ICES DigiCeutical Technical Brief

What is ICES DigiCeutical Technology?

ICES ™ stands for Inductively Coupled Electrical Stimulation. DigiCeutical ® is the future of medicine: pain-free and non-invasive digital electronics that communicate efficiently with cells and tissues to promote health, which is replacing the centuries-old tools of medicine such as drugs, needles, saws and scalpels. ICES and DigiCeutical are trademarks of Micro-Pulse LLC, founded in 2012 by the inventor and owner of the technology, Robert G. Dennis, PhD. ICES DigiCeutical Technology is the product of nearly two decades of intensive research and development, and is now available as a commercial product.

How does it work?

ICES works by using Faraday induction to communicate with cells and tissues deep within a living organism. Unlike TENS stimulation which relies upon direct electrical *conduction* between two electrodes, ICES can penetrate both deeply and much more uniformly into tissues far beneath the skin to reach deep tissue injuries, thus allowing the use of much less power to achieve far superior results. Detailed technical descriptions and comparisons against competing technologies are presented later in this document.

Is ICES really new or is it just a different name for an old technology?

ICES is an entirely new approach to electrotherapeutic stimulation of tissues, cells, and injuries in living organisms. The technology was initially developed under contract for NASA and then further developed with funding from DARPA, and continues to be developed and refined with four recently issued patents. ICES technology is continually being tested both clinically as well as scientifically at independent laboratories. It is a mature but dynamic product that takes full advantage of emerging science to continually improve the technology to keep it far ahead of the competition as the safest, most effective and least expensive electrotherapeutic product to promote tissue healing. Although our current ICES products are a mature and reliable technology, new ICES products are released approximately every 18 to 24 months to incorporate the newest electronic components and the most recent scientific advances in the field.

Patents: Micro-Pulse technology is protected by the following patents: (copies available upon request)
6,485,963 6,673,597 8,029,432 8,137,258 8,137,259 8,376,925

Trademarks: **ICES**, **METS**, and **Digiceutical** are all trademarks of the unique ultra-portable, highly efficient and uniquely effective electrophysical therapy devices manufactured by Micro-Pulse LLC.

Copyrights: All ICES and Digiceutical technologies are protected by international copyright

Scientific Research/Papers: Reports from independent product testing laboratories and reprints of scientific papers are summarized below, with full text versions available upon request.

ICES compared to TENS, PEMF and Static Magnets; Advantages and Limitations

Static Magnets have been in use to promote health almost as far back as recorded history. There are accounts of famous historical figures, such as Cleopatra, using natural magnets, also called *lode stones*, to promote health and longevity. But the scientific evidence to support such uses is somewhat lacking. This is not to say that static magnets "do not work", rather it is most accurate to say that our understanding of how and why static magnets might work is lacking, and strong repeatable clinical data to support the use of static magnets is also somewhat thin and controversial.

TENS: this technology is common, inexpensive, and is technically simple, but it is very limited in effectiveness because it relies on electrical conduction through the skin. If surface electrodes are used then the skin barrier as well as the random conduction paths (shaped like lightning bolts) tend to isolate deep tissue injuries from effective TENS stimulation. For this reason TENS is often applied using hundreds or thousands of times the theoretical signal energy needed to communicate with the tissues, because most of the signal is lost before it reaches the intended target tissue or injury. This is why clinically the practice often involves "cranking the TENS unit up" to the point where the pain is unendurable, then dialing it back down just a bit. People usually report a temporary abatement of pain, but generally only for 20 minutes or less. Some scientists hypothesize that the reduced sensation of pain is simply because the patient is happy to be released from the very uncomfortable stimulation regime most often employed with TENS.

PEMF: Pulsed electro-magnetic fields, also known as PMF (pulsed magnetic fields) are a very common type of therapeutic device, but much less is known about how these devices work, and even if they work at all. There is not any widely accepted theory for how the pulsed magnetic fields actually interact with living cells and tissues. As a result, the internet is filled with wild speculation. In this information vacuum there are many persistent myths about PEMF. But clinicians who use PEMF state that it does work eventually if properly applied. It is often reported that it may take 6 to 9 months to see any benefit from PEMF.

ICES: Technically much more complex than TENS, ICES is based on Faraday Induction (or inductive coupling) between external coils and the electrically conductive spaces within living tissues and organs. Micro-Pulse ICES technology currently dominates this field with its advanced science, comprehensive IP, and product technology far superior to any competitor. ICES employs the use of Faraday Induction generated between paired Helmholtz coils to achieve very deep penetration into tissues. This is because the intermediate magnetic fields in the electromagnetic induction process are not thought to interact with tissues strongly, therefore they can penetrate tissues very deeply without loss of signal. This is unlike TENS where the electrical signals are mostly dissipated by skin resistance. Therefore ICES allows a much deeper and more uniform stimulation of tissues with much lower signal power, leading to much more efficient and safe product designs. For background information see the following resources available on the web:

http://en.wikipedia.org/wiki/Electromagnetic_induction
http://en.wikipedia.org/wiki/Helmholtz_coil

Commercially available Micro-Pulse technology along with research data are available from Micro-Pulse LLC. Professional clinicians and researchers who wish to study the effects of ICES DigiCeutical technology should contact us through our distributor: Pulse-Pet LLC mzd@pulse-pet.com

Scientific Data for ICES (Brief Overview):

ICES technology powerfully reduces acute inflammation.

CRL Study #1: Carrageenan was injected into the hind footpad of rats. Negative control data ("**control**"; **black line, see graph below to right**) shows normal course of edema (footpad volume increase, ml) over 8-hours. Positive control data (**steroid**) show the effect of a large dose of dexamethasone (3mg/kg). ICES treatment data (**ICES**) at *the lowest power setting* on our ICES system very significantly reduces edema.

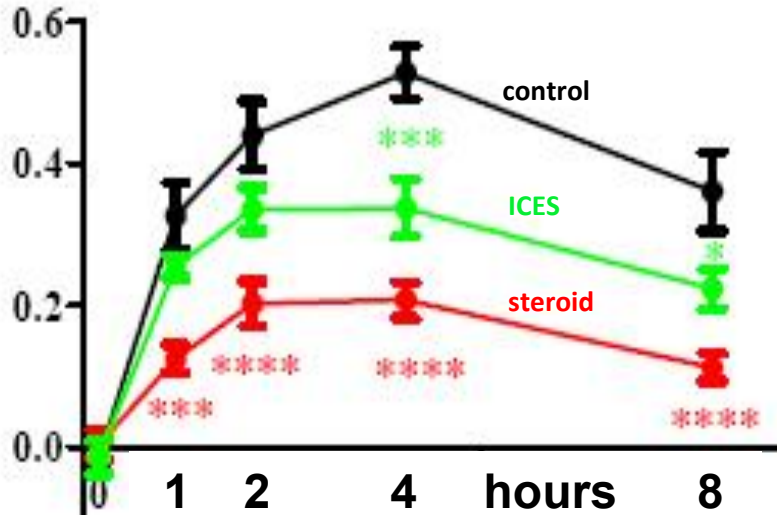
This study protocol (edema with carrageenan challenge) is the *gold standard* for the drug/pharma industry for initial screening of new drugs for their effects on acute inflammation.

NOTES on the Acute Inflammation Study #1:

∞ This test used only the *lowest power setting* on our original ICES system.

∞ The *lowest power setting* on our ICES system reduced swelling more than 60% as effectively as a large dose of anti-inflammatory steroids (dexamethasone).

∞ Note that the effects of ICES treatment begin immediately. Most competing PEMF products instruct users to wait weeks or even months (!) to see any beneficial effects. Micro-Pulse ICES works quickly and effectively to reduce inflammation in specifically targeted tissues.



∞ These studies were conducted by independent contract laboratories with GLP certification. This is the highest available scientific standard for testing the efficacy of drugs and medical devices. The study protocols adhere to the industry standard for assessing new NSAIDs, as required by the US FDA.

CRL Study #2: ICES dose-response study. Same general protocol as CRL Study #1 (above). This second study also serves to verify the results of CRL Study #1 (above)

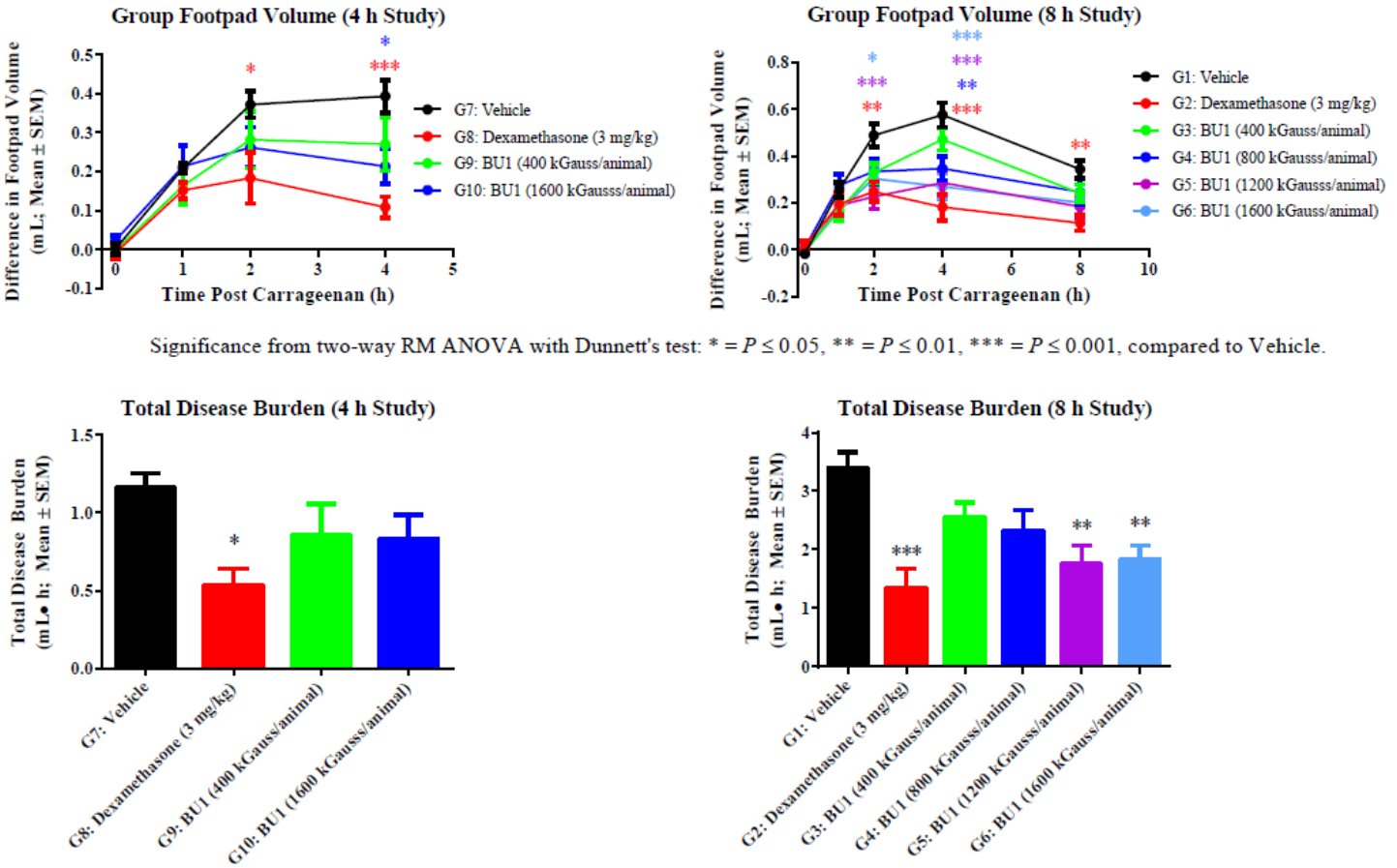
See summary graphs on following page

CRL Study #2 Additional data in preparation:

- Quantitative histopathology slides for all groups
- RNA analysis on specific groups TBD (tissues already collected, awaiting histopathology results).

Confidential

Figure 1. Magnetic Field Effects on Time Course and Disease Burden of Carrageenan-Induced Footpad Edema in CFE-e003



Significance from two-way RM ANOVA with Dunnett's test: * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$, compared to Vehicle.

NOTES on the Acute Inflammation CRL Study #2:

∞ This study suggests optimal slew rate between 1MG/s and 2MG/s, which is squarely in the center of the range that is protected by 4 issued US patents on our ICES system

∞ Note that the effects of ICES treatment begin immediately. Most PEMF systems instruct users to wait weeks or even months to see any beneficial effects. ICES works quickly and effectively to reduce inflammation in specifically targeted tissues.

∞ These studies are conducted by independent contract laboratories with GLP certification. This is the highest available scientific standard for testing the efficacy of drugs and medical devices. The study protocols adhere to the industry standard for assessing new NSAIDs, as required by the US FDA.

ICES technology stimulates stem cell adhesion and gene expression (NASA)

Study: Stem cells in culture were stimulated with ICES technology to determine the effects on cell growth, morphology, and gene expression.

∞ The study found significant effects of ICES technology on gene regulation and cellular activity related to tissue growth and healing.

∞ ICES core technology outperformed *all* other PEMF and static magnets.

For a full copy of the NASA technical brief go to:
http://ston.jsc.nasa.gov/collections/TRS/_techrep/TP-2003-212054.pdf

ICES technology heals refractory tissue injuries.

Study: Surgical critical bone defect in rabbit ulna.

∞ An advanced version of the original NASA-JSC TVEMF system (see above) was used.

∞ The radiograph shows the surgical 1-cm bone excision from the rabbit ulna.

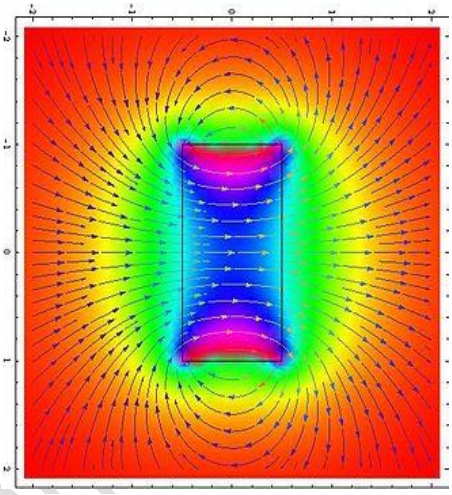
∞ Without ICES treatment the bone gap does not show any signs of healing after 4 weeks, as shown in the 3D-CT scan to the upper right.

∞ With only 4 weeks of ICES treatment the bone gap has closed and is nearly fully healed, see 3D-CT scan to the lower right.

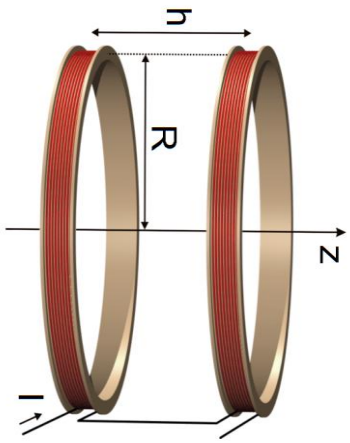
The data from this study, performed at Texas A&M University, have not yet been published.

Data and full reports from all scientific studies, with in-depth scientific analysis, will be made available to our clients upon request.

Electro-magnetic Fields generated during ICES stimulation



The key intermediate steps in ICES are the transformation of signals from the pulse generator unit into magnetic fields, which penetrate the tissues deeply and are then transformed back again into electrical fields by means of Faraday Induction, into electrical signals that stimulate the tissues. Therefore the configuration of the coils and coil placement are important. The electro-magnetic transformations can be modeled (see colorful image to the right, above). The shape and size of the magnetic flux can be controlled by coil size and relative placement of two or more coils, as shown for the Helmholtz coil pair, image at right, middle.



Helmholtz configurations for the coils are comprehensively protected by Micro-Pulse patents. Such configurations allow tissues to be conveniently placed between the coils instead of within a single coil cylinder. It is possible by this means to create convenient and effective ICES stimulation coils, as demonstrated by the image of the Micro-Pulse P2a product image with a Helmholtz coil pair, shown at right, below.

Of critical importance is that the magnetic field penetration deeply into tissue is made possible by inductive coupling. Then, the ICES signaling process is completed by efficient transformation of the magnetic fields into electrical fields deep within the tissue so that the signals can be interpreted as physiologically meaningful by the cells. Because the signal coupling to cells deep within tissues is by the use of magnetic fields generated *between* coils, the field energy outside the coils drops off dramatically, thus ICES products are not considered to be physically significant radiators of electromagnetic energy at any distance from the coils more than 3 or 4 cm. This minimizes unintended radio frequency (RF) energy radiation, thus minimizing energy loss (inefficiency) as well as any undesirable collateral effects of RF energy exposure on the living organism. Taken together, this makes the Micro-Pulse ICES system by far the most efficient tissue stimulation system available. ICES products can operate on a single battery for many hours or days, with peak energy emission well below 1 watt, a very safe level for use with living tissues. Competing systems usually use hundreds or thousands of watts of energy to achieve typically inferior results when compared with Micro-Pulse ICES technology.

A brief history of the development of ICES DigiCeutical technology

The inventor of ICES technology, Robert Dennis PhD, started consulting for NASA in 1997 to develop systems for stimulating stem cells in culture, intended for use in the zero-gravity environment of space. NASA had requested "a TVEMF system to promote stem cell growth in culture". TVEMF stands for *Time Varying Electro-Magnetic Field*. TVEMF is equivalent to the more commonly used designation PEMF, which stands for *Pulsed Electro-Magnetic Field*. Dr. Dennis had recently completed his PhD and was an active scientific researcher in the fields of musculoskeletal tissue engineering, electrical stimulation of tissues, and *in vivo* tissue engineering. Being familiar with the broad field of literature stretching back to Galvani's experiments in 1790's, Dr. Dennis held the commonly accepted belief at that time that magnetic fields basically had no measurable effect on cell function. In preparation for the NASA work, he reviewed over 650 scientific papers reaching back more than 2 centuries and concluded that magnetic field stimulation of cells was based on very questionable and mostly unreliable, poorly conducted science. As a paid consultant, Dr. Dennis advised NASA against such research because he believed that magnetic field stimulation, no matter what it was called (TVEMF, PEMF, PMF, etc.), was a very sketchy field of research that had been stained by poorly conducted science for a very long time. So he began as a staunch skeptic of PEMF and TVEMF.

The scientists at NASA persisted and eventually Dr. Dennis proposed a series of critical experiments, to be conducted under the strictest scientific controls, to determine once and for all whether or not TVEMF could possibly work. It is important to note that there are over ten trillion (10,000,000,000,000) different possible combinations* of electro-magnetic waveforms that could be used, which is more than a million times the number of known chemical substances on earth, so it is impossible to say conclusively TVEMF could *not* work. In fact the scientific literature has more than 1000 papers demonstrating the beneficial effects of electrical stimulation on living tissues, so we do know that direct electrical stimulation when used properly does promote tissue growth and development. Dr. Dennis had published many papers on this topic himself (LINK TO WEB CV). So the major challenge was to determine where to look within the ~ 10 trillion possible TVEMF waveform combinations. In 1997 Dr. Dennis developed a set of scientific protocols and the necessary hardware for NASA that would separate and group the key electro-magnetic stimulation parameters into 7 reduced groups to divide up the 10 trillion possible combinations. This initial testing was performed at NASA under strict double-blind scientific controls.

The first set of experiments at NASA had surprising results. They showed that very sharp but narrow magnetic pulses did in fact have significant effects on human cells grown in culture. These sharp but narrow pulses tended to influence both cell and colony morphology and gene expression in culture. The results were so stunning that Dr. Dennis insisted that the experiments be repeated before publication, which they were, and the results were confirmed. This study was published partially as NASA Tech Brief NASA/TP-2003-212054. Dr. Dennis was not included as an author as he was considered only a “consultant”.

* 10 trillion combinations of 6 waveform parameters assuming a 10% change in any parameter to be a significant change

The NASA technical paper includes gene expression data and images that show very compellingly that a specific subset of the 10 trillion possible electro-magnetic waveform parameters can be used to influence cell growth without the need to directly conduct electricity through the cells in culture. NASA also patented this very early version of the TVEMF technology (U.S. Pat. Nos. 6,485,963 and 6,673,597). Unfortunately the scientists at NASA failed to include RG Dennis as an inventor, for reasons that remain unclear, so the resulting patents did not accurately capture the TVEMF technology. In 2007 after an internal NASA audit the inventorship issue was corrected to include RG Dennis as an inventor. Because of his exclusion on the NASA publications and patents Dr. Dennis decided to develop and study the technology independently. His contribution is clear: Progress on TVEMF research at NASA stopped abruptly at this time.

In 2001 Dr. Dennis was funded by DARPA to further develop the TVEMF technology as well as to determine the underlying biological mechanisms, that is, to find out why these specific electro-magnetic waveforms had such strong and beneficial effects on living cells. The DARPA- funded project was titled: *Metabolic Engineering Program: Guidance of Gene Expression and Metabolism in Excitable Tissues (Muscle) using Time-Varying Micro-Magnetic Fields (TVEMF),* DARPA federal contract number N00173-01-1-G020. The purpose of this project was to test the effects of very low level magnetic fields, less than100 mG (milli-Gauss), which is far less than the typical magnetic field of the earth, on cultured skeletal muscle cells. The results of this work confirmed the earlier NASA results and gave further insights into the underlying mechanisms of action of TVEMF. Each subsequent experiment brought new understanding.

From 2002 onward Dr. Dennis developed a series of increasingly advanced, portable and effective electro-magnetic stimulation systems for use in the treatment of orthopedic injuries. By this time he had been able to narrow down the search from among the 10 trillion possible electromagnetic waveforms, down to just a few thousand scientifically tenable candidates. Over the years he developed a new theory of operation for the devices which in 2012 evolved into the current theory designated *ICES: inductively-coupled electrical stimulation*. Basically, the theory simply states that *magnetic fields do not directly interact with living cells and tissues*, rather they can be used to *induce* tiny electrical currents around individual cells within a large volume of deep tissue, without the need to use needles or conducting electrodes as are necessary with TENS and similar technologies.

In 2007 Dr. Dennis conducted a double-blind controlled scientific study with veterinarians at Texas A&M university that showed dramatic healing of surgically-induced critical bone defects in the rabbit ulna. This pilot study was never fully completed because the private funding for the study was lost about half way through the study. But the results were very compelling: the critical bone defect only healed when properly stimulated. Also, the veterinarians noted that rabbits that were being stimulated with the device were also much more active than rabbits without the device, a clear indication that the post-operative pain and discomfort was reduced significantly, but only for the rabbits being stimulated. One final observation of the

study was that the stimulation must include a parameter designated the *magnetic slew rate* (this is the first time derivative of the magnetic field, for those who are comfortable with calculus), which must be above 300 kGauss/second to be effective. Any waveform with a slew rate below this value was not effective at promoting healing, but waveforms above this threshold were shown to be very effective. The full range of effective slew rates has been patented. Although the full data for this study has not yet been published, it is available from Dr. Dennis for veterinarians, clinicians, and scientists upon request.

In 2009 Dr. Dennis co-founded a company to market the technology as a PEMF device for use in veterinary practice. Ongoing research and development was intended to ultimately also result in an FDA approved device for human use.

In 2012 Dr. Dennis reacquired full ownership of the technology and intellectual property from his business partners and founded Micro-Pulse LLC. Human trials of the device were conducted in Egypt for use with patients to treat post-operative pain and to accelerate healing after craniofacial surgery. These trials were approved and conducted at the University of Alexandria School of Dentistry, which houses the most advanced tissue engineering research facility in the Middle East. This study had to be abandoned eventually because of the problems associated with the civil unrest in Egypt. But before the study ended it was found that every patient who used the device had dramatically reduced pain and accelerated healing, each achieving approximately 6 weeks healing milestones at only 3 weeks post-operative time, as assessed by independent surgical examination. So the post-operative healing rate was doubled, while pain and discomfort was virtually eliminated. This study will be continued to conclusion when conditions permit.

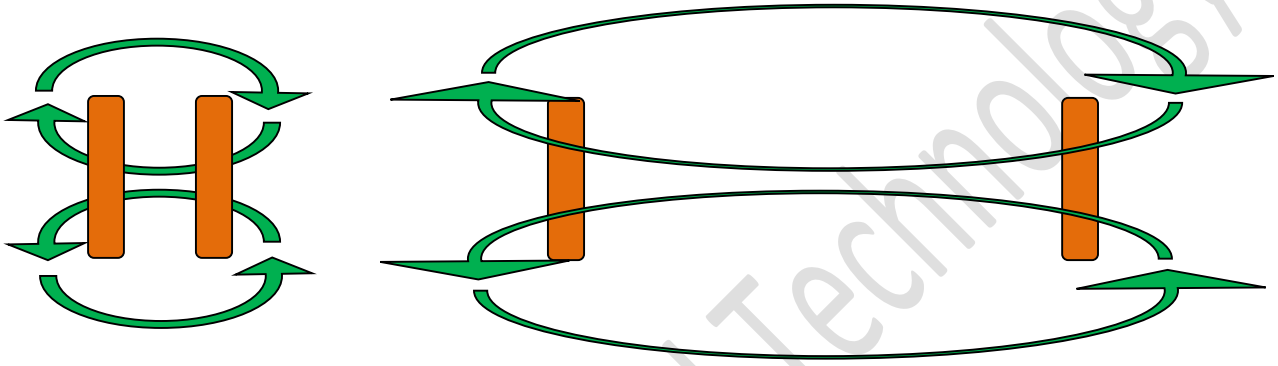
In early 2013 advanced experiments and product R&D resulted in the ICES technology which is currently available commercially as an ultra portable electro-therapeutic device to treat acute and chronic pain and orthopedic injuries. The technology was tested in an animal model at the highly respected independent research laboratory Charles River Labs (CRL) in Research Triangle Park, NC. A summary of the first series of experiments is included below and a complete unedited copy of the independent test results is available upon request. As a brief summary, the lead scientist at CRL informed us that although they had tested many TENS and PEMF devices (specific product names remain confidential) they had never before seen any device that had such a dramatic and significant effect on reducing inflammation and swelling. A summary of this data is presented in this document.

The second CRL study was initiated in early August 2013, and the full report will be made available to our customers upon request. The majority of revenues from our ICES DigiCeutical products is spent on continued advanced R&D, to assure that the product remains at the forefront of the technology.

Possible coil configurations for ICES technologies and products

The primary coil configuration for ICES coils is the Helmholtz coil configuration, as illustrated on the previous page. This is simply placing the coils face-to-face (N-S magnetic polarity is important), with the target tissue in between. Several other coil configurations are frequently used for reasons related to practical clinical considerations. Some of the most common configurations are shown below, where orange shapes are the coils and green arrows indicate the induced magnetic fields:

Coils face-to-face (Basic Helmholtz configuration, and wide-spread configuration with tissue between coils)



Coils side-by-side (Figure "8" configuration or stacked "double coil" configuration):

Individual coil shape can also be changed to achieve the desired magnetic field shape. This is analogous to the complex shapes of wire coils inside electric motors. Basic shapes are intuitively clear but more complex shapes are also practical. These include for example, oval and racetrack shapes, rounded squares and rectangles, and non-planar coils (shaped like a Pringles potato chip, for example). To allow the user to reshape their coils, Micro-Pulse ICES coils are encased in very flexible medical grade synthetic rubber.