a conducting surface as caused by a Helmholtz configured set of PEMF coils. Any path within the circumference of the coils with radius less than the coils will have an induced electric field dictated only by its radius, not its axial position within the coils. Outside the circumference of the coils, the radius of interest must be concentric with the axis of stimulation in order for the plot above to apply. Note that the peak magnetic field is induced around a pathway of radius equal to the stimulating coils. (Right) Representative 2-dimensional slice of the surface on the left showing a cross section of the conical interior and 1/r behaviour of the induced (tertiary or third level) electric field in a conducting surface. The diameter of the representative coils is 50 mm and the plot is constructed for a magnetic flux slew rate of 80 T/s.

The above arguments generally hold true for the simplest of cell geometries: 10 micron diameter spherical cells.

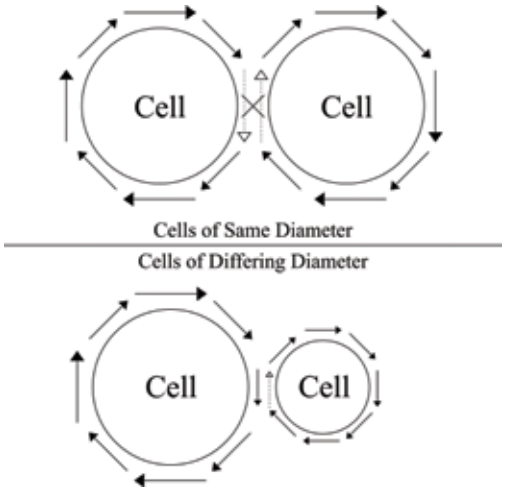

Figure 2. A cartoon of the current flow induced around cells. Top.) Cells of equivalent radius have offsetting electric fields between them, resulting in a net current flow around the perimeter of both cells, but not between them. Bottom.) Cells of different radii of intersection will have a net current flow around their perimeter and in the direction between them determined by the larger cell.

Though this assumption of simple geometry may be adequate for the estimation of tissue properties, such as estimating the number of cells in a given volume of tissue, the spatial details of cell membrane geometry and receptor distribution may well dominate when considering the mechanisms that relate to electrochemical transduction and mechano-transduction in cells and tissues. The assumption of a simple and smooth cellular geometry thus runs the risk of falling into the scientific error known as the "assumption of a spherical cow", a scientific simplification than makes calculations easier at the cost of ignoring the most important details of the system being studied. Many cells in the musculoskeletal system are known to have a complex surface structure containing thin filaments that stretch out into the space between cells. For example, osteocytes (cells in bone tissue) are known to have cytoplasmic processes which extend into canaliculi (tiny canals) in the hard bone matrix (Klein-Nulend et al. 2005; Nordin & Frankel 2001). These thin extensions of the bone cell membrane are known to be involved in the collection of nutrients and elimination of waste, but it is hypothesized that osteocytes may detect mechanical loads through the detection of signaling that arises from the mechanically-induced flow of fluids and ions through the lacuno-canicular network surrounding each osteocyte (Klein-Nulend et al. 2005). It is our working hypothesis that pulsed magnetic field stimulator systems work at this level to emulate the mechanical signals in musculoskeletal tissue systems that would normally induce a functional adaptive response, such as bone growth and remodeling to increase bone density as a result of exercise. We further hypothesize that the emulation of these signals by PEMF stimulators has the additional benefit of employing the natural signal amplification systems within the musculoskeletal system without actually applying the mechanical loads to the tissues being stimulated, thus allowing musculoskeletal tissues to adaptively respond to the emulated signals without also being subjected to the structural micro damage that would otherwise occur from the mechanical loads.

PEMF as a Biological Signal

Biologically relevant signals often have the property of being very low-level; either very low amplitude, low energy, infrequent, or otherwise subtle. As a result these signals are often difficult to detect experimentally. But through millions of years of evolution the molecular or cellular responsiveness to these low-level signals has evolved in many cases to become highly specific and responsive only to a very precisely defined signal, so as to prevent amplification of spurious background noise that might elicit inappropriate cellular or molecular response. Within the receptive bandwidth of these low-level biological signals the signal itself therefore has a high signal-to-noise ratio, with minimal energy being expended upon parameters of the signal that do not contribute to the intended message. This allows all other signals that fall outside of the receptive bandwidth to be essentially ignored. The evolutionary process tends to make good use of such highly selective and efficient processes once they have passed the test of natural selection, so it is reasonable to hypothesize that a signal that might elicit a functional adaptive response in one tissue, for example bone, might also be employed by other tissues for similar purposes. This would be especially true for tissues within the same functional groups such as musculoskeletal tissues, cardiovascular tissues, nerve tissues, etc. On the basis of this reasoning we hypothesize that specific signals that induce tissue growth and regeneration in one tissue in the musculoskeletal system might elicit the same general response in many or all other tissues of the musculoskeletal system. So a specific signal that is known to elicit acceleration of bone repair might also elicit accelerated repair in cartilage, ligament, tendon, and muscle as well. Our review of the literature reveals that this general assumption may be implicit, but is generally not explicitly articulated in the description of any of the PEMF technologies that have been reported. In most cases we believe the PEMF signals that are employed, often referred to as PEMF "waveforms", have been arbitrarily selected and often not developed and refined based upon this line of reasoning. Therefore many PEMF technologies do not take advantage of the inherent natural mechanisms of biological signal amplification, preferring instead to use a brute-force approach to coerce the target tissue toward the desired response rather than employing high fidelity signals that work with innate biological filters and amplifiers. The literature suggests that this latter approach, though crude, is in fact effective to a limited degree. However, this approach has no basis from which to develop increasingly sophisticated, efficient, and effective PEMF signals, and as a result most commercially-available PEMF technologies simply are not improved over time. Once they can be demonstrated to be statistically significant in their intended biological effects the evolution of the PEMF waveform protocols toward increasingly better signals generally does not occur. The unintended consequence of this crude approach to the development of PEMF waveforms has been that most PEMF systems are very inefficient, bulky, costly, and they subject the target tissue to unnecessary levels of electromagnetic energy. But more rational approaches to PEMF waveform design are certainly possible.

PEMF Waveform Shapes

Many different methods exist for inducing an electric field within tissues and all of these have been employed at various times by different PEMF systems. These can be divided into four distinct waveform categories: pure sinusoidal, triangular/sawtooth/trapezoidal/square, asymmetric pulses, and pulsed radio frequency (PRF)/Modulated signals. We will not consider steady (DC) magnetic fields though they are frequently employed, for the reasons stated above. We must also keep in mind that there are three levels of signals, as discussed above. For the following discussion the signal waveforms refer to signals in Level #2—the magnetic field generated by the coils.

Sinusoidal This is by far the most common form of PEMF stimulation, based upon a pure sinusoidal magnetic waveform. In the literature it is well established that tissues typically respond to radio frequencies (RF) from 0 Hz to 10 kHz—outside of this range, tissues and cells are essentially transparent (with the exception of PRF signals). The smallest wavelength of such signals in an electrolyte environment is on the order of 3000 meters—thus cells are unlikely to be acting as antennae at such frequencies. Furthermore, a frequency of approximately 30 THz would be required to induce resonance in a cell of size on the order of 10 μm in a saline solution. Interestingly, because tissues have been found to be responsive in such a low frequency range, one must consider the mechanisms by which cells or

molecules might transduce these signals. Much of the biological response is dependent upon the bulk electrical properties of tissues (direct and reactive impedances), which dictate how electrical energy is absorbed through a medium. In the case of a magnetic field, because the vast majority of mammalian tissues are not known to interact with magnetic fields, one must consider magnetically induced electric field pathways as the primary method in which magnetic fields can interact with tissues. Because the induced electric field is proportional to the rate of change of the magnetic field, the amplitude and frequency of the magnetic field dictates the strength of the cellular response. Thus, higher frequency and amplitude signals should be more effective in eliciting a response. It should be noted that there is significant theoretical evidence that suggests that there is a lower bound for frequencies as well due to the thermal noise threshold (A A Pilla et al. 1994; Weaver & Astumian 1990; David J Muehsam & Arthur a Pilla 2009a). Interestingly, there have been a number of studies that find effects well below the theoretical frequency and amplitude limits predicted mathematically, suggesting either a placebo effect or an alternative transduction mechanism (R Sandyk 1998b; R Sandyk 1997; R Sandyk 1999a; Reuven Sandyk 1993; R Sandyk 1999c; R Sandyk & Iacono 1993; R Sandyk 1998c; R Sandyk 1998a; R Sandyk 1999d; Goodwin et al. 2005; R Sandyk 1999b; R Sandyk 1998d; R Sandyk & Iacono 1994; Weaver & Astumian 1990).

Triangular/Trapezoidal/Square Triangular, trapezoidal and square waves fall into a similar category because they represent Fourier sums. While the multi-frequency aspect of such signals may be a reason that they are effective, it may equally be the case that their efficacy is due to the high slew-rates that can be produced. For practical purposes, pure square waves are impossible to create electronically: there is always a finite rise-time and fall-time for the primary electrical signals—they cannot change instantaneously. Thus, this category of three waveforms can be collapsed into triangle and trapezoidal, which includes square waves which are actually trapezoids because their rising and falling slopes are not perfectly vertical. Both triangular and trapezoidal waveforms provide bipolar induced fields, which depend upon the slope of the sides of each trapezoidal waveform—the main difference being that there is a delay between positive and negative peaks in a trapezoidal pulse given by the length of the signal plateau.

Asymmetric Pulses Asymmetric pulses are typically triangular or trapezoidal in nature, but have a differing rising and falling edge. Such waveforms can be useful for inducing non-equal bipolar induced electric fields. Examples of asymmetric pulses include saw-tooth waves such as those shown in (Figure 3).

PRF/Modulated Signals Pulsed radio frequency (PRF) signals provide a high-frequency method for encoding low-frequency signals, similar to the way in which an FM radio works. Because tissues will integrate low-frequency signals (i.e. they act as a high-pass filter), they can demodulate pulsed PRF signals. The advantage of such a stimulation paradigm is that tissue penetration can be increased. Since radio frequency signals can penetrate tissues easily, PRFs can provide an effective means of stimulating deep tissues without using very strong external fields. The efficacy of PRF stimulation has been explained by Pilla et al. on the grounds of a proposed biochemical model (David J Muehsam & Arthur a Pilla 2009a; David J Muehsam & Arthur a Pilla 2009b; Strauch et al. 2011; a a Pilla 1974; M. Markov & A Pilla 1997; Rohde et al. 2009; M. S. Markov et al. 1993; A A Pilla et al. 1999). Under appropriate stimulation parameters, PRFs can modulate first order kinetics of ion binding to enzymes. Pilla's work is focused on modulating calcium binding to calmodulin in vivo—providing a method by which downstream targets such as endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) can be affected (A A Pilla et al. 1999).

Waveform Parameters All waveform categories and shapes are defined by a set of waveform parameters. These include amplitude, frequency, slew rate, and other parameters. Some waveforms are well described by only two parameters, such as continuous pure sine waves which can be defined by the two parameters amplitude and frequency. Other waveforms are more complex and may require six or more parameters for a complete description. An example of this is asymmetric trapezoidal waves that are generated in short bursts of pulses followed by periods of no stimulation. In this case the waveform would be fully defined by at least twelve parameters: start time, initial slope, peak amplitude, duration (time) held at peak amplitude, final slope, terminal amplitude (can be zero or have opposite sign for bipolar pulses), duration of zero or opposite-sign plateau, return slope (if non-zero), time between pulses, number of pulses in each burst, dwell time between bursts, and at least one additional parameter to define the periodicity of the bursts of asymmetric trapezoidal pulses.

Amplitudes The mechanism for the biological effects of PEMF as they relate to magnetic flux peak amplitude, and thus the relative importance of this parameter, remains slightly ambiguous at this point because there is a large range of experimentally effective amplitudes that fall well below thermal noise limits. However, generally speaking, larger amplitudes are more effective in direct tissue stimulation until high amplitudes that begin to cause collateral tissue damage are reached. This damage is most likely because more energy is dissipated into the tissues in each unit of time. Energy per unit time yields the physical units of power, and electromagnetic power is associated with tissue damage when the power level begins to reach a level with significant thermal effects (temperature rise) within the tissue. This effect is put to positive use in modern surgery when radio ablation is utilized to destroy tumors or other unwanted tissues. Assuming that the RF power is below a damaging level, we have noted in a wide variety of literature that induced electric fields on the order of 0.01 – 10 V/m appear to be most effective in treating chronic pain and inflammation. Generating such field strengths can be done using several magnetic waveforms. It should also be noted that much lower amplitude magnetic fields, on the order of picotesla (10-12 T), have been reported to be clinically effective for treatment of multiple sclerosis and Parkinson's patients (Reuven Sandyk 1993; R Sandyk & Iacono 1994; R Sandyk & Iacono 1993; R Sandyk 1998b; R Sandyk 1999c; R Sandyk 1999a; R Sandyk 1998d; R Sandyk 1997; R Sandyk 1998c; R Sandyk 1998a; R Sandyk 1999d; R Sandyk 1999b). So, we can con-

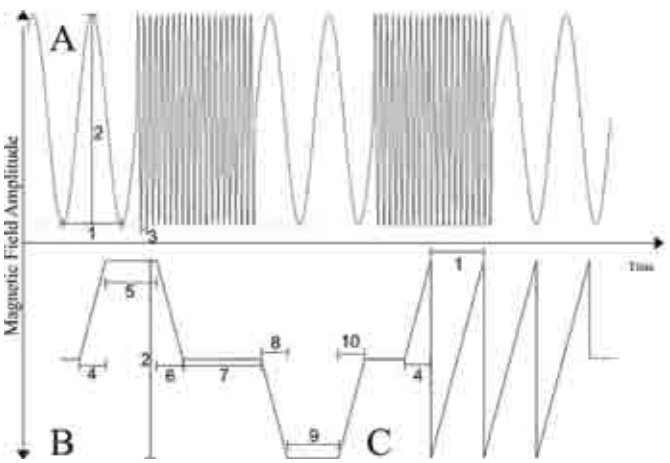

Figure 3. Representative images of waveforms used in PEMF. A.) Sinusoidal waveforms have smoothly varying edges, and can also be pulsed at high frequencies to produce PRF signals. B.) Trapezoidal and square waveforms represent waveforms with large rising and falling edge slopes and non-changing peaks and troughs. C.) Asymmetric pulses, such as the saw-tooth waveform shown, represent waveforms that have large rising and/or falling edge slopes, but provide non-symmetric induced electric fields within tissues of interest. A description of the numbered portions above can be found in Figure 4.

clude that waveform amplitude certainly plays a role in both the efficacy and the potential risk involved in the use of PEMF stimulators, but the precise role and the underlying biological and electromagnetic mechanisms remain to be elucidated.

Frequency The waveform frequency parameter is also considered of vital importance when considering periodic signals. The precise role of frequency is somewhat obfuscated by the imprecise use of this very well-defined engineering term. As noted previously, tissues typically only respond to frequencies below 10 kHz, with the exception being that FM signals can be demodulated by tissues, provided the low frequency encoding falls below 10 kHz. Because the frequency of a sinusoidal magnetic flux signal dictates the time derivative dependence, and therefore the induced electric field magnitude, it follows that higher frequency signals are capable of inducing electric fields with greater peak amplitudes in the target tissue. However, as we shall see later, there are theoretical limits that help narrow down the range of frequencies that would be theoretically effective. For example, a 1 Hz wave would require a peak amplitude of approximately 100 tesla in order to induce an electric field on the order of 1.75 V/m around the perimeter of a 35 mm disk. This peak field strength is approximately 100 times higher than the average field produced in a clinical MRI unit, which is a very large amplitude indeed. One tesla = 10,000 gauss, so a 100 T field = 1 MG, which is about 200 times the average magnetic field strength of the Earth. At higher frequencies the calculus, a simple derivative of the sinusoidal waveform, indicates that significantly lower magnetic flux amplitudes could theoretically become biologically effective. For example, by increasing the frequency from 1 Hz to 1 kHz, the required peak magnetic field becomes approximately 0.1 T, which is more reasonable and technically is much easier and less expensive to achieve—but it remains very large.

Slew Rate As an alternative strategy to employing magnetic fields of very high amplitude it is both possible and sometimes advantageous to use high rates of change (steep slopes) coupled to otherwise low frequency pulses. It is in this use of the term frequency that confusion sometimes arises. For pure sine waves the meaning of the term frequency is defined as "the first time derivative of phase angle", whereas the meaning of the term frequency in reference to non-sinusoidal pulses is "how frequently the individual pulses are generated". Improper or imprecise use of the term frequency can lead to considerable confusion when defining the precise parameters for non-sinusoidal magnetic pulse waveforms. Trapezoidal and triangular magnetic pulses can be generated individually with long periods of inactivity between pulses, but it is possible by this approach to generate very large induced electric fields by driving the trapezoidal waveforms with very steep rising and falling edges, that is, incorporating large slew rates to each edge of each trapezoidal or triangular pulse. Such signals are easily capable of producing 1.5 V/m induced signals while keeping peak magnetic field strength well below 0.1 T provided the pulse can be delivered in a short enough time (approximately 100 μs). Frequency modulated signals provide an alternative method for producing high slew-rate signals by encoding low frequency signals in high frequency (1-27.12 MHz) sinusoidal carrier waves.

The Thermal Noise Threshold

An interesting and important discussion must be had regarding the thermodynamic effects of electric fields. Specifically, as one decreases the magnitude of the induced electric field, there comes a point where thermal fluctuations due to random motion within the sample can easily produce field strengths large enough to mask the applied signal. This masking is referred to as the thermal noise threshold and is on the order of 9x10-2 V/m when signal averaging is not taken into account. However, cells are able to integrate applied signals, which allows the theoretical noise threshold to fall even further to levels as low as 10-3 – 10-5 V/m (Weaver & Astumian 1990).

Review of Past Literature/Focus on Systems/Tissues:

Bone Studies

The majority of the evolution of PEMF therapy in the 20th and 21st century has been driven by the development of bone-growth stimulators. When Fukada and Yasuda discovered that bone is piezoelectric and subsequent studies implicated that bone remodeling could be driven by this property, it was only a matter of time before people began exploring the possibility that applied electromagnetic fields could drive other biological processes. Thus, much of the pioneering work done by Bassett et al. laid the foundation for subsequent work in other tissues.

Cell Studies

Effects of PEMFs on cells have been studied extensively in those cells of bone- or cartilage-derived lineage. In vitro studies on both primary and immortalized cells have been conducted, and there is evidence to suggest that each responds differently to PEMFs (De Mattei et al. 1999). Cell studies done on osteoblast-like cells have mainly focused on the nitric oxide synthase (NOS) pathway of cells such as MC3T3 cells (Diniz, Shomura, et al. 2002; Diniz, Soejima, et al. 2002). Proliferation in several different cell types has been extensively studied and found to be increased in the presence of low-magnitude PEMFs on the order of 0.002 V/m (Pezzetti et al. 1999; Tepper et al. 2004; Liboff et al. 1984; Takahashi et al. 1986; Sollazzo et al. 1997; Robert J Fitzsimmons et al. 2008). In addition to modulating proliferation, PEMFs have been implicated in the upregulation of DNA synthesis , and IGF-2 (osteosarcoma) (R J Fitzsimmons et al. 1995; R. J. Fitzsimmons 1995), FGF-2 (endothelial cells) (Tepper et al. 2004) and BMP-2 mediated osteoblastic differentiation in human mesenchymal stem cells (HMSCs) (Schwartz et al. 2008). In addition to the studies on bone, there have been questions as to the efficacy of PEMFs in nerve regeneration. In particular, a study conducted at NASA by Goodwin and McCarthy (Goodwin et al. 2005) and Dennis (2011) showed that human neuronal cells could be modulated by time-varying electromagnetic fields (TVEMF). They

Summary of Important Secondary Wave Structures Necessary for Fully Defining PEMF Waveforms

Sinusoidal (A)	PRF (A)	Trapezoidal (B)	Asymmetric Pulse (C)
Period (1) Amplitude (2) Peak Slope	Bulk Pulse characteristics Carrier Period (3) Amplitude (2) Encoded frequency Peak Slope	Amplitude (2) Positive Rising Edge Slope Positive Rising Edge time (4) Time at Max (5) Positive Falling Edge Slope Positive Falling Edge time (6) Time at Zero (7) Negative Falling Edge Slope Negative Falling Edge time (8) Time at Minimum (9) Negative Rising Edge Slope Negative Rising Edge time (10) Peak Slope	Period (1) Amplitude (2) Rising Edge Slope Rising Edge time (4) Falling Edge Slope Falling edge time (6) Peak Slope

Figure 4. Summary of important waveform parameters necessary to completely define a PEMF waveform. All numbered items are labeled in figure 3 on their respective waveform type letter. Unlabeled components are those which cannot easily be drawn on a figure, however are absolutely necessary. Trapezoidal waveforms are assumed to be constructed of straight lights—if lines are curved, a function may be required to define the edge slopes. It should be noted that this table is not comprehensive, as more complicated waveforms may require additional information to fully define one full cycle of stimulation.

found differences in cell morphology as well as proliferation rates in cells that were cultured in the presence of TVEMFs. While cell culture studies are important to understanding biochemical and cell-level responses to PEMFs, they cannot provide the tissue and organism level responses that can be gleaned from in vivo, animal and human studies.

Soft Tissue Studies

To understand the effects of PEMF therapy on a system level, we feel it is easiest to break the existing literature into the broader categories of nerve healing and anti-inflammatory studies. Because PEMF is so well established as an effective treatment in bone-healing, we choose not to review that literature—however the reader should be aware that there is a vast literature concerning bone remodeling (a good reference to start with is the 1974 Bassett reference).

Nerve Healing To understand the effects of PEMFs on nerve regeneration, we have broken the in vivo studies into three broad categories: peripheral, spinal cord and cortical studies. We have chosen to separate the cord from central and peripheral studies because it is the junction point for both central and peripheral nerves, and thus has the potential to affect both simultaneously.

Peripheral Nerves The focus of the majority of peripheral nerve studies has been to examine the ability of PEMFs to temper pain and stimulate regrowth. As previously mentioned, the studies performed at NASA by Goodwin et al. indicated that neuronal proliferation could be significantly affected by low frequency pulses much lower in magnitude than the earth's magnetic field. Studies performed by Raji et al. have shown that rat peroneal nerve regeneration can be enhanced by the use of PEMF (a M. Raji 1984; A. Raji & Bowden 1983).

Cord Nerves The majority of the published controlled laboratory studies examine the effects of PEMFs on sciatic nerve lesions. Significant evidence from animal studies suggests that PEMFs are potentially effective in accelerating sciatic nerve healing. Square wave pulses (~600 T/s magnetic flux rate), as studied by Sisken et al. (1989), seem effective in increasing sciatic nerve regeneration regardless of the orientation of the Helmholtz stimulation coils. However, Baptista et al. (2009) showed that there was no significant effect from treating sciatic crush lesions in Swiss mice using a stimulation protocol that induced a 20 kT/s magnetic flux rate—a relatively large stimulus.

Cortical/Central Nerves Finally, it is important to discuss the potential cortical effects of PEMFs. Cortical effects should be considered from two different views: direct stimulation (ex: rTMS, low magnitude PEMF, etc.) which stimulates the brain directly, and indirect stimulation that causes cortical remapping or modulation by stimulating peripherally. Direct stimulation methods such as those used in the studies published by Sandyk et al. have indicated that very small induced fields may be effective in alleviating some of the difficulties associated with multiple sclerosis and Parkinson's disease (Reuven Sandyk 1993; R Sandyk & Iacono 1994; R Sandyk & Iacono 1993; R Sandyk 1997; R Sandyk 1998a; R Sandyk 1998b; R Sandyk 1998c; R Sandyk 1998d; R Sandyk 1999c; R Sandyk 1999b; R Sandyk 1999a; R Sandyk 1999d). However, it should be noted that the field strengths in question fall far below the thermal noise threshold and that the majority of these studies are case studies, not controlled laboratory studies. Unfortunately the literature regarding the central effects of peripherally applied PEMFs on central nerve function is rather sparse. Because peripheral neurons play a very large role via the feedback mechanism in cortical plasticity, it follows that if PEMF affects these neural feedback loops, then fMRI and PET studies would reveal potentially significant effects of peripherally applied PEMF on cortical plasticity.

Anti-inflammatory Effects There are two notable studies that shed significant mechanistic light on the anti-inflammatory and pain reducing effects of PEMF: those of Per Hedén et al. and Christine Rohde et al. Both studies examined the post-operative effects of PEMF on breast augmentation and breast reduction patients respectively. In the former, a pilot study of patients undergoing breast augmentation, PEMF (2-ms bursts of 27.12 MHz PRF, 32 mV/cm peak applied for 30 minutes every 4, 8 or 12 hours on different post-operative days) was shown to significantly reduce pain scores (Hedén & Arthur a Pilla 2008). The second study, performed by Rohde et al. using similar PEMF parameters showed significant pain reduction, and interestingly a drastic reduction in IL1-β levels in wound exudate as compared to sham groups (Rohde et al. 2009). Reduction in inflammatory factors suggests at least one possible biochemical mechanism—perhaps the Ca2+/CaM dependent NOS pathway suggested by Pilla et al. (A A Pilla et al. 1999). It is interesting to note that although these reports and others have demonstrated very significant and repeatable reduction in post-operative pain when PEMF is correctly applied, and that the use of narcotics to manage pain has severe and well documented health and social effects, there does not appear to be any increase in the clinical acceptance of PEMF stimulation for the management pain. Essentially—despite growing support in the peer-reviewed literature, the availability of many commercial PEMF products, and the lack of evidence indicating adverse effects—the use of PEMF for any form of pain management remains outside even the fringe of standard medical practice.

Possible Mechanisms

While there are many possible mechanisms by which PEMFs could influence cells, tissues, organs and whole systems—there are only a few basic mechanisms that are adequately explored in the scientific literature. First is an implicit theory which is not always discussed explicitly: eddy current interactions with signaling proteins. The fundamental idea of this first theory is based on Faraday's law of induction which states that electromagnetic eddy currents can be induced in a conducting surface (such as a slice of tissue) by a time-varying magnetic field. In the presence of a changing magnetic field, the electrolyte surrounding cells can act as a conducing medium and eddy currents can flow in these spaces. If there are free ions in solution, presumably they could be placed into organized motion and their frequency of interaction with their receptors of interest might be preferentially increased or decreased, causing a cell response. Another possibility is that proteins are affected directly—since every biochemical reaction is driven fundamentally by the electromagnetic force, it follows that protein binding pockets could be modulated by induced EMFs or eddy current flow. A more specific proposed mechanism is that put forth by Pilla and his collaborators, which states that PEMFs of the appropriate waveform and pulse duration (specifically pulsed radio frequencies) are able to modulate the Michaelis-Menten binding kinetics of the Calcium-Calmodulin dependent nitric oxide synthases (David J Muehsam & Arthur a Pilla 2009a; A A Pilla et al. 1999; a a Pilla 1974; David J Muehsam & Arthur a Pilla 2009b; M. Markov & A Pilla 1997; Rohde et al. 2009; Hedén & Arthur a Pilla 2008; M. S. Markov et al. 1993; C. a Bassett, R. J. Pawluk, et al. 1974; C. A. L. Bassett, R. J. Pawluk, et al. 1974; Arthur A Pilla 1970). Modulating such a fundamental pathway could result in modulated levels of NO production and therefore have very drastic downstream effects in the body. Finally, for low amplitude magnitude fields, a Larmor precession model is discussed which states that the Larmor precession behaviour of certain atoms or molecules (such as water) can be modulated in the presence of a magnetic field. In the case of water, modifying the Larmor precession can impact the ability of thermal fluctuations to drive chemical reactions—shifting the amount of energy required by a ligand to displace water from a binding site on a target molecule (M. Markov & A Pilla 1997; a Pilla et al. 1997; Barnes & Greenebaum 2007). These three theories are far from complete or comprehensive; however, they serve as a good beginning to the development of an understanding of the basic mechanisms to elucidate the effects of PEMF on the body.

Summary, and the future of PEMF

The PEMF literature is rather sparse when one considers the vast continuum of electromagnetic frequencies and amplitudes. The problem of

organizing and classifying effective PEMF waveforms in tissues is similar to the problem faced by Mendeleev and other chemists who faced the growing problem of classifying elements into the periodic table. More recently a similar problem was faced by subatomic particle physicists such as Glashow, Weinberg and Salam in trying to develop what we now call the Standard Model—a method for classifying and understanding the subatomic particles and their interactions. The problem faced by these influential scientists is not completely held in simply organizing information—it was in taking a large amount of completely unorganized information and convincing a scientific community of an effective means of organizing the information. The importance of such organization is twofold. First, organization helps to circumvent vicious arguments between those seeking answers to the same problems by giving objective grounds on which to make rational arguments. And secondly, possibly more importantly, it allows outside viewers—those not directly involved in the scientific community—the opportunity to understand clearly the methods and goals of the study. If organization can be achieved, then the PEMF community as a whole can make research progress at an incredible pace. As a research community we must apply several simple principles in our experiments and articles that will help to alleviate the questions that are often generated by those not directly involved in the research. First, we must strive to be scientifically rigorous—any published experiment MUST include adequate information to completely replicate the experiment. This means that waveform parameters must be fully and carefully defined such that an induced electric field can be calculated. In some cases the parameters should be measured and determined experimentally, using well-calibrated instruments suitable to the task. Secondly, it is important that authors choose effective and specific titles for articles. Titles such as "PEMF is Not an Effective Means of Treating Rotator Cuff Injury" do not help the already confused literature (unless every single frequency, amplitude, waveform structure and treatment regimen was tested). Consider the possible title for a study in which aspirin (a drug) was found to be ineffective in reducing post-operative pain. The resulting manuscript titled "Drugs are not effective in the treatment of post-operative pain" is non-specific to the point of being both misleading and incorrect. Just as there are many types of drugs, there are vast numbers of different PEMF stimulation protocols. One of the authors of this paper (Dennis) estimates this number to be on the order of 10 trillion different possible PEMF stimulation protocols (unpublished estimate). Therefore, titles should include at minimum a descriptor of the magnetic field waveform such as "75 Hz, 250 mH Sinusoidal PEMF is Not an Effective Means of Treating Rotator Cuff Injury." This allows those in the field to quickly isolate articles based on their treatment parameters, and it gives those outside the field an understanding that different PEMF protocols are used for different reasons. Just as ultrasound has different clinically effective waveforms for different applications (imaging, targeted ablation, ARFI, etc.), both clinical practitioners and the educated public must understand that the same is likely true of PEMF. Secondly, it is important, as the PEMF literature progresses and waveforms are grouped based on efficacy, that we use consistent terms to define PEMF stimulation protocol parameters (Figure 4). Until a well-defined set of terms is established, understanding and forward progress in the use of PEMF will be limited. However, if we are strict with definitions and clear in our methods and scientifically approach the many questions posed by the interactions of PEMFs with tissues, then we can take the field from being in a questionable and disorganized state toward a respected and organized body of knowledge that has earned the respect of scholars and physicians. ■

List of Abbreviations:

ARFI – Acoustic radiation force impulse
BMP-2 – Bone morphogenic protein 2
Ca2+ – Calcium (2+) ion
CaM – Calmodulin
DNA – Deoxyribonucleic acid
eNOS – Endothelial nitric oxide synthase
FGF-2 – Fibroblast growth factor 2
HMSC – Human Mesenchymal derived stem cell
IL1-β – Interleukin-1 Beta
NASA – National Aeronautics and Space Administration
nNOS – Neuronal nitric oxide synthase
NOS – Nitric oxide synthase
PEMF – Pulsed electromagnetic field
PRF – Pulsed radio frequency
rTMS – Repetitive transcranial magnetic stimulation
TVEMF – Time varying electromagnetic fields

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