

## Expanding Use of Pulsed Electromagnetic Field Therapies

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*Various types of magnetic and electromagnetic fields are now in successful use in modern medicine. Electromagnetic therapy carries the promise to heal numerous health problems, even where conventional medicine has failed. Today, magnetotherapy provides a non invasive, safe, and easy method to directly treat the site of injury, the source of pain and inflammation, and a variety of diseases and pathologies. Millions of people worldwide have received help in treatment of the musculoskeletal system, as well as for pain relief. Pulsed electromagnetic fields are one important modality in magnetotherapy. Recent technological innovations, implementing advancements in computer technologies, offer excellent state-of-the-art therapy.*

**Keywords** Pulsed electromagnetic fields; Therapy.

### Introduction

The use of magnetic fields for resolving health problems has a long history. It is difficult to identify the exact time when physicians from ancient Greece, China, Japan, and Europe discovered that some natural magnetic materials were of help in their daily practice. One of the earliest scientific accounts is found in the book *De Magnete*, written in 1600 by William Gilbert, the personal physician of the English Queen (Gilbert, 1600). This brilliant natural philosopher used “lode stones” to treat a variety of health problems of ordinary British citizens and even the Queen of England.

Contemporary magnetotherapy began in Japan immediately after World War II by introducing both magnetic and electromagnetic fields in clinical practice. This modality quickly moved to Europe, first in Romania and the former Soviet Union. During the period of 1960–1985, nearly all European countries designed and manufactured their own magnetotherapeutic systems which utilized various waveshapes. Indeed, the first book on magnetotherapy, written by Todorov, was published in Bulgaria in 1982 summarizing the experience of utilizing magnetic fields for treatment of 2,700 patients having 33 different pathologies (Todorov, 1982).

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During the 1970's, the team headed by C.A.L. Bassett introduced a new approach for the treatment of delayed fractures, employing a very specific biphasic low-frequency signal (Bassett et al., 1974, 1977). This signal was approved by the FDA for application in the U.S. only for non union/delayed fractures. A decade later, the FDA allowed the use of pulsed radiofrequency electromagnetic field (PRF) for treatment of pain and edema in superficial soft tissues.

It is now commonly accepted that selected weak electromagnetic fields (EMF) are capable of initiating various healing processes including delayed fractures, pain relief, multiple sclerosis, and Parkinson's disease (Rosch and Markov, 2004). This proven benefit could be obtained by using both static and time-varying magnetic fields.

This article is focused on the modalities that utilize pulsed electromagnetic fields (PEMF), one type of low-frequency electromagnetic (EMF) signals. Therefore, the scientific and clinical research on effects of static magnetic fields and high-frequency EMF as well as electroporation and electrical stimulation are not included in this article. We can suggest several excellent publications on these stimulation modalities (Ayrapetyan and Markov, 2006; Barnes and Greenebaum, 2006; Gardner et al., 1999; Ojingwa and Isseroff, 2003; Rosch and Markov, 2004; Rushton, 2002; Sluka and Walsh, 2003).

Magnetotherapy includes at least 6 groups of electromagnetic fields, developed and utilized in different countries of the world during the last 50 years: static/permanent magnetic fields, low-frequency sine waves pulsed electromagnetic fields (PEMF), pulsed radiofrequency fields (PRF) transcranial magnetic/electric stimulation, and millimeter waves (Markov, 2004a).

- *Static/permanent magnetic fields* can be created by various permanent magnets as well as by passing direct current (DC) through a coil.
- *Low-frequency sine wave electromagnetic fields* mostly utilize 60 Hz (in the U.S. and Canada) and 50 Hz (in Europe and Asia) frequency in distribution lines.
- *PEMF* are usually low-frequency fields with very specific shapes and amplitudes. The large variety of commercially available PEMF devices makes it difficult to compare their physical and engineering characteristics, presenting a major obstacle when attempting to analyze the putative biological and clinical effects obtained when different devices are used.
- *PRF* utilize the selected frequencies in the radiofrequency range: 13.56, 27.12, and 40.68 MHz.
- *Transcranial magnetic/electric stimulation* is a method of treatment of selected areas of the brain with short but intensive magnetic pulses.
- *Millimeter waves* have a very high-frequency range of 30–100 GHz. In the last ten years this modality has been used for treatment of a number of diseases, especially in the countries of the former Soviet Union.

It is obvious that such a large variety of signals cannot be the subject of one single publication. Therefore, our attention will be concentrated on low-frequency PEMF, discussing the types of signals implemented in different therapeutic devices.

The fundamental question in this biomagnetic technology is related to the biophysical interactions that allow EMF signals to be recognized by cells. The biophysical mechanisms of these interactions and the possibility of the signals to modulate cell and tissue functioning remain to be elucidated. The scientific and medical communities still lack the understanding why the same magnetic fields applied to different tissues can cause different effects.

The medical part of the equation requires proper diagnostics and identification of the exact target as well as the “dose” of EMF that the target needs to receive. Then, physicists and engineers should offer the appropriate protocol and exposure system which will secure that the target tissue received the required magnetic flux density. The bioelectromagnetics community has developed several methods of biophysical dosimetry, including myosin phosphorylation assay (Markov, 2004a,c) which are able to predict which EMF signals could be bioeffective and monitor this efficiency. Therefore, theoretical models and biophysical dosimetry could be instrumental in selection of the appropriate signals and in engineering and clinical application of new PEMF therapeutic devices. Once again, the same signal may have different efficiency depending on the particular target and medical problem to be treated.

Historically, the largest benefit from magnetic field therapy has been reported for victims of musculoskeletal disorders, wounds, and pain. Today, the largest interest in general public is in the potential of EMF to help in the alleviation of pain. The increased life span brings the problem that the geriatric population is mostly interested in age-related pain and discomfort. The National Institutes of Health estimate that more than 48 million Americans suffer chronic pain that results in a \$65 billion loss of productivity and over \$100 billion spent on pain care (Markov et al., 2004). The better part of this money is spent for pain-relief medications with little benefit.

It should be noted that the musculoskeletal disorders, related to bone fractures and chronic wounds, remain another large target for magnetic/electromagnetic field therapy. Recent advances in the magnetotherapy suggest that carefully selected magnetic fields may be helpful in treatment of diseases as Parkinson’s, Alzheimer, as well as Reflex Sympathetic Disorders for which contemporary medicine has little help to offer. While Reflex Sympathetic Disorder is categorized as an “orphan” disease, the number of victims of Parkinson’s and Alzheimer disease shows a tendency of continuously increasing each year.

Even a small improvement would be of great benefit: less suffering, reduced expenses, and decreased duration of treatment should be considered in parallel with individual and social welfare. Thus, the clinical effects of PEMF often constitute the method of choice when all conventional care has failed to produce adequate clinical results.

It should be pointed out that for the majority of pharmaceutical treatments the administered medication spreads over the entire body, thereby causing adverse effects in different organs, which sometimes might be significant. One should not forget that in order to deliver the medication dose needed to treat the target tissue/organ, patients routinely receive medication doses that may be hundreds of times larger than the dose needed by the target. Compared to regular pharmaceuticals, PEMF offers an alternative with fewer, if any, side effects. PEMF modalities are usually applied directly on the targeted area of the body, thereby affecting directly the source of the problem, not its manifestation.

However, regulatory and reimbursement issues have prevented more widespread use of PEMF modalities, especially in the U.S. The FDA policy toward magnetotherapy is unnecessarily restrictive. In concert with this policy, the Center for Medicare Services (CMS) for a period of time refused to allow reimbursement even for modalities cleared by the FDA. It took several years of litigation until CMS reversed its position. This was a result of the pressure from general public and physical therapy communities. In fact, the CMS has now recognized that PEMF is a

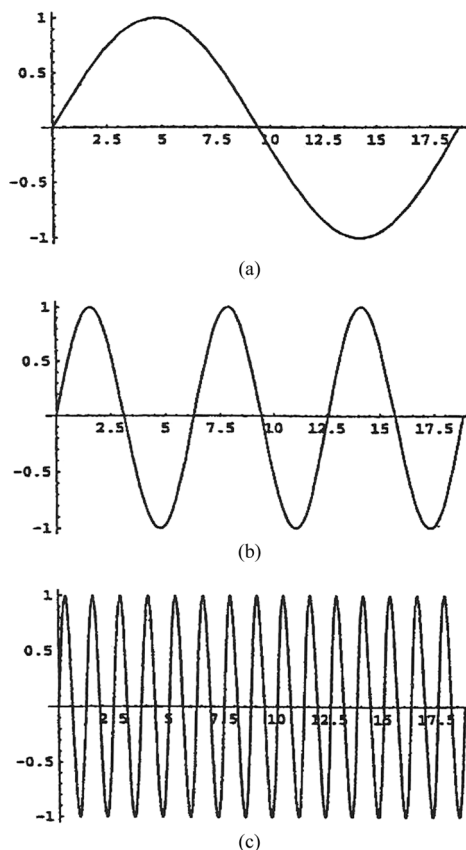
plausible therapeutic modality which produces sufficient clinical outcome to permit, and reimburse for, use in the off-label application of healing chronic wounds, such as pressure sores and diabetic leg and foot ulcers (Pilla, 2006).

## PEMF Signals

An excellent review of the physics and engineering of low-frequency signals was published by Liboff (2004). The PEMF signals in clinical use have a variety of designs, which in most cases are selected without any motivation for the choice of the particular waveform, field amplitude, or other physical parameters. The EMF generating systems are products of intuition and knowledge of engineers. As far as the author knows, the two commercial signals based upon the scientific model of Ion Cyclotron Resonance are those implemented by Orthologic (now manufactured and distributed by DJ Ortho), and by Sistemi srl.

## Sinewave Type Signals

The widely used waveshape is the sine wave with frequency of 60Hz in North America and 50Hz in the rest of the world (Fig. 1).

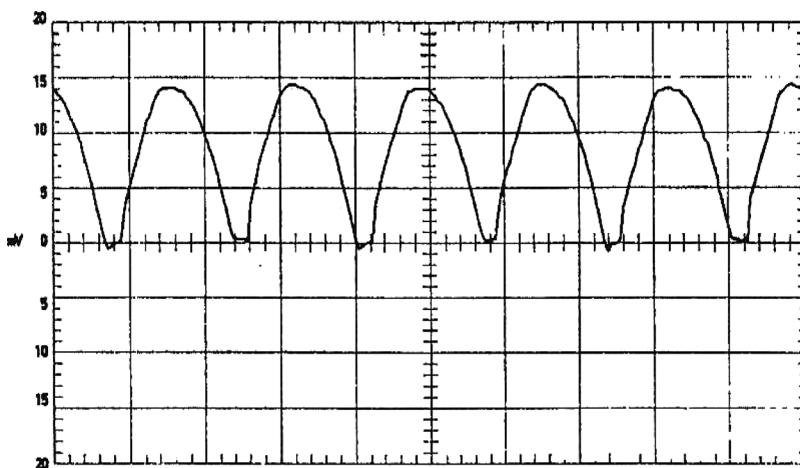


**Figure 1.** Three types of sinewave signals with the same amplitude, but different frequencies.

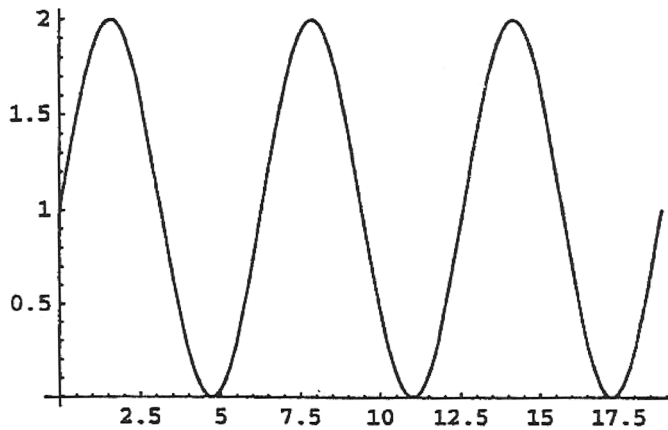
The next step was to move from symmetrical sinewaves to an asymmetrical waveform by means of rectification. The rectification basically flip-flop the negative part of the sinewave into positive, thereby creating a pulsating sinewave. The textbooks usually show the rectified signal as a set of ideal semi-sinewaves. However, such ideal waveshape is impossible to be achieved, because of the impedance of the particular design of the generating system. As a result, the ideal form is distorted and in many cases a short DC-type component appears between two consecutive semi sinewaves (Fig. 2). This form of the signals has been tested for treatment of low back pain and Reflex Sympathetic Disorder. However, the most successful implementation of this signal is shown in animal experiments as causing anti-angiogenic effects (Williams et al., 2001). Investigating a range of amplitudes for 120 pulses per second signal, the authors demonstrated that the 15mT prevents formation of the blood vessels in growing tumors, thereby depriving the tumor from expanding the blood vessel network and causing tumor starvation and death.

In the mid 1980's, the Ion Cyclotron Theory was proposed by Liboff (1985) and Liboff et al. (1987) and shortly after that a clinical device was created based on this ICR model (Orthologic, Tempe, AZ). This device is in current use for recalcitrant bone fractures. The alternating  $40\mu\text{T}$  sinusoidal magnetic field is at 76.6Hz (a combination of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  resonance frequencies). This signal, shown in (Fig. 3) has an oscillating character, but due to the DC magnetic field it oscillates only as a positive signal.

The other types of sinewave-based signals are generated when a sinewave signal is modulated by another signal. Usually, the carrier sine wave signal is with relatively high frequency (in KHz and MHz range), while the modulating signal is a low-frequency signal. This exploits the principle of amplitude modulation, used in radio-broadcasting (Fig. 4). There are also devices that apply two high-frequency signals and the interference of both signal results in an interference magnetic field (Todorov, 1982).



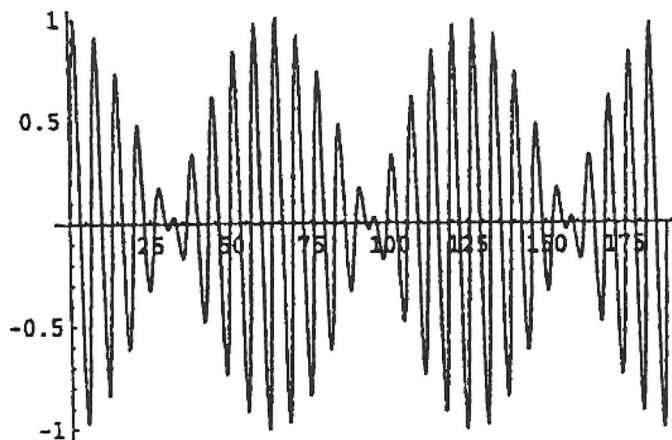
**Figure 2.** Example of real bridge rectified signal: a small DC component occurs between two semi sine waves and a slight distortion of the front part of semi sine wave might be observed.



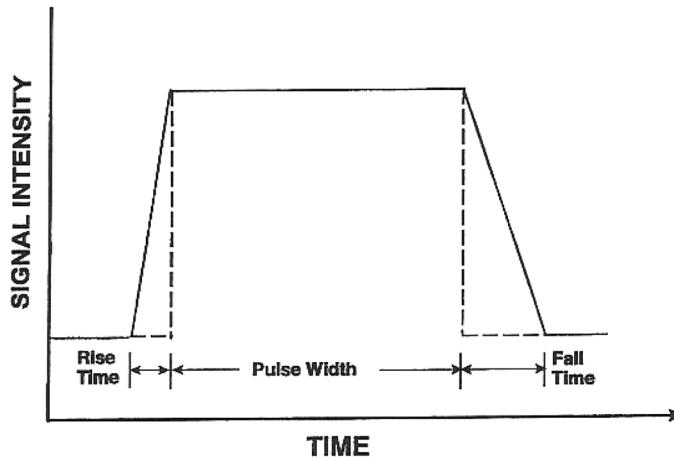
**Figure 3.** Adding a DC signal to sinusoidal signal might cause the positive only signal to originate.

### Rectangular and Trapezoidal Signals

A set of devices which utilize bipolar rectangular signals is available at the market. Probably for those signals the most important thing is that due to the electrical characteristics (mostly the impedance) of the unit, these signals could never be rectangular. There is a short necessary delay both in raising the signal up and in decaying back to zero. The rise-time of such signal can be of extreme importance because the large rate of change of magnetic field, or  $dB/dt$  may induce significant electric current into the target tissue. Some authors consider that the  $dB/dt$  rate is the factor mostly responsible for the observed biological response and the raise time is more important than the frequency or the amplitude of the magnetic field. One way to avoid this problem is to design a signal with relatively slow rise and decay time—this signal usually has a trapezoid form. Recently successful use of such a signal was reported by Kotnik and Miklavcic (2006) (Fig. 5).



**Figure 4.** Example of amplitude modulation of a high-frequency sinusoidal signal.



**Figure 5.** Trapezoid signal minimizes the problems with the rising time in case of rectangular signals.

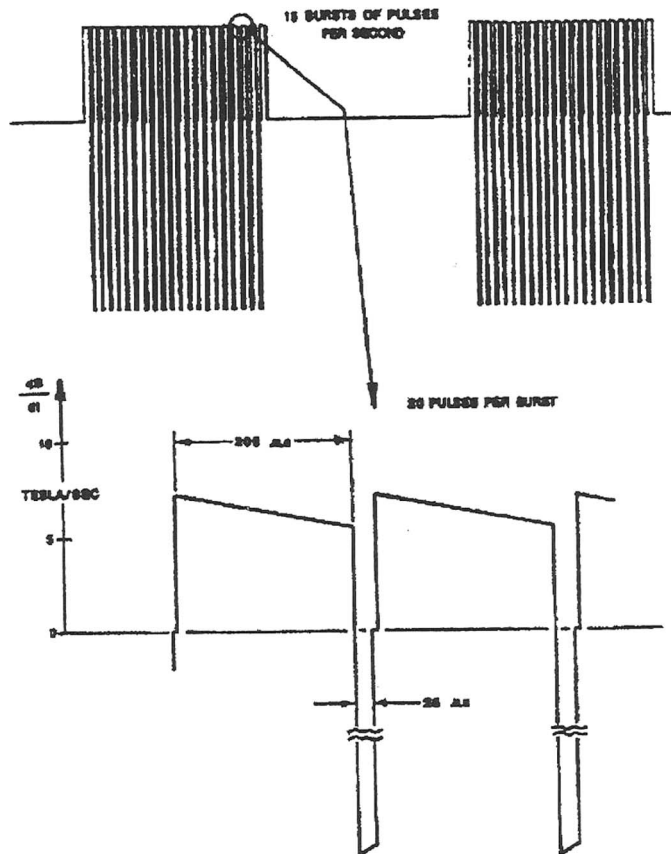
### Pulsed Signals

The first EMF signal cleared by FDA for therapeutic application has a very specific form that exploited the pulse burst approach. Having repetition rate of 15 burst per second, this asymmetrical signal (with a long positive and very short negative component) has more than 30 years of very successful clinical use for healing nonunion or delayed bone fractures (Fig. 6). The philosophy of the team, headed by Bassett, was that the cell will ignore the short opposite polarity pulse and will respond only to the envelope of the burst which had a duration of 5 msec, enough to induce sufficient amplitude in the kHz frequency range (Bassett et al., 1974, 1977). Unfortunately, although approved for delayed fractures, for decades this signal was not allowed to treat fresh fractures.

Another approach in the electromagnetic stimulation is represented by signals that consist of single narrow pulses separated by a long “signal-off” intervals. This approach allows modification not only of the amplitude of the signal, but the duty cycle (time on/time off) as well (Fig. 7).

The pulsed radiofrequency signal originally proposed by Ginsburg (1934) and later allowed by FDA for treatment of pain and edema in superficial soft tissues (Diapulse) utilizes the 27.12 MHz sinusoidal signal in pulsed mode. In Diapulse and further modification, the continuous sinewave is pulsed in short 65  $\mu$ sec bursts and 1,600  $\mu$ sec pause between pulse bursts. The frequency of bursts varies from 80–600 pulses per second with magnetic field amplitude of up to 2 Gauss. The long “time off” allows the heat potentially generated in the target tissue to dissipate, therefore during 30 min use the heat elevation is less than 1°C.

Several systems that exploit different combinations of rectangular pulses have been developed in last decade. The common in these systems is the fact that they utilize a series of rectangular pulses. The systems ([www.QRS.com.sg](http://www.QRS.com.sg); [www.Bemerclinics.com.au](http://www.Bemerclinics.com.au); [www.curatronic.com](http://www.curatronic.com); [www.seqex.com](http://www.seqex.com)) have different duty cycle or amplitude arrangements in low frequency range. Due to restrictive policy of the FDA, such systems are developed outside the U.S. (Singapore,



**Figure 6.** The original signal for treatment of non union fractures proposed by Bassett et al. (1977).

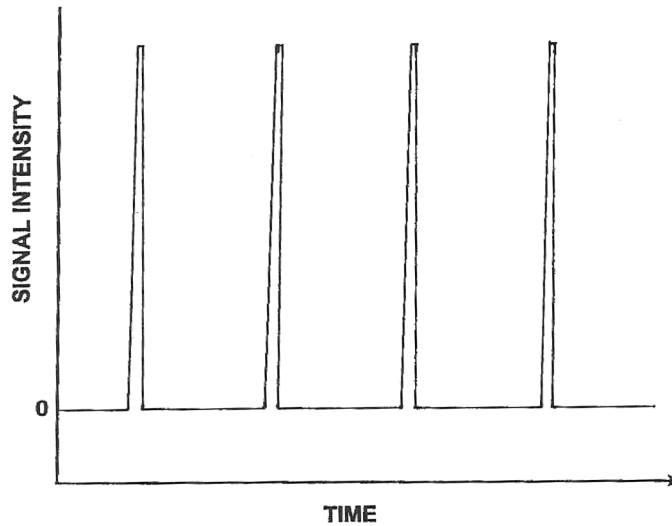
Germany, Israel, Italy) and are utilized elsewhere as therapeutic devices, while in the U.S. they are marketed as wellness items.

Another system developed in Germany, ONDAMED, was cleared by the FDA as a biofeedback device. This system is designed to scan a range of frequency over the human body and select those that are present in the spectrum of individual patient and further applied such frequency assuming that they are resonance frequencies for the patient's body.

Unfortunately, these (and other types) systems that might be found on the Internet sites, lack physics and engineering information, citing the proprietary signals and this makes the biophysical analysis of the systems very difficult.

For example, the SEQEX system is described as an advanced electromedical device developed to provide an Ion Cyclotron Resonance (ICR) therapy. It operates using specific magnetic fields that vary in intensity, frequency, and form. The device allows one to program and produce 30 forms of complex waves characterized by variation of the magnetic field's intensity to a maximum of one Gauss, changing frequency, from 1–80 Hz; periodical and adjustable pauses, as well as automatic inversion, of the field's polarity every 2 min.





**Figure 7.** Some therapeutic modalities use monophasic pulsed (both with low- and high-frequency components) with different duty cycles.

In another example, the QRS device works in a “ramp” shape wave with a “trapeze” wave, stimulating ions only during a change of the intensity in a magnetic field. QRS operates between 0.3 and 10 KHz with a duty cycle of 2:3. Furthermore, the QRS pulsing magnetic field is contracted from 3 main pulses: 200, 23, and 3 Hz.

### *Clinical Benefit*

Since the first FDA cleared device was for treatment of delayed fractures, this modality was largely used in the U.S. with a more than 80% success rate. This fact is even more important in the light of the fact that the conventional therapy failed to heal this fractures for months. The development of therapy that utilize PEMF has resulted in a large number of scientific and clinical studies reporting that PEMF help in bone unification, the reduction of pain, edema, and inflammation, and increasing blood circulation and stimulating the immune and endocrine systems.

Most wound studies involve arterial or venous skin ulcers, diabetic ulcers, pressure ulcers, and surgical and burn wounds. Since cells involved in wound repair are electrically charged, some endogenous EMF signals may facilitate cellular migration to the wound area (Lee et al., 1993), thereby restoring normal electrostatic and metabolic conditions. Because the main goal of any therapy is to restore normal function to the organism, electric, magnetic, or electromagnetic modalities appear suitable to compensate the injury currents. PEMF have also been beneficial in treatment of chronic pain associated with connective tissue (cartilage, tendon, ligaments, and bone) injury and joint-associated soft tissue injury (Hazlewood and Markov, 2006; Harden et al., 2007; Rosch and Markov, 2004).

Numerous cellular studies have addressed effects of EMF on signal transduction pathways (Adey, 2004; Markov, 2002, 2004a). Evidence is collected that selected magnetic fields are capable of affecting the signal transaction pathways via alteration of ion binding and transport. The calcium ion is recognized as a key

player in such alterations. In a series of studies of calcium-calmodulin dependent myosin phosphorylation my group demonstrated that specific static magnetic fields, PEMF and 27.12 MHz PRF could modulate  $\text{Ca}^{2+}$  binding to CaM to a twofold enhancement in  $\text{Ca}^{+2}$  binding kinetics in a cell-free enzyme preparation (Markov, 2004b,c; Markov and Pilla, 1993, 1994a,b; Markov et al., 1992, 1993, 1994). The ion binding target pathway has recently been confirmed in other studies using static magnetic fields (Engstrom et al., 2002; Liboff et al., 2003).

Several randomized clinical trials using PEMF on soft tissues and joints showed that both PEMF and PRF were effective in accelerating healing of skin wounds (Canedo-Dorantes et al., 2002; Comorosan et al., 1993; Ieran et al., 1990; Itoh et al., 1991; Seaborne et al., 1996; Stiller et al., 1992), soft tissue injury (Bental, 1986; Foley-Nolan et al., 1990; Pennington et al., 1993; Pilla et al., 1996; Vodovnik and Karba, 1992), as well as providing symptomatic relief in patients with osteoarthritis and other joint conditions (Fitzsimmons et al., 1994; Ryaby, 1998; Zizic et al., 1995).

Many scientific or clinical articles include statements like this: “Today there is abundance of *in vitro* and *in vivo* data obtained in the laboratory research as well as clinical evidence that time-varying magnetic fields of various configurations can generate beneficial effects for various conditions, such as chronic and acute pain, chronic wounds and recalcitrant bone fractures. This has been achieved with low intensity, non thermal, non invasive time-varying electromagnetic fields, having various configurations within a broad frequency range” (Pilla, 2006). Is there is something wrong with this statement? Only one word is missing “**some**” or “**selected**”. By not saying that some or selected PEMF could initiate plausible therapeutic effects, we simply say that **all** magnetic fields could achieve the goals. This simply is not true. For example, there is evidence obtained when comparing the effects of 10 different signals fort whole body exposure of guinea pigs that blood coagulation and anticoagulation systems are affected by different magnetic fields (Markov and Todorov, 1984; Todorov, 1982).

Which signals are effective and under which conditions? Are some signal parameters better than others? It should be pointed out that many EMF signals used in research and in therapeutic modalities have been chosen in an arbitrary manner. Very few studies assessed the biological and clinical effectiveness of different signals by comparing the physical/biophysical dosimetry and biological/clinical outcomes. With the exponential development of Internet it is easy to find tens, if not hundreds, of devices which promised to cure each and any medical problem. A careful look at these sites would show that no engineering, biophysical, and clinical evidence is given to substantiate the claims.

Any therapy that utilizes magnetic fields should start with:

- evaluation of the clinical problem;
- identification of the source of the problem (i.e., target organ/tissue);
- selection of the appropriate source of the magnetic field.

*More important is to identify the magnetic flux density that needs to be delivered to the desired target tissue.* The ability of the PEMF to modulate biological processes is determined first by the physiological state of the injured tissue, which establishes whether or not a physiologically relevant response can be achieved and, secondly, by achieving effective dosimetry of the applied MF at the target site. It should be remembered that the therapeutic effect depends upon the spatial distribution of MF in the injured site. Therefore, the main question remains: how to properly choose

the magnetic device. It should be pointed out that biologically and clinically relevant characteristic of the effective magnetic field is the field strength at the target site. The three-dimensional dosimetry of the magnetic field is extremely important to analyze and further predict the biological effects at the given target.

It has been three decades since the concept of “biological windows” was introduced. In fact, three groups, unknown to one another, published, almost simultaneously, that during evolution Mother Nature created preferable levels of recognition of the signals from exogenous magnetic fields. These windows could be identified by amplitude, frequency, and/or their combinations. The research in this direction requires assessment of the response in a range of amplitudes and frequencies. It has been shown that at least 3 amplitude windows exist: at 50–100  $\mu$ T (5–10 Gauss), 15–20 mT (150–200 Gauss), and 45–50 mT (450–500 Gauss) (Markov, 2005). Using cell-free myosin phosphorylation to study a variety of signals, my group has shown that the biological response depends strongly on the parameters of applied signal, confirming the validity of the last two “windows” (Markov, 2004b,c). Interestingly, a new PEMF system, developed by Curatron Ltd., generates electromagnetic signals within the range of these amplitude windows and exploit amplitude signals already proven to be biologically and clinically effective ([www.curatron.com](http://www.curatron.com)). Some discussions have occurred about the validity of the term “window” and suggestions have been made that what are described as windows are simply excellent examples of the sort of resonant behavior often observed in physics. The author agrees that “resonance” might be a better term. Indeed, in my first publication (Markov et al., 1975) the author explained the maximum response that was observed within the range of 10–100 mT as an example of resonance. This was done by analogy with resonance levels in the electronic structure of the atom, where some energy will bring the electron to a stable state, and others will not. It should be pointed that the resonance in this sense has nothing to do with models discussed in the next section.

### ***Models of EMF Interactions with Biological Systems***

The biophysical mechanism(s) of interaction of weak electric and magnetic fields with biological systems, as well as the biological transductive mechanism(s), have been vigorously studied by the bioelectromagnetics community. Both experimental and theoretical data have been collected worldwide in search of potential mechanisms of interactions. As of today, a number of mechanisms have been proposed, such as ion cyclotron resonance, ion parametric resonance, free radical concept, heat shock proteins, etc. One of the first proposed models uses a linear physicochemical approach (Pilla, 1972, 1974), in which an electrochemical model of the cell membrane was employed in order to assess the EMF parameters for which bioeffects might be expected. It was assumed that non thermal EMF may directly affect ion binding and/or transport and possibly alter the cascade of biological processes related to tissue growth and repair.

This electrochemical information transfer hypothesis postulated that one plausible way for interactions between the cell membrane and the electromagnetic fields could modulate the rate of ion binding to receptor sites. Several distinct types of electrochemical interactions can occur at cell surfaces, but two deserve special attention: non specific electrostatic interactions involving water dipoles and

hydrated (or partially hydrated) ions at the lipid bilayer/aqueous interface of a cell membrane as well as voltage dependent ion/ligand binding (Pilla et al., 1997).

It should be noted the significant contribution of the late Ross Adey in studying biophysical mechanisms of interactions of EMF with biological membranes which has both fundamental and clinical importance (Adey, 1986, 2004).

Ion cyclotron resonance (ICR) proposed during the mid-1980's by Liboff (1985) and Liboff et al. (1987), described specific combinations of DC and AC magnetic fields which can increase the mobility of specific ions near receptor sites and/or through ion channels.

Over the years, any discussion of the possibility for MF to cause biological/clinical effects involved the problem of thermal noise ("kT"). A number of physicists and physical chemists have rejected the possibility that static and low-frequency magnetic fields may cause biological effects because of "thermal noise" (Muehsam and Pilla, 1996; Pilla et al., 1997; Zhadin, 1998). Bianco and Chiabrera (1992) provided an elegant explanation of the inclusion of thermal noise in the Lorentz-Langevin model which clearly shows the force applied by a magnetic field on a charge moving outside the binding site is negligible compared to the background Brownian motion and therefore has no significant effect on binding or transport at a cell membrane.

To resolve the thermal noise problems in the ICR model, Lednev (1991) formulated an ion parametric resonance (IPR) model which was further developed during the 1990's (Blanchard and Blackman, 1994; Blackman et al., 1995; Engstrom, 1996). In this quantum approach, an ion in the binding site of a macromolecule is considered as a charged harmonic oscillator. It was proposed that the presence of a static magnetic field could split the energy level of the bound ion into two sublevels with amplitudes corresponding to electromagnetic frequencies in the infrared band. The IPR model was sharply criticized by Adair (1992).

For the author, the most important contribution of Lednev is the experiment he designed to estimate the validity of his ICR model: myosin phosphorylation in a cell-free mode (Shuvalova et al., 1991). The calmodulin molecule provides ideal model for investigating ion binding with and without the presence of exogenous magnetic field. This molecule has four molecular clefts ready to bind calcium ion. Moreover, calmodulin undergoes conformational changes at each filling of the binding sites. The experiment proposed by Lednev, and further elaborated by my group (Markov, 2004b,c), allowed Pilla's group to propose a model that overcomes the problem of thermal noise. In addition, evidence has been collected showing both low-frequency sinusoidal magnetic fields, which induce electric fields well below the thermal noise threshold, and weak static magnetic fields, for which there is no induced electric field, can have biologically and clinically significant effects (Engstrom et al., 2002; Liburdy and Yost, 1993; Liboff et al., 2003; Markov and Pilla, 1993, 1994a,b; Markov et al., 1992, 1993, 1994; Shuvalova et al., 1991).

Larmor precession, which describes the effects of exogenous magnetic fields on the dynamics of ion binding, when the ion is already bound, has been suggested as a possible mechanism for observed bioeffects due to weak static and alternating magnetic field exposures (Edmonds, 1993; Muehsam and Pilla, 1994, 1996; Pilla et al., 1997; Zhadin and Fesenko, 1990). The further development leads to the dynamical systems model which assumes the ion binding as a dynamical process wherein the particle has two energetically stable points separated by a few kT (double potential well), either bound in the molecular cleft, or unbound in

the plane of closest approach to the hydrated surface (Helmholtz plane) at the electrified interface between the molecular cleft and its aqueous environment. Ion binding/dissociation is treated as the process of hopping between these two states driven by thermal noise and EMF effects are measured by modulation of the ratio of time bound (in the molecular cleft) to time unbound (in the Helmholtz plane) (Pilla et al., 1997).

The underlying problem for any attempt to explain biological and clinical response of human tissues to weak EMF relates to the signal detection at the molecular/cellular/tissue target in the presence of thermal noise, i.e., signal to thermal noise ratio (SNR).

Numerous animal and *in vitro* studies, as well as clinical experience, suggest the initial conditions of the EMF-sensitive targets determine whether a physiologically meaningful bioeffect could be achieved. For example, when broken bone received treatment with PEMF, the surrounding soft tissues receive the same dose as the fracture site, but physiologically important response occurs only in the injured bone tissue, while changes in the soft tissue have not been observed.

This is a crucially important phenomenon, indicating that magnetic fields are more effective when the tissue is out of equilibrium. Therefore, the experiments with healthy volunteers are not always indicative for the potential response of patients who are victims of injury or disease. The healthy organism has much larger compensational ability than the diseased organism, which in turn would reduce the manifestation of the response.

Support for this notion comes from a study of Jurkat cells in which the state of the cell was found to be important in regard to the response of tissues to magnet fields: normal T-lymphocytes neglect the applied PEMF, while being stimulated by other factors. Furthermore, the response of lymphocytes to magnetic fields clearly shows a dependence on the stimulation with other factors. In other words, it might be approximated with a pendulum effect: the larger the deviation from equilibrium, the stronger the response (Markov et al., 2006; Nindl et al., 2002). For example, Nindl has demonstrated, in an *in vitro* study, that the initial conditions of lymphocytes are important in terms of the biological effects of those cells to magnetic fields.

## The Future

Analyzing the reported biological and clinical data obtained with devices and signals in use for PEMF therapy, one might conclude that some types of signals are more promising for the future development of the magnetic field therapy. It appears that semi sinewaves are more effective compared to continuous sine waves. This approach is based on rectification of the continuous sinusoidal signal, described earlier.

It is too early to generalize, but the future research should clarify the importance of the short DC component between the consecutive semi sinewaves (Fig. 2). In an unpublished study, we have found that the duration of this DC component is associated with different biological response in several outcomes. There have been reported two different approaches for utilization of these signals. One relies on constructing an elliptical or spherical coil which could be moved around the patient body (Williams et al., 2001) and the other, applies the magnetic field on the upper

or lower limbs, assuming that the results appear following systemic effects when the benefit is obtained at sites distant from the site of application (Ericsson et al., 2004).

It is reasonable to expect that the advantages of powerful computer technologies should be used in the designing new magnetotherapeutical devices. At first, it should be the computerized control of the signal and maintenance of the parameters of the signal during the whole treatment session. This has been implemented already in a large number of PEMF systems. Next, is the inclusion of user-friendly software packages with prerecorded programs, as well as with the ability to modify programs depending the patient needs. With appropriate sensors, the feedback information could be recorded and used during the course of therapy. Third, the computer technology provides the opportunity to store the data for the treatment of individuals in a large database and further analyze the cohort of data for particular study or disease.

One example of this very promising approach toward clinical application of PEMF is the Curatron system ([www.curatron.com](http://www.curatron.com)). This system generates a sinusoidal dual rectified waveform, subjected to Fast Fourier Transformation. The signal contains only one frequency component at a given time. The process of creating the pulse waveform, pulsing frequency, zero crossing, timing, and impulse intensity is completely software controlled by the built-in computer. The precise computer-controlled timing for gating of the time window, responsible for the actual pulse frequency, allows the maximum utilization of the energy contents of the modulated sinusoidal signal to be obtained. Very fast pulse rise time guarantees maximum electromagnetic energy transfer deep inside the tissue and cells, explaining the high efficacy for the Curatron. The strength of the PEMF generated by the coil applicators is monitored and controlled by a laser-calibrated Hall-effect sensor.

Yet another example of utilization of the personal computer to enable proprietary software to control the nature of applied signals is the SEQEX system ([www.seqex.com](http://www.seqex.com)). In this case, magnetic field signals act to bring the whole-body impedance into agreement with individual "wellness factors". The PC controls the therapeutic magnetic signal in a feedback arrangement determined by the instantaneous impedimetric measurement.

## Conclusion

Much work remains to be done in designing both technology and methodology of application of magnetotherapeutic devices. The proper diagnosis of the medical problem and the understanding of the biophysical mechanisms of EMF interactions with injured/diseased tissues are the first two steps to be implemented in choosing the type of PEMF stimulation. Further, the design of the appropriate treatment protocol and the choice of clinical outcomes might facilitate the success of the therapy. This requires joint efforts of engineers, biophysicists, biologists, and medical practitioners to further develop the PEMF use for treatment of various health problems.

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