A breakthrough in Cancer Treatment or Cancer cell proliferation is inhibited by specific modulation frequencies but how and why?? Some new findings and a comprehensive but totally independent explanation of the new cancer treatment device used by Zimmerman et al (2013) see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3845545/ and https://www.therabionic.com/

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First published online 21/12/2018

Abstract

The work of Zimmerman et al (2013) is first elucidated in the context of the history of research into the biological effects of electromagnetic fields (EMFs). Dubost's theory of microtubule resonance has been considered by some to account for the effects of TTF (tumour treating frequencies) and although it could be modified to incorporate solitonic (hence higher Q) behaviour it does not immediately elicit a reason or reasons why Zimmerman observed these treatment frequencies to bring about immediate physiological changes in blood pressure and heart rate, see https://www.therabionic.com/therapy-with-the-therabionic-p1-medical-device/#mechanismoffrequencies. Amongst the questions I answer are:

1. **Is the effect of Zimmerman fundamentally different from that of Kirson?**

2. **What is the mechanism of the effect of Zimmerman -they know they produce multiple effects, but they state they do not know how?**

3. **If ion channels are involved, how ?**

4. **How can the downregulation of both XCL2 and PLP2 be explained?**

In answer it is proposed that a variant of Ion Cyclotron resonance accounts for the precise TTF frequencies involved based on allowing for very high harmonic frequencies to develop upon dehydration due to lowered dielectric constant and conservation of angular momentum within ion channels, the model is developed and tested. The importance of GMF (local geomagnetic field) is emphasised. The system is shown to be different from that of Kirson.

The observed down regulation of XCL2 is accounted for in a putative link between inflammation, invasion and metastasis and intra-cellular Ca2+ ion concentration has been proposed wherein it seems the TTF modulated signal is acting rather like the chemotherapy drug Infliximab and in this case causing Ca2+ efflux or slowing Ca2+ entry, hence downregulating XCL2. Either way the action, brought about by the tumour treating frequencies modulated onto the 27.12 MHz signal is deep within the hydrophobic part of the channel as identified by the high ICR harmonics present.

A distinct breakpoint in the spread of the ICR Harmonics for calcium across the TTF frequency spectrum is observed. This is entirely consistent with the progressive and known and literature documented dehydration of calcium as it passes through the pore and is also entirely consistent with a combination of both the dielectric and angular momentum models which I propose.

TTF's also effectively suppress K+ current giving the link for reduced PLP2 and another explanation of the observed damage to the mitotic spindle. Unlike previous authors which only focus on electromagnetic interaction with calcium ions as a second messenger, it is further shown that all sorts of ion channels and transporters can interact through ICR with their ions and/or ligands.

Overall, simple sequential plots of closest to integer ICR harmonic numbers obtained from both the HCC and the Breast Cancer Treatment file yield 'channelopathy' like results showing break-points at places which can be interpreted as corresponding to those of known dehydration such as the narrow pore and selective filter.

The 'channelopathy' hypothesis is especially reinforced by considering the result for voltage gated proton channels where as expected the plots are essential linear and have no sharp breakpoints.

Introduction

Cancer is one of the major diseases of the 21st Century. To identify drug free modalities for treatment which offer patient convenience, significantly less patient trauma and a link with far better cost benefit analysis seems like a pipe-dream. Nevertheless, there is a new system has been trialled in Brazil for HCC (liver) and Breast Cancer which appears to do just that. Zimmerman et al British Journal of Cancer volume 106, pages 307–313 (17 January 2012) describe how cancer cell proliferation is inhibited by specific modulation frequencies. The Zimmerman et al (2012) study with the group's two preceding papers (Barbault et al, 2009; Costa et al, 2011), identify such a modality. Their set of clinical and explanatory laboratory results which achieve outcomes in metastatic patient prognoses as good as modern chemotherapy regimens and downregulation of two specific genes XCL2 and PLP2 remains to be explained. Indeed, the researchers themselves state that there is presently no known physical mechanism for these effects or their method of therapeutic action. It is my present intention to elucidate precisely such mechanism and to make this work freely available on my website in the interests of open innovation and to the benefit of human kind.

It is thus my present contention that we need to first understand this work in the context of the history of research into the biological effects of electromagnetic fields (EMFs).

The beginning of the 20th century saw the first medical applications of electromagnetic fields (EMF), notably in the diagnosis and therapy of various diseases such as cancer. The assumption was that external application of electromagnetic energy could correct disease-causing altered electromagnetic frequencies or energy fields within the body. Abrams (ref) invented various machines with the goal to cure cancer. However, between 1923 and 1924, Scientific American magazine set up a committee to investigate Abrams's results and concluded "the claims advanced on behalf of the electronic reactions of Abrams, and electronic practice in general, are not substantiated"

Lakhovsky developed the Radio-Cellulo-Oscillator in the 1920s this device produced broad band high frequency (RF) EMF around 150 MHz. He postulated that EMF reinforced "the oscillations of the cell." Although a controversial figure in his time, he seems to have had some success with his treatments (refs).

Raymond Royal Rife hypothesized that a number of bacilli were causal factors in many diseases, especially cancer. In the mid 1930s, he developed a microscope able to see these bacilli and invented the Rife Frequency Generator, commonly called Rife Ray Machine, which he claimed could diagnose and eliminate diseases like cancer by tuning into electrical impulses given off by diseased tissue. Rife's machine produced some 400 watts of output power fed into a gas discharge tube antenna. This would have radiated a lot of soft x-rays and ultraviolet light and being very inefficient as a radio antenna, only about 1 watt of RF. The former, especially the u/v could have instrumental in killing bacteria. Although there were anecdotal reports that he had cured someone's cancer, the American Medical Association later condemned Rife's experiment.

Until very recently, virtually all medical devices aimed at treating cancer using low levels of electric and/or magnetic fields were considered nothing more than quackery because of lack of scientific proof.

Yet EMF has, for some time, also been used as a therapeutic modality for osteoarthritis. Alternating electric fields have been used to induce fracture healing, with suggested efficacy similar to that of bone graft. The proposed action of pulsed EMF in this case is through the induction of directed migration and differentiation of bone marrow-derived mesenchymal stem cells.. Currently, RF EMF is used as a therapeutic option in cases ranging from tibial stress fractures to spinal cord injury. Clearly, such successes are evidence of the start of a paradigm change.

High power Radiofrequency ablation (RFA) is a therapeutic option sometimes used to treat malignancies including breast cancer, colorectal cancer, and hepatocellular carcinoma (HCC), and especially surgically unresectable metastases. RFA has been administered with medical devices operating at numerous different frequencies including circa 500KHz, 2.2 MHz, 13.56 MHz, 27.12 MHz and 915 MHz and delivering therapeutic energy to soft tissues. This modality primarily destroys tumor tissue through heat-induced necrosis by raising their temperature to greater than 45 C and often to approximately 100°C for approximately 15 min.

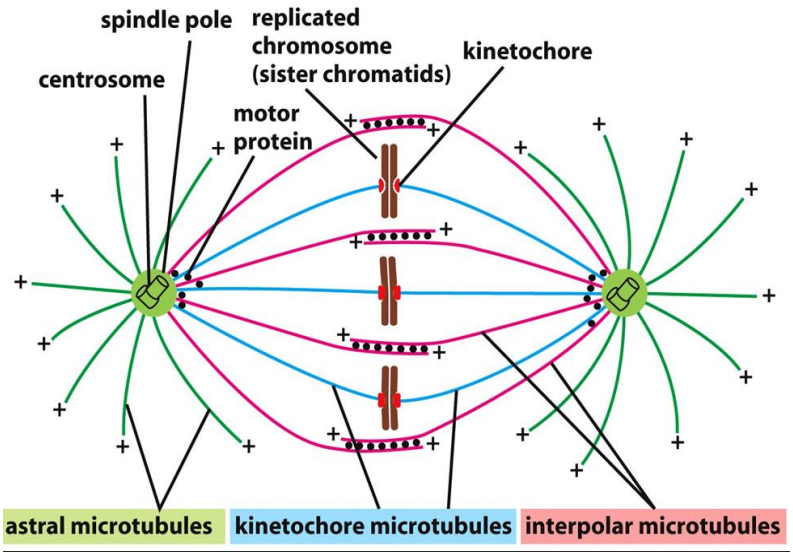
There is a growing body of laboratory and clinical evidence suggests that certain frequencies within the RF EMF range of the spectrum may have antitumor effects without eliciting temperature increase. Such effects are often described as non -thermal or subtle field effects of EMF and RF radiation. Likewise, there is a huge body of evidence that considers the potential dangers of such radiation to biological systems and life in general.

Kirson et al (2004) employed low-intensity, intermediate-frequency (100–300 kHz), alternating electric fields, delivered by means of insulated electrodes, and found them to have a profound inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines. This effect was shown to be nonthermal and to selectively affect dividing cells while quiescent cells are left intact. These fields acted in two modes: arrest of cell proliferation and destruction of cells while undergoing division. Both effects were demonstrated when such fields are applied for 24 h to cells undergoing mitosis that is oriented roughly along the field direction. The first mode of action is manifested by interference with the proper formation of the mitotic spindle, whereas the second results in rapid disintegration of the dividing cells. Both effects, which were frequency dependent, were shown by the authors to be consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. In vivo treatment of tumors in C57BL/6 and BALB/c mice (B16F1 and CT-26 syngeneic tumor models, respectively), resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3–6 days. These findings demonstrated the potential applicability of the described electric fields as a novel therapeutic modality for malignant tumors.

In a second and later study (2007), Kirson dealt with 'Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors'. Their findings on mice led to the initiation of a pilot clinical trial of the effects of TTFields in 10 patients with recurrent glioblastoma (GBM). Median time to disease progression in these patients was 26.1 weeks and median overall survival was 62.2 weeks. The time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes. These were impressive results and they concluded that TTFields are a safe and effective new treatment modality which effectively slows down tumor growth in vitro, in vivo and, as demonstrated in human cancer patients.

Dubost et al (2014) have discussed TTF in terms of microtubule mechanical resonance. The polar and kinetochore microtubules of those cancer cells are 5 to 9 μm long, which provides

good correlation between theory and experimental results using PEFT frequencies of 100 kHz to 200 kHz, i.e. those of Kirson. Dubost also discusses the recent work of Zimmerman et al (refs) where they proposed that cancer cell inhibition in this case is caused by PEFT applied to the straight astral microtubules at their longitudinal mechanical resonance frequencies.



In my opinion, the paper of Dubost is in fact very general and does not account for the manifold yet highly precise combinations of frequencies observed by Zimmerman and Pasche nor does it account for the precise genetic effects observed. Others have noted that microtubules (MTS) and the spaces between act like highly non-linear ionic wires (refs) and I have considered that it may be possible for there to be soliton modes at play here analogous to those proposed by Geesink and Meijner(ref). Pang et al (2016) have experimentally confirmed the existence of soliton modes in collagen in the infra-red and shown a change of binding energy with applied E -field although of course this is a very different frequency range from that considered here.

Sekulic (2011) also considers solitonic ionic waves along the microtubule axis. They conclude that a microtubule plays the role of a biological nonlinear transmission line for ionic currents. They speculate that such currents might be of particular significance in cell division and possibly also in cognitive processes taking place in nerve cells.

Priel et al (2006) propose a new signalling mechanism in the cell, especially in neurons, that involves clouds of ions surrounding protein filaments which may travel without significant decay along the axon or the dendritic tree. Further they state that these signals could be utilized to control various membrane properties, for example, the transition rate of ion channel opening and closing, local membrane conductivity, and vesicle trafficking.

Dubost's theory does not immediately elicit a reason or reasons why the treatment frequencies bring about immediate physiological changes in blood pressure and heart rate, see https://www.therabionic.com/therapy-with-the-therabionic-p1-medical-device/#mechanismoffrequencies.

I propose that ion channels must be involved. Potentially Priel holds the link but I intend to explore that in much more significant detail in a future publication.

Clearly thus there are questions which need urgently to be answered in order to bolster credibility for this potentially, crucially important treatment technique.

The work of Zimmerman et al differs from that of Kirson in that the fundamental applied radio carrier frequency is some two orders of magnitude or so higher and in that the former also applies a range of complex and very specific modulation frequencies. The frequencies were first discovered by Barbault et al (2009). The questions I shall attempt to answers are as follows:

1. Is the effect of Zimmerman fundamentally different from that of Kirson?
2. What is the mechanism of the effect of Zimmerman -they know they produce multiple effects, but they state they do not know how?
3. If ion channels are involved, how ?
4. How can the downregulation of both XCL2 and PLP2 be explained?
5. Is there a way other than the hypothesis of Dubost for explaining the mitotic spindle effects?

At first sight the Zimmerman et al rationale for use of AM modulated 27.12 MHz frequencies for the treatment of cancer seems a little odd. It was based on previously identified several frequencies in patients with chronic insomnia using biofeedback methods. They had demonstrated that the intrabuccal administration of very low and safe levels of 27.12 MHZ (100mW) MHz RF EMF, amplitude-modulated at 42.7 Hz, has a sleep-inducing effect in healthy subjects. However, administration of the same signal to patients with insomnia did not yield any therapeutic benefits. In contrast, administration of a combination of the four frequencies most commonly identified in patients with chronic insomnia (2.7 Hz, 21.9 Hz, 42.7 Hz, and 48.9 Hz) resulted in significant improvements of total sleep time and sleep latency as assessed by polysomnographic evaluation. It is interesting to note that these modulation frequencies are very similar to those employed in biological experiments which have showed frequency, field, and power windowing effects in response to the interaction of either ELF or modulated RF with tissue (refs) and which have been interpreted in terms of the theory of Ion Cyclotron Resonance (ICR) or theoretical derivatives thereof (refs). Taking into account that these experiments were performed in Brazil where the earth's geomagnetic field is of the order of 26 micro-Tesla, it is my view that the frequency of 2.7 Hz is especially poignant. It calculates to be exactly the ICR frequency for the amino acid L-tryptophan the most essential for sleep especially in subjects with insomnia or increased sleep latency, see Hartmann (1982).

They then go on to state that the frequencies discovered with cancer patients were not the same as those effective against insomnia. Further they state that the frequencies were postulated/discovered by Barbualt in an earlier study which they reference as 2001. Every search on the criteria given yield the paper of Barbualt et al (2009). https://www.researchgate.net/publication/24277597_Barbault_A_Costa_F_Bottger_B_Mundeen_R_Bomholt_F_Kuster_N_Pasche_BAmplitude-modulated_electromagnetic_fields_for_the_treatment_of_cancer_discovery_of_tumor-specific_frequencies_and_assessment_of_a_nove

Their stated rationale was because in vitro studies suggest that low levels of electromagnetic fields may modify cancer cell growth, they hypothesized that systemic delivery of a combination of tumor-specific frequencies may have a therapeutic effect.

They undertook a study to identify tumor-specific frequencies and test the feasibility of administering such frequencies to patients with advanced cancer. We examined patients with various types of cancer using a noninvasive biofeedback method to identify tumor-specific frequencies. This involved monitoring heart rate and also patient reporting changes in heart rate! They offered compassionate treatment to some patients with advanced cancer and limited therapeutic options. They examined a total of 163 patients with a diagnosis of cancer and identified a total of 1524 frequencies ranging from 0.1 Hz to 114 kHz. The specific frequencies themselves are not all disclosed. However, all three studies in the Pasche, Zimmerman , Barbault group appear to disclose some frequencies which are common to all the cancers they evaluated.

These are inter-alia 2,221.323 Hz TTF, 6530.24 Hz TTF and 10,454.4 Hz TTF.

They claim most frequencies (57-92%) were specific for a single tumor type. The large range in brackets is not examined. Compassionate treatment with tumor-specific frequencies was offered to 28 patients. Three patients experienced grade 1 fatigue during or immediately after treatment. There were no NCI grade 2, 3 or 4 toxicities. Thirteen patients were evaluable for response.

Clearly there were some interesting results. One patient with hormone-refractory breast cancer metastatic to the adrenal gland and bones had a complete response lasting 11 months. One patient with hormone-refractory breast cancer metastatic to liver and bones had a partial response lasting 13.5 months. Four patients had stable disease lasting for +34.1 months (thyroid cancer metastatic to lung), 5.1 months (non-small cell lung cancer), 4.1 months (pancreatic cancer metastatic to liver) and 4.0 months (leiomyosarcoma metastatic to liver). In essence, their results are comparable with those expected of chemotherapy.

I have made an earlier and somewhat simplified attempt to explain these effects (ref) however, since that explanation new information has come to light which enables a far more comprehensive explanation.

What are Zimmerman's other frequencies?

Besides using the downloadable files, there are three of which, described as; Breast tumour treating frequencies, HCC (liver) treating tumour frequencies and Random frequencies which did not provoke effect, I have also found it instructive to consult the patent literature. BRPI0810084 (A2) — 2014-03-18 discloses an 'Electronic system for influencing cellular functions in a warm-blooded mammalian subject'. Claim 20 discloses A system (11) according to any one of the preceding claims, in which the control information is selected to lead the one or more generator circuits (29) to generate one or more amplitude- modulated low energy electromagnetic emissions, the frequency of which amplitude modulations being controlled by the one or more frequency control generators (31) at frequencies selected from at least one frequency within the range of at least one of the following frequency ranges: 1870 to 1876 Hz, 2218 to 2224 Hz, 3666 to 3672 Hz, 4483 to 4489 Hz, 5879 to 5885 Hz, 6347 to 6353 Hz, 8459 to 8455 Hz, 10453 to 10459 Hz, a combination of two or more frequencies within two or more of said frequency ranges, and a combination of at least one of said frequencies and at least one further determined or predetermined frequency outside of said frequency ranges, and

Claim 21 discloses a system (11) according to claim 20, in which the frequencies are selected from at least one of the following frequencies: 1873.477 Hz, 2221.323 Hz, 3669.513 Hz, 4486.384 Hz, 5882.292 Hz, 6350.333 Hz, 8452.119 Hz, 10456.383 Hz, a combination of two or more of said frequencies, and a combination of at least one of said frequencies and at least one further determined or predetermined frequency.

Rightly or wrongly, I assume that these are the groups of frequencies common to all cancer patients and not the undisclosed remainder of the aforesaid 1524 frequencies.

I have previously postulated that the frequencies have at least in some way a relationship with ion channels or the perturbation thereof, as stimulation of such channels in excitable tissue is the only way to ever elicit the observed biofeedback response. Excitable tissue is defined as being nerve and muscle tissue. There is now considerable evidence that the same types of ion channel that are found in excitable tissue are also expressed in tumour tissue but not in healthy non-excitable tissue. This would then elegantly account for the reason these types of treatment have no adverse effect on healthy tissue. Previously it was thought there was only a handful of ion channels for the main biological ions. However, there is now a significant and growing evidence for a huge number of families and genetic variations in all kinds of ions channels included voltage gated channels, dual pore channels, aquaporins and piezo channels to name but a few. This fits elegantly with the observation of 1524 different treatment frequencies. I postulate there will be a least one per different ion channel and some for special combinations of channels and dual pore channels and the like. On the other hand Schönherr (2005) suggests that although the current pattern of cancer-related ion channels is not arbitrary yet it can be reduced to few members from each ion channel family. Thus I postulate this probably accounts for the observation of the common frequencies mentioned above.

How can modulated RF radiation influence ion channels anyway?

Galvanovskis and Sandblom (1197) showed that even very weak low-frequency electromagnetic signals (<100 Hz and down to 100 microT) may be detected in a cellular system with a large number of ion channels. But what is the evidence for the detection of such systems with higher frequencies or modulated signals?

Bawin and her coworkers have reported changes in binding of calcium after exposure of avian brain tissue to nonionizing electromagnetic radiation. Blackman et al (1979) used the forebrains of newly hatched chickens, separated at the midline to provide treatment-control pairs and labelled them in vitro with radioactive calcium. Samples of tissue were exposed for 20 minutes in a Crawford irradiation chamber to 147-MHz radiation, which was amplitude

modulated sinusoidally at selected frequencies between 3 and 30 Hz. Power densities of incident radiation ranged between 0.5 and 2 mW cm−2. Compared with nonirradiated samples, a statistically significant increase in efflux of calcium ions ($P < 0.01$) was observed in irradiated samples at a modulation frequency of 16 Hz and at a power density of 0.75 mW cm−2. Their data confirmed the existence of the frequency "window" reported by Bawin et al., as well as a narrow power-density "window" within which efflux of calcium ions is enhanced. Such frequency windows can be interpreted in terms of Ion Cyclotron Resonance (ICR).

Habash, Electromagnetic Fields and Radiation: Human Bioeffects and Safety (2018) , describes numerous other examples.

Ramachandran (2007) has shown experimentally that voltage gated ion channels are capable of responding to an 800 MHz RF carrier wave effectively by a process of rectification due to the combination of membrane capacitance and non-linearity in the channel itself.

D'InzeoStefano et al (1993) has discussed a stochastic model of Ionic channel gating under electromagnetic exposure. They considered the membrane channel as a non-deterministic state machine. Its behaviour is fully described by a set of states, a matrix of transition rates, and a vector for the probability of the machine to be in each single state at a certain instant. A stochastic model was developed, generating random processes where the probability for each state is an aleatory variable. The model was tested for both voltage gated and ligand-dependent channels, both unexposed and exposed to EM fields in the ELF range.

Intuitively, I would propose that rectification or demodulation of a modulated HF carrier wave would occur at cell membranes and hence expose ion channels to the modulation envelope frequency component. Indeed, there is evidence to support my claim. Elnasharty et al discuss 'cell membrane analysis using modulated electrophoresis. They describe method of examining this low-frequency region using a low frequency signal to modulate a 1 MHz carrier wave, allowing membrane conductance due to conduction through ion channels and surface conductance of the membrane to be probed in this unusual way for the first time. They produce DEP spectra before and after the application of ion channel blockers.

The technique works because demodulation of the AM signal occurs. The simplest demodulation circuit for amplitude modulation signals consists of a diode and a capacitor. In a

suspended cell, the membrane acts as a capacitor, while there are two methods in which ion channels can act as diodes to demodulate the signal.

Ion channels will normally conduct along a concentration gradient of the particular ion they transport. If there is a much higher concentration of ions inside the cell than outside the cell (or vice versa) making the flow of a particular ion essentially one direction similar to the flow of electrons through a diode. Additionally, some ion channels move ions directionally have an intrinsic selectivity filter only allowing excreting or taking up a particular ion and thus relative to total potential ionic current as a whole behave as a diode even without a concentration gradient. Since an ion needs a characteristic time to be transferred though a particular ionchannel, the electric field will only have an effect on ion channels that transfer change in less than half the period of the signal. This has been modelled as an inductive component in then ion channels response for some time and gives rise to resonance conditions at well defined frequencies. Although Elnasharty et al only focus on the electric field, I conclude that the magnetic field will similarly exhibit resonance effects due to ion cyclotron resonance. These resonance peaks should be detectable in the DEP response of the cell. If the amplitude of a high-frequency carrier wave is modulated using a lower frequency signal, then I would anticipate that where there is a change in conductance to due to ion channel activity, the net force on the cell would be due to the superposition of the low-frequency signal acting across the membrane due to the demodulation effect, plus the effect of the high-frequency signal. This force will also be felt by any piezo channels present in the cell. This high frequency component will depend solely on the interaction between the medium and cytoplasm, the membrane having been bypassed at these frequencies. It is therefore possible to deduct the high-frequency force component by measuring the force acting on cells when exposed to an unmodulated signal at the carrier frequency. Hence, by using a low-frequency signal modulated onto a MHz frequency carrier signal. This is what allowed Elnasharty et al to observe the DEP spectrum of cells at low frequency and observe changes to the spectrum when channel blockers and other chemical agents were used. They observed frequency peaks both in the low tens of Hz and at about 1Khz. The precise frequencies depended on the nature of the channel blocker and/or ionophore.

The work of both D'InzeoStefano and Elnasharty is useful in that it provides a viable physical mechanism for interactions of modulated radio frequencies and biology of which there are lots of experimental observations but few viable explanations. Whereas essentially their work

is interpreted in terms of electric field gating and component we must never forget that in an EM wave the magnetic component is inseparable. Both are candidates for demodulation. We only have to research the earlier pioneers of radio and the magnetic coherer which preceded the cat's whisker to understand this. Moreover, I will show later there are potentially fewer objections in terms of signal to noise ratio in the magnetic case.

Further evidence linking the frequencies with ion channels, initial thoughts.

The average GMF (geomagnetic field) in the USA is some 47.5 micro-tesla. I therefore constructed table 1 below to show the ion cyclotron resonance parameters of all the common biological ions, most taken from Bioengineering and Biophysical Aspects of Electromagnetic Fields (Handbook of Biological Effects of Electromagnetic Fields)20 Oct 200 by Ben Greenebaum and Frank S. Barnes (Chapter 9 Liboff) also found at http://www.sibeonline.com/download/Liboff%20-%20ICR%20interactions%20in%20living%20systems%20-%20SIBE%202013.pdf.
Following this reference, I have obtained the fc/B values for certain tabulated ions and the rest I have calculated from their charge and molecular weights. I have then divided those fc/B values into the given values of tumour treating frequency. When treated in this way each tumour frequency appears about two orders of magnitude higher than expected ICR frequency. One possible explanation for this is that ICR theory needs to be amended to take into account dielectric constant and/or viscosity. I would predict a quasi- harmonic behaviour for each ion if its angular momentum is to be conserved as it descends through the selective filter and into the hydrophobic core. In other words when the ion is in a totally hydrophobic channel environment it will seem has though it has lost mass or waters of hydration. I believe this argument to be justified as follows.

Biological ion channels are nanoscale transmembrane pores. When water and ions are enclosed within the narrow confines of a sub-nanometer hydrophobic pore, they exhibit behaviour not evident from macroscopic descriptions. At this nanoscopic level, the unfavourable interaction between the lining of a hydrophobic pore and water may lead to stochastic liquid vapor transitions, see Aryal et al (2014). These transient vapor states are de-wetted , i.e. effectively

devoid of water molecules within all or part of the pore, thus leading to an energetic barrier to ion conduction. This process, termed hydrophobic gating was first observed in molecular dynamics simulations of model nanopores, where the principles underlying hydrophobic gating (i.e., changes in diameter, polarity, or transmembrane voltage) have now been extensively validated.

Previous observations of ICR have been in solution. Calcium ICR can exhibit hyperfine splitting effects due to hydronium and hydroxyl, see for example but not exclusively Sheykina 2016.

'Characterisation of weak magnetic field effects in an aqueous glutamic acid solution by nonlinear dielectric spectroscopy and voltammetry.' It is my contention that when experimenters have attempted to apply ICR frequencies in biological situations they have used these solutions determined frequencies which are those of hydrated ions. Whereas they may be a handful of biological situations where this is relevant (refs) it is clearly not the case here. There is another essential difference also. The Q-factors observed for ICR elsewhere are low. The bandwidth is of the order +/- 10% of the fundmanetal frequncy. In the TTF case here Q values of apparently between 10^4 and 10^5 are seen at least in terms of the requirement to produce biofeedback. I will show that the difference can be understood in terms of the difference between bulk and structured water, ion cages and dehaydration following for example Del Giudice. Pazur (2018) also consders calcilum ICR in water cages and finds the oscillations of the Belousov–Zhabotinsky chemical reaction are significantly reduced under Ca^{2+} ICR application. Secondly an "oscillator" of calcium ions appears to be able to itself couple coherently and predictably to large-scale coherent regions in water. This system appears able to regulate ion fluxes in response to very weak environmental electromagnetic fields. See Fulltext http://www.tandfonline.com/eprint/KYKEqMetHpz7sKwakZct/full.

f (27.065) Brazil average

Ion	Q/M	fc/B	f (47.5)	Ratio /K+	TTF	Ratio /K+
			(Hz)		Hz	ttf
H+	95.76	15.24	723	38.76		
Li+	13.78	2.19	104	5.58	10456	5.58
OH-	11.13	1.773	84	4.5	8455	4.51
Mg 2+	7.93	1.27	60.3	3.21	5880	3.13
H3O+	5.04	0.803	38.1	2.04		
Ca2+	4.81	0.77	36.55	1.94	3668	1.95
Na+	4.16	0.662	31.42	1.91		
Cl-	2.69	0.428	20.3	1.1	2220	1.18
K+	2.47	0.39	18.5	1	1873	1
Glu-	0.65	0.103	4.83	0.26		

H+	412.46
Li+	59.27
OH-	47.98
Mg2+	34.37
H30+	21.7
Ca2+	20.83
Na+	17.917
Cl-	11.58
K+	10.55
Glu-	2.787

Table 1

It can be clearly seen that the ratios of frequencies observed from the TTF'S (modulation frequencies applied to 27 MHz carrier) reference potassium as a base frequency (Table 1 column 7) are highly compatible with the ratios obtained from the more classically reported Ion Cyclotron resonance frequencies (Table 1 column 5). Although it is believed this has never been attempted by any authors or research groups previously, it is relatively easy to account for the high harmonic content observed. Several have commented that ICR cannot properly apply in the hydrated case. There are strong viscous forces on the ion. Indeed Halgamuge et al (2009) have highlighted the signal to noise ratio problem with the basic ICR model and has also noted that theoretically true ICR did not ought to be able to occur for ions in a viscous medium at frequencies below about 2000 Hz due to the number of collisions per second they are encountering. Lednev (ref) amended the ICR model and came up with the IPR model

which overwhelms the SNR problem and has similar predicted frequencies. The same mathematical prediction can be obtained using a different theoretical approach: the analysis of the velocity of the damped ion under the influence of the Lorentz force, see Vincze et al (2008). In both cases, the prediction of a dependence on specific values for B AC/B DC has been tested in several experiments.

Liboff and McLeod (1988) first considered the cyclotron resonance model for channel ion transport in weak magnetic fields is extended it to include damping losses. Their model leads to discrete modes of vibration (eigenfrequencies) in the ion-lattice interaction, such that $\omega n = n\omega c$. The presence of such harmonics is compatible with recent results by Blackman et al. [1985b] and McLeod et al. [1986] with the interesting exception that even modes do not appear in their observations. Especially relevant to the present interpretation in my work, their model has ***no restriction whatsoever on n.*** Further their harmonic formalism is also consistent with another reported phenomenon, that of quantized multiple conductances in single patch-clamped channels.

Liboff et al (2106) have made recent observations of low-frequency electromagnetic oscillations in water which suggest an inductive structural component. Accordingly they assumed a helical basis enabling them to model water as an LC tuned oscillator. A proposed tetrahedral structure consisting of three water molecules and one hydronium ion was incorporated into the Boerdijk-Coxeter tetrahelix to form long water chains that are shown to have resonance frequencies consistent with observation. Their model also serves to explain separately reported claims of ion cyclotron resonance of hydronium ions, in that the tetrahelix provides a built-in path for helical proton-hopping. For this reason I shall include hydronium ions in my list of biological ions for later analysis of Zimmerman and Pasche's data.

If I take the LC model, it is logical to suppose the resonant frequency may depend inversely on the square root of the dielectric constant. Thus as we descend into the hydrophobic region epsilon falls from 80 to as low as 2-6. If ICR or ICR like and water cluster resonance cohere,

as has been suggested by Del Giudice (ref) we should expect an increase of up to 7 fold in frequency. If the angular momentum of the ion entity is conserved I would similarly expect a frequency to be proportion to the inverse of the square root of the effective radius. For a loss of 6 water molecules this represents approximately a five fold increase in frequency. Much larger water clusters are reported in biological systems so theoretically this could easily double. For example, often the binding of two protein molecules seems to be mediated by clustered water. It is known, for example, that the crystal structure of trypsin and trypsin inhibitor don't fit together perfectly and the amino acid side chains conflict. In order to form a tight complex, these side chains must change their conformations. Mobile water structures along the proteins' surfaces link the two proteins by binding to each. To do this these water structures are organized as fragmented dodecahedrons (12-sided figures), 9–15 Ångstroms long, enough to accommodate 30 or more molecules. There are similar events in the biochemistry of myoglobin.

Combining the dielectric constant idea and the conservation of angular momentum could thus easily account for the observation of an ICR frequency some seventy times higher than expected. Previously ICR harmonics as high as about 15 have been reported, see for example Pazur (2004) who note ICR for glutamic acid at 4.14 Hz but note other frequencies worthy of remark are 62, 78 and 94 Hz, being four folds of the used base ICR resonance frequency 4.14 Hz.

Further, I would perhaps expect there to be special conditions where higher harmonics still could match the ICR frequency of more than one type of ion simultaneously as in, for example, their lowest common multiple. Since Zimmerman and Pasche's biofeedback frequency registration technique relies on stimulating excitable tissue, I would naturally expect these 'LCM' conditions to produce a strong stimulus. Under such special conditions one may well have frequencies which drive these ICR's in phase with mechanical resonance of other structures within cells or their organelles.

Furthermore, due to the vast number of different types and families of ion channels in biology I would expect an almost pseudo-random distribution of harmonics of each specific ion's ICR Frequency depending on type of channel, size and shape of the selective filter and pitch of the helices involved. For example some channels are more conical than others. In fact, this is exactly what the data shows.

It is well known that the components of ion channels execute coupled movements, see for example Horn (2002). For example; there has to proper co-ordination between the S4,5 and 6 sub-units in the open and closed states. There is experimental evidence to suggest some of these movements are rotational, see Horn (2000).

Thus the channel itself or its various sub-units will have finite angular momentum and will hence behave as a harmonic oscillator.

Placing additional angular momentum on the traversing ions by means of ICR at its fundamental or harmonic frequencies will lead to superposition behaviour effectively there will be regions of motional enhancement and regions of motional restriction depending on the harmonic frequency. Due to the very precise structure and bonding requirements in a moving ion channel it is plausible to visualise how high Q responses with in phase and antiphase dehydrated ion motions might be achieved.

Previous discussions of the interaction of EMF and biology has only considered ion channel enhancement (refs). Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects, see Pall et al (2013). Usually only calcium channels either inwardly or outwardly rectifying voltage gated types have been considered (refs). Hence it has been stated and experimentally shown in some cases that application of ELF (refs) or even modulated 147 MHz (ref) causes increased calcium efflux/influx (check refs). The ICR or similar models have been used to explain this on the grounds that ions on

the membrane surface and close to pore entrances are encouraged en-route as it were. Influx or efflux is encouraged depending on the type of ion channel and the initial membrane or ligand surface concentration of ions. The frequencies or modulation frequencies employed have exclusively been low (Hz or tens of Hz). There is sufficient body of scientific evidence to suggest that application of calculated ICR frequencies has real biological effect, with one of the earliest and most profound papers being that of Smith and Liboff et al (1987) dealing with Calcium Cyclotron Resonance and Diatom Mobility. This is elegant because it shows downstream effects of ICR controlling simple molecular machinery.

There is also evidence form the field of plant biology. Smith et al (1995) tested the ion cyclotron resonance theory of electromagnetic field interaction with odd and even harmonic tuning for cations on seeds of Raphanus sativus, var. Cherry Belle. The seeds were exposed to combined parallel static and sinusoidal 60 Hz, 40 μT peak-peak ac fields turned to the fundamental, 2nd and 3rd cyclotron resonance harmonics for calcium and potassium ions. Other seeds were exposed to similar fields tuned to the fundamental and 5th harmonic for magnesium. Concurrent controls consisted of seeds exposed to the ac field only, and to ambient geomagnetic and stray 60 Hz ac fields. After 21 days plant height, aboveground weight, root weight, stem diameter, leaf length, leaf width and length/width aspect ratio were measured and compared to in-group controls. Calcium slowed germination, potassium speeded it, and magnesium left it unaffected. Calcium and magnesium tunings were generally stimulatory to growth, while potassium tuning was inhibitory, except for root weight. Controls (ac only) were unchanged from the ambient field controls. Fields at the 2nd harmonic were ineffective, except for potassium 2N, which appeared similar to a weak calcium effect.

Comisso et al (2005) studied dynamics of the ion cyclotron resonance effect on amino acids adsorbed at the interfaces. They reproduced the Zhadin experiment, which consists of the transient increase of the electrolytic current flow across an aqueous solution of L-arginine and L-glutamic acid induced by a proper low frequency alternating magnetic field superimposed to a static magnetic field of higher strength. Further they identified the mechanisms that were at the origin of the so-far poor reproducibility of the above effect: the state of polarization of the electrode turned out to be a key parameter. The electrochemical investigation of the system

shows that the observed phenomenon involves the transitory activation of the anode due to ion cyclotron frequency effect, followed again by anode passivation due to the adsorption of amino acid and its oxidation products.

The relevant conclusion here was that there will be the likely occurrence of similar ion cyclotron resonance (ICR) phenomena at biological membranes and hence the implications not only for common small ion circulation but also for amino acid circulation in living matter under the consequent impact of environmental magnetic fields.

A useful analogue for ion channelling and downstream control is to imagine the building a six mile high dam around the deepest part of the ocean. Now picture what a cell does when it reduces calcium ions to 20,000-fold lower levels inside the cell than surrounding the cell. Uncontrolled Ca2+ leaks induce cell death, whereas controlled Ca2+ entry triggers an enormous array of actions, ranging from secretion to cell division.

Ion channels are the electrical switches that control these actions. One ion channel directs the flow of ~10 million ions per second, in turn rapidly changing intracellular Ca2+ levels. The human genome contains more than 300 genes encoding ion channels, effectively these are the cell's transistors.

Although demonstrated in plants few are probably unaware of ICR effects in mammalian and human biology under the influence of environmental fields other than what has been reported on Calcium channel effects. Hence probably why Elnasharty et al suggest that the potassium channel too may be a target for electronic modification as though this in itself were a rather radical proposition..

However, I will show herein that not only a numerous different voltage and ligand gated ion channels for all common biological ions are effected by the Zimmerman and Pasche TTF's but also and for the first time, that high harmonics of ICR act in a manner contrary to that associated with ELF application. In other words under some conditions Ca2+ entry can be slowed rather than accentuated. This is entirely consistent with both the angular momentum hypothesis and the dehydration hypothesis above. Using the same experimental data due to Zimmerman and Pasche, I will also show that high ICR harmonics also effect amino acid transporter channels too. Finally, I will also show that under some conditions K+ can also be suppressed.

Suppressing Ca2+ current will be shown to account for the genetic effects in XCL2 and suppressing of K+ current will also be shown to be responsible for the genetic effects on PLP2 expression.

There has been comment by Teplan et al (2017) that the Q factors seen with Pasche and Zimmermann's TTF's are unrealistically high. However if one treats the system as a mechanically resonant system with viscoelastic damping and considering the de-wetting phase of ions one can consider the transition from water to vapour viscosity.

Evaluating the resonance condition one arrives at $Qv/Qw = \text{Eta w/ Eta v}$

And it is also known that the viscosity and viscous shear forces in nanoconfined water can be orders of magnitudes larger than in bulk water if the confining surfaces are hydrophilic, whereas they greatly decrease when the surfaces are increasingly hydrophobic. This decrease of viscous forces is quantitatively explained with a simple model that includes the slip velocity at the water surface interface, see Ortiz-Young et al (2013).

The two processes above are sufficient to account for the high Q'S observed.

The ultimate aim is to know exactly how to control ions in the transport channels of living cells opens up a fantastic new era and paradigm for both the diagnosis and treatment of human disease. The advent of the drug free channel blocker is upon us. Not only that but we may also finally be able to properly and fully evaluate the true hazard or otherwise of radio communication systems on biological systems and moreover even design safer such systems for the future.

Connection with Royal Rife?

There have been so many versions of the so called Rife machine and so many published frequency lists that it is virtually impossible to tell which are 'original' and which are 'fake'.

However one version of the machine appeared to modulate multiple sidebands at a frequency of about 20-21 KHz onto a 3.3 or 3.8 MHZ carrier wave. Calculation of this frequency as an ion yields the 29^{th} harmonic of proton ICR for a GMF of 47.5 micro-tesla. The machine would not have had the benefit of modern DDS stability and hence one can postulate that with frequency drift and jitter it could have occasionally excited ICR in multiple types of ion channels.

Another version of the machine was described by one of Rife's associates, namely John Crane in 1973. He tried to patent the 'Frequency Instrument'. Here are some extracts from the patent application:

"It has been well known by Rife, myself and others that a specific cancer virus causes the cancer which was long ago isolated by Royal R. Rife and cancer was cured by Rife in animals and in clinical tests with people and was published by the Smithsonian Report for 1944 on pages 193-220 as written by R. E. Seidel, M.D. (and see U.S. Government Printing Office Publication No. 3781 which has 5 plates of Rife's microscopes). It was observed that electromagnetic energy utilizing a frequency of 2127 cycles per second modulated on a carrier wave of 4150 kilocycles (4.15 Mhz) at 200 watts was lethal to cancer.''

Here the modulation frequency of 2127 Hz would seem extremely close to that seemingly causing ICR in chloride channels as used by Zimmerman et al at least from the simplified interpretation in Table 1 above. Moreover a quick calculation shows this frequency to be the third harmonic of the hydrogen ICR, the 20th harmonic of the Lithium ion ICR **and** the 57th

harmonic of the calcium ICR assuming an average geomagnetic field of 46.58 micro-tesla, not unreasonable for North America.

Detailed interpretation of the Zimmerman and Pasche frequencies.

Because the geomagnetic field in Sao Paulo is estimated to be between 20-30 micro-Tesla it is not appropriate to develop a detailed interpretation either from Table 1 above or by normalisation because the field will vary on a day by day basis. I thus considered in much greater detail the downloadable files, there are three of which, described as; Breast tumour treating frequencies, http://drchrisbarnes.co.uk/BREAST.pdf and HCC (liver) treating tumour frequencies. http://drchrisbarnes.co.uk/HCC.pdf and Random frequencies which did not provoke effect, http://drchrisbarnes.co.uk/RAND.pdf. These files are used as follows;

The extreme left column is the so called TTF (tumour treating frequency as identified by the reflex response of the patient directly or by physiological monitoring of changes to patient vital signs such as heart rate and blood pressure. The remaining columns are the precise ICR frequencies and harmonics for the known common biological ions and common amino acids at the GMF according to hydrogen. Where there are precise or extremely close numeric (frequency) matches between the TTF and the ICR harmonic this has been indicated/highlighted in green. Lesser matches in yellow and lesser matches still in orange. No match is just left as bare print, black on white.

Plugging in a value of 25uT for the GMF yields approximately 380 Hz for the first ICR value of the proton. In the 'breast' file the nearest frequency to this is 414.817 Hz. In the HCC file the nearest frequency 410.231 Hz. I thus interpret these frequencies as being the fundamental ICR for protons and I interpret the differences not as 'patient specific' as suggested by Zimmerman and Pasche et al but rather simply being due to a difference in the local GMF

when the treatment was given. Accordingly dividing these two frequencies by Fc/B (15.24) for the proton yields the precise value of GMF in each case, namely 27.21895858 uT in the Breast file and 26.91804 uT in the case of the HCC file. I the utilise these GMF's to calculate the expected fundamental ICR frequencies for a significant number of other common relevant biological ions including: H+, Li+, OH- , H3O+, Mg2+, Ca2+, Na+, Zn2+, Cl-, K+ and a number of small amino acids. I then divide these fundamental frequencies into each of the stated 194 TTF frequencies to find the harmonic number for each ion. I define a harmonic as being valid if it falls as an integer or close thereto. For higher harmonics I allowed a maximum deviation of +/- 0.1 on the harmonic number. I then count the number of harmonics for each specific ion which fulfils this chosen condition. I have set no upper bound on harmonic number but essentially my chosen precision gets sharper and sharper in an arithmetic progression. The results are available in XL spreadsheets. Proton ICR harmonics from 1-45 are observed. Much higher harmonics of heavier ions and amino acids are observed, tantamount with the dehydration hypothesis above.

The random file contains 237 random frequencies and it is stated none are closer than .5 Hz of an actual treatment frequency. For the random file I took the GMF as being the average of the GMF for the two treatment files. I used the same criteria for the definition of an ion specific ICR harmonic. The result is available in an XL spreadsheet.

For all three files I then went on to calculate the percentage of frequencies that fulfilled ICR or ICR harmonic conditions for each specific ion and have showed these results in a separate spreadsheet, an extract of which is included in table 2 below:

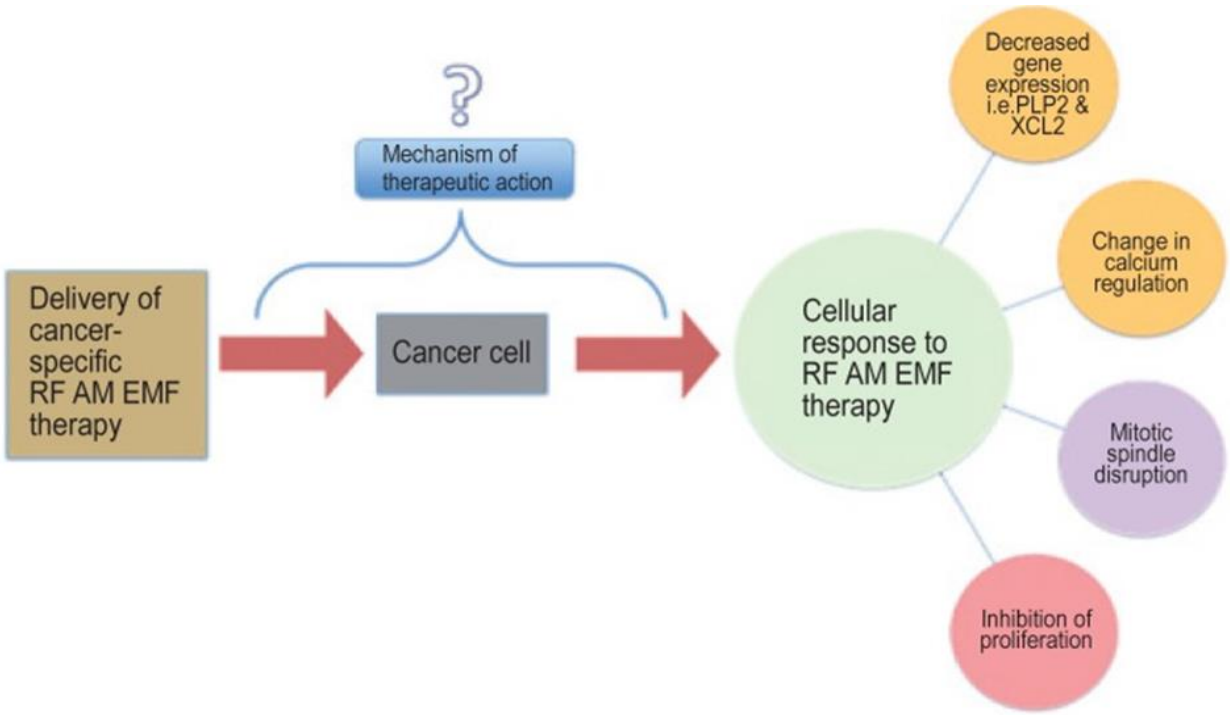
/194	H+	Li 6 35	Li 7 49	OH 39	H30 42	Mg 39	ca 40/42	Na 47	zn 64/35	cl35 40	K39/38	arg 28	ASN 42	Glu 36	tyr 29	ser 35	Hist 34	h3po42-	HCO32-
						24												39	40
HCC	10.26%	17.95%	25.13%	20.00%	22%	20%	21.53%	24.10%	17.95%	20.51%	19.48%	14.36%	21.53%	19.07%	14.90%	17.95%	17.43%	20%	20.62%
																			0.2062
	16H+	25 Li 6	30 Li 7	41 OH	47 H3 0	37 Mg24	43 Ca 40	35 Na 23	51 Zn 64	Cl 35 39	48 K39	41/41	39 Asn	50 Glu	34 Tyr	41 Ser	40 Hist	HPO42-	HCO3 39
																		-41	
RAND	6.75%	10.55%	12.66%	15.18%	19.83%	16.88%	18.14%	14.76%	21.94%	16.40%	20.25%	17.30%	0.1645	21.34%	14.35%	17.30%	16.90%	17.30%	16.46%
/237																			
BREAST	25 H+	34LI6	30LI7	38OH	38 H30	39Mg24	47 Ca40	31Na	34ZN 64	34 ZN/CL	39 k39	35 Arg	26 ASN	40 Glu	35 Tyr	37Ser	39 Hist	40 hpo4	38 HCO3
/194	12.88%	17,52%	15.46%	19.59%	19.59%	20.10%	24.23%	15.38%	17.53%	17.53%	22.16%	18.04%	13.32%	20.62%	18.04%	19.07%	20.10%	20.62%	19.59%

I have used green to represent a low or lowest percentage for the tabulated ion and orange to represent high and highest percentages. It can be clearly seen that the ions which give rise to action potentials in excitable tissue have more ICR harmonics in the treatment files than in the random file. This is totally consistent with perturbation of ions, their channels, the ICR resonance condition and /or a downstream event being the cause of the biofeedback registration in the treatment cases and the lack of registration upon application of random frequencies. There are also some far more profound observations which I will discuss later in this present paper. I also considered hydrogen polarisation models, see and was unable to fit the results in any way, see Halgamuge et al (2009) .

Can ion channel modulation explain Zimmerman's results?

Zimmerman et al categorically state that there are known known mechanisms for their results which sadly downplays their excellent work and makes their system less likely to be commercially exploitable.

Human nature tells us if you buy something you want to know how it works. Like a drug you don't know how or why it works then it could simply be placebo! I have included Zimmerman's graphic to show where they are at.



I will spend the rest of this paper attempting to explain Zimmerman et al's observations of downregulated PLP2 and XCL2 genes and mitotic spindle disruption especially with regard to HCC liver cancer.

XCL2 and Calcium regulation

XCL2 is the other member of the C-chemokine subfamily, XCL1 being the first and more well-known member. Further, XCL2 is responsible for G protein-coupled receptor activation while the dimeric form is important for GAG binding. Despite their high structural similarity, XCL2 displays a slightly higher affinity for heparin than XCL1. Because their in vitro

functional profiles are virtually identical, distinct physiological roles for XCL1 and XCL2 are probably encoded at the level of expression, see Fox et al (2014). Since Chemokines are immune modulators it is possible the expression of this gene fell in response to there being less overall metastases. For instance, the Chemokine Network has a role in the Development and Progression of Ovarian Cancer and is hence a potential Pharmacological Target, see Barbieri et al (2009). Chronic inflammation is a also a risk factor for several gastrointestinal malignancies, including colorectal cancer. Recent epidemiological studies and clinical trials demonstrate that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) markedly reduced the relative risk of colorectal cancer. Chronic inflammation associated with development of cancer is partly driven by the chemokine system. They are also involved in gliomas, melanomas, and breast cancer, see Memtlein et al (2013) who also discusses Chemokines as a possible target.

XCL2 and CX3CL1 expression in lung cancers and adjacent non-cancerous tissues has been studied by Zhou et al (2016) using quantitative PCR and ELISA. The relative expression of both chemokines in lung cancers in different pathological stages was compared by immunohistochemical assay. The expression of XCL2 and CX3CL1 increases with increasing degree of malignancy, indicating that both chemokines might be important targets in gene therapy for lung cancer. Their study demonstrated that XCL2 and CX3CL1 expression in lung cancers were significantly higher compared to adjacent normal tissues. Moreover, expression of both chemokines was significantly stronger with higher pathological stages. **They speculated that XCL2 and CX3CL1 synergistically promote the development of lung cancer.**

Tthe paradigm of cancer development and metastasis has been redefined to encompass a more comprehensive interaction between the tumor and microenvironment within which the tumor cells reside. Despite the realization that this more comprehensive relationship has changed the current paradigm of cancer research, the struggle continues to more completely understand the pathogenesis of the disease and the ability to appropriately identify and design novel targets for therapy. Chemokines and chemokine receptors in general are being investigated for their role in tumor development and metastasis and may prove to be useful therapeutic targets. The chemokine family is a complex network of molecules that are ubiquitously expressed and perform a variety of functions most notably regulating the immune system. Here we review the

importance of chemokines in the tumor-stromal interaction and discuss current concepts for targeting the chemokine network.

XCL2 encodes for a protein that enhances chemotactic activity for lymphocytes and downregulation of XCL2 has been shown to be associated with good prognosis in patients with breast cancer (Teschendorff et al, 2007; Teschendorff and Caldas, 2008).

XCL2 is structurally similar to XCL1, displaying metamorphic interconversion. The monomeric form of XCL2 activates XCR1 and has a similar potency to XCL1.

Perhaps the most important question here is can **any direct** link be established between RF ion channel modulation and XCL2 expression or is the fall in the latter simply a consequence of cancer cell destruction by another mode. The papers in the Barbault and Zimmerman family categorically state that effects could not be elicited at other modulation frequencies so we are left to consider whatever mechanism must differ from that of Kirson et al.

The drugs Etanercept and Infliximab are capable of Modulating Proinflammatory Genes in Activated Human Leukocytes. Etanercept is a recombinant human tumor necrosis factor

receptor [p75]: Fc fusion protein. Infliximab is a chimeric anti-tumour necrosis factor α monoclonal antibody. Two chemokines are downregulated by etanercept, XCL1 and XCL2, have been identified as two isoforms of lymphotactin.

Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease an autoimmune condition. Conversely, anti-tumor Necrosis Factor Alpha (Infliximab) attenuates Apoptosis, Oxidative Stress, and Calcium Ion Entry Through Modulation of Cation Channels in Neutrophils of Patients with Ankylosing Spondylitis, an auto inflammatory disease, see Ugan et al (2016).

In conclusion, their current study suggests that infliximab is useful against apoptotic cell death and oxidative stress in neutrophils of patients with AS, which seem to be dependent on increased levels of intracellular Ca2+ through activation of TRPM2 and VGCC.

TRPM2-mediated Ca2+ influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration.

Transient receptor potential (TRP) channels, have been implicated in tumour cell migration and the metastatic cell phenotype, see Prevarskaya (2011).

TRPV1 and TRPV4 channels provide Ca2+ entry pathways in HepG2 liver cancer cells. HGF/SF increases Ca2+ entry via TRPV1, but not via TRPV4. This rise in [Ca2+]i may constitute an early response of a signalling cascade that gives rise to cell locomotion and the migratory phenotype, see Vriens et al (2003).

Store-operated calcium entry (SOCE) is the main Ca2+ influx pathway involved in controlling proliferation of the human hepatoma cell lines Huh-7 and HepG2, see Boustany et al (2008).

Now we have a putative link between inflammation, invasion and metastasis and intra-cellular Ca2+ ion concentration. It seems the TTF modulated signal is acting rather like Infliximab and in this case causing Ca2+ efflux or slowing Ca2+ entry, hence downregulating XCL2. Either way the action, brought about by the tumour treating frequencies modulated onto the 27.12 MHz signal is deep within the hydrophobic part of the channel as identified by the high ICR harmonics present. The higher ICR Harmonics for calcium seem to be evenly spread across the TTF frequency spectrum. This is consistent with the progressive dehydration of calcium as it passes through the pore and as documented in the literature and is equally consistent with both the dielectric and angular momentum models. Mitosis or S-phase in cancer cells is usually associated with Ca2+ entry which augments depolarisation and provides an internal store of calcium to operate calcium operated potassium efflux channels leading to cell shrinkage before division. Hence interfere with Ca2+ entry will interfere with mitosis which is what is observed. Running in tandem the TTF's also block sodium entry see Table 2, augmenting the same mechanism.

PLP2

This gene also called Phosducin-like Protein 2 encodes an integral membrane protein that localizes to the endoplasmic reticulum in colonic epithelial cells. The encoded protein can multimerize and may function as an ion channel. A polymorphism in the promoter of this gene may be linked to an increased risk of X-linked mental retardation. A pseudogene of this gene is found on chromosome 5. [provided by RefSeq, Jan 2010]

PLP2 is usually expressed in yeasts and hepatitis and several other viruses. A functional role for PLP2/A4 has been suggested by Lee et al (2004) in the chemotactic processes via CCR1.

Proteolipid protein 2 (PLP2) has been shown to be upregulated in several cancers, including breast cancer, hepatocellular carcinoma, osteosarcoma, and melanoma. PLP2 specifically binds to phosphatidylinositol 3 kinase to activate the protein kinase B pathway to enhance cell proliferation, adhesion, and invasion in melanoma cells , see Ding et al (2015). They speculated that PLP2 exhibits oncogenic potential. However, they also reported that the regulatory mechanisms of PLP2 in cancer cells remain unclear.

Sonoda et al (2010) were able to show that knockdown of PLP2 with an artificial microRNA reduced growth and metastasis in B16BL6 melanoma cells.

Cadmium a heavy metal poison is now shown as being able to regulate gene expression. It induces modifications of the expression level of genes coding for members of stress response-, mitochondrial respiration-, MAP kinase-, NF–κB-, and apoptosis-related pathways. Longo et al (2012) showed that PLP2 (proteolipid protein-2)was a novel member of the list of Cd-upregulated genes. Further, through the application of transfection techniques with specific antisense oligonucleotides, they demonstrated that such over-expression may be an upstream event to some of the changes of gene expression levels already observed in Cd-treated cells, thus unveiling new possible molecular relationship between PLP2 and genes linked to the stress and apoptotic responses.

Del Marmol (PhD Thesis 2016) has shown that Plp2 amplifies the magnitude and slows down the kinetics of the Piezo1 mechano-sensing ion channel. Another protein, Cd63, is also a transmembrane protein that only amplifies the magnitude of Piezo1 currents, with no modification of its kinetics, in heterologous expression. Given the remarkably large set of functions that have been attributed to Piezo channels 6,7,8,9 in the very few years since its discovery, and how little we still know of its functional mechanisms, the identification of novel modulators provides a crucial next step in elucidating the molecular basis of mechano-sensation.

One recently published study proposed some intriguing effects of music on the well-known breast cancer cell line MCF-7. The authors of this study reported that exposing MCF-7 cells to sound pressure of 70–100 dB induces changes in cell cycle, cell viability and morphological changes. Despite this interesting observation, perhaps a better understanding of Piezo 1 and Plp2 will lead to an explanation for these findings in vitro?

Mechanical tension generated within the cytoskeleton of living cells is emerging as a critical regulator of biological function in diverse situations ranging from the control of chromosome movement to the morphogenesis of the vertebrate brain, see Chicurel (1998).

Mutant forms plp2-ts cells have increased sensitivity to cytoskeletal destabilizing drugs such as Benomyl and Latrunculin, see Stirling et al (2007), and are larger than wild-type cells. (A) Benomyl and latrunculin sensitivity of plp2-1 and plp2-2 mutants relative to wild-type (PLP2) cells, as determined by relative clearance caused by drug-inoculated paper discs when grown at the semi permissive temperature of 30°C.

Latrunculin A is isolated from the nudibranch Chromodoris sp. Houssen et al (2006) studied its effects on the electrophysiological properties of cultured dorsal root ganglion neurones. Latrunculin A alone had no effect on intracellular Ca2+. However, under voltage-clamp conditions, significant and dose-dependent suppression of K+ current was seen with 10–100 μM latrunculin A. See, Na+/Ca2+ selectivity in the bacterial voltage-gated sodium channel NavAb Research article Biophysics Computational Biology Ben Corry Published February 12, 2013.

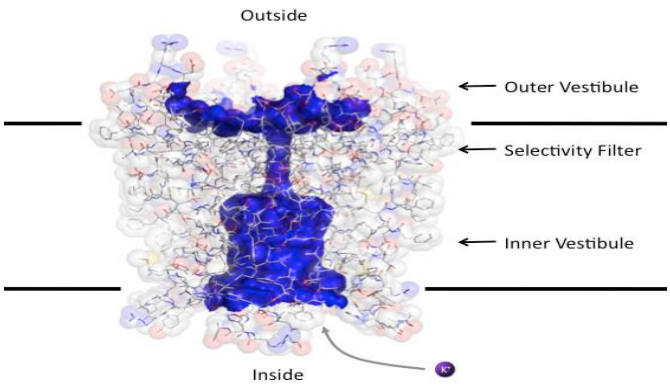
I thus hypothesise that the frequencies employed have a similar effect on PLP2 to Latrunculin and this is because they effectively suppress K+ current. Hence we have the link for reduced PLP2 **and** another explanation of the observed damage to the mitotic spindle. With TTF's the K+ efflux may be being suppressed as a product of the reduced calcium influx but also directly by blocking of the Potassium channel in the selective filter and/or hydrophobic regions of the channels. Once again, this is entirely consistent with the theory.

Besides electromagnetic waves it may even be possible to produce similar effects with sound or modulated ultrasound.

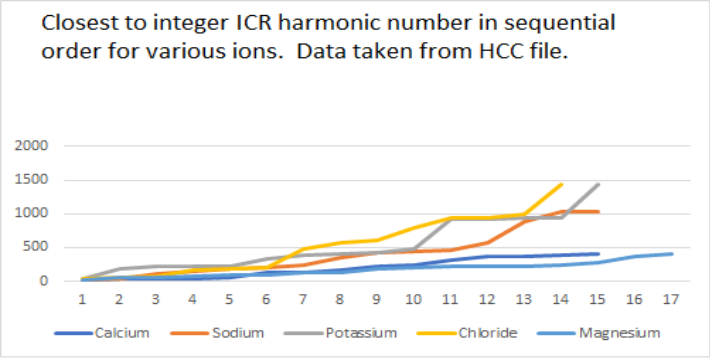
The biological effects of electromagnetic waves are widely studied, especially due to their harmful effects, such as radiation-induced cancer and to their application in diagnosis and therapy. However, the biological effects of sound, another physical agent to which we are frequently exposed have been considerably disregarded by the scientific community. Although a number of studies suggest that emotions evoked by music may be useful in medical care, alleviating stress and nociception in patients undergoing surgical procedures as well as in cancer and burned patients, little is known about the mechanisms by which these effects occur. It is generally accepted that the mechanosensory hair cells in the ear transduce the sound-induced mechanical vibrations into neural impulses, which are interpreted by the brain and evoke the emotional effects. In the last decade; however, several studies suggest that the response to music is even more complex. Moreover, recent evidence comes out that cell types other than auditory hair cells could response to audible sound. However, what is actually sensed by the hair cells, and possible by other cells in our organism, are physical differences in fluid pressure induced by the sound waves. Therefore, there is no reasonable impediment for any cell type of our body to respond to a pure sound or to music. Hence, the aim of the present study was to evaluate the response of a human breast cancer cell line, MCF7, to music. The results' obtained suggest that music can alter cellular morpho-functional parameters, such as cell size and granularity in cultured cells. Moreover, our results suggest for the 1sttime that music can directly interfere with hormone binding to their targets, suggesting that music or audible sounds could modulate physiological and pathophysiological processes. I hypothesise that Piezo 1 and 2 are responsible for the above.

Further Discussion and Advanced Analysis.

It is documented that potassium loses all water in the selectivity filter.



This is entirely consistent with the great majority of close integer ICR harmonics for potassium falling at the highest TTF frequencies. I propose antiphase interference in the selectivity filter limits the K+ current suppressing PLP2 causing loss of cytoskeleton and interference with mitosis. I further propose that disturbance to potassium current suppresses kinesin motors. This is documented at least in the neuronal case, see Barry et al (2013).



Plot 1

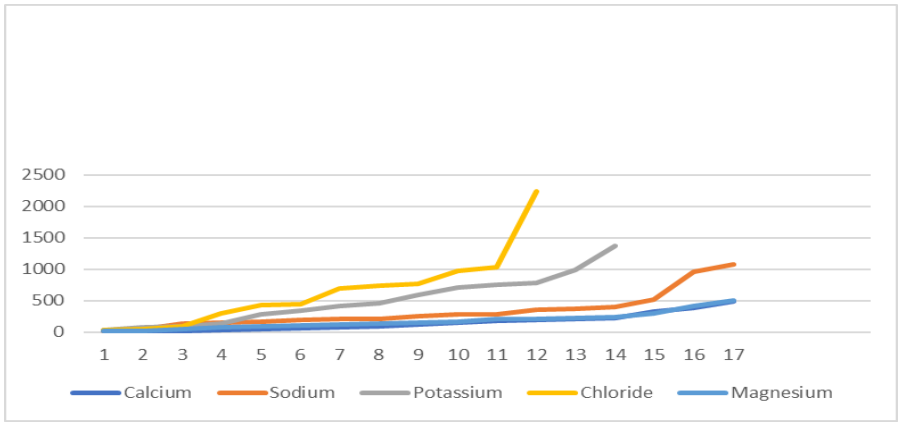
On the other hand the literature teaches us that sodium ions are mostly hydrated in the wide pore and for the most part one can see from Plot 1 above that for the greater part of the TTF frequency range the sodium curve falls well below potassium indicating more hydration.

Additionally, the literature teaches that chloride in ion channels is totally dehydrated and for 78% of the TTF range we see that chloride has higher integer like ICR harmonics than all the other ions exactly as predicted by both the dielectric model and/or the angular momentum model.

Finally, the literature teaches us to expect that Calcium should be slightly less hydrated than magnesium upon deeper progression into the pore with 3-4 water molecules as opposed to 6 and once again this appears to borne out by the result wherein from some 60% through the TTF frequency range from low to high, calcium overtakes magnesium in terms of the magnitude of near integer ICR harmonic values. Although at very high TTF frequencies magnesium appears as though it is overtaking calcium as it starts to be stripped of water in the selectivity filter.

Whereas the fundamental ICR frequency will be a property of ions in isolation, the harmonic frequencies will be very much a product of ion and channel in tandem. There are multiple types of each channel expressed due to genetic variation in excitable tissue and tumour tissue.

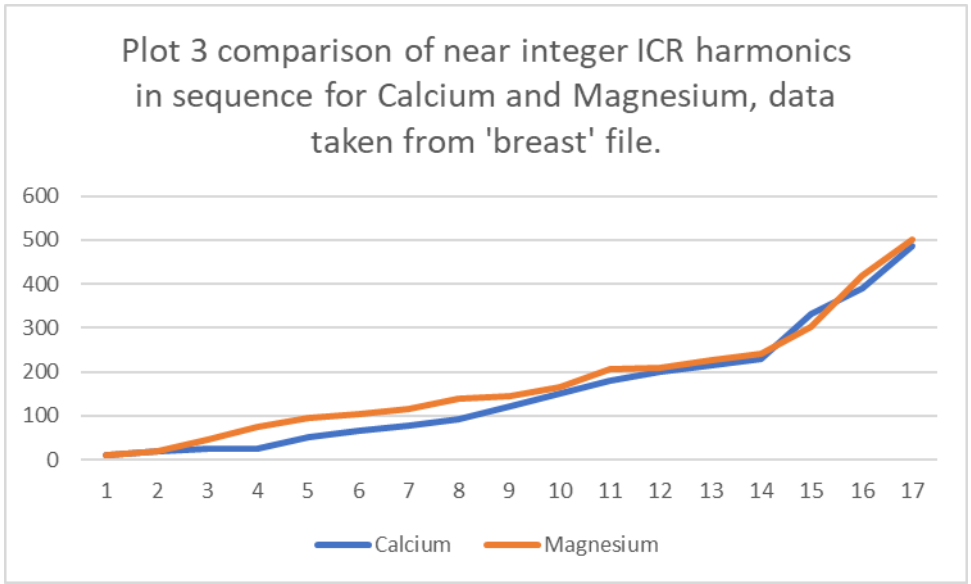
Plot 1 is an a sense a snapshot of total 'channelopathy' for HCC. We should therefore expect to see some similarities form what is known of ion channels in general and some differences in the case of breast cancer. Additionally, different genetic variations of ion channels are expressed and utilised by cancer cells at different stages of metastasis.



Closest to integer ICR harmonic number in sequential order for various ions. Data taken from breast file

Plot 2

Considering plot 2 then, the result for breast cancer. The same general trends are present Chloride, Potassium and Sodium as with HCC Plot 1. At first sight, however, on the scale of plot 2 calcium and magnesium appear indistinguishable. It is thus instructive to plot them on a more appropriate scale. See Plot 3 below:



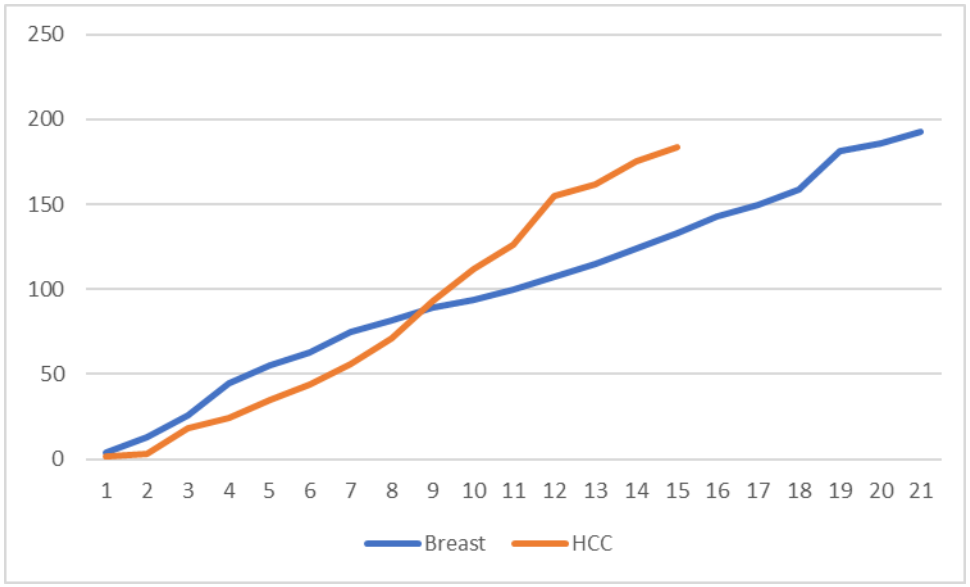
The literature teaches us that magnesium has 6 water molecules in the pore whereas calcium has 7. I would this expect calcium to show lower near integer ICR harmonics then magnesium

which is exactly as is observed. Moreover, magnesium loses more water in the selectivity filter, borne out by its slight tendency to overtake calcium at the very highest TTF's.

From between circa 30-50% the TTF frequency range magnesium is higher than calcium by a factor of circa 1.56. The radius of the entity has increased by a factor of about 1.16. Thus the volume of the entity has increased by 1,16^3 =1.56. A near perfect agreement.

Furthermore if I treat the system as a spherical mass and spherical capacitor this is totally supportive of the combined dielectric and angular momentum hypothesis which I initially advanced.

Voltage gated proton channels are almost unique in that the proton is transported as simply the native bear entity and not as H3O+ as in solution (ref). This is the case even in water filled gramicidin pores (ref). I would thus expect the sequential plot for near perfect ICR harmonic fits to be virtually linear across the range of TTF'S.



Plot 4 : Near perfect ICR harmonic fits TTF range frequency number versus sequence number

It is seen from plot 4 that there is considerably more linearity when compared with ions that suffer staged dehydration through the channel, i.e plots 1-3. This is exactly as predicted.

Using the specific frequency files to inform on specific cancers

By extension of the hypotheses developed and tested above one can make the following additional and testable assumption which is that ICR at the fundamental frequency only requires an ion in water as for example with observations on glutamic acid (refs), but that very large ICR harmonics are only observed with ion channels where the water structure is very different from the bulk and/or where there is angular momentum coupling. There is some limited evidence in the literature of ICR at low to moderate harmonic frequencies without reference to ion channels and I suspect this is because these are the ICR frequencies associated with smaller than usual water clusters.

Extending the above assumption to its natural conclusion suggests that the more close to integer higher harmonic frequencies of ICR there are present for a particular ion channel in a particular patient with a particular cancer then the more of these channels there will be physically expressed. This is highly testable by referring to table 2.

Pasche and Zimmerman have stated that the random frequencies did not elicit a biofeedback response in any patients and moreover that the TTF frequencies did not elicit a blood pressure or pulse rate biofeedback response in patients without cancer.

If we consider the random frequencies then all we can do is to calculate the harmonics of ICR and see where they fall. It is logical to suppose that there will be genetic variations of ion channels expressed in the excitable tissue of cancer patients which are also expressed in their tumours. Therefore the immediate upshot of this would be to expect to find a greater percentage of very close or reasonably close integer fits to ICR harmonics related to excitable tissue types in the HCC and Breast cancer treatment files than in the random file. The voltage ion channels associated with muscle include for instance; sodium, calcium, magnesium,

chloride and proton. All of which show up significantly more very close or reasonably close integer fits to ICR harmonics in both the HCC file and the breast file than in the HCC file, see figure 2. Very interestingly zinc channels appear to be depleted in both the cancer TTF files in contrast with zinc channels expected on a random basis, circa 17.5% fits are found as opposed to circa 22% in the random case. Costello and Franklin (2014) have discussed the basis is presented for characterizing HCC malignancy as zinc transporter ZIP14-deficient tumours, and its requirement to prevent zinc cytotoxic effects on the malignant cells. They also discuss the potential for an efficacious zinc treatment approach for HCC. In this respect not only are TTF's shown to be a treatment modus operandi but also one of diagnosis. Indeed, zinc deficiency may be a hallmark of several cancers.

Besides cell membrane channels we may also consider TTF activation of mitochondrial channels. The main channel of interest is VDAC1 which favours chloride in the open state and small cations in the closed state. Inhibiting VDAC1 cause apoptosis. The proapoptotic effect of VDAC1 is due to its physical interaction with the IP3 receptor and to its formation of the molecular route for transferring Ca2+ signals to mitochondria in apoptosis. I postulate that high ICR harmonic chloride TTF's favour the closed (inhibited) state. It is very exciting to note that the anti-fungal drug Itraconazole inhibits in the same manner and has recently been shown highly effective against bowel cancer. I view TTF as the physical equivalent of this drug in the case of this ion channel.

I will now deal specifically with HCC and breast cancer in turn.

HCC Specific Observations

Referring then to table 2, Sodium channels would appear to be far more expressed in the HCC case than the breast case, 24.1% as opposed to 15.38% of the total 194 treatment frequencies considered give very close or reasonably close integer fits to ICR harmonics. ASIC1α is overexpressed in HCC tissues and associated with advanced clinical stage. is overexpressed in HCC tissues and associated with advanced clinical stage. ASICS can non-selectively transport sodium. Scn2a1 sodium channel is also involved in HCC, see Zuniga-Garcia (2015). NaV sodium channels are known to be associated with proliferation, see Rao et al (2015).

However, no specific reference can be found to sodium channels of any specific kind being solely associated with HCC.

Again, referring to Table 2 there are an apparent large expression (25% of the TTF's) of Lithium channels, some 10% greater than random. Whether there is a specific human lithium channel is unclear (check) but ASIC1 is known to be an excellent lithium transporter and is know to be overexpressed in HCC with poor outcome, see Jin et al (2015) and Jin et al (2017). Strangely lithium has been used in the treatment of some human cancers but is known to cause changes in Micro RNA so could be a double-edged sword?

Both magnesium and chloride show approximately 20% of the total 194 frequencies as close or reasonably close integer harmonic fits and calcium 21.5%, some 3.4% greater than random. All three of these well exceed the results for the random file. HCC CSCs overexpress the calcium channel $\alpha 2\delta 1$ subunit, see Sainz (2013). Calcium channel blockers have been used in HCC treatment (refs). Cell migration and invasion are two prerequisites for tumor metastasis, in which TRPM7 in HCC plays an important role, see Chen et al (2016). Chloride intracellular channel 1 participates in migration and invasion of hepatocellular carcinoma by targeting maspin, see Wei et al (2014).

Relative to other neutral amino acid transporters, the expression levels of ASCT2 and LAT1, are co-ordinately elevated in a wide spectrum of primary human cancers. There seems to be a greater percentage of asparagine harmonics in the HCC case and the ASCT2 transporter would be the candidate here. Likewise, they can transport serine also found to be elevated, see Table 2.

Next, I consider small amino acid ions. Serine and glutamine and arginine appear to be suppressed relative to the random expectation. Asparagine appears to be elevated.

Hirayama et al (1987) studied plasma amino acid levels in 23 patients with HCC in comparison with 16 normal subjects and 17 patients with liver cirrhosis. Patients with hepatocellular

carcinoma had elevated levels of the aromatic amino acids and lowered levels of the branched-chain amino acids, as seen in liver cirrhosis; however, they had lowered levels of alanine and glutamine as compared with normal subjects and with liver cirrhosis patients. Following treatment with intraarterial chemotherapy and/or transcatheter arterial embolization, plasma levels of alanine and glutamine recovered. These results suggest that the consumption of alanine and glutamine increase in hepatocellular carcinoma. Moreover, among the other amino acids, asparagine, citrulline, ornithine, and cysteine were also elevated.

Thus, I have shown the TTF technique not only to be a treatment technique but also a powerful diagnostic technique with the power to make a certain amount of differential diagnosis.

Breast Cancer Specific Observations

In the case of the breast cancer file and near of very near harmonic ICR fits, I conclude that the three most overexpressed ion channels are Calcium, 24.2% of TTF, Potassium 22.1% of TTF, and Magnesium 20.1% of TTF. These represent increases of 6%,5,8% and 3.22% over the randomly hit ICR harmonics.

Interestingly, Tamoxifen (Tx) has been used in breast cancer treatment and prophylaxis because of its antiestrogenic activity however it has also been shown to inhibit voltage-gated calcium current and contractility in vascular smooth muscle from rats, see Song et al (1996).

Store-operated calcium (Ca2+) entry (SOCE) mediated by STIM/Orai proteins is a ubiquitous pathway that controls many important cell functions including proliferation and migration. STIM proteins are Ca2+ sensors in the endoplasmic reticulum and Orai proteins are channels expressed at the plasma membrane. The fall in endoplasmic reticulum Ca2+ causes translocation of STIM1 to subplasmalemmal puncta where they activate Orai1 channels that mediate the highly Ca2+-selective Ca2+ release-activated Ca2+ current (ICRAC). Whereas Orai1 has been clearly shown to encode SOCE channels in many cell types, the role of Orai2 and Orai3 in native SOCE pathways remains elusive. Motiani et al (2010) analyzed SOCE in ten breast cell lines picked in an unbiased way. They used a combination of Ca2+ imaging, pharmacology, patch clamp electrophysiology, and molecular knockdown to show that native

SOCE and ICRAC in estrogen receptor-positive (ER+) breast cancer cell lines are mediated by STIM1/2 and Orai3 while estrogen receptor-negative (ER−) breast cancer cells use the canonical STIM1/Orai1 pathway. The ER+ breast cancer cells represent the first example where the native SOCE pathway and ICRAC are mediated by Orai3. Future studies implicating Orai3 in ER+ breast cancer progression might establish Orai3 as a selective target in therapy of ER+ breast tumors.

I have already shown that the TFF's are acting in a way either to block calcium influx or cause efflux, see earlier.

Abdul et al (2003) working with MCF 7 breast cancer cells showed that some 85% had high or moderate expression of Kv 1.3. Potassium channel openers enhanced their proliferation whereas potassium channel blockers dequalinium and amiodarone showed a remarkable 90% inhibition. I have already suggested that the TTF frequencies employed have a similar effect on PLP2 to Latrunculin and this is because they effective suppress K+ current. Hence not only did I provide the link for reduced PLP2 and offer another explanation of the observed damage to the mitotic spindle but this type of argument is now also supported from the above.

Moreover Woodfork et al (1995) investigated nine different potassium channel antogonists with regard to differential sensitivity of cell proliferation and cell cycle progression and conclude that ATP-sensitive potassium channels in these human mammary carcinoma cells reversibly arrests the cells in the GO/G1 phase of the cell cycle, resulting in an inhibition of cell proliferation.

Trapani et al (2013) discuss magnesium. In vivo, magnesium deficiency, and the resulting inflammation, can trigger both anti- and pro-tumour effects. Recent experimental evidence indicates that altered expression of the transient receptor potential melastatin, type 7 (TRPM7) epithelial magnesium channel is a frequent finding in cancer cells and human tumour tissues,

and correlates with cell proliferation and/or migration. Guilbert et al (2009) also provide evidence that TRPM7 is required for breast cancer cell proliferation. This supports the notion of it showing up in the TTF spectrum.

A few references discuss raised sodium channel expression in breast cancer but this does not appear to be borne out for the TTF file provided.

Finally, I considered some common amino acid ions as there transporters are also common and important in biology. Regarding the Breast TTF file I show that Tyrosine and Histidine are some 4% higher than the random expectation, serine is come 2% higher and glutamine and asparagine.

The observation regarding serine is interesting. Serine is of course a component of the protein kinase C (PKC) family of serine/threonine kinases has been intensively studied in cancer since their discovery as major receptors for the tumor-promoting phorbol esters (ref). PKC comprises 10 phospholipid-dependent serine-threonine kinases grouped into three subclasses: the "classical" (PKC α, βI, βII, and γ), which can be stimulated by Ca2+ and diacylglycerol (DAG) or phorbol esters; the "novel" (PKC δ, ε, η, and θ), which can be activated by diacylglycerol or phorbol esters but are Ca2+ independent; the "atypical" (PKC ζ and λ/ι), which are unresponsive to Ca2+, diacylglycerol, and phorbol esters. The structure of classical PKCs includes four conserved domains (referred as C1–C4) interrupted by five variable regions (V1–V5). The C1 region contains cysteine-rich zinc-finger-like motifs responsible for phosphatidylserine, DAG, and phorbol esters binding. An autoinhibitory pseudosubstrate (Ps) sequence is located at the N-terminal region of PKCs that is involved in autoinhibition. The C2 region in classical PKCs is rich in acidic residues and binds Ca2+. The C3 and C4 regions form the ATP- and substrate-binding lobes. Novel PKCs have an altered C2 region unable to bind Ca2+, and atypical PKCs are insensitive to Ca2+ and have only one cysteine-rich zinc-finger-like motif that is unable to bind DAG or phorbol ester.

Next considering tyrosine, mapping of homozygous deletions on human chromosome 10q23 has led to the isolation of a candidate tumor suppressor gene, PTEN, that appears to be mutated at considerable frequency in human cancers. In preliminary screens, mutations of PTEN were detected in 31% (13/42) of glioblastoma cell lines and xenografts, 100% (4/4) of prostate cancer cell lines, 6% (4/65) of breast cancer cell lines and xenografts, and 17% (3/18) of primary glioblastomas. The predicted PTEN product has a protein tyrosine phosphatase domain and extensive homology to tensin, a protein that interacts with actin filaments at focal adhesions. These homologies suggest that PTEN may suppress tumor cell growth by antagonizing protein tyrosine kinases and may regulate tumor cell invasion and metastasis through interactions at focal adhesions. The HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells, see Pietras et al (1995). Of course tyrosine is one of its major components and so we have another link here.

Finally, considering glutamine which appears to be in short supply rather as zinc. These findings suggest that dietary GLN supplementation suppresses mammary carcinogenesis by activation of apoptosis in tumor cells and this probably is a result of GSH down-regulation. Todorova et al (2004) have shown that at least in rats, dietary GLN supplementation suppresses mammary carcinogenesis by activation of apoptosis in tumour cells and this probably is a result of GSH down-regulation.

Once again, I have highlighted the depth and power of the TTF technique.

Link between mechanical models, solitons and ICR frequencies.

The first evidence I shall borrow is from a discussion of action potential in neuronal membrane, see El Hady and Machta (2015). Many diverse studies have shown that a mechanical displacement of the axonal membrane accompanies the electrical pulse defining the action potential (AP). In their model, mechanical displacements arise from the driving of surface wave modes in which potential energy is stored in elastic properties of the neuronal membrane

and cytoskeleton while kinetic energy is carried by the axoplasmic fluid. Further surface waves are driven by the travelling wave of electrical depolarization characterizing the AP, altering compressive electrostatic forces across the membrane. This driving leads to co-propagating mechanical displacements, which we term Action Waves (AWs). The shape of the AW that accompanies any travelling wave of voltage, is in excellent agreement with results from several experimental systems. This model is useful in understanding the effects of TTF as there would seem to be very predictable phase relationships. This can link ICR frequencies and MT mechanical resonance ideas.

JA Tuszyński (2004) has also discussed ionic waves in actin filaments. Gelens et al (2014) discuss the link between ionic waves and mitotic waves in theor paper 'Spatial trigger waves: positive feedback gets you a long way.'

Prindle et al (2015) show that ion channels **conduct long-range electrical signals** within bacterial biofilm communities through spatially propagating waves of potassium. These waves result from a positive feedback loop, in which a metabolic trigger induces release of intracellular potassium, which in turn depolarizes neighbouring cells. Propagating through the biofilm, this wave of depolarization coordinates metabolic states among cells in the interior and periphery of the biofilm. Deletion of the potassium channel abolishes this response. As predicted by a mathematical model, we further show that spatial propagation can be hindered by specific genetic perturbations to potassium channel gating. Together, these results demonstrate a function for ion channels in bacterial biofilms, and provide a prokaryotic paradigm for active, long-range electrical signalling in cellular communities.

Becchetti (2011) provides a convincing demonstration that ion channels modulate cell proliferation which ultimately relies on results showing that their activity is absolutely key to regulation of the cell cycle checkpoints.

Little wonder then that TTF's via their here proven interference on ion channels alter the mitotic spindle. Some have attempted to show that the TTF mode of interaction is purely

one of mechanical resonance. The fact that biology exhibits long range solitonic transport and positive feedback means we cannot escape the TTF interaction with the ion channel, whether chicken or egg.

Conclusions

1. A new hypothesis of ICR allowing for very high harmonic frequencies to develop upon dehydration due to lowered dielectric constant and conservation of angular momentum is developed and tested. The importance of GMF (local geomagnetic field) is emphasised.
2. A plausible hypothesis for the involvement of ion channels in the TTF technique of Zimmerman and Pasche had been tested and strongly supported.

3. The system has been shown to be different from that of Kirson.
4. A putative link between inflammation, invasion and metastasis and intra-cellular Ca2+ ion concentration has been proposed wherein it seems the TTF modulated signal is acting rather like Infliximab and in this case causing Ca2+ efflux or slowing Ca2+ entry, hence downregulating XCL2. Either way the action, brought about by the tumour treating frequencies modulated onto the 27.12 MHz signal is deep within the hydrophobic part of the channel as identified by the high ICR harmonics present. There is a distinct breakpoint in the spread of the ICR Harmonics for calcium across the TTF frequency spectrum. This is consistent with the progressive dehydration of calcium as it passes through the pore and as documented in the literature and is also equally consistent with a combination of both the dielectric and angular momentum models which I have proposed.

5. Unlike previous authors which only focus on electromagnetic interaction with calcium ions as a second messenger, it has been shown that all sorts of ion channels and transporters can interact through ICR with their ions and/or ligands. Indeed I have shown that the TTF's also effectively suppress K+ current giving the link for reduced PLP2 and another explanation of the observed damage to the mitotic spindle.

6. Simple sequential plots of closest to integer ICR harmonic numbers for the two treatment files yield ‘channelopathy’ like results showing break-points at places which can be interpreted as corresponding to those of known dehydration such as the narrow pore and selective filter.

7. (5) above is reinforced by considering the result for voltage gated proton channels where as expected the plots are essential linear and have no sharp breakpoints.

8. Detailed cancer specific observations of overexpressed and under expressed channels and transporters for the two cancers compared with the random file have been made and full explanations in terms of the known biochemistry have been offered. Considerable success is also shown when considering amino acids.

Further work

It is envisaged that the technique will be developed as a new realm of contactless and drug free electronic medicine, not only for cancer treatment but also for all kinds of other medicine where antagonist or protagonist modification of specific ion transit in membrane channels may be desirable or advantageous.

I am presently conducting further studies based on re-analysis of Zimmerman’s data in comparison with the soliton condensate frequencies supplied by Geesink and Meijner (G&M) in an to unify the frequencies of the ion hypothesis developed here with the notions of Priel (2006) and Sekulic (2011) considering both solitonic ionic waves along the microtubule axis and the transition rate of ion channel opening and closing, local membrane conductivity, and vesicle trafficking.

G&M have recently made such a comparison and concluded there is no such correlation. However, I believe their argument to fundamentally flawed as they do not seem to appreciate the crucial dependence of the ICR frequencies on geomagnetic field.