

# Extended use of superconducting magnets for bio-medical development

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## Abstract

Magnetic fields interact with biological cells affecting them in variety of ways which are usually hard to predict. Among them, it was observed that strong fields can align dividing cells in a preferred direction. It was also demonstrated that dividing cancer cells are effectively destroyed by applying electric fields in vivo with a success rate dependent on the cell-to-field orientation. Based on these facts, the present note aims to suggest the use of magnetic and electric fields for improved cancer treatment. Several possibilities of generating the electric fields inside the magnetic field volume are reviewed, main tentative approaches are described and discussed. Most if not all of them require special magnet configuration research which can be based on existing magnet systems in operation or in development.

## 1 Introduction

Developments in High Energy Physics (HEP) have significant impact on our society though it may not be well realized. For understandable reasons, the most recognizable and appreciable contributions are arguably in the field of medicine. Particle beams are used for cancer treatment, isotope production and equipment sterilization ; particle detectors are used for imaging diagnostics (PET scanners) and strong superconducting magnets (typically researched and then produced “en masse” for HEP accelerators) are used in magnetic resonance imaging (MRI) systems. The significance of these applications and the fact that they, inevitably, rely on interdisciplinary knowledge and support of sciences can not be overstated. Such an interaction is healthy for the respected fields and is probably a key for faster progress in many areas of life and science. Not least it is much better accepted in view of the public opinion than pure field applications which is important for the support of fundamental studies.

One of the mentioned contributions of HEP is the development of magnets of variable complexity. Such devices are part of MRI which guiding principle is basically based on the re-alignment of (hydrogen) nuclei in a magnetic field. This effect is well founded and precisely calculable. It is much more difficult to predict and even more to calculate what the bio-physical effect of magnetic field on living organisms would be. Experiments conducted on living organisms in fact show that at least some form of bio-cell alignment is observed in many cases. These include but are not limited to red blood cells [1], smooth muscle cells [2], nerve cells [3], bone (collagen, osteoblasts) [4, 5], bio-crystals (in fish and algae) [6], frog eggs [7], yeast [8] and even particular cancer cells studied [9]. The studies suggest that stronger the field strength better the (average) cell alignment with it. This is not surprising by itself as any (diamagnetic) material but also ion flow would react to a sufficiently strong magnetic field.

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Symmetries in cells are what makes the process worth the attention in this note. Quickly dividing cell cultures, like yeast, are of particular interest as dividing cells by definition possess clearly defined symmetry axes. The fact that such cells align is easier to observe, explore and apply to cell populations sharing similar features. Analogy to cancer cells is implied though ultimately every cell culture of interest needs to be tested.

Fairly recently it was shown that alternating electric fields, above some intensity and with optimal frequency, fight cancer [10]. It was also emphasized that the effects (albeit with hard to strictly prove underlining mechanisms) of cell proliferation and cell growth rates were dependent on the cell alignment to the electric field. It is clear that if cell orientation could have been enforced results from electric field exposure would have been improved as well. Magnetic fields can be used as such an alignment tool. However they are much more than that - they themselves can induce the electric potential needed. Magnetic fields present the opportunity to enhance the applications and extend of cancer treatment by exploring the intrinsic physical duality of the electro-magnetic field.

It is fair to shed some light on the interaction between magnetic fields with living organisms. It is generally agreed there are no lasting effects of fields up to at least 8 T on individual cells, cell structures or metabolism (see for instance US Food and Drug Administration /FDA/ Guidelines in [11]). However variety of significant temporary effects do exist and in some cases cell cultures are severely affected. Effects are discussed in ref. [12], [13], [14], [15], [16], [17]. Complete systematic studies on the effects of magnetic fields (strong dipole, gradient, variable/pulsed) on living tissue are in fact not available. As the reviews referenced also suggest, magnetic fields by their own affect cancer growth though studies are incomplete and inconclusive. It is worth emphasizing the value of such investigations - they are a likely by-product of the type of studies suggested by this document.

The current note discusses particular applications of strong external magnetic fields, in combination or not with electric and acoustic fields, to quickly expanding (dividing) bio-tissue. It is argued that they greatly enhance the available approaches to fight cancer given already proved mechanisms of anti-cancer action. It is also argued that a successful development requires technological research on magnets as well as extended collaborations with expertise in variety of fields in science.

## 2 Targeting the process of cell division

One of the main discriminators between cancer and non-cancer cells is the continuous rapid reproduction of the former and thus the fact that cancer cells are much more often in a state of division. Targeting cell/nucleus division (mitosis) and the structures supporting it was recognized as an anti-cancer tool long ago (see [18]) and various approaches along this line were explored. More recently it was suggested that the targeting can be accomplished by alternating electric fields [10]. Indeed, the method (a.k.a TTF or Tumor Treating Field) is now accepted in the USA by the FDA and in other parts of the world. The suggested physics explanation behind the success of this new treatment has to do with the inhomogeneity of the induced electric field inside a cell during mitosis together with the natural alignment of highly polarized molecules and likely the ion flow in the process. As a result of applied field of  $\sim 1$  V/cm, with a chosen frequency of hundreds of kHz, extended period for the mitosis and ultimately cell death were observed. As it was emphasized the field achieved slight alignment of the cells but overall multiple sources from different directions had to be applied to mitigate the effect of random angle distribution. As demonstrated and as expected cells aligned to the direction of the electric field were most susceptible to destruction.

The TTF method shows (overall) the same success rate as drugs (chemotherapy)<sup>1</sup> and in combination they are shown to improve the medical outcomes [19]. Most treatments, even if very successful, could not continue indefinitely for variety of reasons. It is worth emphasizing a general feature of tumor masses that makes them hard to deal with. Starting with relatively small number of cells the number grows exponentially but as cells have to compete for resources (like limited number of blood cells feeding them) a limit is slowly reached for that cell culture. Although there is no universal description for the process the Gompertz model can be used to approximate it [20]:

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<sup>1</sup>However there are much less adverse effects with TTF and thus the quality of life is better.

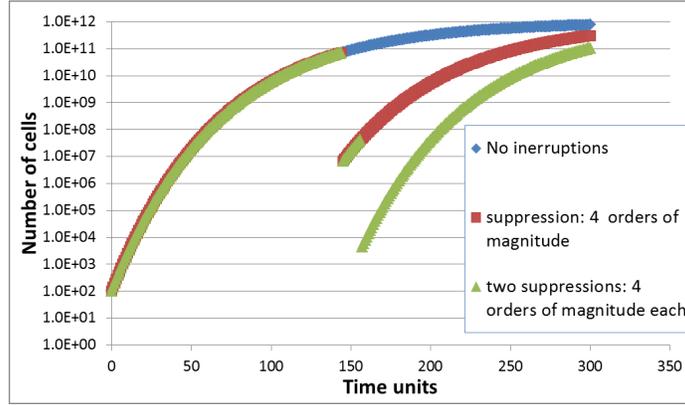


Figure 1: Uncontrolled cell growth according to the Gompertz model (see text) with parameters  $N_\infty = 10^{12}$ ,  $B = 10$  and  $C = 0.015(\text{time unit})^{-1}$ . Two instantaneous suppression models are shown together with no suppression model. The figure is for illustrative purposes only.

$$N(t) = N_\infty e^{-Be^{-Ct}} \quad (1)$$

, where  $N_\infty$  is the asymptotic limit,  $B$  defines the initial condition,  $C$  is the growth rate and  $t$  is time. Figure 1 compares the cell growth development for unperturbed population and two cases with one and two instantaneous population reductions of 99.99% (each is a “4-log-kill” which would be considered a very very successful outcome). Not only the population quickly recovers but, as the growth rate depends on the population, higher the kill rate quicker the recovery rate! Such a figure suggests why only a complete cancer cell obliteration is a long term remedy.

### 3 Magnetic field applications

There are studies showing that the magnetic field - constant, gradient or alternating (or pulsed) - itself could have anti-cancerous effect. A review can be found in ref. [12]. The current note is not about these but rather about the simultaneous application of external magnetic field for proper cell alignment and an electrical field, external or not, on the sensitive cell ingredients. As mentioned, in first order even very strong magnetic fields are harmless to multi-cell living organisms and field strengths of at least several tesla start to impose significant alignment on dividing cells depending on their type. Then considering the presence of magnetic field we find additional ways to induce electric field on or inside the dividing cells and thus disrupt the process of division. Hence the set of available options is enriched and the probability that technological obstacles can be overcome is increased.

There are more subtle points about (dividing) cell orientation that are best to be understood when a technique is developed. Even though preferred orientation is statistically confirmed in cultures we ultimately need all cells to be properly aligned. In order to do that an understanding of the process for individual cells is necessary. As observed in many cases a cell division plane follows symmetry laws - the cell orientation in absence of external forces depends on the cell orientation of the previous generation(s). Ref. [21] presents a mathematical model of cell division orientation from generation to generation for a particular culture (frog eggs) with or without influence of magnetic field. Cell orientation is modeled following observations. A more detailed practical method for mitotic spindle orientation analysis is suggested in ref. [22]. It is important to find how much in common different relevant cultures have and more importantly to try to understand where differences from physical point of view come from. Models describing the effects of magnetic fields and possibly understanding of the processes would allow for much better planning of the type and strengths of magnetic fields needed to exert an optimal alignment effect on the cultures in question. Throughout the text we will neglect these fine but important details and just assume that the magnetic fields orient cells with some (high) efficiency.

The electric field applied in the TTF method acts best when dividing cells have their division plane perpendicular to the electric field direction. However it was also shown that there were significant effects on cells even when the electric field was parallel to the division plane. This brings up two important points. Ideally a magnetic field aligns dividing cells such that the division plane is perpendicular to the field direction. Then an electric field would be applied that is perpendicular to the division plane (so parallel to the magnetic field in this case). Both cases are not necessarily unique in all cultures. Although there is seemingly cylindrical symmetry in a dividing cell internal structures may have hidden symmetries. Still it is feasible to assume that the division plane is a symmetry plane. Hence in general a magnetic field is expected to orient cell division planes either perpendicular or parallel (due to internal symmetries) to the magnetic field. Then the electric field disrupts the process of division very efficiently if normal to the division plane, less efficiently when parallel to it and the effect is further suppressed when in mid-angle situation [10]. Combining expectations and observations, we can conclude that for a given culture the requirement is to have the electric and the aligning magnetic field either parallel or perpendicular to each other, with the former most often the case.

### 3.1 External magnetic and electric fields

An obvious though potentially technically challenging approach is the separate application of a strong constant dipole magnetic field and variable electric field. Ideally the only difference with TTF is the presence of (properly oriented) magnetic field. It maybe be difficult to operate a finely tuned electrical device inside a strong magnetic field. If this is the case an option is to apply the magnetic and then the electric field consequently. It is applicable as long as the characteristic times of de-orientation of bio-molecules is much larger than the periods of time with no magnetic field. Typical times of de-orientation of cells are high, often hours [23]. De-orientation of the mitotic apparatus, if misaligned with respect to natural markers, can take ten and more minutes [24]. Thus the approach with variable alignment field should be applicable for cycles of at least several minutes and possibly much more. With or without interruptions in the magnetic field the method is the most straightforward to implement and can be a proof of concept as long as it is rendered technically operational. A drawback of the method (just as for TTF) is that the area where the electric field is applied can not be customized easily and usually includes undesired regions of space.

### 3.2 External magnetic and acoustic fields

It was already suggested that magnetic and acoustic fields can be used together for cancer treatment [25] though cell alignment to the magnetic field was not considered. Acoustic pressure causes molecular movements in tissue and in the presence of magnetic field which is not parallel to the movement direction an electric field perpendicular to both the movement and magnetic field directions is induced. The following equations relate the acoustic pressure  $p$  with particle velocity  $v_{part}$  in a medium and the intensity  $I$  of the ultrasound field:

$$p = Zv_{part} \quad (2)$$

$$I = pv_{part} \quad (3)$$

with  $Z$  the specific acoustic impedance of the medium. For water (and approximately for tissue)  $Z = 1.5MN_s/m^3$ . At  $I = 100W/cm^2$  (the most powerful pulsed devices achieve two orders of magnitude more [26]) one gets  $p \sim 1MPa$  and  $v_{part} \sim 1m/s$ . We associate that velocity to the amplitude of the cell velocity during the cell's cyclic movement under the sound pressure. The following equation gives the induced electric field  $E$  in the cell in the presence of magnetic field with flux density  $B$ :

$$E = Bv_{part} \quad (4)$$

In 10 T field the maximal electric field amplitude is  $E = 0.1V/cm$ . Although it is lower than the minimal external electric field giving the desired effects in TTF it can be regulated by the acoustic intensity and also it should be noted that lower induced electrical fields may be needed to achieve the same results with respect to external fields (where the membrane capacitance plays an important role). This subject can be addressed only experimentally. The point being made is that experimental approaches to resolve the problem are within reach.

To minimize the effect of absorption the ultrasound should be with lower frequency. Even few tens of kHz allows for a fairly well spacial resolution. To maximize the effect in the desired region and suppress it elsewhere multiple (properly synchronized) acoustic sources could be used and directed toward the area of interest (as noted in [25] as well). To minimize undesired effects of sound reflection tissue and the front-end of the acoustic device(s) should have similar specific acoustic impedance with air excluded as a medium. One of the advantages of this method is that a small, of the order of one cubic cm, region of space can be targeted by the ultrasound with either crossing collimated beams or a focused beam, leaving the remaining area less affected.

The estimations performed above imply that the magnetic and the induced electric fields are perpendicular to each other. There is clearly an obstacle in the case where the aligning magnetic field and the induced electric field should be in parallel. To resolve this problem we consider a constant aligning dipole magnetic field and a variable (or pulsed) dipole magnetic field in perpendicular direction (that is - a “skew” dipole field component). Then each magnetic and the induced electric fields are perpendicular to each other with the sound direction in parallel to the alignment field. The variable/pulsed magnetic field should be strong enough (order of 1-10 T) and still devised in such a way as to leave the average cell orientation induced by the alignment field unperturbed<sup>2</sup>. Nevertheless when multiple sound sources are used both magnetic fields have contributions to the induced electric field inside the cell creating a more complex distribution of it (with unknown consequences to the cell division process).

### 3.3 Variable magnetic fields

We consider a time-dependent dipole field in the direction of the cell division axis - the case with perpendicular field (“skew” component) was already discussed. Variable magnetic field induces (non-conservative) electric field in the bio-tissue. This variation could be a modulation on top of a strong dipole field and can consist of large amplitude pulses. Modulation of the field will likely mean two separate magnets otherwise technological difficulties will prevail. To give an estimate of the induced electric field we assume that a dividing cell has a characteristic length (diameter)  $d$  and that it defines the relevant sensitive area. The electric field  $E$  induced at the cell is given by

$$E \sim \frac{d}{4} \frac{\partial B}{\partial t} \quad (5)$$

and if we assume that 1 V/cm is the desired magnitude for the induced electric field then 0.1 T/ms rate of change of the field is needed to reach it. This is very much achievable in pulsed magnets where values of tens of tesla are reached within tens of milliseconds<sup>3</sup>. These are one or two orders of magnitude higher than needed for the purposes discussed. The combined effect of the pulsed magnetic field and the constant field should be strong enough to align cells which gives additional degrees of freedom in terms of relative field strengths and variable field frequency and duty cycle. An alternative to this approach is to apply two variable uni-directional magnetic fields - one pulsed with low frequency and another operating during the “non-active” part of the cycle of the first magnet. Such a solution may be preferable with respect to simultaneous operation of the two magnets.

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<sup>2</sup>As mentioned, this can be achieved because the processes associated with cell redistribution are relatively slow

<sup>3</sup>There are many pulsed magnet facilities in the world; one of the leading ones is the Los Alamos National Laboratory in New Mexico - [www.lanl.gov](http://www.lanl.gov)

### 3.4 Gradient and higher order harmonics magnetic fields

Electrical field will be induced by gradient magnetic field in moving bio-cells based on the following relation:  $E \sim \frac{d}{4} \frac{\partial B}{\partial s} v_{part}$ , where  $\frac{\partial B}{\partial s}$  is the field gradient. Typical velocities and achievable field gradients result in orders of magnitude lower electric fields compared to the methods already discussed. Gradient fields could exert additional force on molecules due to their magnetic dipole moments and if any, this is the effect that might be of use in obstructing cell division. In practice large gradients can be created by multipole magnets. Higher order field harmonics themselves are of no direct gain except if very peculiar field configurations are required. We are not considering these here.

### 3.5 Technical aspects about magnets

In the most trivial case a strong dipole magnet with sufficiently large aperture should be able to operate for hours. The magnetic field should be able to reach at least 10 T so that field strength dependent effects could be investigated - this also concerns all other cases later. A high frequency electrical TTF-type device should be able to operate inside the field. There is nothing special about the magnet requirements and as long as the TTF device is operational the configuration can be build by the help of existing magnets or magnet prototypes. In most cases here and later we are implying superconducting devices though there may as well be exceptions (in particular - pulsed magnets).

The first development issue comes with the requirement to have two perpendicular field components with one of them dominant (it should define the cell alignment axis). These fields should be delivered to the same area simultaneously or semi-simultaneously (relying on short period cell immobility). This is not a regular requirement and magnets of such a type should be manufactured. Moreover the second magnet should be either with variable magnetic field or based on high power pulses. Especially in the latter case this is likely to affect the normal operation of the first superconducting magnet. The most probable solution is to operate the two magnets in repeated cycles (thus both of them will be producing variable fields). There are no obvious obstacles to mechanically devise the two magnets fitting together as the two fields are perpendicular to each other. The more challenging task is to resolve potential operational issues.

If we only need uni-directional two-component field this still means two separate magnets as high frequency/pulsed magnets come with much different parameters than constant field magnets (notably - inductance). In effect we search for such a configuration as to produce a modulated magnetic field in the area of interest. This is not a trivial task given the desired characteristics of the field - essentially a strong (semi-)constant component and powerful pulses with the same field direction. It is a major technological challenge to overcome but there is nothing suggesting it can not be done.

The above gives the basic idea of the type of developments needed in order to make further progress. The technological means are available and most often the requirements are away from the edge of technology. To fully appreciate future experiment outcomes we argue that the complete set of options should be considered and tested.

## 4 Research and collaboration

Because of the strong magnetic field required only superconducting devices can be used for tests. Superconducting magnets are typically expensive and not trivial to manufacture and operate. On the other hand existing devices, including very high field MRI and many HEP magnets, would meet the loose requirements for initial tests. As discussed a systematic study requires different types of devices possibly with characteristics to be varied. The optimal approach to this problem is to use facilities that have good expertise and practise with such devices and eventually operate/test variety of them. As already mentioned HEP experiments require huge production of superconducting magnets with different characteristics. It seems a viable collaboration between HEP organizations involved in magnet fabrication on one side and biology/medical institutions on another can be formed. If properly planned such a collaboration will inevitably deliver valuable results and hopefully crucial observations and insights for further development.

Effects of magnetic field on living organisms and on humans in particular are not fully understood and there is no clarity on the safety of strong (including gradient/alternating) magnetic fields. There is a lack of systematic investigation and safety rules guidance does not extrapolate far enough. Yet stronger and stronger fields are tested and some of them are also needed for medical purposes. The point of systematic information gathering, likely needed for performing the studies outlined and thus constituting a by-product, has its own significance. It could easily be a part of a more general systematic research on living organisms in strong magnetic fields though this is not necessarily related to the main subject of this note. It is related however to the mentioned type of collaborations needed to accomplish such a goal.

## 5 Conclusions

We have presented and discussed the possibility of more efficient cancer treatment based on external magnetic, electric and acoustic fields. All revolve around the ability of strong magnetic fields to align dividing cells combined with simultaneous application of electric field to disrupt the cell division. Both effects are known in the literature and in practice. A sufficiently strong magnetic fields are needed which requires superconducting devices and supporting facilities. Several viable options exist to create the necessary electric field and part of them necessitate development of magnets with special characteristics. It was shown that overcoming technical obstacles is within the reach of current technologies. A comprehensive research and analysis implies forming strong interdisciplinary collaborations.

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