Ion Cyclotron Resonance interactions in living systems

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Introduction

The interaction of weak magnetic fields, with intensities on the order of the geomagnetic field, is a very interesting subject that only recently, in the last few decades, has received much scientific attention.

In the late 1970s a number of independent studies showed, counter to scientific prediction, that magnetic fields on the order of the geomagnetic field (GMF) appeared capable of interacting with living things. The first of these was the impressive data on bird sensitivity brought to the fore by husband-and-wife Wolfgang and Roswitha Wiltschko, by Beason and Semm, and by other ornithologists. Quite independently, an epidemiological study by Wertheimer and Leeper found that leukemia in children increased with proximity to the 60 Hz frequencies emitted by power lines, implicating magnetic intensities below 5μT, ten times less than maximum geomagnetic levels. Most critically, an experiment designed by Adey (Fig. 1) and Bawin studying radiofrequency effects on chick brain (Bawin et al, 1978), later modified by Blackman, discovered that calcium transport is profoundly affected when the radiofrequency was modulated by specific extremely low frequencies (ELF). Much of the subsequent research along these lines was not motivated by any interest in geomagnetic interactions, but by health concerns.

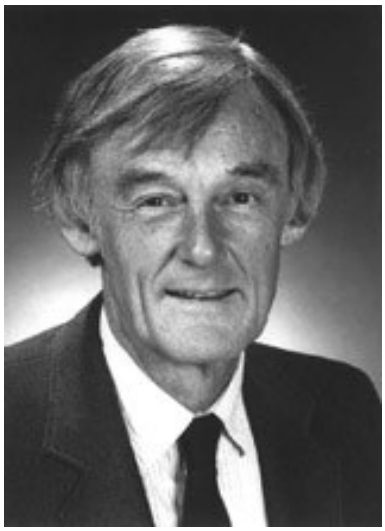

Fig. 1. W. Ross Adey, 1922-2004.
One of the first to bring attention to weak electromagnetic field bioeffects.

These seemingly unconnected discoveries illuminate the puzzling nature of weak-field biomagnetic interactions. On the one hand, there is a large body of literature on animal navigation showing that weak ***static*** magnetic fields are biologically interactive.

On the other hand, there is an equally large body of literature showing that biological systems are sensitive to ELF magnetic fields that are tuned resonantly to various biological ions. It seems that sensitivity to the earth's magnetic field occurs in two very general ways, either from recognition of magnetostatic changes for purposes of navigation, hunting, or other biological advantage, or very differently, from physiological effects connected to low-frequency perturbations of the GMF. In the first case the sensitivity is manifested in the nervous system, but in the second, the ELF effects are system-wide. This dichotomy is reflected in the type of cellular response: whereas only certain cells in the visual system are affected by altered magnetostatic levels, certain low-frequency magnetic fields appear capable of affecting all types of cells.

The first type of effect, the magnetic interaction in the visual pathway, is associated with two distinct types of photoreceptive proteins found in the retina. The opsin and cryptochrome protein moieties are central to the question of sensitivity to electromagnetic fields that is associated with both the biological clock as well as orientation and navigation.

ION	**Q/M** (C/kg) x 10^{-6}	**f/B_0** (Hz/μT)
H^+	95.76	15.241
Li^+	13.90	2.212
Mg^{2+}	7.937	1.263
H_3O^+	5.066	0.807
Ca^{2+}	4.814	0.766
Zn^+	2.951	0.470
K^+	2.447	0.393
arg^{2+}	1.235	0.197
asn^+	0.838	0.133
glu^+	0.747	0.119
tyr^+	0.591	0.094

Table 1 - Ion cycloton resonance frequencies, as derived from the expression $f=(1/2\pi)(q/m)B_0$, corresponding to a selected group of potentially biologically interactive ions. The charge to mass ratios are calculated from handbook values. The third column lists the ICR frequency in Hz for each □T of magnetic field. For example, the calcium ion in regions where the GMF is 35 μT will exhibit a resonance frequency of 26.8 Hz.

For the second type of effect, which is responsive to low frequency electromagnetic oscillations, an extensive variety of cell types have been studied, often in terms of proliferation or calcium uptake.

Mostly effects on lymphocytes and fibroblasts have been reported, but also on tumorigenic lines such as neuroblastoma, bone sarcoma, and HeLa cells. Human leukemic cells included Jurkat, HL-60, and U937. Other human cell types studied electromagnetically include epithelial and cardiac stem cells.

Bone cells (osteoblasts), pinealocytes, thymocytes, liver cells (hepatocytes), and salivary gland cells have all proven to be electromagnetically sensitive.

For the most part, the cells that have been mainly studied were from typical sources such as mouse, rat, rabbit, hamster, etc, but it is clear that human cells, although used less frequently, are equally responsive. A variety of exposure signals have been employed in these experiments, including pulsed magnetic fields (PMF) initially, sinusoidal fields, and later, ion cyclotron resonance (ICR) field combinations. Table 1 is a list of ion cyclotron resonances for various biological ions.

In studying the effects of magnetic fields, different components of the cell's signaling apparatus are probed by cell biologists, with magnetic fields applied instead of the usual added biochemicals or enzymes. A favorite for such experiments is calcium concentration, a well-recognized variable in cellular activity. Thus, many studies have followed the interplay between cellular calcium and magnetic fields. No other cell type has been studied more for its response to weak low frequency magnetic fields than human lymphocytes. These are obtained from blood, with readily reproduced protocols for preparation and culture. One technique is to measure the relative proliferation, with and without field, resulting from certain lectins that are known to act as spurs for cell division. The degree of proliferation is conveniently measured by determining the cellular uptake of tritiated thymidine[*]. In this manner, it was found that low-frequency pulsed magnetic fields (PMF) are able to restore lymphocyte proliferation in aged subjects to levels consistent with proliferation from much younger subjects. The stimulating lectin in this case was PHA (phytohaemagglutinin). This test, normally performed without any specific constraint on magnetic field, is a key measure of immune response in an individual, a measure that is known to fall drastically with age.

∗*Thymidine is one of the nucleotides that makes up DNA. When cells are dividing rapidly, more thymidine is required. In tritiated thymidine, many of the hydrogen atoms are replaced with the isotope of hydrogen,* ${}_1H^3$.

Theoretical difficulties

Although many scientists (Liboff, Chiabrera, Lednev, Blanchard, Blackman, Zhadin, Vincze, Szasz, Pilla, Meuhsam, Del Giudice) have attempted to find a proper explanation for the ICR effect, no one has succeeded.

The original ICR hypothesis by Liboff (1985) suggested that calcium and potassium ions were specifically activated to enhance their transport through membrane ion channels, thereby altering signaling mechanisms and cellular function. However, the notion that cyclotron resonance occurs within ion channels is subject to criticism on physical grounds. Nevertheless, there can be no question concerning the overwhelming evidence that ions are indeed stimulated in a highly specific manner directly related to their charge-to-mass ratios, an atomic parameter that is equivalent to a defining fingerprint.

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The theoretical shortcomings of the ICR hypothesis, coupled to the lack of any other possible explanation, have sometimes been used to deny the extensive research findings that have been reported. Some investigators have chosen to avoid reporting such work as even connected to a resonance effect, instead using other terms to describe the results. Thus one finds some scientists using the term CMF for combined magnetic fields. Others merely provide the parameters of the interactive field, without pointing out that these parameters were chosen because of their resonance capability.

One finds in the literature numerous robust effects of ion resonance exposures on cell culture that are not referred to as such. All of this represents a denial of reality. We continue to use ICR as an umbrella phrase to encompass the many experimental reports showing that biological effects occur when one sets the ratio of magnetic field frequency to magnetostatic field equal to the ionic charge-to-mass ratio.

Resonance stimulation has proven to be a powerful tool when probing the molecular nature of biomagnetic interactions. Quite apart from helping demonstrate that weak magnetic fields affect cells in vitro, one very useful aspect of ICR applications lies in the rational experimental design it makes possible. The ICR hypothesis provides a strong empirical tool with which to probe living cells. There is now undeniable evidence that living things make use of ICR in the way that they function. This means that if we can understand the underlying ICR processes in biology then these processes can perhaps be controlled and used in matters of wellness.

One addition to the ICR picture, first pointed out by Liboff (1997), was that the interaction should work equally well if one uses an ELF *electric* oscillation instead of a magnetic signal. The importance of this is that this implies the possibility of a "natural" ICR effect, that is, one that will occur without any human application of a magnetic field.

Biological pathways

The possibility of such a "natural" ICR effect must necessarily involve the geomagnetic field. A better understanding of the internal cellular processes responsible for cellular responses can also help shed light on the potential for geomagnetic sensitivity. Ishido (2001), examining the melatonin-induced changes in different biochemical pathways, was able to deduce that the effect was traceable to the fact that weak magnetic fields interact with the signal transfer in these pathways.

There is a vast array of signaling mechanisms in living things, with different aspects reflected in the great variety of biochemical reactions found among their organic constituents. Cells have an extraordinary capacity to convert one type of stimulus into another, using cascades of biochemical reactions involving enzymes that are first activated by specific molecules that serve as messengers. It is in this manner that molecular messages such as epinephrine, insulin, and estrogen are employed by the endocrine system. The resulting cascades are referred to as transduction pathways (Fig. 2).

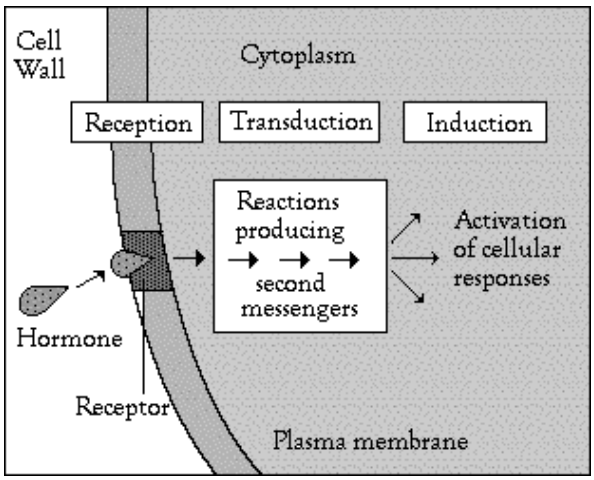

Fig. 2. Hormones such as insulin are used as signals that can interact with specialized receptors at the cell surface resulting in second messengers and reaction cascades within the cytoplasm directing the cell to respond appropriately.

Second messengers are small diffusible molecules, in some cases simply ions, that serve to activate one or more of the individual proteins links making up the cascade. They are primarily involved in processes whereby ions or molecules external to the cell interact with different molecules at the membrane of the cell to signal a large range of specific activities within the cell or within the nucleus. This is achieved either by the presence of specific receptors at the cell surface or channels that traverse the cell membrane. One prominent ionic second messenger is the cellular calcium ion, Ca^{2+}.

Other commonly studied messengers are cAMP (cyclic AMP), cGMP (cyclic guanosine monophosphate), IP_3 (inositol triphosphate) and nitric oxide (NO). Because the experimental requirements for studying calcium effects are rather direct and also because the effects of calcium manipulation are well known in cell biology, many studies on cell magnetosensitivity have focused on calcium.

THE Ca^{2+} ICR RESPONSE

A large fraction of the body's calcium is found in the extracellular space, where it plays a surprisingly active role in conveying information to the cells. One can think of this extracellular concentration as an infinite pool of calcium ions, where changes in concentration involved in moving ions in and out of the cell through membrane channels and membrane pumps are inconsequential, even though slight changes in calcium within the cell are recognized as important information. The vanishingly low cytoplasmic concentrations of calcium are due to the fact that there are also very active membrane pumps acting to keep the cell interior free of calcium ions. There results an enormous difference in concentration, inside the cell and out, a difference that allows whatever slight changes in interior calcium that do occur to be used as signals. Hence the term, *second messenger.*

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It is in this context that attention is drawn to the long list of reports that found calcium-related changes in cell culture due to ICR weak field exposures. A selection of these reports is presented in Table 2. Considering the wide variety of model systems employed, using different cell lines and different calcium-dependent endpoints, it is very clear that weak low-frequency magnetic fields indeed couple to calcium ions in cells in ways that influence cell function. The significance of this q/m signature is borne out by the fact that experiments conducted using isotopic calcium, Ca^{45}, require a 12% change in ICR tuning compared to those merely utilizing Ca^{40}.

One important example (among many) of a calcium messenger-initiated cascade is the activation by calmodulin of cyclic nucleotide phosphodiesterase (PDE) which in turn breaks down cAMP (cyclic adenosine monophosphate) to form inorganic phosphate. This reaction involves two ubiquitous second messengers, calcium and cAMP.

REFERENCE	**FREQ Hz**	**DC FIELD μT**	**RATIO Hz/μT**	**EFFECT**
Smith et al (1987)	16.0	20.9	0.765	Diatoms; motility
Liboff et al (1987)	14.3	21.0	0.68	Lymphocytes; Ca uptake
Rozek et al (1987)	14.3	20.9	0.68	Lymphocytes; channel blocking
Ross (1990)	100	130	0.77	Fibroblasts; proliferation
Rochev et al (1990)	16	20.9	0.765	Fibroblasts; proliferation
Lyle et al (1991)	13.6	16.5	0.82	Three cell lines; Ca uptake
Yost &Liburdy (1992)	16	23.4	0.68	Lymphocytes; mitogen activation
Horton et al (1993)	15.3	20	0.765	Neurons; differentiation
Ryaby et al (1993)	15.3	20	0.765	Chondrocytes; TGF β-inhibition
Fitzsimmons et al (1994)	15.3	20	0.765	Bone cells; IGF-II & DNA
Tofani et al (1995)	32	42	0.76	Lymphocytes; micronuclei
Blanchard et al (1997)	45	59	0.76	Neurites; outgrowth
Gaetani et al (2009)	7.65	10	0.765	Stem cells; differentiation
Ledda et al (2013)	7.65	10	0.765	Cancer cell line; differentiation

Table 2 - Reports of cellular effects due to weak magnetic fields tuned to calcium ion resonance. Note that some studies utilized isotopic calcium, Ca^{45}, requiring a slightly smaller q/m ratio. The charge-to-mass ratio for chemical calcium, Ca^{40}, in SI units is 4.814 x 10^{-6} Coulombs/kilogram.

Calmodulin (Figs. 3,4), found in all living organisms, is a small molecule (16.7 kD) belonging to a unique group of proteins called calcium binding proteins. This type of protein serves as a sort of calcium switch, reacting to changes in calcium concentration by activating or deactivating other molecules. In the absence of calcium, it has four available binding sites for calcium. With increasing concentrations of calcium these sites become occupied altering the conformation of the molecule, thereby allowing it to activate other molecules.

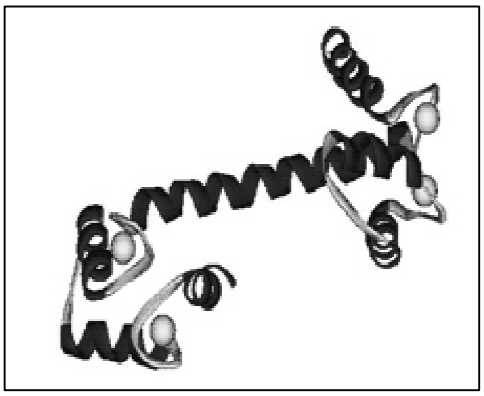

Fig. 3. The calmodulin molecule consists of a middle helical polypeptide backbone and calcium binding sites at either end, indicated here as empty circles. When these four sites are filled, the molecule undergoes a conformational change in shape allowing it to react with other molecules. The net effect is that calmodulin acts as a switch, turning reactions within the cell on and off depending on calcium concentration.

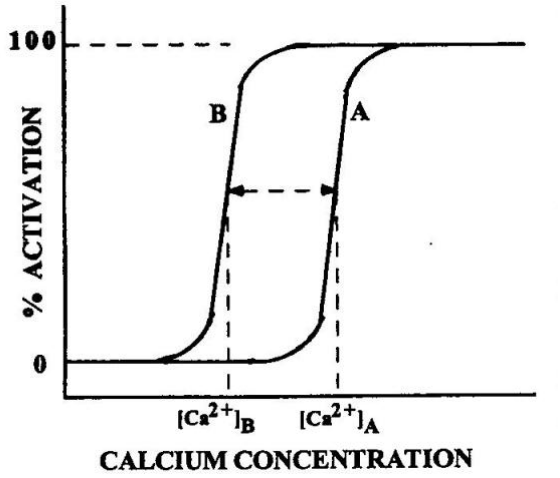

Fig. 4. Hypothetical role of magnetic field in calmodulin activation. Activation curve A is determined at zero magnetic field, where the concentration $[Ca^{2+}]_A$ is required to initiate activation. Exposure to a non-zero magnetostatic field results in a second activation curve B, with the free calcium concentration required to initiate activation correspondingly lowered to $[Ca^{2+}]_B$. (Liboff et al, 2003).

Attention was drawn to calmodulin by Lednev (1991) who proposed an important advance over Liboff's original version of the ICR hypothesis, suggesting that it is the primary site of the resonance interaction.

He invoked an effect called *parametric resonance*, a well-known phenomenon observed in atomic spectroscopy. This approach places the ELF resonance interaction site at the calcium-binding molecule instead of the ion channel.

But, even of greater importance, Lednev's model allowed one to calculate the effectiveness of the local AC magnetic intensity, a consideration that did not appear in the earlier ICR explanation. Thus, when designing a resonance experiment, in addition to making use of the fundamental charge-to-mass signature, one could now also choose a proper intensity for the AC magnetic field.

ICR multiplicity

Another, very different example of weak-field resonance effects involving calcium did not come from cell culture, but has also been linked to a calcium-binding event. This involves a large body of work (Thomas et al, 1985; Lovely et al, 1993 ; Zhadin et al, 1999) dealing with Ca^{2+} ICR effects on rat behavior. The discovery that this behavior is altered by exposure to ICR-tuned magnetic fields led to replicative experiments that examined this effect in greater detail. One of the ways this effect was studied was to also determine the behavioral effect when the ionic resonance was tuned to Mg^{2+} instead of Ca^{2+}. A profoundly different type of behavior results from this change. When the magnesium ion is tuned for instead of calcium, greater aggressiveness and exploratory behavior is seen in rats, compared to increased submissiveness and reduced memory for Ca^{2+} tuning. Lovely, who first reported this difference, made the point that both changes, those associated with Ca^{2+} and those with Mg^{2+}, were each very different from the control condition, where neither ion was stimulated.

This discovery of this strange sensitivity to the species of the stimulated ion, where one can create an opposite result by merely tuning for a different ion, was first demonstrated by Smith in his study on diatoms, when he found an increase in motility with Ca^{2+} tuning and a decrease with K^{+}. Other investigators (Table 3) have also observed this ICR effect.

MODEL	REFERENCE	FREQUENCY Hz	B_0 FIELD μT	ION	RESPONSE
Diatom motility	Smith et al (1987)	16 16	20.9 41.0	Ca^{2+} K^{+}	Motility ↑ Motility ↓
Embryonic bone	Smith et al (1991)	16 16	20.9 40.7	Ca^{2+} K^{+}	Growth ↑ Growth ↓
Plant growth	Smith et al (1993)	60 60	78.3 153.3	Ca^{2+} K^{+}	Growth ↑ Growth ↓
Rat behavior	Zhadin et al (1999)	63 38	50 50	Mg^{2+} Ca^{2+}	Activity ↑ Activity ↓
Gravitropic response	Belova & Lednev (2000)	35.8 54.7	46.5 46.5	Ca^{2+} K^{+}	Direction ↑ Direction ↓
Cartilage explant	Regling et al (2002)	16 16	20.9 40.7	Ca^{2+} K^{+}	GAGS ↑ GAGS ↓

Table 3 - ICR results from a variety of sources showing that opposite outcomes can be achieved by merely tuning to different ions. In all but one case the static field B_0 was less than the GMF intensity.

We have suggested (Liboff, 2010) that this "opposite" effect may point to a property of living things where various resonances are occurring simultaneously, with each resonance properly weighted. One is reminded of the effect in plants where competing pytohormones act in concert, balancing mechanisms of both enhancement and inhibition to reach desired outcomes.

Under the assumption that multiple ion resonances occur in similar fashion, one can write the response R from the simultaneous application of a group of ionic stimulations applied together as $R = \Sigma a_i R_i$, where the R_i represent the partial response corresponding to each of the ionic species and a_i the relative weight of each ionic stimulation. In the most general way, we can associate the various contributions to R made up of the individual ICR frequencies Ω_i, with the result that the overall response becomes

$$R = a_1\Omega_1 + a_2\Omega_2 + a_3\Omega_3 + a_4\Omega_4 + \ldots = \Sigma a_i\Omega_i.$$

Since the general expression for the ICR frequency is $\Omega = B_0$ (q/m), this enables us to factor out the static field B_0 and rewrite R as

$$R = B_0 \Sigma a_i (q/m)_i .$$

This indicates that the overall response to a group of separate ICR frequencies applied simultaneously at a given point on the earth's surface is directly proportional to the local GMF intensity B_0. Therefore, one can also say that the earth's magnetic field plays a key role in matters of biological regulation.

The point has already been made that the oscillatory component of the ICR electromagnetic field combination can be an electric field and, further that the noise distribution of the electric field at the cell membrane may include various ionic resonance frequencies. It is therefore not difficult to imagine that the expression for R given above in terms of the sum of different Ω_i describes a situation at the cell surface where the frequencies Ω_i correspond to electric-field oscillations rather than magnetic.

Recent ICR updates

More recently, two additional ion cyclotron resonance observations have been made. First, it was shown that the cellular effect may be transitory, and second, it was discovered that the ICR interaction continues to be effective down to very small magnetic intensities, well below 100 nT (0.1 μT).

Pazur and Rassadina (2009), while studying the ICR activation of calcium-binding proteins in plants using bioluminescence, showed conclusively (Fig. 5) that the effects of the ICR stimulation only last for about 20 minutes. Application of an ICR signal for a longer period is apparently not recognized by the biological system. It remains to be shown whether this transient response occurs in animals as well as plants. We note that two different ICR therapeutic applications, for bone repair and by Seqex, both suggest treatment times of roughly 30 minutes.

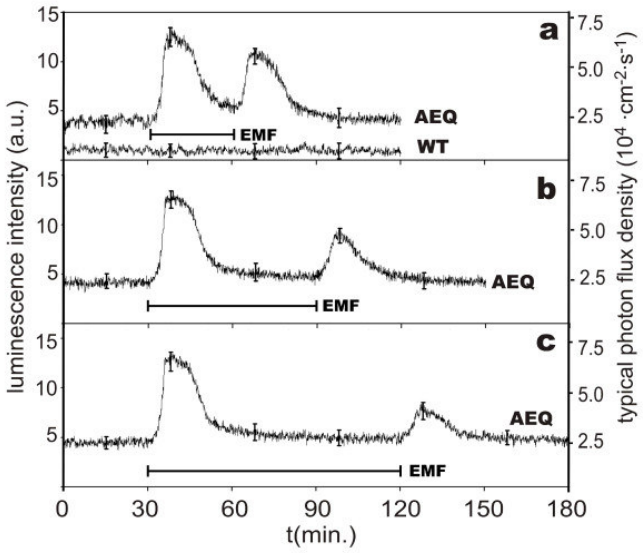

Fig. 5. Cyclotron resonance (50 Hz, 65.8 □T) stimulation of Ca^{2+} in plant cytoplasm is transitory, lasting for about 20 minutes following both application and removal of magnetic field. AEQ refers to aeqourin, a bioluminescent substance expressed in the A thaliana strain used here. (Pazur and Rassadina, 2009).

The second discovery showed conclusively that the ICR effect can occur at ultralow magnetic intensities. This remarkable effect occurs at intensities so small (~40 nT) that special shielding is required to detect this effect; otherwise the background AC magnetic intensity would hide it. This property, discovered by Zhadin (1998) using cell-free substances, has since been replicated in three other laboratories (Alberto et al 2008, Pazur 2004, Commisso, 2006). When measuring the electrical conductivity of polar amino acids such as glu^+, everyone finds a sharp spike in conductivity (Fig. 6) at the ICR frequency predicted by the charge to mass ratio of the amino acid.

This work has now been applied in various ways, particularly by V V Novikov. For example, he used an ultrasmall ICR magnetic intensity to hydrolyze various proteins, i.e., break them up into their constituent amino acids (Novikov and Fesenko, 2001). One very interesting series of reports indicate that this approach is successful in dissolving the □-amyloid plaque found in Alzheimers patients (Bobkova et al, 2005).

The fact that 40 nT ICR magnetic intensities are biologically effective is fascinating. For one thing it is consistent with the apparent magnetosensitivity of birds and other animals, presently believed to be in the 10-100 nT range. It is also consistent with the widely reported effects on humans due to geomagnetic changes resulting from solar storms, effects that include suicides and heart attacks. We have recently suggested (Liboff, 2013) that these very weak magnetic interactions may be linked to the solar response by serving as a surrogate for the clock-like response of sunlight in the upper atmosphere.

Ion Cyclotron Resonance interactions in living systems

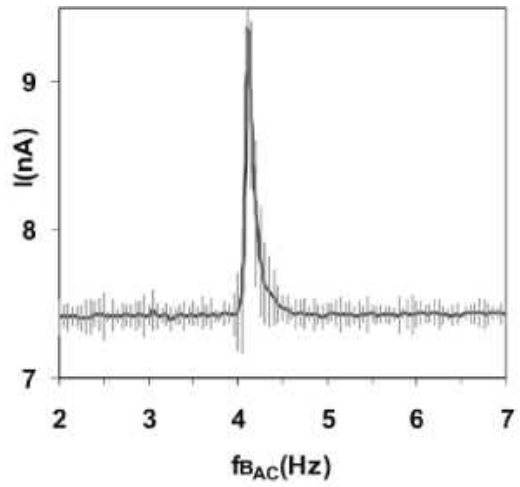

Fig. 6. Typical result showing the ICR response when the AC magnetic field is only 40 nT. The electrical conductivity of glutamic acid ions (glu^+) in aqueous solution is plotted vertically and the horizontal axis shows a slow scan of the applied frequency. The sharp peak occurs at a value very close to the predicted ICR frequency for the charge-to-mass ratio of the glu^+ ion. (Pazur, 2004).

The weak-field biomagnetic responses that were reported by Zhadin and are also found in birds probably stem from early evolutionary recognition of the diurnal change in the GMF shown in Fig. 7. This diurnal change outperforms the sun itself in that it happens independently of cloudy skies. Acting as a back-up for the solar biological clock, this would have lent itself to the development of early magnetic detection mechanisms that, in time, not only would have evolved differently for different genera but would have provided opportunities for additional advantageous adaptations. This concept does not provide an answer to the exact nature of the mechanism, but instead makes it reasonable to think that it must have first appeared in the earliest organisms, perhaps explaining why these effects are found in present-day organisms.

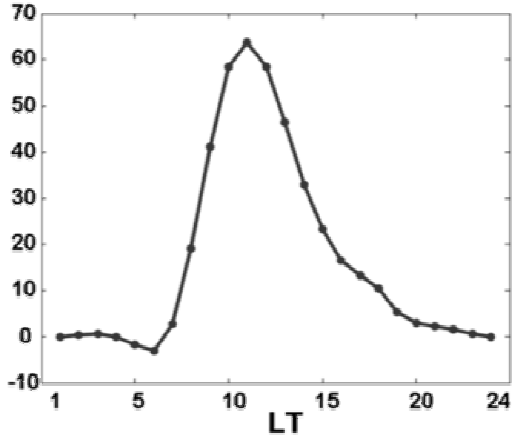

Fig. 7. Change in the horizontal component of the GMF, measured in nT, plotted against local time in hours (LT) clearly showing the 24-hour variation. Change is most prominent during daytime hours, and is measurable only at times when there are no solar storms that can swamp this small (65 nT) swing in intensity.

The Geomagnetic Field as Ausfaher

What does all of this strange data mean? It shows that the geomagnetic field is intertwined with living things in a very fundamental way. It is important to understand that because all of life on earth, since the earliest organisms, has evolved in the presence of the GMF, it is reasonable to think that this field has very likely been used to assist in the evolutionary process, with interactive processes that are as old as the earliest life on earth. In short we should not be surprised to find that there are "natural" biomagnetic interactions .

Our conclusion is that the earth's magnetic field is an ***aufsaher*** for life on earth. That is to say, the GMF supervises the way living things function. In part, it exercises its control through interactions such as ion cyclotron resonance, but this GMF oversight of living things not limited to the ICR response.

Indeed, we find two separate pathways by which the GMF exercises control over living things. The first is through the eyes, where specialized proteins (melanopsin and cryptochrome) in the retina use the ambient *magnetostatic* intensity to help regulate the biological clock and assist in tasks such as bird navigation. There is no evidence to think that the ICR interaction is involved in this process. This type of sensitivity is instead explained through a radical pair mechanism, one that is strictly dependent on the level of magnetostatic field.

In sharp contrast, the second pathway, which can affect the entire body, is responsive to low frequency magnetic oscillations of the sort given by ICR fields. These resonances are determined by the combination of just two things: the local geomagnetic field intensity and the electric oscillations in the cell membrane. This interaction is endogenous, independent of any applied signals except those supplied in nature.

All of this is part of what can be called *geomagnetic homeostasis*, whereby the cellular transport processes for the variety of ionic types in the cell are subject to ICR-directed continuous balancing and adjustment. In this view, *electric-field* ICR acts with the GMF coupling to many different species of ions at the same time, recognizing each ionic type through its q/m signature, while making use of the appropriate frequencies contained in the noise spectrum of the cell membrane's electric field.

The geomagnetic field is therefore deeply involved in the living state. It acts as a universal overseer in two ways, not only keeping all organisms phased into the daily solar cycle but also working continuously to maintain homeostasis at the cellular level.

The big question is how to make use of this response to the GMF. To a small degree we have already succeeded, using ICR in therapeutic ways. But I suspect there are even greater possibilities that are to be derived from the aufsayer interactions. There are undoubtedly important advances in human wellness yet to be made by learning more about how the earth's magnetic field controls life on earth.

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