THERORETICAL AND EXPERIMENTAL RESEARCH REGARDING MAGNETIC STIMULATION OF THE SPINAL CORD

Scientific description of the project: (Max. 10 pages)

The main goal (maximum 100 words):

The present project suggests how to implement and model some magnetic stimulation procedures, in order to treat the patients who suffer of lower limbs paralysis. The electric stimulation will also be performed to compare and validate the obtained results. The stimulation of the lumber spinal cord, that is responsible for the activation of neuronal structures which control the lower limb movement, is the main objective of this research.

The importance and relevance of the scientific content.

The initial **motive** of this project consists of assistance of paraplegic patients, through the stimulation on magnetic or electric way of the lumber spinal cord, for generating a lumbar locomotive pattern.

Before practice implementation of such a device, is necessary to unfold an intense research and testing activity, which will lead to the enrichment of the existing knowledge in medical, electrotechnical, numerical methods and information technology field. Thus, this project represents **an interdisciplinary research project** with a strong impact over the health. The research will lead towards implementing of the numerical methods in computing the electric field induced in spinal cord tissue during stimulation, and evaluating the nervous response at these stimuli. Because of the problem complexity (the human tissue is extremely non-homogeneous), the only method to obtain a precisely estimation of the electromagnetic field, consists in numerical method implementation in order to determine this field (Method of the Finite Element – MFE, Method of Finite Differences – MFD, etc.)

Severe spinal cord injury can cause the total or partial loss of descending tracts from the brain motor structures to the lumbar spinal cord that is responsible for the activation of lower limb muscles. The result is the loss of control over voluntary movements and the ability to stand and walk. Independently from the spinal cord injury, there are locomotor’s centers within the lumbar spinal cord with the inherent property to control stepping-like movements that still exist below the lesion level.

At the Medical University of Vienna, there is a collectivity who’s working in this field, under the mentorship of Prof. Milan R. Dimitrijevic. The Austrian researchers has been able to prove that lumbar spinal cord electrical stimulation with electrodes implanted in the epidural space (inside the vertebral canal – figure 1, but outside of the spinal cord) could produce functional lower limb movements in individuals with complete absence of brain motor control. They have demonstrated that the human lumbar locomotor circuitries, placed in lumbar area, responded to the electrical stimulation with a constant frequency (25-50Hz) – without any existence of a stimulation pattern - with the generation of stepping-like alternating flexion and extension movements as well as with standing-like extensor patterns. However, the invasive nature of the placement of epidural electrodes has limited this method of spinal cord stimulation to be widely used in rehabilitation practice [15, 16, 18, 23-25].

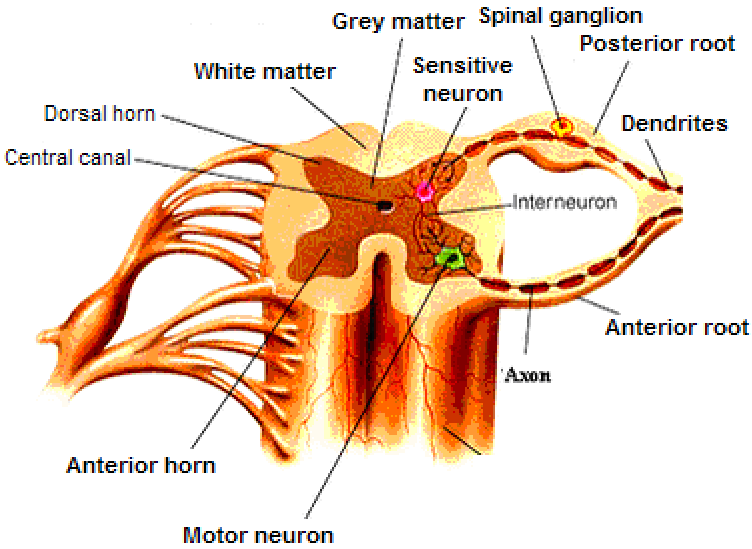


Figure 1: Anatomy of vertebra column and spinal cord

The recent works have developed a novel non-invasive method of electrical stimulation that utilizes surface electrodes and stimulators which are routinely used in physical medicine [12-14, 17, 19-22].

As in the case of implanted electrodes, it was demonstrated that, because of the anatomical area geometry and the electrical properties of the anatomical fluids, the dorsal horns of the spinal cord are not activated but posterior nervous roots placed in lumbar area. Through this non-invasive method can't be obtained the same effect as in the first case, because the intensity of the applied stimulus should surpass the pain threshold of the patient. The studies in this field advance in the direction for neuromodulation of lumbar cord functions to facilitate functional motor activities, including standing and stepping in paralyzed people. One of these techniques, that can produce the expected effects, is the magnetic stimulation, which is a non-invasive method that can directly stimulate the spinal cord, because the electromagnetic field can traverse layers of high resistivity, for example the vertebral bone.

Magnetic stimulation generates an action potential in the excitable cells through an electric current that drives the charged ions to pass thru the cell's membrane. The physical phenomenon of magnetic stimulation has recently entered the neurology field [Polson, 1982]. The magnetic stimulation is based on induction of an electric current in the nervous tissue by placing a coil driven by time varying current over the fiber that needs to be stimulated. The principle is presented in figure 2.

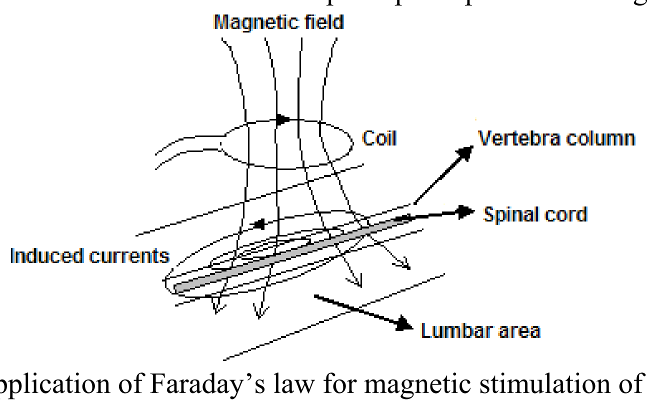
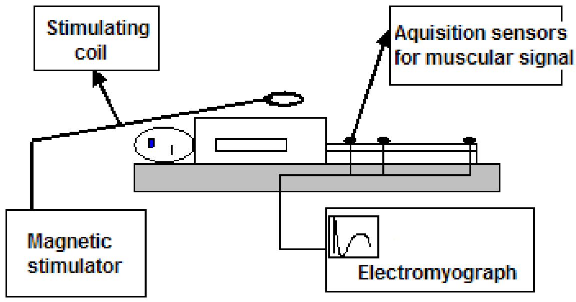
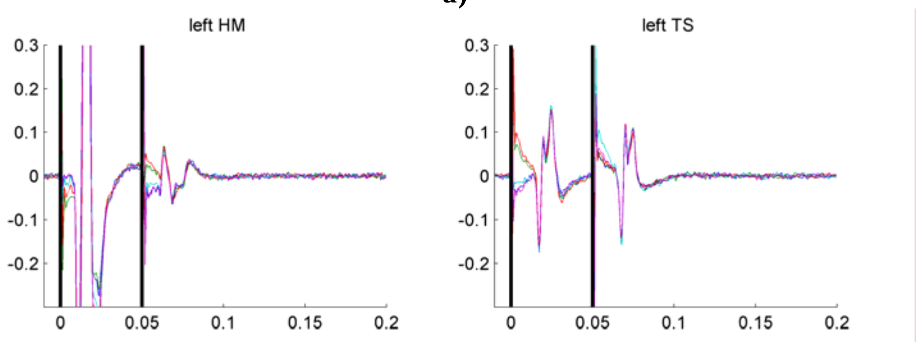


Figure 2: Application of Faraday's law for magnetic stimulation of nervous fibers

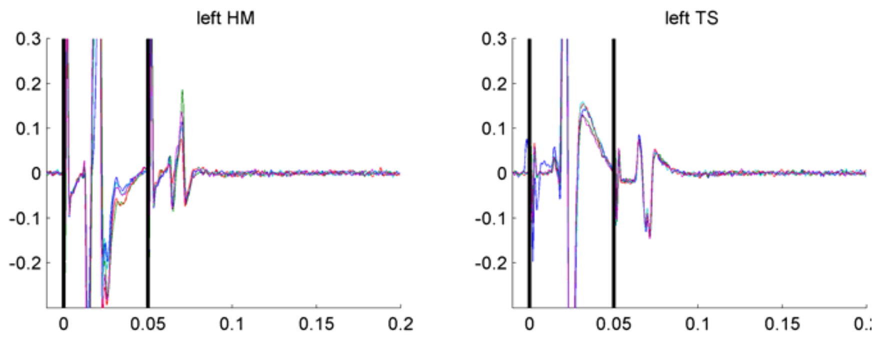
In the latest years, the interest for magnetic stimulation has grown considerably because the method has proven utility and applicability both in diagnostic and treatment [8]. The preliminary tests of the lumbar area magnetic stimulation have proven a good concordance between the results obtained through this method and the same obtained with electrical stimulation. The experiment presented in figure 3 was performed with the researchers from the Medical University of Vienna, whom experience in the electrical stimulation field is very rich [16-25] Figure 3-a) explains the principle of the experiment: a stimulation coil is placed over the lumbar area (in this case, a circular coil was used, placed in the area of T12 vertebra). The nervous impulse generated in this area is propagated through nervous pathways to the hands and feet, commanding muscular contractions of limbs. The muscular response was recorded through electromyography. The muscular response recorded in the area of Hamstring and Triceps surae muscles are represented in figure 3-b). Figure 3-c) illustrates the recording of the same muscles, for the same patient, but in the case of the electrical stimulation of the lumbar area (T11-T12 vertebras).



a)



b)



c)

Figure 3: Experiment realized to determine the muscular response for HM and TS muscles during magnetic stimulation (b) and electrical stimulation respectively (c) of the lumbar area

Figure 4 illustrates the simplest configuration of a magnetic stimulation circuit: the stimulation coil is placed parallel to the tissue, approximated to a conductive semi space, considered homogenous, and the nervous fiber is embedded in this medium. Also, there is depicted the cable model for the nervous fiber, in wich the cellular membrane properties are modeled like an electric circuitry with distributed parameters.

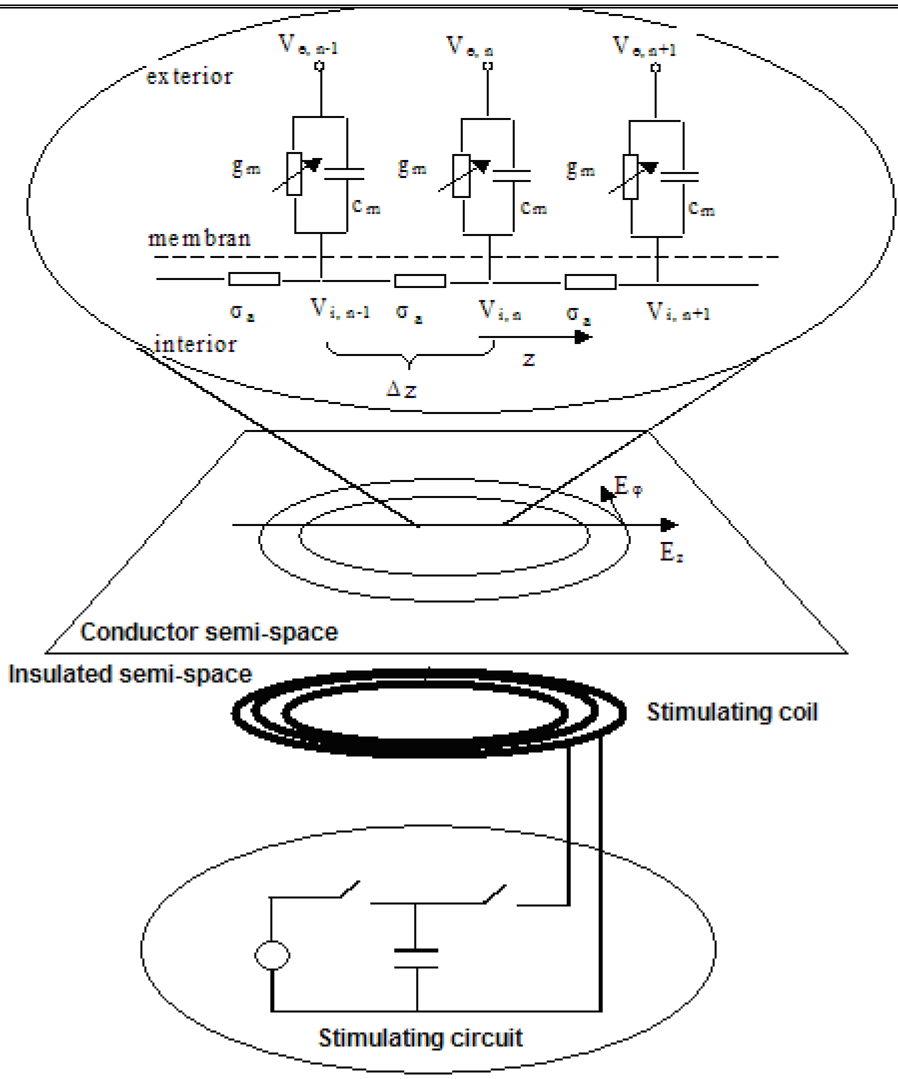


Figure 4: The stimulation circuit [11]

Modeling of magnetic stimulation of nerve fibers can be achieved in a combination of 3 steps:

1. Calculation of the space distribution of induced electric field by time depending variable magnetic field produced by the coil. The distribution of the electric field depends on the geometry of the coil and its determination can be done through electromagnetic field analysis [1], [2], [3].
2. Calculation of distribution in time of the stimulation field by analyzing the transitory regime of the source circuit. The coil is driven by the excitation circuit, witch also contains: the capacitor – element for accumulation of energy from the electric source – and the switches witch control the charging and discharging of the capacitor. The time varying magnetic field – caused by the current that runs through the coil during the discharge of the capacitor – produces electric field in the conductive medium placed in the vicinity of the coil.
3. Modeling the neural substance using compartment structuring and by representing the membrane properties through equivalent electric scheme. Depending on the type of fiber (myelinized or non myelinized), the model and the cable equations change accordingly.

The biological medium modeled, relative to the medical application, can have different idealized forms: semi space conductor for the chest or back, cylinder – for the limbs, sphere – in the case of the head. Depending on the complexity of the model, determination of the induced electromagnetic field in the tissue is done analytically or numerically.

The temporal part of the electric field can be separated from the spatial one. This derives from the premise that the tissue is purely resistive, a correct approximation at the working frequencies. The temporal characteristic of the induced field is described by the rate of change of the current in the stimulation circuit, thus depending on its parameters (the circuit can be modeled as an RLC series circuit – see fig. 4). The effect of spatial and temporal distribution of the induced field can be determined by combining those field calculations with the models of the neuronal structures, incorporating the calculated field into the "cable equation", equation's solution being the transmembranar potential along the nervous fiber.

Concerning the modeling of the nervous fiber, it is done by using a compartment structure. This modeling depends also on the aspects of the neuronal structure: myelinized or not. In figure 4 is described the model for the non myelinized fiber model. In addition to this model, the myelinized model contains the representation of the Ranvier nodes and of the internodes zone included in the myelin casing (considered as a perfect isolator layer [McNeal 1976], or, in other articles as an isolator with losses [Frijsn, 1994]).

The main research directions start from certain minuses of techniques, observed experimentally. We remind the following: week focalization of the induced field high costs of the stimulator – because of very high currents on the order of kA (impulses), significant energy losses because of heating of the coil and low efficiency in energetic transfer between coil and tissue. Current research directions in the world are thus mainly focused on:

- Optimal design of the stimulation coil in order to obtain a better energy transfer from coils to the stimulated tissue (from design) [4-6];
- Modernization of the stimulating circuit through increasing the efficiency of the stimulating coils [10];
- A more realistic modeling of the biological medium (non linear and inhomogeneous) with the aim to obtain correct analytical and numerical solutions, witch produce results as close as possible to the ones determined experimentally [7-9].

Theoretical contributions included in this project are in the frame of present researches tendencies. Nevertheless, about the stipulated computer simulations and an adequate design of the coil for this specific medical application, the experimental estimations will bring an important practical contribution.

To further enhance rehabilitation of locomotor's capabilities; the availability of a clinical system for spinal cord stimulation can become an important assistive device for retraining of standing and walking. Even if the final objective of researches cannot be reach (the complete regainment of control over the lower limbs), this technique can be used to train the unused muscles and to maintain their functionality.

From the point of medical view, the neurologists from medical clinics of Cluj-Napoca have already express their availability in testing these devices in volunteers.

In what concerns the practical applicability of the method described above, appears evident the fact that the main beneficiary are the medical institutions and the patients they are treating. Till now, the complete recovery of patients who suffer of spinal cord paralysis wasn't possible, therefore any contributions are very important and it should support and finance.

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Objectives, methodology and expected results of the project.

The main objective of this research project is the modulation and testing of a new treatment technique: magnetic stimulation of spinal cord for patients with lower limbs paralysis. **In Romania**, this technique was never implemented or applied until now. **On a global scale**, the scientific papers mention different clinical studies comparing the effect of functional electrical and magnetic stimulation over paralysis patients. Nevertheless, it has be mentioned the in the paper [16], developed at the Ludwig-Maximillians University from Munchen, is tested technique of direct magnetic stimulation of peripheral nerves, that activates the muscles of lower limbs (coils are placed on the patients feet).

The majority of these techniques are still in the experimental status, even in other countries still working to solve different technical aspects that this project is also trying to solve. Hereby, **the research objectives** can be **synthesized** as follows:

- Computation of the spatial distribution of the electric field induced in the spinal cord and in the adjacent tissues by the magnetic stimulation. It tries to model, as accurately as possible, the biological media, for different shapes of the target tissue (half-space conductor – thorax modelling; two (or more) concentric cylinders – the column vertebra and the spinal cord – in the case of more concentric cylinders can be simulated the cerebral-spinal of high conductivity, etc…). The model that includes non-homogeneities of the human body represents a step forward for the future researches [1-3, 10].
- Actualization of the cable model by taking into consideration the modification of cell's membrane properties along the neural fibber and its geometrical irregularities and taking into account of an activation function (the axial derivative of the induced electric field along the nervous fibber).

When the cable model was proposed [Hodgkin, Huxley - 1952], [McNeal - 1976], they took into consideration several simplifications hypothesis, in order to permit the passing from a three - dimensional model to this one - dimensional model. The re-evaluation of those hypotheses, in the light of the last experimental determinations, is the base premises for improving this model.

First, the natural undulation of nervous fibbers - although known for over 200 years, is in general neglected. Few bibliographical articles consider this undulation as " a sinusoid of variable frequency and amplitude", with wave length between 0,1 - 0,4 mm [Haninec,1986], or a sinusoid wave, with the undulation wave length between 0,1 - 0,3 mm and amplitude between 0,02 – 0,05 mm [Zachary,1993]. The most recent bibliographic reference in this field [1], referees to the modelling of the nervous structure starting from a perfectly straight fibber and reaching - step by step - to a sinusoidal form with amplitudes up to 0, 2 mm and wave length between 0, 2 – 5 mm. This undulation is modelled in plane, suggesting a further study for modelling the nervous fibber as a three dimensional spiral.

Adding this two modifications into the cable model give us the decrease of the activation threshold of the nervous cell up to five times over the classical model [2].

Another two hypotheses which are imposed to be considered, is regarding the modeling of the nervous fiber as infinite long and with uniform membrane properties all over the fiber.

The first hypothesis can be considered correct in the case of peripheral nerves, because the length of these nerves is at least five times greater than the distance between the stimulation coil and the fiber. The problem occurs when the cortical stimulation is studied. Thus, Nagarajan in [7] states that it is absolutely necessary to use two supplementary differential equations in order to describe the transmembrane potential at the ends of the cable.

As far as the consideration of the membrane properties as being constant along the fiber, [Struijk, 2000] reaches the conclusion that the excitation threshold to the models that include the alteration of the membrane parameters differs up to 20 % from the standard model (for the variation of a single parameter).

- Modeling of the active dorsal nervous roots. On magnetic way, the efficiency of the energetic transfer from the coil to the tissue is realized through the optimal design of the stimulating coil and the influence of the coil geometry over the excited tissue. This way, the design of different coils geometries is tried in this project, in order to permit a better focalization of the induced electric field, through the control of amplitude and stimulus localization. Till now, the optimization of coil shape was realized relative to the value of the induced electric field [3, 17], so the present project proposes this optimization relative to the proper nervous fibber activation (this phenomenon represents the object of the research, and this is not an intermediate like the value and distribution of the induced electric field). Of course, the optimal design of the coil is a very difficult problem which involves solving the electromagnetic inverse problem and the use of shape optimization algorithms (e.g.: genetic type).
- Comparative analysis of different types of stimulators, by: inductivity calculation, dimensioning of the impulse generator in order to obtain the best repeating rate of the stimulus, determination of the circuit's electric energy consumption and the dissipated magnetic energy in the coil and control of the coil heating. The experience of the director project in this field is great, her results can be verified by analysing the list of the articles presented and published at prestigious scientific manifestations in the bio-engineering field [18-20].
- Once the optimal geometry of the stimulating coil for this specific application is determined (all scientific papers in the field [11] stipulate that every medical application determines the proper configuration of the applicator, there isn't a valid solution), the present project centred upon elaboration of the technical project concerning the practical execution details of this coil. Our objective is not to produce in our country such a coil because of its high complexity (turns position inside the coil must be accurate determined, so that the coil can support the high transient values of the stimulated currents, the intense electromagnetic forces inside the coil). Magstim Company, producer of the magnetic stimulator from our University, can provide a practical realization of such applicators, in accordance with clear specifications elaborated by research institutes. Moreover, there is a good compatibility between the existing stimulator and the coil that will be produced.
- A great part of the time of this research project will be dedicated to practical experiments of the described method. The project director has already participated to measurements, effectuated in Cluj, together with specialists in functional electric stimulation from the Medical University of Vienna. This first experiment consists of testing muscular reactions (recorded through electromyography) to electric and magnetic stimulation of the lumbar spinal cord. The obtained results make obvious a good accordance between these two distinctive methods. Nevertheless, an essential criterion is the

repeatability and generality of the obtained effects for a lot of patients. That's way, these experimental studies are laborious and of long durability. The final purpose consists in obtaining the movements of standing and walking for paralyzed patients.
- From medical point of view, neurologists from Clinics in Cluj expressed their interest in the therapeutic results quantification for neurological and psychical diseases, reminded through clinical studies

Besides the existing magnetic stimulation coils, the purpose of the project manager is to bring **improvements** by performing an intense researching activity.

A field computation tool, specific for the medical application to which the stimulator is designed, is foreseen. This instrument will allow for the evaluation of the electric field induced in the human tissue (both location and amplitude), depending on the coil's configuration. This way one can estimate the stimulus beaming, and if its duration and strength are sufficient to producing the activation of the nerve fiber. The behavior of the nervous fiber will be studied using the cable model, which the director of the project hopes to improve according to the project objectives.

The other scientific contributions, the project wants to bring in, mainly refer to achieving **the optimization of the energetic transfer from the coil to the nervous tissue**; **different new configurations of the stimulation coil** will thus be tested and **optimal geometries will be determined**, depending on the intended medical application.

Also, depending on the evaluated stimulator's performances, the dimensioning of the stimulating circuit can be finalized. The results of the theoretical studies will be validated through laboratory tests. Depending on the results of these tests, the settled optimal coil configurations can be patented and the information will be disseminated in the whole scientific community, in order to implement the obtained solutions technique to medical clinics.

The high complexity level of the project (electromagnetic field computation, modeling of coupled problems, field-circuit, electric-thermal field, coils design, design of the electric circuit of the stimulator (in the model phase), laboratory tests, identification of potential applications of this technique in medicine) requires an experience and ability that the project director has already proved.

To develop the new technology in Romania, it will be used:
- Existing endowment of the University with computation and numerical data processing equipments, and high performance medical instruments
- Computation tools for modeling, calculation and visualization of the electromagnetic field, developed in scientific software (MATLAB, MATHEMATICA) and implemented models in engineering tools (FEMLAB, COMSOL, MAXWELL 3D)
- Effective experience and competences of the project directors who worked in this field and obtained outstanding results, published at national or international conferences. During some learning stages performed abroad, the project director worked in the magnetic stimulation field, having a practical experience in this field, too.

The absolute novelty of the implementation of this technique in our country will involve the training of the medical personal for adopting the method and using it on a large scale.

The present project wants to bring to Romania a new, noninvasive instrument for diagnostic and treatment. Before its implementation, several research and testing activities will be performed, increasing the existing knowledge of medical science, electrotechnics, numerical methods and information technology. Therefore, this is a real complex project with a high impact for health.

According to the project's course, the intermediate results can be verified on the basis of some **criterions** ("**indicators**"). Among these:
- Confrontation of the induced electric field results with the ones obtained by worldwide outstanding research teams (CWRU Cleveland-USA, University of Sheffield-England)
- Improved configuration and optimal design of the stimulation coils, superior effective power of the energetic transfer from the coil to the tissue
- Realization of a configuration for the magnetic stimulation coil adapted to a specific medical application
- Publication, in journals or international conferences, of an average number of two papers/year (which will confirm the novelty character of the papers).

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Degree of originality/novelty/innovation and expected impact of the project.

The approach of the problem is original since, until now, electrical and magnetic stimulation were never combined in solving a medical problem (it is considered that each method has its own area of applicability). Although these methods use distinct stimulation techniques, they may be combined to obtain improved results.

This research problem implies a highly multidisciplinary character of the activities. Knowledge are needed from: the theory of electromagnetic field, computer programming (software), medicine (anatomy), numerical methods, engineering.

The problem is solved in a modern way: The first step consists of modeling magnetic stimulation and performing a set of computer simulations to anticipate the way the human body will respond to this stimulation. These computations also permit an optimization of the electrical devices used in magnetic stimulation, in order to increase the efficiency of the stimulation and reduce possible negative side effects (pain, local heating, etc.). Validation of obtained theoretical results is done by experiments (clinical studies).

The novelty brought by this project consists in performing a magnetic stimulation of the lumbar spinal cord, another procedure than the one used until now (electric stimulation). This one can lead to positive results given the characteristic of electromagnetic fields to pass even through highly resistive layers (such as the vertebral bone). Considering that the problem approach is new, both scheduled simulations and experiments represent a novelty in this area. We do not mean that such computations of induced electric field inside the tissue were never performed before (even the PhD thesis of the project manager, as well as her paper and research projects are focused on such computations), but this specific medical application requires a particularization of the software for the problem geometry (determined by the anatomy of the area). The stimulation protocols that are to be used are also new; very few specifications are present in the literature [Gerasimenko, 2009].

Considering the objectives of this research project, one can fairly say it represents a joint effort of medicine and engineering to improve people’s health (rehabilitation). The project answers to a highly important goal expressed by the European Commission.