Comment of Dr. Dimitris J. Panagopoulos to the HHS Request for Information on EMFs, RF Radiation and Wireless Technologies

Docket HHS-OASH-2026-0397. Filed October 12, 2026. Posted by HHS as Comment ID HHS-OASH-2026-0397-3190: https://www.regulations.gov/comment/HHS-OASH-2026-0397-3190 (the 11 attached papers are listed there). Text below reproduced exactly as submitted.

Comment of Dr. Dimitris J. Panagopoulos, PhD, EMF biophysicist, Choremeion Research Laboratory, Medical School, National and Kapodistrian University of Athens, Greece. Submitted on his behalf and with his written permission by Nicolas Pineault, citizen journalist and author. The content is Dr. Panagopoulos's own published work and his written interview, attached without alteration.

Q2 (perspective): research entity. Basis: peer-reviewed research, cited with links.

Questions addressed: 5(p), 6, 12, 16.

Q5(p), signal characteristics a classification system should account for. All digital wireless communication signals are emitted as on/off pulses repeated at extremely low frequency (ELF) rates, with intense variability in amplitude, shape, duration and repetition frequency; they are not continuous-wave radiofrequency carriers. These ELF pulsations were recorded directly from a Wi-Fi router and from 4G and 5G phones in Panagopoulos, Litovsky and Chamberlin 2026 (Electromagnetic Biology and Medicine, https://doi.org/10.1080/15368378.2026.2654072; response to comments: https://doi.org/10.1080/15368378.2026.2707966). Human-made fields are also fully polarized and coherent, unlike natural fields (Panagopoulos, Johansson and Carlo 2015, Scientific Reports, https://doi.org/10.1038/srep14914). Modulation, pulse characteristics, duty cycle, polarization and low-frequency variability therefore belong in any exposure classification.

Q6 and Q12, evidence of effects below current limits, and a mechanism. In human peripheral blood lymphocytes, a 15-minute exposure to real mobile phone emissions at a power density about 136 times below the current ICNIRP limit was genotoxic by itself and significantly enhanced the chromosomal damage induced by gamma radiation, beyond the sum of the two exposures (Panagopoulos 2024, General Physiology and Biophysics, https://doi.org/10.4149/gpb_2023036). Related findings: synergy with a high caffeine dose (2020, https://doi.org/10.4149/gpb_2020036) and comparison of DNA damage from mobile telephony versus power-line fields in Drosophila cells (2019, https://doi.org/10.1016/j.mrrev.2019.03.003). The Ion Forced Oscillation and Voltage-Gated Ion Channel mechanism explaining how these fields trigger oxidative stress and DNA damage is set out in Panagopoulos et al. 2021 (International Journal of Oncology, https://doi.org/10.3892/ijo.2021.5272) and 2025 (Frontiers in Public Health, https://doi.org/10.3389/fpubh.2025.1585441), both open access.

Q16, research priorities. Combined exposure to wireless fields with other stressors (ionizing radiation, chemicals) produced more damage than the sum of the separate exposures in the studies above. Research on combined exposures, and standardized measurement of the ELF components of wireless emissions, are the gaps these results point to.

The attached interview (Pineault, September 18, 2024, https://theemfguy.com/emf-dangers-panagopoulos) sets out Dr. Panagopoulos's views on these questions in his own words.

Attached: the interview; PDFs of the cited papers. Edited volume: Electromagnetic Fields of Wireless Communications: Biological and Health Effects, CRC Press, 2022, https://www.routledge.com/Electromagnetic-Fields-of-Wireless-Communications-Biological-and-Health-Effects/Panagopoulos/p/book/9781032061764. Full publication list: https://www.researchgate.net/profile/Dimitris-Panagopoulos-3

EMF Dangers: “The Evidence Today Is Overwhelming And Indisputable”

Interview with EMF-biophysicist Dr. Dimitris J. Panagopoulos

By Nick Pineault | Published September 18, 2024 | https://theemfguy.com/emf-dangers-panagopoulos/

Years after writing “The Non-Tinfoil Guide to EMFs”, where I argued that our current use of human-made EMFs (cell phones, Wi-Fi, Bluetooth, cell towers, etc.) is reckless, irresponsible and one of the very likely root causes of the modern epidemic of chronic disease… I still find myself regularly arguing with “skeptics” who tell me that:

- There are no credible scientific studies showing that human-made EMFs cause harm
- Anyone who argues that EMFs might be dangerous should wear a tinfoil hat and is delusional or paranoiac
- There are *zero* known mechanisms that could explain how “low levels” of EMFs can cause harm
- Human-made EMFs from phones, Wi-Fi or Bluetooth gadgets are “non-ionizing”, and therefore cannot possibly damage your DNA or cause any kind of harm
- Sunshine exposes you to an incredible amount of of radiation, which demonstrates that cell phones could not possibly harm you at such low levels of power

I see one form or another of the arguments above being used by PhDs in physics, medical doctors, professional “skeptics”, science writers, and of course, electrical engineers.

Instead of arguing with them – Hey, I’m just a citizen journalist trying my best to figure things out after all! – I decided to ask one of the most recognized scientists in the field of the biological and health effects of EMFs what *he* thinks.

Are human-made EMFs safe or dangerous? Are there mechanisms that could explain EMF damage? Have I lost my mind? Was Elon Musk right after all?

I sent several questions to **EMF-biophysicist Dr. Dimitris J. Panagopoulos.** Here’s what he had to say.

EMF-biophysicist Dr. Dimitris J. Panagopoulos works at the Choremeion Research Laboratory, Medical School, National Kapodistrian University of Athens, Greece. His experiments were among the first that showed damaging effects of microwaves and other types of man-made EMFs on DNA and reproduction. His theory on the biophysical mechanism of action of EMFs on cells also known as “ion forced-oscillation mechanism” is considered the most plausible. He has explained why man-made polarized EMFs are much more damaging than natural unpolarized EMFs, and why highly varying Real exposures from mobile phones and other microwave devices are much more damaging than simulated exposures with invariable parameters.[1]

Definitions:

- WC: Wireless Communication (mobile/smart phones, Wi-Fi, Bluetooth, cell towers, etc.)

- EMFs: Electromagnetic Fields
- RF: Radio-Frequency radiation (mobile/smart phones, Wi-Fi, Bluetooth, cell towers, etc.)
- VGICs: Voltage-Gated Ion Channels
- mV: Millivolts
- ROS: Reactive Oxygen Species
- OS: Oxidative Stress
- EHS: Electro-hypersensitivity
- AC: Alternating Current
- Anthropogenic EMFs: Human-made electromagnetic fields (including Wireless Communication, but also other types like dirty electricity, AC electric fields, AC magnetic fields, power line electric and magnetic fields, etc.)
- MT: Mobile Telephony (mobile/“smart” phones)
- km: Kilometers

1) Your recent paper “Mobile telephony radiation exerts genotoxic action and significantly enhances the effects of gamma radiation in human cells” showed that radiofrequency radiation enhanced the genotoxic action of gamma radiation.

Considering that planes are now filled with Wi-Fi (radiofrequency) emissions, what are the implications of this study on pilots or flight attendants, or passengers?

The experiments described in this paper showed that wireless communication (WC) electromagnetic fields (EMFs)/radiation act synergistically with ionizing (gamma) radiation. Similarly, previous experiments (Panagopoulos 2020)[3] have shown that they also act synergistically with caffeine. **This means that combined exposure to various stressors induces significantly more biological damage than the exposure to the separate stressors.**

And, in fact, more than that: The combined exposure in both cases (with gamma or caffeine) induced more aberrations than the sum of the aberrations induced by the separate exposures. Today, people are exposed daily not only to WC EMFs, but also to a variety of other stressors like chemicals, pharmaceuticals, psychological stress, etc.

On airplanes during flights, people are exposed to increased levels of ionizing radiation of cosmic and solar origin. Every form of ionizing radiation is significantly more genotoxic and carcinogenic than man-made EMFs. The use of “smart” phones, tablets, and other devices connecting wirelessly to the Internet during flights makes all people exposed in the plane even more vulnerable to the increased ionizing radiation.

Moreover, the electromagnetic radiation from the WC devices gets trapped and increased within the metallic cage of the plane which acts like a “Faraday cage” exposing every passenger and crew member to significant EMF levels. **If authorities were to protect public health, the use of WC devices should be strictly prohibited not only in airplanes but also in all public transport vehicles (trains, buses, etc.).**

I should also say that all types of WC EMFs (from mobile/cordless phones, Wi-Fi, etc.) are not simply radiofrequency (RF) emissions. They consist of modulated RF (300 kHz-300 GHz) EMFs emitted in the form of on/off pulses repeated at various Extremely Low Frequency (ELF: 0-3000 Hz) rates, and displaying intense variability in intensity, frequency and other parameters, mainly in the Ultra Low Frequency (0-3 Hz) band. In other words they are a combination of high and low (RF/ELF/ULF) frequency emissions.

2) It has been claimed recently that “power level is irrelevant” when it comes to the biological effects of man-made electromagnetic radiation.

The argument included, for example, the idea that “It takes little or no power to interfere with life” and that “low power can be more harmful than high power”.

Do you agree with these statements?

No, I do not agree.

The effects of all anthropogenic EMFs, including WC, are dose-dependent and increasing with increasing power density (intensity) levels in the vast majority of the cases. **But they are not always increasing linearly (doubling the exposure level does not necessarily double the effect).** Occasionally, so-called “window” effects have been reported in the literature – where an effect can become maximal within certain values of the exposure parameters and be diminished for both lower and higher values. Several scientists including myself have reported such effects (Panagopoulos et al. 2010).[4]

The “window” effects are due to the fact that living tissue does not always respond linearly to an applied stressor/EMF. For example, the voltage-gated ion channels (VGICs) which are the natural EMF-sensors in all animal and plant cell membranes do not respond to any voltage change in the membrane, but only to membrane voltage changes of approximately between 30 and 100 millivolts (mV).

For greater voltage changes, the ion flow through the channel saturates. This is an energy saving mechanism which acts as a natural protection for the cell. I have argued that the explanation behind the “window” effects reported for a long time in the literature is actually the existence of this corresponding window (30-100 mV) in the gating (opening/closing) of the VGICs (Panagopoulos et al 2021)[5], and possibly also other biological “windows” or resonance phenomena that have not been yet discovered or are not yet understood.

In conclusion, the existence of non-linear effects in biology is a fact, but this does not justify statements that the power level is irrelevant.

If the power level was irrelevant, that would mean that whether you are exposed to a cellular base station antenna at a distance of 1 kilometer (km) or at a few meters would make no difference. That would also mean that keeping a mobile phone at a distance by using the speakerphone function or air-tube headsets during calls makes no difference compared to using the mobile phone close to the head/body, which is a totally misleading and dangerous idea.

That also would justify the current absence of any precaution in the use of WC devices, and the current practice of installing antennas anywhere close to houses and workplaces without keeping a safe distance of at least several hundred meters – depending on the emitting power.

3) In 2021, you published a landmark paper[6] where you demonstrated to have arrived at a "complete picture […] of how human-made EMF exposure may indeed lead to DNA damage and related pathologies, including cancer."

Can you please explain, in layman terms, how these human-made EMF exposures (including WC/wireless communications) impact human cells?

This paper addresses the biophysical mechanism of action of EMFs on cells. It explains how polarized and coherent (human-made) EMFs, including WC EMFs, can cause dysfunction of voltage-gated ion channels (VGICs). The VGICs (the natural EMF sensors in living organisms) are the most abundant class of ion channels in all animals (and plants), which demonstrates that all living organisms are basically electromagnetic in nature.

All processes in cells are initiated and mediated by ion flows (endogenous electric currents) through cells, tissues, and cell membrane ion channels. Irregular opening and closing (dysfunction) of VGICs as shown by this mechanism alters ionic concentrations in cells, triggering the (over)production of reactive oxygen species (ROS) by specific enzymes in the cells which normally produce ROS for physiological purposes, as e.g. protection from infectious microorganisms.

These enzymes are activated by alterations in the concentrations of various ions in the cells, like calcium, potassium, sodium, or proton ions. Prolonged overproduction of ROS in the cells is a condition of irritation/inflammation called oxidative stress (OS) which may easily result in various pathologies.

A relatively mild such "pathology" is what is called Electro hypersensitivity (EHS) at its first stages. Actually, in my view, this is not a pathology but a healthy reaction to an unnatural exposure which is the totally polarized and coherent (man-made) EMFs. If the person does not minimize the exposure at the early stages of EHS occurrence, the initial healthy reaction may become a serious pathology with unbearable symptoms. Continuing OS/ROS overproduction due to continuing exposure is connected with DNA damage induced by certain ROS which are particularly damaging, like the hydroxyl free radical or the peroxynitrite[7].

Those ROS can easily damage DNA and any other critical biomolecule. Irreparable DNA damage can lead to cell death or mutations, which in turn may lead to reproductive problems, organic diseases and cancer. Therefore, the biophysical mechanism initiates a cascade of biochemical events resulting in oxidative stress (OS) in the cells and the various pathologies reported in the literature. The OS was long ago reported to be induced by anthropogenic EMF exposure, and this paper explained why and how this occurs.

The same biophysical mechanism explains most if not all reported EMF bioeffects, including the "window" effects. It has also explained the ability of sensitive individuals to sense upcoming thunderstorms (Panagopoulos and Balmori 2017)[8] and the ability of certain animals to sense upcoming earthquakes (Panagopoulos et al 2020)[9] – through the action of the natural EMFs associated with these phenomena.

Lately, the same mechanism has explained one of the most known scientific problems: How migrating animals orient and navigate over thousands of kilometers (km) on Earth, finding exact locations by sensing the intensity and the direction of the geomagnetic field. Unfortunately, my coworkers and I have had problems publishing this paper – just like we had problems publishing other papers before (papers that have now become widely accepted and cited by hundreds of other studies).

Sadly, conflicts of interest and corruption in science have not left many of the major science journals unaffected. Certain people do not want this mechanism to be widely known and established. Instead, they favor other theories which are complicated and impossible, leading science nowhere. In fact, the adverse biological and health effects of human-made EMFs can now be thoroughly explained and confirmed, but they do not want this fact to be widely accepted – even though every true expert admits it.

They prefer to seed confusion, doubt, and ignorance in the public. Many scientists also promote this confusion in various ways whether they know it or not, by supporting, for example, impossible theories that lead nowhere.

4) I keep coming across statements like “non-ionizing radiation cannot possibly cause DNA damage” (from PhDs in physics), even though you and many of your colleagues have proven this to be completely false decades ago.

How do you think we’ll be able to pierce this veil of ignorance?

Such erroneous statements are made because some physicists and engineers confuse living tissue with inanimate matter. Living tissue does not respond to EMFs and other stressors like inanimate matter. It is far more complicated than that. A relevant statement would be “non-ionizing radiation cannot *directly* cause DNA damage”. But it can do that *indirectly* in living cells by causing VGIC dysfunction, which alters ionic concentrations in the cells – triggering the production of ROS as I explained above.

Then, the ROS can readily damage DNA and other critical biological molecules, as shown by many experimental studies where animals and cells were exposed to man-made EMFs. **Actually, Wireless Communication (WC) EMFs from mobile phones and other devices/antennas cause oxidative stress (OS) and DNA damage within minutes.** This in turn explains epidemiological studies that have connected man-made EMF exposure with cancer. [Nick’s note: For example, this 2018 review from Miller et al. shows that radiofrequency radiation should be re-classified as a Class 1 Definite carcinogen][10]

The above provides a full explanation of the biological mechanisms, but furthermore, the confidence of some people/scientists who claim that anthropogenic EMFs, at frequencies below those of infrared radiation, cannot cause ionization (break chemical bonds), comes from the erroneous and misleading assumption of modern quantum physics that any EMF consists of photons, regardless of how it is generated.

Based on this assumption, microwaves and other forms of anthropogenic EMFs, which have lower frequencies than infrared and visible light, “do not possess enough energy in their photons” to produce ionization. But **anthropogenic EMFs do not consist of photons**, as I have argued before (Panagopoulos 2018).[11]

They consist of continuous waves like those described by classical electromagnetism, not quantum physics. Continuous waves are not instantaneous emissions (photons). They can have durations that are trillions of times longer, and therefore, they may possess much greater energy than that of a photon, even when their frequency is much lower.

5) In your 2019 paper “Comparing DNA damage induced by mobile telephony and other types of man-made electromagnetic fields”[12], you confirmed your previous work that real mobile telephony (MT) devices cause more DNA damage than other types of man-made EMFs (ELF 50/60 Hz magnetic or electric fields).

Can you explain why these tests were conducted on Drosophila (fruit flies), and how applicable these results are to human beings?

These experiments were conducted on fruit flies because this insect is one of the best-studied and one of the most common laboratory animals in biology. They are small, clean and easy to keep in the lab, with a very good timing of developmental processes under controlled conditions, and a lifetime of about a month – which allows us to observe systemic (whole body) effects much faster than in humans or other animals, on top of many other advantages.

Most importantly, their cells – like in all insects – are essentially the same as mammalian (including human) cells. **They have identical types of cell membranes, proteins, ion channels, intracellular organelles, nuclei, DNA, and the same ions controlling all cellular processes.**

Considering that all biological and health effects are initiated within the cells, an effect found in Drosophila is absolutely expected to be found in mammals, including humans, and vice-versa. Even though its lifetime is too short to develop cancer, this animal is used for cancer research due to its genetic similarities with mammals and humans.

In my experiments, DNA damage was found in both fruit fly and human cells, to a similar degree, after they were exposed to mobile phone radiation or other types of human-made EMFs. As you noted, it was shown that mobile phone EMFs cause more damage than power line EMFs [Nick’s note: AC electric and magnetic fields], which have been linked to cancer for a long time.[13]

6) Many EMF scientists have faced systematic attacks throughout their career.[14]

Considering that you co-authored and edited the most thorough book[15] ever written on the biological and health effects of human-made EMFs in 2023, do you feel that things are changing, now that the published literature is becoming harder and harder to ignore?

Indeed, some of the pioneer scientists who first reported DNA damage and other important biological effects in the 1990s and early 2000s after exposing biological samples to anthropogenic EMFs were unethically attacked by hired “scientists”. They were even accused that they had falsified their data!

Today, hundreds of peer reviewed published studies have confirmed these effects. Sadly, as far as I know, those who accused them did not face legal consequences and the harm made to the scientists was not restored. **The evidence today is overwhelming and indisputable, and, as you said, it is becoming harder and harder to ignore.**

The recent book is an evidence-based source of knowledge for all those who want to know the truth in this highly battled scientific field, those who want to understand the science, and protect themselves, their people, and the environment. I very strongly recommend it to everyone.

References

1. https://www.researchgate.net/profile/Dimitris-Panagopoulos-3
2. https://pubmed.ncbi.nlm.nih.gov/38099580/
3. https://pubmed.ncbi.nlm.nih.gov/33226362/
4. https://pubmed.ncbi.nlm.nih.gov/20397839/
5. https://pubmed.ncbi.nlm.nih.gov/34617575/
6. https://pubmed.ncbi.nlm.nih.gov/34617575/
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2248324/
8. https://pubmed.ncbi.nlm.nih.gov/28558424/
9. https://pubmed.ncbi.nlm.nih.gov/32070887/
10. https://pubmed.ncbi.nlm.nih.gov/30196934/
11. https://www.researchgate.net/publication/327578880_Man-Made_Electromagnetic_Radiation_Is_Not_Quantized
12. https://pubmed.ncbi.nlm.nih.gov/31416578/
13. https://iopscience.iop.org/article/10.1088/0952-4746/21/3/604
14. See a few examples here: https://www.memon.eu/en-EN/blog/mobile-phone-study
15. https://www.routledge.com/Electromagnetic-Fields-of-Wireless-Communications-Biological-and-Health/Panagopoulos/p/book/9781032061757

Human-made electromagnetic fields: Ion forced-oscillation and voltage-gated ion channel dysfunction, oxidative stress and DNA damage (Review)

DIMITRIS J. PANAGOPOULOS[1-3], ANDREAS KARABARBOUNIS[4], IGOR YAKYMENKO[5,6] and GEORGE P. CHROUSOS[2]

[1]Laboratory of Health Physics, Radiobiology and Cytogenetics, Institute of Nuclear and Radiological Sciences and Technology, Energy and Safety, National Center for Scientific Research 'Demokritos', 15310 Athens; [2]Choremeion Research Laboratory, Medical School, National and Kapodistrian University of Athens, 11527 Athens; [3]Electromagnetic Field-Biophysics Research Laboratory, 10681 Athens; [4]Department of Physics, Section of Nuclear and Particle Physics, National and Kapodistrian University of Athens, 15784 Athens, Greece; [5]Institute of Experimental Pathology, Oncology and Radiobiology of National Academy of Science of Ukraine, 03022 Kyiv; [6]Department of Public Health, Kyiv Medical University, 02000 Kyiv, Ukraine

Received July 9, 2021; Accepted August 23, 2021

DOI: 10.3892/ijo.2021.5272

Abstract. Exposure of animals/biological samples to human-made electromagnetic fields (EMFs), especially in the extremely low frequency (ELF) band, and the microwave/radio frequency (RF) band which is always combined with ELF, may lead to DNA damage. DNA damage is connected with cell death, infertility and other pathologies, including cancer. ELF exposure from high-voltage power lines and complex RF exposure from wireless communication antennas/devices are linked to increased cancer risk. Almost all human-made RF EMFs include ELF components in the form of modulation, pulsing and random variability. Thus, in addition to polarization and coherence, the existence of ELFs is a common feature of almost all human-made EMFs. The present study reviews the DNA damage and related effects induced by human-made EMFs. The ion forced-oscillation mechanism for irregular gating of voltage-gated ion channels on cell membranes by polarized/coherent EMFs is extensively described. Dysfunction of ion channels disrupts intracellular ionic concentrations, which determine the cell's electrochemical balance and homeostasis. The present study shows how this can result in DNA damage through reactive oxygen species/free radical overproduction. Thus, a complete picture is provided of how human-made EMF exposure may indeed lead to DNA damage and related pathologies, including cancer. Moreover, it is suggested that the non-thermal biological effects attributed to RF EMFs are actually due to their ELF components.

Correspondence to: Dr Dimitris J. Panagopoulos, Laboratory of Health Physics, Radiobiology and Cytogenetics, Institute of Nuclear and Radiological Sciences and Technology, Energy and Safety, National Center for Scientific Research 'Demokritos', Patr. Grigoriou E' and 27 Neapoleos Street, Agia Paraskevi, 15310 Athens, Greece
E-mail: dpanagop@biol.uoa.gr

Abbreviations: DECT, digitally enhanced cordless telecommunications; ELF, extremely low frequency; EMF, electromagnetic field; MT, mobile telephony; OS, oxidative stress; RF, radio frequency; ROS, reactive oxygen species; ULF, ultra low frequency; VGICs, voltage-gated ion channels; VGCCs, voltage-gated calcium channels; WC, wireless communications; Wi-Fi, wireless fidelity; 2G/3G/4G/5G, second/third/fourth/fifth-generation of mobile telephony

Key words: EMF, ion forced-oscillation, VGICs, free radicals, OS, ROS, DNA damage, cancer

Contents

1. Introduction
2. Biophysical action of polarized/coherent EMFs resulting in voltage-gated ion channel (VGIC) dysfunction and disruption of cell electrochemical balance
3. Biochemical processes activated by irregular gating of VGICs, leading to DNA damage
4. Discussion

1. Introduction

Experimental and epidemiological findings connecting exposure of living organisms to ELF and complex RF human-made EMFs with genetic damage, infertility and cancer. There is a plethora of experimental findings connecting the *in vivo* or *in vitro* exposure of experimental animals or cells to extremely low frequency (ELF) (3-3000 Hz) or radio-frequency (RF)/microwave (300 kHz-300 GHz) electromagnetic fields (EMFs), with genetic damage/alterations

(DNA damage, chromosome damage and mutations, among others), cell death and related effects (1-4). Most findings concern exposure to wireless communication (WC) EMFs [from mobile phones/antennas, cordless domestic phones (DECT: digitally enhanced cordless telecommunications), internet (Wi-Fi: wireless fidelity) or 'Bluetooth' wireless connections, among others], which necessarily combine RF/microwave carrier frequencies with ELF pulsing and modulation, and ultra low frequency (ULF) (0-3 Hz) random variability of the signal. Today, almost all technical RF EMFs (not only of WC, but also from radars, radio and television antennas, among others) contain ELF/ULF components in the form of on/off pulsations, modulation, and signal variability. These are usually called simply 'RF', but actually they are a combination of RF and ELF/ULF (4).

The number of experimental-laboratory studies showing genetic damage and related effects induced by human-made ELF or RF (combined with ELF) EMFs on a variety of organisms/cell types under different experimental conditions has rapidly increased, especially in recent years (5-55).

Several of the aforementioned findings involve DNA damage and consequent cell death in reproductive cells of different animals, resulting in decreased reproduction. In particular, the effects of pulsing WC EMFs on the DNA of reproductive cells, as reported by different studies on a variety of animals (25,30,31,36,40,41,46), display a marked similarity and explain other findings that connect WC EMF exposure with insect, bird and mammalian (including human) infertility (56-64), or declines in bird and insect populations (especially bees) during the past 15 years (65-69). A significant decrease in reproduction (decrease in egg laying or embryonic death) after exposure to mobile telephony (MT) radiation was identically observed in fruit flies (30,40,57,58), chicken eggs (61), birds (65-67), and bees (63). Similar effects are reported for amphibians (70,71), rats (31,62), and human sperm (decreased number and motility of spermatozoa) (59,60). These markedly similar findings in different organisms by different research groups can be explained by the observed cell death in reproductive cells after DNA damage, as seen in fruit fly ovarian cells (30,40,41,46), human sperm cells (36), mouse and rat sperm cells (25,31). Decreased reproduction after DNA damage and cell death in reproductive cells or embryonic death induced by purely ELF EMF-exposure is also reported (4,9,14,22,47).

At the same time, epidemiological/statistical studies increasingly link man-made EMF exposure with health problems, genetic damage and cancer in human populations. More specifically, ELF EMFs from power lines and high-voltage transformers (mainly 50-60 Hz plus additional frequencies due to harmonics, noise and discharges, among others) are linked with childhood leukemia (72-82) for magnetic field intensities down to 2 mG (0.2 μT) (76,82), or distances from power lines up to 600 m (81), and electric field intensities down to 10 V/m (78). RF exposure from various antennas always containing ELF components, especially MT antennas, is linked to various forms of cancer. Hallberg and Johansson (83) found a connection between skin cancer (melanoma) incidence in humans and residential exposure to radio broadcasting antennas, while two recent studies found significantly increased genetic damage in the peripheral blood lymphocytes of people residing in the vicinity of MT base antennas (84,85). During the past 15 years, epidemiological studies have found an increasing association between mobile or cordless phone use and brain tumors in humans (86-98). Moreover, during the past 20 years, statistical studies have found associations between exposure to MT base station antennas and devices, and reported symptoms of un-wellness referred to as 'microwave syndrome' or 'electro-hypersensitivity' (EHS). The symptoms include headaches, fatigue, sleep disorders, etc. (99-107). A high percentage (~80%) of EHS self-reporting patients were recently found with increased oxidative stress (OS) [intracellular increase in free radicals/reactive oxygen species (ROS)] in their peripheral blood (108).

A review of studies involving exposure to complex RF EMFs with ELF pulsation/modulation revealed that 93% of them reported induction of OS/ROS overproduction in biological systems (109).

Induction of cancer in experimental animals by long-term MT exposure, including ELF pulsations, has also been reported (110,111). A recent study of the USA National Toxicology Program (NTP) found that rats exposed for 2 years, 9 h per day, in the near-field of simulated 2nd generation (2G) or 3rd generation (3G) MT emissions, developed brain cancer (glioma) and heart cancer (malignant schwannoma), with both lower and higher radiation levels than the officially accepted limits (112). Moreover the study found significantly increased DNA damage (strand breaks) in the brains of exposed animals (113), confirming that DNA damage is closely related to carcinogenesis. An Italian life-span exposure study of rats in a simulated 2G MT far-field also found induction of heart schwannomas and brain glial tumors, confirming the results of the NTP study (114).

These findings on animal carcinogenicity along with the epidemiological cancer findings on humans, the DNA damage and OS findings, and the adverse effects on reproduction due to DNA damage in the gametes or embryonic death, point towards the same direction, i.e., that human-made EMF exposure causes OS and DNA damage that may lead to cancer, reproductive declines and related diseases. It is important to note that the exposure levels in the vast majority of all the aforementioned studies (1-114) were significantly below the officially accepted exposure limits for ELF and RF EMFs, which have been set to prevent discharges on humans in the case of ELF and heating of living tissues in the case of RF (115,116).

At the same time, several other studies have reported no effects of ELF or RF EMFs in all the aforementioned end-points (1-4,47,57,115-124), especially studies that employed simulated MT/WC exposure from generators with invariable parameters (intensity, frequency and pulsations, among others) and no modulation or random variability. By contrast, more than 95% of the studies that employed real-life MT/WC exposure from commercially available devices (mobile/cordless phones and Wi-Fi, among others) with high signal variability found effects (4,121,122). Regardless of real-life or simulated exposure, the majority of experimental studies (more than 70%) both in the RF (combined with ELF) and purely ELF bands do find effects (4,109,123,124). In a recent review of 138 RF studies with frequencies >6 GHz evaluating potential effects of the under deployment 5th generation (5G) MT/WC system, it was not specifically examined whether there were

ELF components in the exposure and what type, or whether there was any similarity between the signals produced by generators in the studies, and those of the 5G, apart from the carrier frequency. While most of the reviewed studies reported effects, they were criticised in this review for not being 'independently replicated' and for employing 'low quality methods of exposure assessment and control' (125). Thus, despite the incomplete review methodology, the authors of the review attempted to downgrade any reported effects.

Under the increasing weight of scientific evidence, the International Agency for Research on Cancer (IARC) has for a long time now classified both ELF and RF EMFs as possibly carcinogenic to humans (group 2B) (117-119). Based on additional scientific evidence after the 2011 IARC classification for RF EMFs, several studies have suggested that RF/WC EMFs should be re-evaluated and classified as probably carcinogenic (group 2A) or carcinogenic (group 1) to humans (92,97,126,127). As already emphasized, in the vast majority of studies characterized as 'RF', the ELF/ULF components were present.

While the reported effects in the vast majority of the above studies (1-124) induced by ELF or complex RF (containing ELF) EMFs were not accompanied by any significant heating of the exposed living tissues, it is well established that purely RF/microwave EMFs cause heating of exposed materials (e.g. microwave ovens). The heating becomes significant for high power/intensity (≥0.1 mW/cm^2) and high frequency (at GHz range) microwaves (128). In addition, purely RF EMFs, which are of very limited technological use, are scarcely reported to induce non-thermal effects, and it is questionable in such cases, whether the presence of any ELFs was carefully excluded (129).

DNA damage and related pathologies. It is well documented that DNA damage is connected with cell senescence (cell aging and loss of replicative capacity), cell death, neurodegenerative diseases and aging of an organism, and is the main cause of carcinogenesis induced by environmental stressors (3,130-138). DNA damaging events take place at any time in the cells of any living organism due to a variety of events (such as exposure to ultraviolet radiation, natural radioactivity or cytotoxic chemicals), but efficient DNA repair mechanisms have evolved to provide protection. Damage in the DNA is any modification in a nucleotide base, deoxyribose, a break in a covalent bond between deoxyribose and nucleotide base, or a break in a phosphodiester bond in one or both strands (3,130-139).

Replication of damaged (or inaccurately repaired) DNA that may occur before repair or blocking can lead to gene mutations, which will then give rise to altered proteins. Mutations in oncogenes, tumor-suppressor genes, DNA repair genes or genes that control the cell cycle can generate a clonal cell population with a distinct ability to proliferate. DNA methylation that may prohibit the expression of DNA repair genes and synthesis of related proteins can result in inaccurate ('error-prone') DNA repair. Many such events, which may accumulate over a long period of time in cases of chronic exposure to carcinogens, can lead to genomic instability and cancer (133,134,136,139).

When the genomic DNA of a cell is damaged by an external stressor and the damage is either not reparable or inaccurately repaired, the following outcomes are possible: i) The cell dies (necrosis) or is led to suicide (induced apoptosis). In the case of cell types with the ability to proliferate, the organism compensates for their loss by creating new cells, practically with no adverse consequences apart from energy consumption, which may lead to accelerated aging when such events occur at a high rate. In the case of cell types that do not have ability to proliferate, such as neural cells or chondrocytes, the loss of a significant number of cells will probably result in the inability of certain tissues/organs to operate normally. In the case of neural cells, this may lead to neurodegenerative diseases such as Alzheimer and Parkinson, and autoimmune disorders, among others. ii) The cell does not die but survives with modified DNA. In the case of somatic cells that proliferate, the modified genome will reproduce itself. Even though the organism may recognize such mutant cells as foreign and try to isolate them and remove them, they strive to survive and may start proliferating uncontrollably, initiating cancer. In the case of reproductive cells (oocytes and spermatocytes), this may lead to mutated new organisms that may be problematic in many ways or cancer-prone. In both cases (somatic or reproductive cells) cell senescence is an alternative pathway for eliminating surviving genetically defective cells. Thus, cells with irreparably damaged genomic DNA will result in cell senescence, cell death, cancer or mutated offspring, depending on cell type and specific biological/environmental conditions (3,4,122,130-132,135-137).

The duration of cancer development (latency period) after irreparable DNA damage may be a number of years, depending on the organism and the type of cancer. The latency period for gliomas (a type of brain cancer) is usually >20 years in humans (140). This probably explains why only during the past ~15 years epidemiological studies have started showing an association between mobile phone use and cancer (86), whereas cancer from power lines, which are several decades older than MT/WC, has been indicated long before (72).

Purpose of the present study. As aforementioned, a growing number of experimental and epidemiological/statistical findings connect man-made EMF exposure with genetic damage and cancer, and this involves the breakage of chemical/electronic bonds in molecules/atoms, in other words ionization. The human-made EMFs with frequencies up to the lower limit of infrared (0-3×10^{11} Hz) discussed in the present study cannot directly cause ionization, except for very strong field intensities (≥10^6 V/m) (141,142). Such field intensities rarely exist environmentally, apart from atmospheric discharges (lightning) or in very close proximity to high-voltage power lines and transformers. The question therefore is how human-made EMFs at environmental intensities are capable of damaging DNA and other biological molecules. Obviously they have the ability of breaking chemical bonds indirectly through the action of some primary biophysical mechanism(s) and subsequent initiation of intracellular biochemical processes.

Visible and infrared natural light cannot break chemical bonds, even though they expose us at higher frequencies and radiation intensities than human-made EMFs in daily life (143). There must be a unique property of the human-made EMFs that makes them capable of inducing

adverse biological/health effects and ionization, in contrast to natural infrared and visible light. This unique property is that human-made EMFs/radiation are totally polarized and coherent, meaning that they possess net electric and magnetic fields, apart from radiation intensity, which exert forces on any electrically charged (or polar) particle/molecule such as mobile/dissolved ions and charged macromolecules in any biological system (143).

The purpose of the present study is to suggest a realistic primary biophysical mechanism for polarized and coherent EMFs at environmentally relevant intensities, to impair cellular function and initiate plausible intracellular biochemical processes resulting in genetic damage and carcinogenesis, as reported in the aforementioned studies.

2. Biophysical action of polarized/coherent EMFs resulting in voltage-gated ion channel (VGIC) dysfunction and disruption of cell electrochemical balance

It has been shown that polarized/coherent EMFs, even at very low field intensities in the ULF and ELF bands, can cause irregular gating of electro-sensitive ion channels or VGICs on the cell membranes through the 'ion forced-oscillation mechanism' (143-146), with consequent disruption of the cell's electrochemical balance (the electrical and osmotic equilibrium maintained by specific concentrations of all dissolved/mobile ions across all cell membranes according to the Nernst equation) (144,147,148). Since, as explained, ELF/ULF components exist also in the complex WC/RF EMFs, this mechanism, which will be thoroughly reviewed next, accounts for the biological effects of the vast majority of human-made (polarized and coherent) EMFs.

The mechanism is based on molecular/physical data, and the forces on mobile ions, in the vicinity of the voltage-sensors of VGICs, exerted by an applied polarized oscillating EMF. The oscillating field will force mobile ions to oscillate on parallel planes and in phase with the field. This coordinated motion of electrically charged particles exerts electric forces on the voltage-sensors, similar to the forces exerted on them by changes in the transmembrane electric field known to physiologically gate these channels, and thus the channels are gated irregularly by the applied EMF. The forces are proportional to the amplitude of the forced-oscillation, and thus, the amplitude is a direct measure of the bioactivity of the applied EMF. It has been shown that the amplitude (bioactivity) is proportional to EMF intensity, inversely proportional to EMF frequency and doubles for pulsed EMFs. The validity of the proposed mechanism has been verified by numerical testing, while other previously suggested mechanisms have failed to pass the same test (149,150). Repeated irregular gating of electro-sensitive ion channels disrupts cellular electrochemical balance and homeostasis (147,148), leading to overproduction of ROS/free radicals as described next.

It is known from a plethora of experimental data that the most bioactive EMFs are the lower frequency ones (ELF/ULF). In numerous cases of induced biological effects by complex RF EMFs modulated by ELFs, it has been found that the modulation (ELF) and not the carrier (RF) is responsible for the recorded effects. In addition, it has been repeatedly found that pulsing RF EMFs with ELF pulse-repetition rates are more active biologically than continuous (non-pulsed) fields of identical other parameters (1-5,44,45,47,151-159). These findings are in direct agreement with the described mechanism.

Biological molecules of critical importance such as ions, water molecules, proteins, nucleic acids and lipids, among others, are either polar or carry a net electric charge (147,148). The net electric field from an infinite number of individual electric pulses of random polarization and/or random phase (as e.g. photons of natural light) tends to zero at any moment (and similarly the net magnetic field).

$$\lim_{n\to\infty}\sum_{i=1}^{n}\vec{E}_i = \quad \vec{E}_1+\vec{E}_2+\vec{E}_3+\ldots+\vec{E}_n = 0 \qquad (1)$$

Thus, non-polarised/incoherent EMFs (as e.g. light and cosmic microwaves) at any radiation intensity cannot cause any parallel/coherent oscillation of charged/polar molecules (143). On the contrary, polarized and coherent (human-made) oscillating EMFs force all charged/polar molecules in biological tissue to oscillate on planes parallel to their polarization and in phase with them. This is crucially important for understanding the mechanism described. The forced-oscillation will be most intense on the mobile ions, the smallest charged particles dissolved in large concentrations in the cytosolic and extracellular aqueous solutions in all living cells/tissues controlling practically all cellular/biological functions (147,148).

Even though all molecules move randomly with much greater velocities/displacements due to thermal energy, this has no biological effect other than increasing tissue temperature. By contrast, a polarized and coherent oscillation of much lower energy than average thermal molecular energy can initiate biological effects (143-145).

The majority of cation channels (Ca^{2+}, K^+, Na^+ and H^+, among others) on the membranes of all animal cells are voltage-gated (147,148). These ion channels convert between open and closed states when the electrostatic force on their voltage sensors, due to transmembrane voltage changes, exceeds some critical value. The voltage sensors are four symmetrically arranged, transmembrane, positively charged α-helices, each one named S4. The S4 helices occupy the 4th position in a group of 6 parallel α-helices (S1-S6). The channel consists of four identical such groups in symmetrical positions around the pore of the channel. The S5-S6 helices of the four groups form the pore walls (147,148). More specifically, the sensors are positive Lys and Arg amino acids in the S4 helices. Changes in the transmembrane voltage of the order of ~30 mV are normally required to gate electrosensitive channels (change their status from opened to closed and vice-versa) (160,161). Among the S1-S4 α-helices, the S4 helices are the closest to the pore-forming S5-S6 helices, being <1 nm in distance from the pore (162,163). Several ions may interact simultaneously at any instant with an S4 sensor from a distance of the order of 1 nm, as, except for the ion(s) that may be passing through the pore any moment or are just outside the gate ready to pass, a few more ions are bound close to the pore at specific ion-binding sites (e.g. three in potassium channels) (164,165). Proton voltage-gated channels studied more recently also contain S4 transmembrane helices with charged Arg residues as voltage-sensors, similar to the metallic cation channels (166,167).

Let us consider four identical mobile ions at distances of the order of 1 nm from the channel-sensors (S4) and an externally applied oscillating EMF. The average electric (and magnetic) force on each ion due to any non-polarized EMF is zero (Eq. 1). By contrast, the force due to a polarized field with an electrical component E, is $F=Ezq_e$, (with zq_e the electric charge of the ion).

In the most usual and simplest case of a sinusoidal alternating electric field, $E=E_o\ sin\omega t$, the motion (forced-oscillation) equation of a mobile ion is as follows (143-146):

$$m_i \frac{d^2r}{dt^2} + \beta \frac{dr}{dt} + m_i\, \omega_o^2\, r = E_o\, z\, q_e\ sin\omega t \tag{2}$$

where m_i is the mass of the ion, r is the displacement of the ion due to the forced-oscillation, z is the valence of the ion (z=1 for K^+, Na^+ or z=2 for Ca^{2+} ions), q_e=1.6×10^{-19}C is the elementary charge, β is the damping coefficient (being within channels $\beta = \frac{E_m z q_e}{u_o} \cong 6.4z\times10^{-12}$ kg/s, with E_m (~10^7 V/m) the transmembrane electric field, and u_o=0.25 m/s the velocity of the ion through an open channel calculated from patch-clamp measurements of channel ion-currents). $\omega_o=2\pi\nu_o$ (ν_o the ion's oscillation self-frequency accepted to be equal to the recorded spontaneous intracellular ionic oscillation frequencies on the order of 0.1 Hz), $\omega=2\pi\nu$ (ν the frequency of the applied field) and E_o is the intensity amplitude of the applied oscillating field. Detailed calculations of the parameters are provided in Panagopoulos *et al* 2000 (144).

The right part of Eq. 2 is the force on the ion due to the applied E-field. The first term of the left part ($m_i\frac{d^2r}{dt^2}$) is the resultant force on the ion, the second term ($\beta\frac{dr}{dt}$) is a damping force and the third term ($m_i\ \omega_o^2\ r$) a restoration force exerted by the medium (144,145). While an oscillating ion close to the S4 sensors exerts gating forces on them, it receives zero opposite force, as the S4 charges are paired with opposite charges from adjacent helices of the channel (148). Eq. 2 is a second-order linear differential equation with constant coefficients, which is solvable once we know the values of the different parameters.

The general solution of Equation 2 (144) is:

$$r = \frac{E_o z q_e}{\beta\omega}\ cos\ \omega t + \frac{E_o z q_e}{\beta\omega} \tag{3}$$

The constant term $\frac{E_o z q_e}{\beta\omega}$ in the solution represents a constant displacement of the ion and has no effect on the oscillating term $\frac{E_o z q_e}{\beta\omega} cos\omega t$. This constant displacement represents a jump of the whole oscillation at a distance equal to the amplitude, in other words it doubles the amplitude $\frac{E_o z q_e}{\beta\omega}$ of the oscillation at the moment when the field is applied or interrupted. For pulsed fields (such as the vast majority of human-made complex RF/microwave EMFs, especially those employed in modern WC), this interruption/repetition occurs constantly with every repeated pulse. Therefore, pulsed fields are predicted to be twice as bioactive as continuous/non-pulsed fields of the same other parameters, and this explains a plethora of experimental findings showing increased bioactivity of pulsed compared with non-pulsed RF EMFs, which were previously unexplained (44,45,154, 155,157-159).

Ignoring the constant term in Eq. 3, the amplitude of the forced-oscillation is:

$$A = \frac{E_o z q_e}{\beta\omega} \tag{4}$$

An oscillating ion of charge zq_e (whose motion is described by Eq. 3) close to the S4 helices of a voltage-gated channel exerts a force F on the effective charge q of each S4, as described by Coulomb's law: $F=\frac{1}{4\pi\varepsilon\varepsilon_o}\cdot\frac{q\cdot zq_e}{r^2}$, ($r$ here is the distance of the oscillating ion from the S4). The ion displaced by dr during its oscillation, induces an additional force dF on each S4 sensor:

$$dF = -\frac{q\cdot zq_e}{2\pi\varepsilon\varepsilon_o r^3}\, dr \tag{5}$$

While in the case of a random/chaotic movement of the ion due to e.g. thermal motion $\lim\sum d\vec{r} = 0$, and $\lim\sum d\vec{F} = 0$, in the case of a coordinated polarized and coherent forced-oscillation, the sum force on each S4 from all four ions, is:

$$4dF = -2\frac{q\cdot zq_e}{\pi\varepsilon\varepsilon_o r^3}\, dr \tag{6}$$

The effective charge of each S4 domain is found to be: q=1.7q_e (161). The force on this charge exerted by a change of 30 mV in the transmembrane voltage required normally to gate the channel, is calculated to be (144): dF=8.16×10^{-13} N.

The displacement of one single-valence ion within the channel corresponding to this minimum force, according to Eq. 5 (for z=1, $\varepsilon \cong 4$, and r ~1 nm), is: dr=4×10^{-12} m.

The dielectric constant within proteins is significantly lower than in the aqueous solutions (4/80), and ion concentration in cells is of the order of 1 ion per nm^3 (144,147,148).

For 4 single-valence ions oscillating on parallel planes and in phase with an applied polarized (and coherent) oscillating field, the minimum displacement is (according to Eq. 6) reduced to: dr=10^{-12} m. The corresponding necessary displacement for ions outside the channel would be about 20-fold higher due to the higher dielectric constant of the aqueous solutions.

Thus, a crucial finding has been reached: Any external polarized and coherent oscillating EMF (like all technical/human-made EMFs) able to force mobile ions to oscillate with amplitude

$$\frac{E_o z q_e}{\beta\omega} \geq 10^{-12}\ \text{m} \tag{7}$$

is able to irregularly gate VGICs on cell membranes.

For z=1 (e.g. K^+ ions), and replacing q_e, β by their values in Condition 7, we get:

$$E_o \geq 0.25\nu\times10^{-3} \qquad (8) \qquad (\nu \text{ in Hz}, E_o \text{ in V/m})$$

For double-valence cations (z=2) (e.g. Ca^{2+}) the condition becomes:

$$E_o \geq 1.2\nu\times10^{-4} \qquad (9) \qquad (\nu \text{ in Hz}, E_o \text{ in V/m})$$

For pulsed fields (such as all MT/WC fields) the right part of Condition 9 is further divided by 2, becoming:

$$E_o \geq 0.6\nu\times10^{-4} \qquad (10) \qquad (\nu \text{ in Hz}, E_o \text{ in V/m})$$

It is clear that the amplitude of the forced-oscillation given by Eq. 4 is the critical parameter to determine the ability of a polarized/coherent EMF to induce biological/health effects. We shall name it 'Bioactivity of the EMF' or 'EMF-Bioactivity'. Thus:

$$\text{EMF-Bioactivity} = \frac{E_o z q_e}{\beta \omega} = k \cdot \frac{E_o}{\nu} \quad (11)$$

where $k = \frac{zq_e}{2\pi\beta} = \frac{u_o}{2\pi E_m} \cong 4\times10^{-9}$ C·s/kg is a constant quantity (depending upon the membrane electric field E_m and the velocity of the ion through an open channel u_o), E_o is the intensity amplitude and ν is the frequency of the applied electric field. We shall name k the 'bioactivity constant'.

Thus, a most reasonable and elegant result is reached, that the bioactivity of a polarized oscillating EMF is proportional to its maximum intensity (E_o) and inversely proportional to its frequency (ν), meaning that lower frequency fields are predicted to be more bioactive than higher frequency ones of the same intensity and waveform. Although this result was obtained considering the most usual/simple case of harmonically oscillating polarized EMFs, it is evident that non-harmonically oscillating polarized fields can also be approximately described in terms of their bioactivity by Eq. 11.

For pulsed EMFs with harmonically oscillating carriers, the amplitude doubles and so does the bioactivity:

$$\text{Pulsed EMF-Bioactivity} = 2k \cdot \frac{E_o}{\nu} \quad (12)$$

The same mechanism explains the biological action of polarized oscillating magnetic fields as well, if we replace in Eq. 2 the electric force $F_E=Ezq_e$, by a magnetic force:

$$F_B = B\, u\, zq_e \quad (13)$$

exerted on an ion with charge zq_e, moving with velocity u, vertically to the direction of a magnetic field of intensity B (in which case the magnetic force is maximum). In the simplest (and most usual) case of an alternating magnetic field $B=B_o sin\omega t$ with intensity amplitude B_o and based on the same reasoning as aforementioned, corresponding bioactivity conditions are obtained for an oscillating magnetic field.

For one single-valence ion moving through an open channel vertically to the direction of the applied magnetic field with $u=u_o=0.25$ m/s (the velocity calculated for ions moving through an open channel) (144) and for the case of a continuous oscillating magnetic field, the corresponding bioactivity condition is:

$$\frac{B_o u_o q_e}{\beta \omega} \geq 4\times10^{-12}\,\text{m} \quad (14) \quad (\omega \text{ in rad/s}, u \text{ in m/s}, B_o \text{ in T}),$$

from which is obtained:

$$B_o \geq 4\times10^{-3}\,\nu \quad (15) \quad (\nu \text{ in Hz}, B_o \text{ in T}), \text{ or}$$

$$B_o \geq 4\times10^{3}\,\nu \quad (16) \quad (\nu \text{ in Hz}, B_o \text{ in } \mu\text{T})$$

For double-valence ions the right part of Condition 16 is divided by 2:

$$B_o \geq 2\times10^{3}\,\nu \quad (17) \quad (\nu \text{ in Hz}, B_o \text{ in } \mu\text{T})$$

For double-valence ions and pulsing magnetic field the right part of Condition 17 is further divided by 2, and the bioactivity condition becomes:

$$B_o \geq 10^{3}\,\nu \quad (18) \quad (\nu \text{ in Hz}, B_o \text{ in } \mu\text{T})$$

It should be noted that apart from the drift velocity of the ion through the channel (u_o=0.25 m/s) that is accepted as initial velocity, the ion will acquire an additional velocity dr/dt due to the forced-oscillation. From Eq. 3, the following is obtained:

$$\frac{dr}{dt} = -\frac{E_o z q_e}{\beta} \sin \omega t \quad (19)$$

(or respectively: $\frac{dr}{dt} = -\frac{B_o u_o z q_e}{\beta} \sin \omega t$ for a sinusoidal magnetic field)

The corresponding magnetic force due to this additional velocity, $Bzq_e(dr/dt)$, is negligible (more than 10^8 times smaller) compared with the damping force $\beta(dr/dt)$, and thus, it is not taken into account in Eq. 2.

The maximum ($\frac{E_o z q_e}{\beta}$ or $\frac{B_o u_o z q_e}{\beta}$) of this additional velocity is independent of the frequency of the field (ω), and is much smaller for usual field intensities than the ion velocity through an open channel (u_o=0.25 m/s), which in turn is more than 10^3 times smaller than its corresponding average thermal velocity u_{kT} (168). Thus, the described ion forced-oscillation does not add to tissue temperature and this mechanism is 'non-thermal', in contrast to the known heating ability of the high intensity microwaves (128). The non-thermal nature of human-made EMF-bioeffects, including those of low power modulated/pulsing RF/microwaves, in contrast to high power microwaves, has also been discussed in previous studies (169,170).

This theory allows certain predictions for the bioactivity of some human-made EMFs widely present in the modern environment: For the sinusoidal alternating (continuous) 50-Hz E and B fields of high-voltage power lines with intensities of the order of E ~10 kV/m and B ~0.1-1 G (or ~10-100 μT) at close distances (10-20 m) from such lines the conditions 9 and 17 for double valence cations (e.g. Ca^{2+}) give: $E_o \geq 6\times10^{-3}$ V/m or $E_o \geq 6$ mV/m (which is satisfied by more than 10^6 times), and $B_o \geq 10^5$ μT, which is not satisfied, showing that the recorded effects from high-voltage power lines are due to the electric rather than the magnetic component of the resultant EMF, in contrast to what is usually considered. Thus, the electric component of power line EMFs is certainly capable of inducing biological effects in living organisms according to the mechanism presented, even for intensities down to 1-10 V/m, which exist in most homes and work places.

For the pulsing ELF E and B fields of MT/WC EMFs with a pulsing repetition frequency of ~100 Hz (3G/4G MT, DECT), E ~10 V/m and B ~1 mG (or ~0.1 μT) (30,40,54,55), the bioactivity conditions 10 and 18 respectively give: $E_o \geq 6\times10^{-3}$ V/m or $E_o \geq 6$ mV/m, which is satisfied by more than 10^3 times, and $B_o \geq 10^5$ μT, which is not satisfied for direct action, but it may be satisfied by the magnetically induced electric field, which is significant in this case due to the short rise/fall times of the pulses (143). Similar results are obtained for the 217-Hz pulsing E/B fields of 2G MT (30,40).

For Wi-Fi and Bluetooth wireless connections with a pulsing frequency of ~10 Hz, E ~1 V/m and B ~0.1 mG

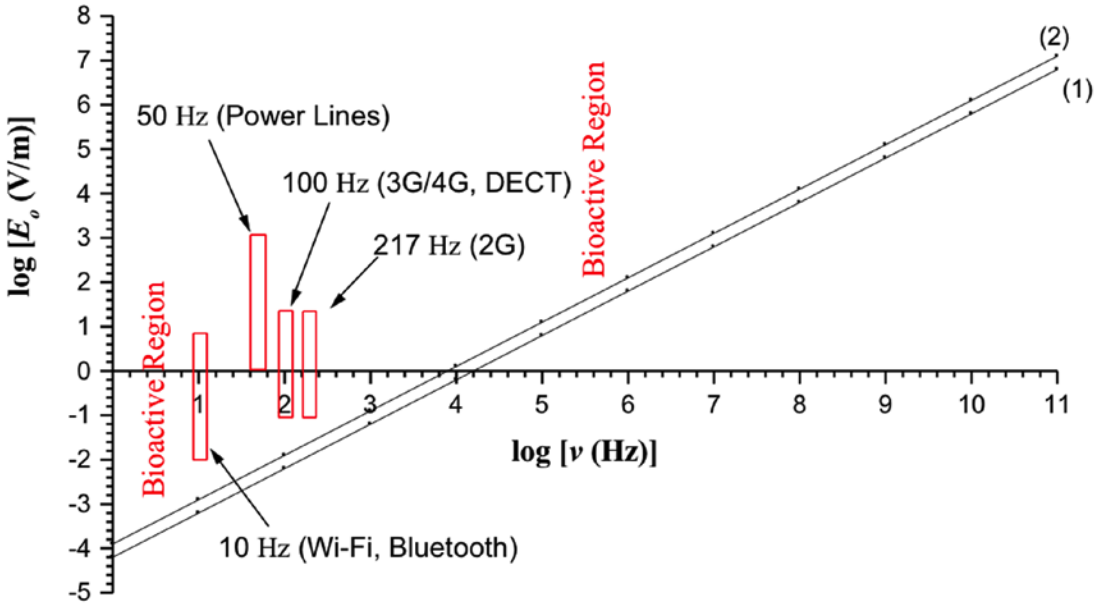


Figure 1. E-field bioactivity diagram showing the bioactive combinations of electric field intensity and frequency capable of inducing biological/health effects according to the ion forced-oscillation mechanism for dysfunction of voltage-gated ion channels in cells. The ELF electric fields of power lines, 2G/3G/4G MT, DECT, Wi-Fi and Bluetooth, are within the bioactive region (above lines 1 and 2). Line 1 refers to pulsed fields, such as the ELF pulsations of WC EMFs (Condition 10), while line 2 refers to continuous (non-pulsed) fields such as those from power lines (Condition 9).

(or ~0.01 μT) (171), the bioactivity conditions 10 and 18 respectively give: $E_o \geq 0.6 \times 10^{-3}$ V/m or $E_o \geq 0.6$ mV/m, which is satisfied by more than 10^3 times, and $B_o \geq 10^4$ μT, which is not satisfied for direct action.

The aforementioned numerical examples show that it is the electric field that seems to be the bioactive component of an EMF and not the magnetic field, in contrast to what has been considered before by health agencies (117). The magnetically induced electric field can also be bioactive in the case of ELF pulses of WC signals with short rise/fall times (143).

The bioactivity conditions 9 and 10 for continuous and pulsed electric fields respectively are depicted in Fig. 1. The region above line 1 (including the line) represents the bioactive combinations of intensity amplitude (E_o) and frequency (ν) for pulsed fields, and above line 2 (including the line) for continuous fields. The ELF electric field of power lines, 2G/3G/4G MT, DECT, WiFi and 'Bluetooth', lie within the bioactive region predicted by the presented theory.

3. Biochemical processes activated by irregular gating of VGICs, leading to DNA damage

Irregular gating of ion channels and ROS. Irregular gating of VGICs by oscillating polarized and coherent ELF EMFs as described [and originally in (143-146)] has been verified experimentally for calcium (Ca^{2+}), potassium (K^+) and sodium (Na^+) VGICs (172-174). This can alter intracellular ionic concentrations, disrupting the electrochemical balance of the cell and leading to DNA damage by OS/ROS overproduction (175-179).

Most ROS are free radicals. Free radicals are highly unstable molecules containing an unpaired electron, which is denoted by a dot ($^\bullet$), and have a tremendous tendency to chemically react with surrounding molecules and/or with each other in order to couple the unpaired electron and become stable. This is the reason why they have extremely short lifetimes. Most ROS react rapidly with surrounding biomolecules inducing chemical alterations (180). Overproduction of ROS in living cells due to EMF exposure has been reliably documented, with two important ROS found after EMF exposure being superoxide anion ($O_2^{\bullet-}$) and nitric oxide ($NO^\bullet$) (109). These may result in hydroxyl radical ($OH^\bullet$) and peroxynitrite ($ONOO^-$) correspondingly, both of which ROS are very reactive with biological molecules and specifically DNA, as discussed next. $ONOO^-$ may interact directly with DNA, as, similarly with $NO^\bullet$, it can be diffused everywhere in the cell (181). Superoxide anion radical ($O_2^{\bullet-}$) is catalyzed by superoxide dismutase enzymes in the cytosol or the mitochondria and is converted to hydrogen peroxide (H_2O_2) (109,182):

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (20)$$

H_2O_2 is a critical molecule in oxidative damage since it can move to any intracellular site (including the nucleus), where it can be converted to the most potent $OH^\bullet$, which can damage any biological molecule, including DNA (183-187).

DNA damage by ROS leading to mutations and disease has been well studied (188,189). Pall (190), in a review of EMF-bioeffects studies with calcium channel blockers, noted a connection between voltage-gated calcium channels (VGCCs) and $NO^\bullet$/$ONOO^-$ overproduction. This verified earlier observations of EMF-induced effects on intracellular calcium concentrations, and the unique role of VGCCs (1,151-153,191,192).

It is known that the intracellular redox status can activate Ca^{2+}, Na^+ and K^+ channels in order to reinstate homeostasis (178), and inversely, activation of these channels determines the redox status and the electrochemical balance

of the cell (179). Multiple studies have found connections between the impaired function of calcium, potassium, sodium and chloride channels with the induction of OS and related pathologies (175-177). These studies provide additional evidence for the validity of the presented biophysical mechanism (143-146).

Calcium signaling and mitochondrial ROS production. Alteration of intracellular ionic concentrations will affect key cellular signaling pathways, including the Ca^{2+} signaling system, which regulates a variety of cellular functions including cell proliferation, differentiation, the ROS regulatory system and apoptosis (192-196). Impaired function of VGCCs in the plasma or in the mitochondrial membranes leading to critical changes in cytosolic or mitochondrial concentrations of Ca^{2+} ions, such as those following EMF exposure, is connected with pathogenesis and cytotoxicity (195,196).

Voltage-gated anion channels in the outer membrane of the mitochondria regulate Ca^{2+} entry into the intermembrane space and in the matrix, which is crucial for mitochondrial ROS production. Increased level of Ca^{2+} stimulates $O_2^{\bullet-}$ production by the electron transport chain in the mitochondria and/or activation of nitric oxide synthase (NOS), to generate more $NO^{\bullet}$. $NO^{\bullet}$ inhibits complex IV of the electron transport chain, triggering production of even more ROS (109,193). ROS overproduction in the mitochondria can damage DNA both in the mitochondria and the nucleus, and initiate a signaling cascade leading to apoptosis, as found in human spermatozoa after MT EMF exposure (36). Moreover, increased concentrations of $NO^{\bullet}$ in living cells due to activation of NOS at different locations of the cell may lead to formation of $ONOO^-$ (181,182).

Regulation of apoptosis is crucial for anticancer control (197). However, excessive apoptosis, induced by increased ROS levels, is connected with inflammatory diseases and cancer (198). When overproduction of ROS in a cell overloads the capacity of the antioxidant system of the cell, the cell/organism is under OS. This condition may lead to significant DNA damage with consequent genomic instability and carcinogenesis (182,183,194-198).

K^+ channels have also been shown to be involved in the activation of apoptosis (194), and voltage-gated Ca^{2+} and K^+ channels have been shown to be connected with cell proliferation and carcinogenesis (199). Thus, cytosolic concentrations of Ca^{2+} and K^+ ions play major roles in cellular function and metabolism. In addition, voltage-gated calcium and potassium channels play important roles in iron entry into the cells. Iron catalyzes the production of $OH^{\bullet}$ via the Fenton reaction and thus, impaired function of these channels can promote cellular toxicity (200-202).

NADPH oxidase and ROS production. Apart from the effect of EMFs on metallic cation voltage-gated channels (such as Ca^{2+}, Na^+ and K^+), proton (H^+) voltage-gated channels will be affected as well, as they operate in a very similar way (166,167). This in turn would affect the function of NADPH oxidase, a plasma membrane enzyme found in abundance in all cells, which normally generates ROS for the elimination of invading microorganisms (203,204). The activity of NADPH oxidase is strongly associated with H^+ channels and it may even act directly as a H^+ voltage-gated channel due to its $gp91^{phox}$ transmembrane subunit (205,206). NADPH oxidase generates an electron flux for the reduction of extracellular O_2 to $O_2^{\bullet-}$ (203,207).

NADPH oxidase is activated by cytosolic Ca^{2+} and possesses a Ca^{2+}-binding site in addition to its H^+ voltage-gated channel ($gp91^{phox}$ transmembrane region) (204). Thus, perturbation of intracellular concentrations of either H^+ or Ca^{2+}, after irregular gating of their voltage-gated channels, will affect the function of NADPH oxidase and trigger irregular ROS production.

NADPH oxidase has been reasonably suggested as a primary target of EMF exposure in living cells. In 2007, Friedman *et al* (208) found rapid ROS production in cultured cells after a few min of exposure to RF EMF emitted by a generator.

Na^+/K^+-ATPase and ROS production. Impaired function of Na^+, K^+, Mg^{2+} and Ca^{2+} voltage-gated channels may also affect the function of the Na^+/K^+ pump (ATPase) and Ca^{2+} pumps in the plasma membranes of all cells. The ion pumps (active ion transporters) across all cell membranes in coordination with the ion channels (passive ion transporters) determine the membrane voltage, the volume of the cell and the electrochemical balance (147,148). A positive-feedback amplification loop between Na^+/K^+-ATPase signaling and ROS production by the mitochondria was experimentally demonstrated in primary cultures of cardiac myocytes (209). Na^+/K^+-ATPase became a target for ROS-initiated signaling, and in turn, stimulation of Na^+/K^+-ATPase signaling function led to increased ROS production. This model can definitely be associated with dysfunction in living cells under EMF-exposure.

Therefore, it is clearly indicated that irregular gating of VGICs on plasma and intracellular membranes due to EMF-exposure will most likely trigger ROS overproduction and consequent cellular damage. Although plenty of data connecting ion channel dysfunction and the induction of cell death or cancer have been available for a long time (194,199), the connection between the dysfunction of VGICs and ROS overproduction (175-179,190-192) leading to DNA damage has not perhaps gained the attention it deserves.

Apart from action via ROS/free radicals, DNA damage may be brought about by irregular activation of DNases after alteration of intracellular ionic concentrations. Of the two forms of endonucleases implicated in the initiation of apoptosis, one of them is Ca^{2+}-dependent (DNase I). An increased level of intracellular Ca^{2+} in some cases is associated with increased apoptosis, possibly due to the activation of DNase I (210). Thus, the possible activation of DNase I by increased levels of intracellular Ca^{2+} may be an alternative way for DNA damage and related pathologies.

ROS and DNA damage. $OH^{\bullet}$ is considered the most potent oxidant of DNA. The main mechanism for $OH^{\bullet}$ production involves the iron-catalyzed conversion of H_2O_2 via the Fenton reaction (211): Fe^{2+} is oxidized by H_2O_2 to Fe^{3+}, producing an $OH^{\bullet}$ radical and a hydroxide ion (OH^-) (Eq. 21). Fe^{3+} is then reduced back to Fe^{2+} by another molecule of H_2O_2, producing a hydroperoxyl radical and a proton (Eq. 22).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad (21)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO^{\bullet} + H^{+} \quad (22)$$

The net effect is the conversion of two hydrogen peroxide molecules to produce two different oxygen-radical species, with water ($H^+ + OH^-$) as a byproduct.

$$2H_2O_2 \rightarrow OH^{\bullet} + HOO^{\bullet} + H_2O \quad (23)$$

The $OH^{\bullet}$ radical reacts with any biological molecule in its immediate environment, including DNA. For example, it can break macromolecules (R-R or R-H) or abstract atoms from them (such as the various hydrogen atoms of the deoxyribose) by breakage of covalent bonds. This results in chemical alterations of the macromolecules and production of new free radicals ($R^{\bullet}$ or $RO^{\bullet}$):

$$R\text{-}R + OH^{\bullet} \rightarrow ROH + R^{\bullet} \quad (24)$$

$$RH + OH^{\bullet} \rightarrow R^{\bullet} + H_2O \quad (25)$$

$$\text{or } RH + OH^{\bullet} \rightarrow RO^{\bullet} + H_2 \quad (26)$$

The new free radicals will further react with other molecules resulting in additional chemical alterations. Corresponding evidence for DNA damage by $ONOO^-$ is available as well (181).

In conclusion, there is a clear sequence of events starting from the irregular gating of VGICs by EMFs up to DNA damage and related pathologies, including carcinogenesis.

4. Discussion

The present study reviewed experimental and epidemiological findings connecting exposure to purely ELF, and RF (containing ELF) human-made EMFs, with DNA damage and related pathologies, including cancer. It is documented that both such types of human-made EMF-exposure can induce OS (3,34,36-39,43,45,109), DNA damage (1-55,84,85) and infertility (56-71). It is also documented that the same types of EMF-exposure are linked with increased cancer risk both in humans and experimental animals (72-83,86-98,110-114).

We attempted to provide a complete, plausible explanation of these DNA damage-related findings on a biophysical and biochemical basis. According to the ion forced-oscillation mechanism for dysfunction of VGICs (143-146), human-made (polarized and coherent) ELF/ULF EMFs or the ELF/ULF modulation/pulsing/variability components of modern RF/WC EMFs can alter intracellular ionic concentrations by irregular gating of VGICs on cell membranes. This leads to immediate OS by ROS (over)production in the cytosol and/or the mitochondria, which can damage DNA when cells are unable to reinstate electrochemical balance (normal intracellular ionic concentrations). Consequently, DNA damage can lead to reproductive disabilities, neurodegenerative diseases, aging, genetic alterations and cancer.

According to the presented biophysical mechanism, the bioactivity of a polarized/coherent EMF is proportional to its intensity, inversely proportional to its frequency and doubles for pulsed fields, meaning that the ELF/ULF EMFs and even more the pulsing RF EMFs with ELF pulsations such as all WC EMFs, are predicted to be the most bioactive. This explains the recorded effects of purely ELF EMFs (1-5,9,13-18,22,47,50,72-82,117,212) and those of modulated/pulsing/variable RF EMFs (1,3,4,6-8,19-21,23-46,48,49,51-55,57-71,84-107,109-114,118,121-126). As emphasized, all types of RF exposure from all types of antennas and WC devices (WC EMFs) necessarily combine RF carrier signals with ELF/ULF components in the form of pulsing, modulation and random variability. The RF carrier signal alone does not contain information. The information is always contained in the ELF signals that modulate the RF (4). Significant experimental evidence shows that the bioactive parameters in a complex signal are its ELF components, and that non-modulated and non-pulsed RF signals alone do not usually induce biological effects (4,44,45,151-159), apart from heating when they possess high enough frequency and intensity (128,168-170). Therefore, the present study suggests that the vast majority of non-thermal effects attributed till now to various types of RF EMF-exposure, are actually due to their ELF/ULF components.

The presented biophysical mechanism and the provided numerical examples show that it is the direct ELF electric fields (and the magnetically induced electric fields in the case of sudden pulses), not the magnetic, that are the bioactive components, in contrast to what has been considered before by health agencies (117), and in agreement with previous experimental findings (191). Although electric fields are less penetrating in living tissue than magnetic fields, penetration depends upon the inverse square root of frequency, and thus ELF electric fields are significantly penetrating. Penetration depends also upon the inverse square root of the medium conductivity (213). Even though seawater is much more conductive than living tissue, ELF electromagnetic waves (thus both the electric and the magnetic parts of the waves) are penetrating several meters into seawater, accommodating communications with submarines (214). Moreover, it is known that isolated tissues respond to externally applied pulsed or sinusoidal ELF electric fields at very low thresholds (~10^{-3} V/m) similar to those predicted by this theory (143,215-217). This evidence shows that ELF electric fields penetrate enough to induce effects into living tissue, even at very low field intensities. Finally, skin cells, nerve terminals, eyes and organs close to the surface, such as the brain and heart, are directly exposed to externally applied EMFs. For all these reasons, no distinction is made between externally applied ELF electric fields and internally induced ones.

The ion forced-oscillation mechanism/theory was described in the present study by realistic equations based on the forces exerted on mobile ions in the vicinity of the voltage-sensors of VGICs on cell membranes by externally applied human-made (polarized) EMFs. The solution of the basic Eq. 2 resulted in bioactivity conditions connecting the intensity of an applied polarized EMF with its frequency. The bioactivity conditions 8-10, and 16-18, provided the bioactive intensity-frequency combinations for continuous and pulsed electric and magnetic fields. The final numbers explain almost all the experimental and epidemiological findings connecting biological/health effects with human-made EMF-exposure.

Although the mechanism was first published in 2000 (144) based on the available data on the structure and function of the

VGICs, newer details on the roles of S1-S6 helices, channel structure, relaxation, hysteresis and gating, have not refuted but verified and extended that knowledge (162,163,165,218-221).

What is more difficult to explain is the existence of non-linear phenomena such as the increased bioactivity 'windows' reported occasionally in the EMF-bioeffects literature, where certain effects are intensified within certain values of an EMF-exposure parameter (intensity in most cases, or frequency) (1,40,151-153,222). The existence of 'windows' shows that the response of living cells/organisms to EMFs is not generally proportional to the aforementioned EMF-parameters. Non-linear responses of living cells have not been explored in depth and it will take a number of years until they are. A possible explanation of observed intensity 'windows' according to the described mechanism has been suggested as being due to an existing upper limit in the membrane gating voltage change (222). Indeed, such an upper limit seems to exist. The VGICs respond to membrane voltage changes from ~30 mV (minimum) to ~100 mV (maximum) where the conductivity of the channel saturates (218,221). Apart from this possible explanation, no other explanation for the observed 'window' effects has been provided so far.

An effect not included in the bioactivity Eqs. 11 and 12 is the increased bioactivity of highly and unpredictably varying exposure such as those from WC devices (including mobile phones and Wi-Fi) and corresponding antennas (4,121,122). The described mechanism results in accurate predictions when the applied EMFs have constant parameters (intensity and frequency, among others). When the parameters are highly and unpredictably variable, the mechanism, and any possible mechanism, can only estimate effects according to the average and maximum exposure values of the varying EMFs. Finally, the bioactivity equations include field (and tissue) parameters and not exposure variables such as exposure duration or intermittence, which are also very important (16,17,19,41,55,122). One way to include such parameters is to multiply the right parts of Eqs. 11 and 12 by certain coefficient(s), which would be estimated experimentally. This could be a subject for future development of the theory.

This theory has successfully explained for the first time the sensing of upcoming earthquakes by animals, and the sensing of upcoming thunderstorms by sensitive individuals through the action of the partially polarized natural EMFs associated with these phenomena (146,223).

Any 'mechanism' in science (particularly in physics) must be based on simple and reasonable postulates, and must necessarily be expressed quantitatively (by solvable equations and numbers). The values of the different parameters in the equations must be based on physical/molecular data. Qualitative descriptions alone or incomplete quantitative descriptions based on incomplete or unsolvable equations do not constitute a 'mechanism'. The presented biophysical mechanism (143-146) is the only one that fulfills the aforementioned criteria in the case of EMF-induced bioeffects. Previous important attempts on mechanisms focusing on ions moving inside membrane channels or other proteins (224-227) were not successful, mainly for the following reasons: i) They had not taken into account damping and restoration forces (224,226), or did not calculate them (225,227). The difficulty was not related with considering such forces, as this is standard in oscillation mechanics, but with calculating their parameters such as β and ω_o, or the maximum velocity of the ion (u_o) within a channel. ii) They did not consider coordinated motion of several ions oscillating in parallel and in phase due to polarization and coherence, exerting additive forces on channel sensors, which prevail against the greater but chaotic forces due to the random thermal motion of the ions. iii) They focused on magnetic fields and magnetically induced electric ones, and ignored externally applied electric fields, which eventually seem to be more bioactive (191). iv) They did not result in numbers for field intensity versus frequency necessary to affect cells, although some experimental reports have indicated bioactive frequencies close to those predicted by Liboff's ion cyclotron resonance (ICR) model (224,228), possibly indicating some additional/secondary resonance mechanism involving ICR phenomenon (169). v) Apart from the study by Balcavage *et al* (226), there was no focus on the gating of VGICs, which is by far a more probable event to initiate biological effects, but simply on the motion of ions within channels/proteins.

Several other suggestions on possible mechanisms also face problems on fundamental issues (229-231). What is termed by Pall 'VGCC activation mechanism' and presented as his own discovery is none other than the mechanism presented here. A commentary paper/letter to the editor was published on this major ethical issue (129). An extended review of suggested mechanisms has been written by Creasey and Goldberg (169).

It has been claimed that the ELF components of complex RF-ELF EMFs of WC need to be 'demodulated' in order to be sensed by living organisms (232). 'Demodulated' or not, the fact is that the ELF components of modulated/pulsed WC signals can be directly sensed by both ELF meters/spectrum analyzers and living organisms (40,55).

Although there have been successive publications of this mechanism since 2000 (144), the subject is of great importance and in each consecutive publication additional important aspects are elucidated and/or refined. In our previous study in 2002 (145), the mechanism was extended to include oscillating magnetic fields and the thermal noise problem was discussed in more depth, while in 2015 (143) the mechanism was applied to reveal the importance of polarization/coherence in the bioactivity of man-made EMFs. In 2017 (223) and 2020 (146), it was applied to explain the sensing of upcoming thunderstorms and earthquakes, respectively, by sensitive humans/animals. In the present study, several aspects are further refined, including: i) The distance of S4 sensors from the channel pore; ii) more details on damping coefficient β and bioactivity constant k (Eq. 11); iii) further explanation of the role of the constant term in the solution (Eq. 3); iv) the similarity of proton voltage-gated channels with the other VGICs; v) numerical examples demonstrating the ability of the pulsing ELF electric and magnetic fields of 2G/3G/4G MT, DECT, Wi-Fi, Bluetooth, and the power line ELF fields to induce biological/health effects; vi) the velocity of oscillating ions; vii) bioactivity diagram extended to intensities down to 10^{-5} V/m; and viii) discussion on other suggested mechanisms.

Moreover, the present study documented how the impaired function of VGICs on the membranes of living cells triggers (over)production of free radicals/ROS, such as the most potent

$OH^{\bullet}$ produced by H_2O_2 via the Fenton reaction, and $ONOO^-$ produced by $NO^{\bullet}$. These are considered the main damaging species for DNA and other critical biological molecules. It is estimated that approximately two-thirds of the DNA damage caused by ionizing radiation is due to $OH^{\bullet}$ (233,234). Although $OH^{\bullet}$ can only diffuse at distances comparable to the length of a macromolecule, H_2O_2 can move to any intracellular site. Thus, even though the most potent $OH^{\bullet}$ due to its high reactivity has an extremely short lifetime (of the order of 10^{-9}-10^{-4} s depending on the presence of other molecules) it can be formed by H_2O_2 at any location within the cell (including the nucleus) and act instantly upon DNA or other macromolecules (233,234). As for $NO^{\bullet}$/$ONOO^-$, they can be diffused anywhere in the cell and thus directly affect any molecule, including DNA (181). Even though the present study identified specific pathways of ROS overproduction or the release of DNases connected with disrupted ionic concentrations in EMF-exposed cells, the exact molecular mechanisms need to be further explored and elucidated.

Finally, the present study discussed how unrepaired/misrepaired DNA lesions/damage such as strand breaks, covalent bond breakage or nucleotide base damages, lead to cell senescence, cell death or mutations, and related pathologies, including cancer. Even though effective mechanisms have evolved in all animals/cells for repairing DNA damage induced by environmental stressors, it is very different when the damaging events are isolated or random (e.g. radioactive particles or γ-photons of cosmic/natural radioactivity, or sporadic x-ray diagnostic exposure), compared with persisting/repeated exposure to cytotoxic agents, even when these agents are relatively weaker. Exposure to human-made EMFs and especially to the most detrimental ones from WC antennas/devices and high-voltage transmission lines (4) has become a new reality in modern life. Billions of people are exposed to such EMFs on a daily basis. Although they are less cytotoxic than radioactivity or certain cytotoxic chemicals, they represent the most persistent daily cytotoxic stressors against which any repair mechanisms cannot be efficient enough. By contrast, previously existing cytotoxic agents expose us randomly as isolated events. When an organism is constantly under OS due to a totally new cytotoxic agent such as human-made EMFs, no protective mechanism, evolved in the billions of years of biological evolution to protect from natural (non-polarized) EMFs/radiation or isolated hazardous events, can be effective enough.

The repair capability of cells in response to DNA damage is crucial for the final outcome. The threshold of damage above which it becomes irreparable depends on cell type and the health and status of the organism. An organism with poor health and/or under stress and inflammation due to OS is expected to have decreased repair capability and increased cancer risk. Epigenetic effects such as altered gene expression may also lead to cellular dysfunction and carcinogenesis (133,235,236).

Both DNA damage and alterations in protein synthesis, especially increased levels of stress proteins, are reported to be induced similarly by both ELF and pulsing RF EMFs (237,238). However, the effects of pulsing RF were attributed to the carrier frequency, and it was not considered that perhaps in both cases (ELF and pulsing RF) the ELF components might be responsible for the effects, as suggested now by the present study.

To the best of our knowledge, the present study provides for the first time a complete and precise biophysical/biochemical picture to explain the great number of experimental and epidemiological findings connecting human-made EMF exposure with DNA damage and related pathologies such as cancer, infertility and neurodegenerative diseases.

The long-existing experimental and epidemiological findings connecting exposure to human-made EMFs and DNA damage, infertility and cancer, are now explained by the presented complete mechanism. The present study should provide a basis for further research and encourage health authorities to take measures for the protection of life on Earth against unrestricted use of human-made EMFs.

Acknowledgements

Not applicable.

Funding

The study is supported by the Special Account for Research Grants of the National and Kapodistrian University of Athens (grant number 16599).

Availability of data and materials

Not applicable.

Authors' contributions

DJP designed the study and wrote the main manuscript. AK verified all equations and calculations. IY coauthored section 3 on biochemical processes. GPC reviewed and evaluated all data. All authors have read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Goodman EM, Greenebaum B and Marron MT: Effects of electromagnetic fields on molecules and cells. Int Rev Cytol 158: 279-338, 1995.
2. Santini MT, Ferrante A, Rainaldi G, Indovina P and Indovina PL: Extremely low frequency (ELF) magnetic fields and apoptosis: A review. Int J Radiat Biol 81: 1-11, 2005.
3. Phillips JL, Singh NP and Lai H: Electromagnetic fields and DNA damage. Pathophysiology 16: 79-88, 2009.
4. Panagopoulos DJ: Comparing DNA damage induced by mobile telephony and other types of man-made electromagnetic fields. Mutat Res Rev Mutat Res 781: 53-62, 2019.
5. Delgado JMR: Biological effects of extremely low frequency electromagnetic fields. J Bioelectricity 4: 75-92, 1985.

6. Garaj-Vrhovac V, Horvat D and Koren Z: The effect of microwave radiation on the cell genome. Mutat Res 243: 87-93, 1990.
7. Garaj-Vrhovac V, Horvat D and Koren Z: The relationship between colony-forming ability, chromosome aberrations and incidence of micronuclei in V79 Chinese hamster cells exposed to microwave radiation. Mutat Res 263: 143-149, 1991.
8. Garaj-Vrhovac V, Fucić A and Horvat D: The correlation between the frequency of micronuclei and specific chromosome aberrations in human lymphocytes exposed to microwave radiation in vitro. Mutat Res 281: 181-186, 1992.
9. Ma TH and Chu KC: Effect of the extremely low frequency (ELF) electromagnetic field (EMF) on developing embryos of the fruit fly (*Drosophila melanogaster* L.). Mutat Res 303: 35-39, 1993.
10. Sarkar S, Ali S and Behari J: Effect of low power microwave on the mouse genome: A direct DNA analysis. Mutat Res 320: 141-147, 1994.
11. Lai H and Singh NP: Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. Bioelectromagnetics 16: 207-210, 1995.
12. Lai H and Singh NP: Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol 69: 513-521, 1996.
13. Lai H and Singh NP: Acute exposure to a 60 Hz magnetic field increases DNA strand breaks in rat brain cells. Bioelectromagnetics 18: 156-165, 1997.
14. Svedenstål BM, Johanson KJ and Mild KH: DNA damage induced in brain cells of CBA mice exposed to magnetic fields. In Vivo 13: 551-552, 1999.
15. Koana T, Okada MO, Takashima Y, Ikehata M and Miyakoshi J: Involvement of eddy currents in the mutagenicity of ELF magnetic fields. Mutat Res 476: 55-62, 2001.
16. Ivancsits S, Diem E, Pilger A, Rüdiger HW and Jahn O: Induction of DNA strand breaks by intermittent exposure to extremely-low-frequency electromagnetic fields in human diploid fibroblasts. Mutat Res 519: 1-13, 2002.
17. Ivancsits S, Diem E, Jahn O and Rüdiger HW: Intermittent extremely low frequency electromagnetic fields cause DNA damage in a dose-dependent way. Int Arch Occup Environ Health 76: 431-436, 2003.
18. Winker R, Ivancsits S, Pilger A, Adlkofer F and Rüdiger HW: Chromosomal damage in human diploid fibroblasts by intermittent exposure to extremely low-frequency electromagnetic fields. Mutat Res 585: 43-49, 2005.
19. Diem E, Schwarz C, Adlkofer F, Jahn O and Rüdiger H: Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro. Mutat Res 583: 178-183, 2005.
20. Mausset-Bonnefont AL, Hirbec H, Bonnefont X, Privat A, Vignon J and de Sèze R: Acute exposure to GSM 900-MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. Neurobiol Dis 17: 445-454, 2004.
21. Ji S, Oh E, Sul D, Choi JW, Park H and Lee E: DNA damage of lymphocytes in volunteers after 4 h use of mobile phone. J Prev Med Public Health 37: 373-380, 2004.
22. Hong R, Zhang Y, Liu Y and Weng EQ: Effects of extremely low frequency electromagnetic fields on DNA of testicular cells and sperm chromatin structure in mice. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 23: 414-417, 2005 (In Chinese).
23. Belyaev IY, Hillert L, Protopopova M, Tamm C, Malmgren LO, Persson BR, Selivanova G and Harms-Ringdahl M: 915 MHz microwaves and 50 Hz magnetic field affect chromatin conformation and 53BP1 foci in human lymphocytes from hypersensitive and healthy persons. Bioelectromagnetics 26: 173-184, 2005.
24. Markovà E, Hillert L, Malmgren L, Persson BR and Belyaev IY: Microwaves from GSM mobile telephones affect 53BP1 and gamma-H2AX foci in human lymphocytes from hypersensitive and healthy persons. Environ Health Perspect 113: 1172-1177, 2005.
25. Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM and King BV: Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline. Int J Androl 28: 171-179, 2005.
26. Nikolova T, Czyz J, Rolletschek A, Blyszczuk P, Fuchs J, Jovtchev G, Schuderer J, Kuster N and Wobus AM: Electromagnetic fields affect transcript levels of apoptosis-related genes in embryonic stem cell-derived neural progenitor cells. FASEB J 19: 1686-1688, 2005.
27. Zhang DY, Xu ZP, Chiang H, Lu DQ and Zeng QL: Effects of GSM 1800 MHz radiofrequency electromagnetic fields on DNA damage in Chinese hamster lung cells. Zhonghua Yu Fang Yi Xue Za Zhi 40: 149-152, 2006 (In Chinese).
28. Lixia S, Yao K, Kaijun W, Deqiang L, Huajun H, Xiangwei G, Baohong W, Wei Z, Jianling L and Wei W: Effects of 1.8 GHz radiofrequency field on DNA damage and expression of heat shock protein 70 in human lens epithelial cells. Mutat Res 602: 135-142, 2006.
29. Ferreira AR, Knakievicz T, Pasquali MA, Gelain DP, Dal-Pizzol F, Fernández CE, de Salles AA, Ferreira HB and Moreira JC: Ultra high frequency-electromagnetic field irradiation during pregnancy leads to an increase in erythrocytes micronuclei incidence in rat offspring. Life Sci 80: 43-50, 2006.
30. Panagopoulos DJ, Chavdoula ED, Nezis IP and Margaritis LH: Cell death induced by GSM 900-MHz and DCS 1800-MHz mobile telephony radiation. Mutat Res 626: 69-78, 2007.
31. Yan JG, Agresti M, Bruce T, Yan YH, Granlund A and Matloub HS: Effects of cellular phone emissions on sperm motility in rats. Fertil Steril 88: 957-964, 2007.
32. Yao K, Wu W, Wang K, Ni S, Ye P, Yu Y, Ye J and Sun L: Electromagnetic noise inhibits radiofrequency radiation-induced DNA damage and reactive oxygen species increase in human lens epithelial cells. Mol Vis 14: 964-969, 2008.
33. Yadav AS and Sharma MK: Increased frequency of micronucleated exfoliated cells among humans exposed in vivo to mobile telephone radiations. Mutat Res 650: 175-180, 2008.
34. Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, Krstic D, Cvetkovic T and Pavlovic V: Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J Radiat Res 49: 579-586, 2008.
35. Lee KS, Choi JS, Hong SY, Son TH and Yu K: Mobile phone electromagnetic radiation activates MAPK signaling and regulates viability in *Drosophila*. Bioelectromagnetics 29: 371-379, 2008.
36. De Iuliis GN, Newey RJ, King BV and Aitken RJ: Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. PLoS One 4: e6446, 2009.
37. Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E and Sharma R: Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: An in vitro pilot study. Fertil Steril 92: 1318-1325, 2009.
38. Mailankot M, Kunnath AP, Jayalekshmi H, Koduru B and Valsalan R: Radio frequency electromagnetic radiation (RF-EMR) from GSM (0.9/1.8 GHz) mobile phones induces oxidative stress and reduces sperm motility in rats. Clinics (Sao Paulo) 64: 561-565, 2009.
39. Luukkonen J, Hakulinen P, Mäki-Paakkanen J, Juutilainen J and Naarala J: Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872 MHz radiofrequency radiation. Mutat Res 662: 54-58, 2009.
40. Panagopoulos DJ, Chavdoula ED and Margaritis LH: Bioeffects of mobile telephony radiation in relation to its intensity or distance from the antenna. Int J Radiat Biol 86: 345-357, 2010.
41. Chavdoula ED, Panagopoulos DJ and Margaritis LH: Comparison of biological effects between continuous and intermittent exposure to GSM-900-MHz mobile phone radiation. Detection of apoptotic cell death features. Mutat Res 700: 51-61, 2010.
42. Guler G, Tomruk A, Ozgur E and Seyhan N: The effect of radiofrequency radiation on DNA and lipid damage in non-pregnant and pregnant rabbits and their newborns. Gen Physiol Biophys 29: 59-66, 2010.
43. Tomruk A, Guler G and Dincel AS: The influence of 1800 MHz GSM-like signals on hepatic oxidative DNA and lipid damage in nonpregnant, pregnant, and newly born rabbits. Cell Biochem Biophys 56: 39-47, 2010.
44. Franzellitti S, Valbonesi P, Ciancaglini N, Biondi C, Contin A, Bersani F and Fabbri E: Transient DNA damage induced by high-frequency electromagnetic fields (GSM 1.8 GHz) in the human trophoblast HTR-8/SVneo cell line evaluated with the alkaline comet assay. Mutat Res 683: 35-42, 2010.
45. Campisi A, Gulino M, Acquaviva R, Bellia P, Raciti G, Grasso R, Musumeci F, Vanella A and Triglia A: Reactive oxygen species levels and DNA fragmentation on astrocytes in primary culture after acute exposure to low intensity microwave electromagnetic field. Neurosci Lett 473: 52-55, 2010.

46. Panagopoulos DJ: Effect of microwave exposure on the ovarian development of *Drosophila melanogaster*. Cell Biochem Biophys 63: 121-132, 2012.
47. Panagopoulos DJ, Karabarbounis A and Lioliousis C: ELF alternating magnetic field decreases reproduction by DNA damage induction. Cell Biochem Biophys 67: 703-716, 2013.
48. Liu C, Gao P, Xu SC, Wang Y, Chen CH, He MD, Yu ZP, Zhang L and Zhou Z: Mobile phone radiation induces mode-dependent DNA damage in a mouse spermatocyte-derived cell line: A protective role of melatonin. Int J Radiat Biol 89: 993-1001, 2013.
49. Pesnya DS and Romanovsky AV: Comparison of cytotoxic and genotoxic effects of plutonium-239 alpha particles and mobile phone GSM 900 radiation in the *Allium cepa* test. Mutat Res 750: 27-33, 2013.
50. Mihai CT, Rotinberg P, Brinza F and Vochita G: Extremely low-frequency electromagnetic fields cause DNA strand breaks in normal cells. J Environ Health Sci Eng 12: 15, 2014.
51. Daroit NB, Visioli F, Magnusson AS, Vieira GR and Rados PV: Cell phone radiation effects on cytogenetic abnormalities of oral mucosal cells. Braz Oral Res 29: 1-8, 2015.
52. Banerjee S, Singh NN, Sreedhar G and Mukherjee S: Analysis of the genotoxic effects of mobile phone radiation using buccal micronucleus assay: A comparative evaluation. J Clin Diagn Res 10: ZC82-ZC85, 2016.
53. D'Silva MH, Swer RT, Anbalagan J and Rajesh B: Effect of radiofrequency radiation emitted from 2G and 3G cell phone on developing liver of chick embryo-a comparative study. J Clin Diagn Res 11: AC05-AC09, 2017.
54. Panagopoulos DJ: Chromosome damage in human cells induced by UMTS mobile telephony radiation. Gen Physiol Biophys 38: 445-454, 2019.
55. Panagopoulos DJ: Comparing chromosome damage induced by mobile telephony radiation and a high caffeine dose: Effect of combination and exposure duration. Gen Physiol Biophys 39: 531-544, 2020.
56. Magras IN and Xenos TD: RF radiation-induced changes in the prenatal development of mice. Bioelectromagnetics 18: 455-461, 1997.
57. Panagopoulos DJ, Karabarbounis A and Margaritis LH: Effect of GSM 900-MHz mobile phone radiation on the reproductive capacity of *Drosophila melanogaster*. Electromagn Biol Med 23: 29-43, 2004.
58. Panagopoulos DJ, Chavdoula ED, Karabarbounis A and Margaritis LH: Comparison of bioactivity between GSM 900 MHz and DCS 1800 MHz mobile telephony radiation. Electromagn Biol Med 26: 33-44, 2007.
59. Wdowiak A, Wdowiak L and Wiktor H: Evaluation of the effect of using mobile phones on male fertility. Ann Agric Environ Med 14: 169-172, 2007.
60. Agarwal A, Deepinder F, Sharma RK, Ranga G and Li J: Effect of cell phone usage on semen analysis in men attending infertility clinic: An observational study. Fertil Steril 89: 124-128, 2008.
61. Batellier F, Couty I, Picard D and Brillard JP: Effects of exposing chicken eggs to a cell phone in 'call' position over the entire incubation period. Theriogenology 69: 737-745, 2008.
62. Gul A, Celebi H and Uğraş S: The effects of microwave emitted by cellular phones on ovarian follicles in rats. Arch Gynecol Obstet 280: 729-733, 2009.
63. Sharma VP and Kumar NR: Changes in honey bee behaviour and biology under the influence of cell phone radiations. Curr Sci 98: 1376-1378, 2010.
64. La Vignera S, Condorelli RA, Vicardi E, D'Agata R and Calogero AE: Effects of the exposure to mobile phones on male reproduction: A review of the literature. J Androl 33: 350-356, 2012.
65. Balmori A: Possible effects of electromagnetic fields from phone masts on a population of white stork (*Ciconia ciconia*). Electromagn Biol Med 24: 109-119, 2005.
66. Balmori A and Hallberg O: The urban decline of the house sparrow (*Passer domesticus*): A possible link with electromagnetic radiation. Electromagn Biol Med 26: 141-151, 2007.
67. Everaert J and Bauwens D: A possible effect of electromagnetic radiation from mobile phone base stations on the number of breeding house sparrows (*Passer domesticus*). Electromagn Biol Med 26: 63-72, 2007.
68. Bacandritsos N, Granato A, Budge G, Papanastasiou I, Roinioti E, Caldon M, Falcaro C, Gallina A and Mutinelli F: Sudden deaths and colony population decline in Greek honey bee colonies. J Invertebr Pathol 105: 335-340, 2010.
69. Cucurachi S, Tamis WL, Vijver MG, Peijnenburg WJ, Bolte JF and de Snoo GR: A review of the ecological effects of radio-frequency electromagnetic fields (RF-EMF). Environ Int 51: 116-140, 2013.
70. Balmori A: The incidence of electromagnetic pollution on the amphibian decline: Is this an important piece of the puzzle? Toxicol Environ Chem 88: 287-299, 2006.
71. Balmori A: Mobile phone mast effects on common frog (*Rana temporaria*) tadpoles: The city turned into a laboratory. Electromagn Biol Med 29: 31-35, 2010.
72. Wertheimer N and Leeper E: Electrical wiring configurations and childhood cancer. Am J Epidemiol 109: 273-284, 1979.
73. Savitz DA, Wachtel H, Barnes F, John EM and Tvrdik JG: Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. Am J Epidemiol 128: 21-38, 1988.
74. Coleman MP, Bell CM, Taylor HL and Primic-Zakelj M: Leukaemia and residence near electricity transmission equipment: A case-control study. Br J Cancer 60: 793-798, 1989.
75. Feychting M and Ahlbom A: Magnetic fields and cancer in children residing near Swedish high-voltage power lines. Am J Epidemiol 138: 467-481, 1993.
76. Feychting M and Ahlbom A: Magnetic fields, leukemia, and central nervous system tumors in Swedish adults residing near high-voltage power lines. Epidemiology 5: 501-509, 1994.
77. Feychting M and Ahlbom A: Childhood leukemia and residential exposure to weak extremely low frequency magnetic fields. Environ Health Perspect 103 (Suppl 2): S59-S62, 1995.
78. Coghill RW, Steward J and Philips A: Extra low frequency electric and magnetic fields in the bed place of children diagnosed with leukaemia: A case-control study. Eur J Cancer Prev 5: 153-158, 1996.
79. Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, Linet M, McBride M, Michaelis J, Olsen JH, *et al*: A pooled analysis of magnetic fields and childhood leukaemia. Br J Cancer 83: 692-698, 2000.
80. Greenland S, Sheppard AR, Kaune WT, Poole C and Kelsh MA: A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood leukemia-EMF study group. Epidemiology 11: 624-634, 2000.
81. Draper G, Vincent T, Kroll ME and Swanson J: Childhood cancer in relation to distance from high voltage power lines in England and Wales: A case-control study. BMJ 330: 1290, 2005.
82. Kheifets L, Ahlbom A, Crespi CM, Draper G, Hagihara J, Lowenthal RM, Mezei G, Oksuzyan S, Schüz J, Swanson J, *et al*: Pooled analysis of recent studies on magnetic fields and childhood leukaemia. Br J Cancer 103: 1128-1135, 2010.
83. Hallberg O and Johansson O: Melanoma incidence and frequency modulation (FM) broadcasting. Arch Environ Health 57: 32-40, 2002.
84. Gulati S, Yadav A, Kumar N, Kanupriya, Aggarwal NK, Kumar R and Gupta R: Effect of GSTM1 and GSTT1 polymorphisms on genetic damage in humans populations exposed to radiation from mobile towers. Arch Environ Contam Toxicol 70: 615-625, 2016.
85. Zothansiama, Zosangzuali M, Lalramdinpuii M and Jagetia GC: Impact of radiofrequency radiation on DNA damage and antioxidants in peripheral blood lymphocytes of humans residing in the vicinity of mobile phone base stations. Electromagn Biol Med 36: 295-305, 2017.
86. Hardell L, Carlberg M, Söderqvist F, Mild KH and Morgan LL: Long-term use of cellular phones and brain tumours: Increased risk associated with use for > or =10 years. Occup Environ Med 64: 626-632, 2007.
87. Hardell L, Carlberg M and Hansson Mild K: Epidemiological evidence for an association between use of wireless phones and tumor diseases. Pathophysiology 16: 113-122, 2009.
88. Khurana VG, Teo C, Kundi M, Hardell L and Carlberg M: Cell phones and brain tumors: A review including the long-term epidemiologic data. Surg Neurol 72: 205-214, 2009.
89. Hardell L and Carlberg M: Mobile phones, cordless phones and the risk for brain tumours. Int J Oncol 35: 5-17, 2009.
90. Hardell L, Carlberg M, Söderqvist F and Mild KH: Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones. Int J Oncol 43: 1036-1044, 2013.
91. Hardell L, Carlberg M, Söderqvist F and Mild KH: Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. Int J Oncol 43: 1833-1845, 2013.

92. Hardell L, Carlberg M and Hansson Mild K: Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology 20: 85-110, 2013.
93. Wang Y and Guo X: Meta-analysis of association between mobile phone use and glioma risk. J Cancer Res Ther 12 (Suppl): C298-C300, 2016.
94. Carlberg M and Hardell L: Evaluation of mobile phone and cordless phone use and glioma risk using the bradford hill viewpoints from 1965 on association or causation. Biomed Res Int 2017: 9218486, 2017.
95. Hardell L: Effects of mobile phones on children's and adolescents' health: A commentary. Child Dev 89: 137-140, 2018.
96. Momoli F, Siemiatycki J, McBride ML, Parent MÉ, Richardson L, Bedard D, Platt R, Vrijheid M, Cardis E and Krewski D: Probabilistic multiple-bias modelling applied to the Canadian data from the INTERPHONE study of mobile phone use and risk of glioma, meningioma, acoustic neuroma, and parotid gland tumors. Am J Epidemiol 186: 885-893, 2017.
97. Miller AB, Morgan LL, Udasin I and Davis DL: Cancer epidemiology update, following the 2011 IARC evaluation of radiofrequency electromagnetic fields (Monograph 102). Environ Res 167: 673-683, 2018.
98. Miller AB, Sears ME, Morgan LL, Davis DL, Hardell L, Oremus M and Soskolne CL: Risks to health and well-being from radio-frequency radiation emitted by cell phones and other wireless devices. Front Public Health 7: 223, 2019.
99. Santini R, Santini P, Danze JM, Le Ruz P and Seigne M: Study of the health of people living in the vicinity of mobile phone base stations: I. Influences of distance and sex. Pathol Biol 50: 369-373, 2002.
100. Navarro A, Garcia JS, Portoles M and Gómez-Perretta G: The microwave syndrome: A preliminary study in Spain. Electromagn Biol Med 22: 161-169, 2003.
101. Salama OE and Abou El Naga RM: Cellular phones: Are they detrimental? J Egypt Public Health Assoc 79: 197-223, 2004.
102. Hutter HP, Moshammer H, Wallner P and Kundi M: Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. Occup Environ Med 63: 307-313, 2006.
103. Abdel-Rassoul G, El-Fateh OA, Salem MA, Michael A, Farahat F, El-Batanouny M and Salem E: Neurobehavioral effects among inhabitants around mobile phone base stations. Neurotoxicology 28: 434-440, 2007.
104. Blettner M, Schlehofer B, Breckenkamp J, Kowall B, Schmiedel S, Reis U, Potthoff P, Schüz J and Berg-Beckhoff G: Mobile phone base stations and adverse health effects: Phase 1 of a population-based, cross-sectional study in Germany. Occup Environ Med 66: 118-123, 2009.
105. Viel JF, Clerc S, Barrera C, Rymzhanova R, Moissonnier M, Hours M and Cardis E: Residential exposure to radiofrequency fields from mobile phone base stations, and broadcast transmitters: A population-based survey with personal meter. Occup Environ Med 66: 550-556, 2009.
106. Kundi M and Hutter HP: Mobile phone base stations-effects on wellbeing and health. Pathophysiology 16: 123-135, 2009.
107. Shahbazi-Gahrouei D, Karbalae M, Moradi HA and Baradaran-Ghahfarokhi M: Health effects of living near mobile phone base transceiver station (BTS) antennae: A report from Isfahan, Iran. Electromagn Biol Med 33: 206-210, 2014.
108. Irigaray P, Caccamo D and Belpomme D: Oxidative stress in electrohypersensitivity self-reporting patients: Results of a prospective *in vivo* investigation with comprehensive molecular analysis. Int J Mol Med 42: 1885-1898, 2018.
109. Yakymenko I, Tsybulin O, Sidorik E, Henshel D, Kyrylenko O and Kyrylenko S: Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn Biol Med 35: 186-202, 2016.
110. Tillmann T, Ernst H, Streckert J, Zhou Y, Taugner F, Hansen V and Dasenbrock C: Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model. Int J Radiat Biol 86: 529-541, 2010.
111. Lerchl A, Klose M, Grote K, Wilhelm AF, Spathmann O, Fiedler T, Streckert J, Hansen V and Clemens M: Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans. Biochem Biophys Res Commun 459: 585-590, 2015.
112. National Toxicology Program: Toxicology and carcinogenesis studies in Sprague Dawley (Hsd:Sprague Dawley SD) rats exposed to whole-body radio frequency radiation at a frequency (900 MHz) and modulations (GSM and CDMA) used by cell phones. Natl Toxicol Program Tech Rep Ser: NTP-TR-595, 2018.
113. Smith-Roe SL, Wyde ME, Stout MD, Winters JW, Hobbs CA, Shepard KG, Green AS, Kissling GE, Shockley KR, Tice RR, *et al*: Evaluation of the genotoxicity of cell phone radiofrequency radiation in male and female rats and mice following subchronic exposure. Environ Mol Mutagen 61: 276-290, 2020.
114. Falcioni L, Bua L, Tibaldi E, Lauriola M, De Angelis L, Gnudi F, Mandrioli D, Manservigi M, Manservisi F, Manzoli I, *et al*: Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission. Environ Res 165: 496-503, 2018.
115. International Commission on Non-Ionizing Radiation Protection: Guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz to 100 kHz). Health Phys 99: 818-836, 2010.
116. International Commission on Non-Ionizing Radiation Protection: Guidelines for limiting exposure to electromagnetic fields (100 kHz to 300 GHz). Health Phys 118; 483-524, 2020.
117. IARC: Non-ionizing radiation, part 1: Static and extremely low-frequency (ELF) electric and magnetic fields. Vol. 80. World Health Organization. IARC Press, Lyon, 2002.
118. IARC: Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields. Vol. 102. IARC Press, Lyon, 2013.
119. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Islami F, Galichet L and Straif K; WHO International Agency for Research on Cancer Monograph Working Group: Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol 12: 624-626, 2011.
120. Verschaeve L: Misleading scientific papers on health effects from wireless communication devices. In: Microwave Effects on DNA and Proteins. Geddes CD (ed). Springer, Cham, pp159-233, 2017.
121. Panagopoulos DJ, Johansson O and Carlo GL: Real versus simulated mobile phone exposures in experimental studies. Biomed Res Int 2015: 607053, 2015.
122. Panagopoulos DJ: Mobile telephony radiation effects on insect ovarian cells. The necessity for real exposures bioactivity assessment. The key role of polarization, and the 'ion forced-oscillation mechanism'. In: Microwave Effects on DNA and Proteins. Geddes CD (ed). Springer, Cham, pp1-48, 2017.
123. Manna D and Ghosh R: Effect of radiofrequency radiation in cultured mammalian cells: A review. Electromagn Biol Med 35: 265-301, 2016.
124. Leach V, Weller S and Redmayne M: A novel database of bio-effects from non-ionizing radiation. Rev Environ Health 33: 273-280, 2018.
125. Karipidis K, Mate R, Urban D, Tinker R and Wood A: 5G mobile networks and health-a state-of-the-science review of the research into low-level RF fields above 6 GHz. J Expo Sci Environ Epidemiol 31: 585-605, 2021.
126. Hardell L and Nyberg R: Appeals that matter or not on a moratorium on the deployment of the fifth generation, 5G, for microwave radiation. Mol Clin Oncol 12: 247-257, 2020.
127. Hardell L and Carlberg M: Health risks from radiofrequency radiation, including 5G, should be assessed by experts with no conflicts of interest. Oncol Lett 20: 15, 2020.
128. Metaxas AC: Microwave heating. Power Eng 5: 237-247, 1991.
129. Panagopoulos DJ: Comments on Pall's 'Millimeter (MM) wave and microwave frequency radiation produce deeply penetrating effects: The biology and the physics'. Rev Environ Health: Jul 12, 2021 (Epub ahead of print). doi: https://doi.org/10.1515/reveh-2021-0090.
130. Ames BN: Endogenous DNA damage as related to cancer and aging. Mutat Res 214: 41-46, 1989.
131. Lieber MR: Pathological and physiological double-strand breaks: Roles in cancer, aging, and the immune system. Am J Pathol 153: 1323-1332, 1998.
132. Helleday T, Loc J, van Gentd DC and Engelward BP: DNA double-strand break repair: From mechanistic understanding to cancer treatment. DNA Repair (Amst) 6: 923-935, 2007.
133. Lahtz C and Pfeifer GP: Epigenetic changes of DNA repair genes in cancer. J Mol Cell Biol 3: 51-58, 2011.
134. Yao Y and Dai W: Genomic instability and cancer. J Carcinog Mutagen 5: 1000165, 2014.
135. Bernstein C, Prasad AR, Nfonsam V and Bernstein H: DNA damage, DNA repair and cancer. In: New Research Directions in DNA Repair. Clarc C (ed). InTech, Rijeka, pp413-465, 2013.
136. Basu AK: DNA damage, mutagenesis and cancer. Int J Mol Sci 19: 970, 2018.

137. von Zglinicki T, Saretzki G, Ladhoff J, d'Adda di Fagagna F and Jackson SP: Human cell senescence as a DNA damage response. Mech Ageing Dev 126: 111-117, 2005.
138. Shah DJ, Sachs RK and Wilson DJ: Radiation-induced cancer: A modern view. Br J Radiol 85: e1166-e1173, 2012.
139. Rodgers K and McVey M: Error-prone repair of DNA double-strand breaks. J Cell Physiol 231: 15-24, 2016.
140. Nadler DL and Zurbenko IG: Estimating cancer latency times using a weibull model. Adv Epidemiol 2014: 746769, 2014.
141. Francis G: Ionization Phenomena in Gases. Butterworths Scientific Publications, London, 1960.
142. Gomer R: Field Emission and Field Ionization. Harvard University Press, Cambridge, 1961.
143. Panagopoulos DJ, Johansson O and Carlo GL: Polarization: A key difference between man-made and natural electromagnetic fields, in regard to biological activity. Sci Rep 5: 14914, 2015.
144. Panagopoulos DJ, Messini N, Karabarbounis A, Filippetis AL and Margaritis LH: A mechanism for action of oscillating electric fields on cells. Biochem Biophys Res Commun 272: 634-640, 2000.
145. Panagopoulos DJ, Karabarbounis A and Margaritis LH: Mechanism for action of electromagnetic fields on cells. Biochem Biophys Res Commun 298: 95-102, 2002.
146. Panagopoulos DJ, Balmori A and Chrousos GP: On the biophysical mechanism of sensing upcoming earthquakes by animals. Sci Total Environ 717: 136989, 2020.
147. Alberts B, Johnson A, Lewis J, Raff M, Roberts K and Walter P: Molecular Biology of the Cell. Garland Publishing, Inc., New York, 1994.
148. Stryer L: Biochemistry. 4th edition. Freeman WH (ed). Freeman and Company, New York, NY, 1995.
149. Halgamuge MN and Abeyrathne CD: Behavior of charged particles in a biological cell exposed to AC-DC electromagnetic fields. Environ Eng Sci 28: 1-10, 2001.
150. Panagopoulos DJ and Karabarbounis A: Comments on study of charged particle's behavior in a biological cell exposed to AC-DC electromagnetic fields, and on comparison between two models of interaction between electric and magnetic fields and proteins in cell membranes. Environ Eng Sci 28: 749-751, 2011.
151. Bawin SM, Kaczmarek LK and Adey WR: Effects of modulated VHF fields, on the central nervous system. Ann N Y Acad Sci 247: 74-81, 1975.
152. Bawin SM, Adey WR and Sabbot IM: Ionic factors in release of $^{45}Ca^{2+}$ from chicken cerebral tissue by electromagnetic fields. Proc Natl Acad Sci USA 75: 6314-6318, 1978.
153. Blackman CF, Benane SG, Elder JA, House DE, Lampe JA and Faulk JM: Induction of calcium-ion efflux from brain tissue by radiofrequency radiation: Effect of sample number and modulation frequency on the power density window. Bioelectromagnetics 1: 35-43, 1980.
154. Frei M, Jauchem J and Heinmets F: Physiological effects of 2.8 GHz radio-frequency radiation: A comparison of pulsed and continuous-wave radiation. J Microw Power Electromagn Energy 23: 85-93, 1988.
155. Bolshakov MA and Alekseev SI: Bursting responses of Lymnea neurons to microwave radiation. Bioelectromagnetics 13: 119-129, 1992.
156. Penafiel LM, Litovitz T, Krause D, Desta A and Mullins JM: Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells. Bioelectromagnetics 18: 132-141, 1997.
157. Huber R, Treyer V, Borbély AA, Schuderer J, Gottselig JM, Landolt HP, Werth E, Berthold T, Kuster N, Buck A and Achermann P: Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11: 289-295, 2002.
158. Höytö A, Luukkonen J, Juutilainen J and Naarala J: Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants. Radiat Res 170: 235-243, 2008.
159. Mohammed HS, Fahmy HM, Radwan NM and Elsayed AA: Non-thermal continuous and modulated electromagnetic radiation fields effects on sleep EEG of rats. J Adv Res 4: 181-187, 2013.
160. Noda M, Ikeda T, Kayano T, Suzuki H, Takeshima H, Kurasaki M, Takahashi H and Numa S: Existence of distinct sodium channel messenger RNAs in rat brain. Nature 320: 188-192, 1986.
161. Liman ER, Hess P, Weaver F and Koren G: Voltage-sensing residues in the S4 region of a mammalian K^+ channel. Nature 353: 752-756, 1991.
162. Tombola F, Pathak MM and Isacoff EY: How does voltage open an ion channel? Annu Rev Cell Dev Biol 22: 23-52, 2006.
163. Schmidt WF and Thomas CG: More precise model of α-helix and transmembrane α-helical peptide backbone structure. J Biophy Chem 3: 295-303, 2012.
164. Miller C: An overview of the potassium channel family. Genome Biol 1: REVIEWS0004, 2000.
165. Zhang XC, Yang H, Liu Z and Sun F: Thermodynamics of voltage-gated ion channels. Biophys Rep 4: 300-319, 2018.
166. DeCoursey TE: Interactions between NADPH oxidase and voltage-gated proton channels: Why electron transport depends on proton transport. FEBS Lett 555: 57-61, 2003.
167. Seredenina T, Demaurex N and Krause KH: Voltage-gated proton channels as novel drug targets: From NADPH oxidase regulation to sperm biology. Antioxid Redox Sign 23: 490-513, 2015.
168. Panagopoulos DJ, Johansson O and Carlo GL: Evaluation of specific absorption rate as a dosimetric quantity for electromagnetic fields bioeffects. PLoS One 8: e62663, 2013.
169. Creasey WA and Goldberg RB: A new twist on an old mechanism for EMF bioeffects? EMF Health Rep 9: 1-11, 2001.
170. Belyaev IY: Non-thermal biological effects of microwaves. Microw Rev 11: 13-29, 2005.
171. Zhou R, Xiong Y, Xing G, Sun L and Ma J: ZiFi: Wireless LAN discovery via ZigBee interference signatures. MobiCom'10, September 20-24, Chicago, Illinois, USA, 2010. Proceedings of the 16th Annual International Conference on Mobile Computing and Networking. doi: 10.1145/1859995.1860002.
172. Piacentini R, Ripoli C, Mezzogori D, Azzena GB and Grassi C: Extremely low-frequency electromagnetic fields promote in vitro neurogenesis via upregulation of Ca(v)1-channel activity. J Cell Physiol 215: 129-139, 2008.
173. Cecchetto C, Maschietto M, Boccaccio P and Vassanelli S: Electromagnetic field affects the voltage-dependent potassium channel Kv1.3. Electromagn Biol Med 39: 316-322, 2020.
174. Zheng Y, Xia P, Dong L, Tian L and Xiong C: Effects of modulation on sodium and potassium channel currents by extremely low frequency electromagnetic fields stimulation on hippocampal CA1 pyramidal cells. Electromagn Biol Med 40: 274-285, 2021.
175. Batcioglu K, Uyumlu AB, Satilmis B, Yildirim B, Yucel N, Demirtas H, Onkal R, Guzel RM and Djamgoz MB: Oxidative stress in the in vivo DMBA rat model of breast cancer: Suppression by a voltage-gated sodium channel inhibitor (RS100642). Basic Clin Pharmacol Toxicol 111: 137-141, 2012.
176. Ramírez A, Vázquez-Sánchez AY, Carrión-Robalino N and Camacho J: Ion channels and oxidative stress as a potential link for the diagnosis or treatment of liver diseases. Oxid Med Cell Longev 2016: 3928714, 2016.
177. O'Hare Doig RL, Chiha W, Giacci MK, Yates NJ, Bartlett CA, Smith NM, Hodgetts SI, Harvey AR and Fitzgerald M: Specific ion channels contribute to key elements of pathology during secondary degeneration following neurotrauma. BMC Neurosci 18: 62, 2017.
178. Akbarali HI: Oxidative stress and ion channels. In: Systems Biology of Free Radicals and Antioxidants. Lahers I (ed). Springer, Berlin, Heidelberg, pp355-373, 2014.
179. Kourie JI: Interaction of reactive oxygen species with ion transport mechanisms. Am J Physiol 275: C1-C24, 1998.
180. Lushchak VI: Free radicals, reactive oxygen species, oxidative stress and its classification. Chem Biol Interact 224: 164-175, 2014.
181. Pacher P, Beckman JS and Liaudet L: Nitric oxide and peroxynitrite in health and disease. Physiol Rev 87: 315-424, 2007.
182. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M and Telser J: Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44-84, 2007.
183. Halliwell B: Biochemistry of oxidative stress. Biochem Soc Trans 35: 1147-1150, 2007.
184. Balasubramanian B, Pogozelski WK and Tullius TD: DNA strand breaking by the hydroxyl radical is governed by the accessible surface areas of the hydrogen atoms of the DNA backbone. Proc Natl Acad Sci USA 95: 9738-9743, 1998.
185. Cadet J, Delatour T, Douki T, Gasparutto D, Pouget JP, Ravanat JL and Sauvaigo S: Hydroxyl radicals and DNA base damage. Mutat Res 1424: 9-21, 1999.
186. Cadet J and Wagner JR: DNA base damage by reactive oxygen species, oxidizing agents, and UV radiation. Cold Spring Harb Perspect Biol 5: a012559, 2013.
187. Tsunoda M, Sakaue T, Naito S, Sunami T, Abe N, Ueno Y, Matsuda A and Takénaka A: Insights into the structures of DNA damaged by hydroxyl radical: Crystal structures of DNA duplexes containing 5-formyluracil. J Nucleic Acids 2010: 107289, 2010.

188. Cooke MS, Evans MD, Dizdaroglu M and Lunec J: Oxidative DNA damage: Mechanisms, mutation, and disease. FASEB J 17: 1195-1214, 2003.
189. Barzilai A and Yamamoto K: DNA damage responses to oxidative stress. DNA Repair (Amst) 3: 1109-1115, 2004.
190. Pall ML: Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. J Cell Mol Med 17: 958-965, 2013.
191. Liburdy RP: Calcium signaling in lymphocytes and ELF fields. Evidence for an electric field metric and a site of interaction involving the calcium ion channel. FEBS Lett 301: 53-59, 1992.
192. Walleczek J: Electromagnetic field effects on cells of the immune system: The role of calcium signaling. FASEB J 6: 3177-3185, 1992.
193. Brookes PS, Yoon Y, Robotham JL, Anders MW and Sheu SS: Calcium, ATP, and ROS: A mitochondrial love-hate triangle. Am J Physiol Cell Physiol 287: C817-C833, 2004.
194. Lang F, Föller M, Lang KS, Lang PA, Ritter M, Gulbins E, Vereninov A and Huber SM: Ion channels in cell proliferation and apoptotic cell death. J Membr Biol 205: 147-157, 2005.
195. Görlach A, Bertram K, Hudecova S and Krizanova O: Calcium and ROS: A mutual interplay. Redox Biol 6: 260-271, 2015.
196. Lombardi AA, Gibb AA, Arif E, Kolmetzky DW, Tomar D, Luongo TS, Jadiya P, Murray EK, Lorkiewicz PK, Hajnóczky G, *et al*: Mitochondrial calcium exchange links metabolism with the epigenome to control cellular differentiation. Nat Commun 10: 4509, 2019.
197. Lowe SW and Lin AW: Apoptosis in cancer. Carcinogenesis 21: 485-495, 2000.
198. Ikwegbue PC, Masamba P, Oyinloye BE and Kappo AP: Roles of heat shock proteins in apoptosis, oxidative stress, human inflammatory diseases, and cancer. Pharmaceuticals (Basel) 11: 2, 2017.
199. Becchetti A: Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer. Am J Physiol Cell Physiol 301: C255-C265, 2011.
200. Gaasch JA, Geldenhuys WJ, Lockman PR, Allen DD and Van der Schyf CJ: Voltage-gated calcium channels provide an alternate route for iron uptake in neuronal cell cultures. Neurochem Res 32: 1686-1693, 2007.
201. Chattipakorn N, Kumfu S, Fucharoen S and Chattipakorn S: Calcium channels and iron uptake into the heart. World J Cardiol 3: 215-218, 2011.
202. Salsbury G, Cambridge EL, McIntyre Z, Arends MJ, Karp NA, Isherwood C, Shannon C, Hooks Y; Sanger Mouse Genetics Project, Ramirez-Solis R, *et al*: Disruption of the potassium channel regulatory subunit KCNE2 causes iron-deficient anemia. Exp Hematol 42: 1053-1058.e1, 2014.
203. Gamaley I, Augsten K and Berg H: Electrostimulation of macrophage NADPH oxidase by modulated high-frequency electromagnetic fields. Bioelectrochem Bioenerg 38: 415-418, 1995.
204. Panday A, Sahoo MK, Osorio D and Batra S: NADPH oxidases: An overview from structure to innate immunity-associated pathologies. Cell Mol Immunol 12: 5-23, 2015.
205. Henderson LM: NADPH oxidase subunit gp91phox: A proton pathway. Protoplasma 217: 37-42, 2001.
206. Musset B, Cherny VV, Morgan D and DeCoursey TE: The intimate and mysterious relationship between proton channels and NADPH oxidase. FEBS Lett 583: 7-12, 2009.
207. DeCoursey T, Morgan D and Cherny V: The voltage dependence of NADPH oxidase reveals why phagocytes need proton channels. Nature 422: 531-534, 2003.
208. Friedman J, Kraus S, Hauptman Y, Schiff Y and Seger R: Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. Biochem J 405: 559-568, 2007.
209. Pratt RD, Brickman CR, Cottrill CL, Shapiro JI and Liu J: The Na/K-ATPase signaling: from specific ligands to general reactive oxygen species. Int J Mol Sci 19: 2600, 2018.
210. Nitahara JA, Cheng W, Liu Y, Li B, Leri A, Li P, Mogul D, Gambert SR, Kajstura J and Anversa P: Intracellular calcium, DNase activity and myocyte apoptosis in aging Fischer 344 rats. J Mol Cell Cardiol 30: 519-535, 1998.
211. Fenton HJH: Oxidation of tartaric acid in presence of iron. J Chem Soc Trans 65: 899-911, 1894.
212. Bawin SM and Adey WR: Sensitivity of calcium binding in cerebral tissue to weak environmental electric fields oscillating at low frequency. Proc Natl Acad Sci USA 73 1999-2003, 1976.
213. Jackson JD: Classical Electrodynamics. 2nd edition. John Wiley & Sons, Inc., New York, NY, 1975.
214. Barr R, Llanwyn Jones D and Rodger CJ: ELF and VLF radio waves. J Atmos Sol-Terr Phys 62: 1689-1718, 2000.
215. McLeod KJ, Lee RC and Ehrlich HP: Frequency dependence of electric field modulation of fibroblast protein synthesis. Science 236: 1465-1469, 1987.
216. Cleary SF, Liu LM, Graham R and Diegelmann RF: Modulation of tendon fibroplasia by exogenous electric currents. Bioelectromagnetics 9: 183-194, 1988.
217. Lee RC, Canaday DJ and Doong H: A review of the biophysical basis for the clinical application of electric fields in soft-tissue repair. J Burn Care Rehabil 14: 319-335, 1993.
218. Sandipan C and Baron C: Basic mechanisms of voltage sensing. In: Handbook of Ion Channels. Zheng J and Trudeau MC (eds), CRC Press, London, 25-39, 2015.
219. Groome JR and Bayless-Edwards L: Roles for countercharge in the voltage sensor domain of ion channels. Front Pharmacol 11: 160, 2020.
220. Shi YP, Thouta S and Claydon TW: Modulation of hERG K^+ channel deactivation by voltage sensor relaxation. Front Pharmacol 11: 139, 2020.
221. Villalba-Galea CA and Chiem AT: Hysteretic behavior in voltage-gated channels. Front Pharmacol 11: 579596, 2020.
222. Panagopoulos DJ and Margaritis LH: The identification of an intensity 'window' on the bioeffects of mobile telephony radiation. Int J Radiat Biol 86: 358-366, 2010.
223. Panagopoulos DJ and Balmori A: On the biophysical mechanism of sensing atmospheric discharges by living organisms. Sci Total Environ 599-600: 2026-2034, 2017.
224. Liboff AR: Cyclotron resonance in membrane transport. In: Interactions between Electromagnetic Fields and Cells. Chiabrera A, Nicolini C and Schwan HP (eds). Plenum Press, London, pp281-296 1985.
225. Bianco B, Chiabrera A, Morro A and Parodi M: Effects of magnetic exposure on ions in electric fields. Ferroelectrics 86: 159-168, 1988.
226. Balcavage WX, Alvager T, Swez J, Goff CW, Fox MT, Abdullyava S and King MW: A mechanism for action of extremely low frequency electromagnetic fields on biological systems. Biochem Biophys Res Commun 222: 374-378, 1996.
227. Zhadin MN: Combined action of static and alternating magnetic fields on ion motion in a macromolecule: Theoretical aspects. Bioelectromagnetics 19: 279-292, 1998.
228. Liboff AR: Ion cyclotron resonance in biological systems: Experimental evidence. In: Biological Effects of Electromagnetic Fields. Stavroulakis P (ed). Springer, Berlin, pp76-113, 2003.
229. Lednev VV: Possible mechanism for the influence of weak magnetic fields on biological systems. Bioelectromagnetics 12: 71-75, 1991.
230. Kirschvink JL: Magnetite biomineralization and geomagnetic sensitivity in higher animals: An update and recommendations for future study. Bioelectromagnetics 10: 239-259, 1989.
231. Brocklehurst B and McLauchlan KA: Free radical mechanism for the effects of environmental electromagnetic fields on biological systems. Int J Radiat Biol 69: 3-24, 1996.
232. Sheppard AR, Swicord ML and Balzano Q: Quantitative evaluations of mechanisms of radiofrequency interactions with biological molecules and processes. Health Phys 93: 365-396, 2008.
233. Hall EJ and Giaccia AJ: Radiobiology for the Radiologist. 6th edition. Lippincott Williams & Wilkins, Philadelphia, PA, 2006.
234. Coggle JE: Biological Effects of Radiation. Taylor & Francis, 1983.
235. Hanahan D and Weinberg RA: The hallmarks of cancer. Cell 100: 57-70, 2000.
236. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
237. Blank M and Goodman R: Electromagnetic fields stress living cells. Pathophysiology 16: 71-78, 2009.
238. Blank M and Goodman R: DNA is a fractal antenna in electromagnetic fields. Int J Radiat Biol 87: 409-415, 2011.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 04 June 2025
DOI 10.3389/fpubh.2025.1585441

Check for updates

OPEN ACCESS

EDITED BY
George Louis Carlo,
Longwood University, United States

REVIEWED BY
Ugo Cappucci,
Sapienza University of Rome, Italy
Victor Alan Leach,
Oceania Radiofrequency Scientific Advisory Association, Australia

*CORRESPONDENCE
Dimitris J. Panagopoulos
✉ dpanagop@biol.uoa.gr

RECEIVED 28 February 2025
ACCEPTED 21 April 2025
PUBLISHED 04 June 2025

CITATION
Panagopoulos DJ, Yakymenko I, De Iuliis GN and Chrousos GP (2025) A comprehensive mechanism of biological and health effects of anthropogenic extremely low frequency and wireless communication electromagnetic fields.
Front. Public Health 13:1585441.
doi: 10.3389/fpubh.2025.1585441

COPYRIGHT
© 2025 Panagopoulos, Yakymenko, De Iuliis and Chrousos. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A comprehensive mechanism of biological and health effects of anthropogenic extremely low frequency and wireless communication electromagnetic fields

Dimitris J. Panagopoulos[1,2]*, Igor Yakymenko[3], Geoffry N. De Iuliis[4] and George P. Chrousos[1,5]

[1]Choremeion Research Laboratory, 1st Department of Paediatrics, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [2]Electromagnetic Field-Biophysics Research Laboratory, Athens, Greece, [3]Department of Ecology and Ecomanagement, National University of Food Technologies, Kyiv, Ukraine, [4]Reproductive Science Group, School of Environmental and Life Sciences, College of Engineering, Science and Environment, University of Newcastle, Callaghan, NSW, Australia, [5]University Research Institute of Maternal and Child Health and Precision Medicine and UNESCO Chair on Adolescent Health Care, National and Kapodistrian University of Athens, Medical School, Aghia Sophia Children's Hospital, Athens, Greece

Exposure to anthropogenic electromagnetic fields (EMFs), especially those of wireless communications (WC) has increased tremendously. This is an unprecedented phenomenon throughout biological evolution because, all anthropogenic EMFs, being fully polarized, coherent, and, especially WC EMFs, highly variable, differ substantially from the natural EMFs. WC EMFs consist of Microwave (MW) carrier waves, modulated, by Extremely Low Frequency (ELF) signals, and included in on/off pulses repeated at various ELF rates. Moreover, they exhibit intense random variability, mainly in the Ultra Low Frequency (ULF) band. Thus, WC EMFs are a combination of MW and ELF/ULF EMFs. The combination of polarization/coherence and intense low-frequency (ELF/ULF) variability seems to be the key to EMF-bioactivity. Epidemiological and laboratory studies highlight a connection between ELF or WC EMF exposure and cancer, infertility, electro-hypersensitivity, and various other pathologies. Studies also find DNA damage and Oxidative Stress (OS) which explain these pathologies. While man-made EMFs cannot directly ionize molecules, they are capable of doing this indirectly in biological tissue, by triggering the biosynthesis of Reactive Oxygen Species (ROS) which can damage biomolecules, including DNA. The (over)production of ROS and the consequent OS are triggered by irregular gating of Voltage-Gated Ion Channels (VGICs) in the cell membranes as described by the Ion Forced Oscillation (IFO)-VGIC mechanism: Mobile ions within VGICs forced to oscillate by the applied ELF/ULF EMFs exert forces on the voltage sensors of the VGICs, similar to or greater than the forces that physiologically gate those channels, resulting in their irregular gating (dysfunction). Dysfunction of ion channels disrupts intracellular ionic concentrations. This triggers ROS overproduction and OS by the ROS-generating systems/enzymes in the cells, such as the electron transport chain (ETC) in the mitochondria, or the NADPH/NADH oxidases (NOXs), the Nitric Oxide synthases (NOS), etc. The IFO-VGIC mechanism and the consequent OS constitute a comprehensive mechanism that explains all known adverse biological and health effects reported to be induced by anthropogenic EMFs.

KEYWORDS

electromagnetic fields, voltage-gated ion channels, oxidative stress, ion forced oscillation, IFO-VGIC mechanism, ROS, DNA damage

1 Introduction

1.1 Unique physical properties of anthropogenic and especially WC EMFs: Polarization/coherence, combination of frequency bands, modulation, pulsation, variability

All man-made electromagnetic fields (EMFs) and corresponding electromagnetic radiation (EMR) are fully polarized and coherent as they are produced by electric/electronic circuits/antennas with specific geometrical shapes. Moreover, most anthropogenic EMFs and especially those generated by Wireless Communication (WC) devices/antennas [mobile/"smart" phones and corresponding base antennas, cordless domestic (DECT: Digitally Enhanced Cordless Telecommunications) phones, "wireless fidelity" (Wi-Fi) routers for wireless Internet connection, "bluetooth" wireless connection among electronic devices etc.], are oscillating and highly variable at each moment, especially in their intensity. All types of WC EMFs consist of Microwave (MW) carrier waves (300 MHz-300 GHz), modulated, mainly by Extremely Low Frequency (ELF: 3–3,000 Hz) or Very Low Frequency (VLF: 3–30 kHz) signals, and included in on/off pulses repeated at various ELF rates. Moreover, they exhibit intense random variability in their signal amplitudes with frequencies in the Ultra Low Frequency (ULF: 0–3 Hz) band. The MW band is part of the wider Radio Frequency (RF: 300 kHz–300 GHz) band. Therefore, even though all WC EMFs are usually referred to simply as "RF" EMFs, in fact they are a combination of RF/MW, ELF and ULF EMFs (1–4). Figure 1A shows 2nd generation (2G) mobile telephony (MT) Global System for Mobile telecommunication (GSM) basic frame repetition, nominally 217 Hz, pulsations. Variability in both pulse amplitude and repetition frequency is evident as in all real-life WC signals. Newer systems 3G, 4G, 5G have basic frame repetition frequency (nominally) at 100 Hz and exhibit increasing variability in their pulsations/signals due to the increasingly higher amounts of variable information they carry (speech, images, video, Internet, etc.) (3). Figure 1B shows 100 and 200 Hz pulsations from a DECT phone.

These unique features make all anthropogenic, and most of all WC EMFs very different than the natural EMFs which only in specific cases are partially polarized and/or partially coherent to a small degree (3, 5). The geomagnetic field (GMF) and geoelectric field (GEF) are significantly polarized and coherent but static, with no significant variability. During magnetic storms, approximately every 11 years, there is a variability of about 20% in their normal intensities and then there are increased rates of disease and mortality in the human/animal populations (6).

It seems that the combination of polarization/coherence and low-frequency variability is the key to EMF-bioactivity. Polarized and coherent EMFs/EMR (in contrast to, e.g., light and other types of natural EMFs/EMR) possess net electric and magnetic fields, in addition to radiation intensity, which exert forces on every electrically charged/polar particle/molecule such as the mobile ions and the charged/polar macromolecules in all biological systems. It is those unique features that make all anthropogenic EMFs, and most of all WC EMFs, significantly more adversely bioactive than natural EMFs (3, 5, 7).

It has been repeatedly documented that modulated (especially in amplitude) or pulsed RF EMFs are significantly more bioactive than non-modulated or non-pulsing fields of the same carrier frequency and the same intensity with that of the pulses (8–29). [For reviews see (3, 30)]. In all cases, the reported effects were not accompanied by any significant heating of the exposed biological tissues, in other words they were "non-thermal." This evidence implies that the non-thermal biological effects of WC EMFs are due to the included ELF pulsation/modulation.

In addition, ELF EMFs alone have been found independently to be bioactive, similarly to RF EMFs modulated or pulsed by ELFs,

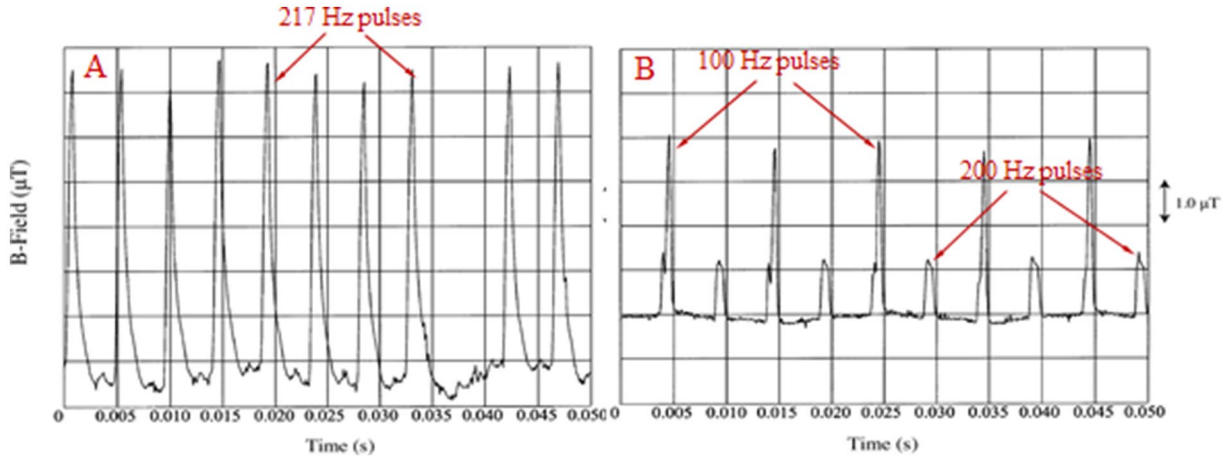


FIGURE 1
(A) 217 Hz ("frame repetition") pulses from a GSM mobile phone. **(B)** 100 and 200 Hz pulses from a cordless domestic (DECT) phone [adapted from Pedersen (4)].

providing additional confirmation that actually the ELF pulsation and modulation EMFs are responsible for the non-thermal effects of WC EMFs and not the RF carrier EMFs (11, 18, 31–48). Again, in all cases, the described effects were non-thermal.

The evidence that the ELF/ULF and not the RF carriers of the anthropogenic/WC EMFs are those that induce the non-thermal effects, is in line with the fact that the physiological electrical activity in all forms of life is restricted to ULF/ELF EMFs. There is no physiological RF EMF in the living organisms, neither in the natural environment, despite the confusion and misinformation among the scientific community for the opposite (6, 49–52). The so called "cosmic microwaves" are actually infrared radiation reaching the Earth with a lower frequency due to the Doppler effect (50, 53). Thus, it is evident that the non-thermal biological and health effects attributed to "RF" EMFs are actually due to their included ELF pulsations, modulation, and variability. And there is practically no RF EMF in any technical application that is not combined with ELFs. All modern digital "RF" EMFs contain ELF pulsations, i.e., not only WC systems but also radars and radio/television broadcasting systems (3, 4, 7, 50, 54–56). Even though this is well documented it has escaped attention, and still authors look for different mechanisms for ELF and "RF" EMFs (57–59). Authors who report that they have found non-thermal EMF effects by non-modulated and non-pulsed RF carrier signals alone but do not provide the signal waveform [as, e.g., (60)], either are unaware of the existence of pulsations produced by almost every existing RF generator, or the effects they report are due to the onset and offset of the RF exposure (18, 56).

1.2 Anthropogenic ELF and WC EMFs: Biological and health effects

Multiple experimental findings associate exposure of laboratory animals or cells to man-made ELF or WC EMFs/EMR with Oxidative Stress (OS) due to Reactive Oxygen Species (ROS) overproduction, genetic damage/alterations (DNA damage, chromosome damage, mutations, etc.), cell senescence (cell aging and loss of replicative capacity), cell death, and related effects [see reviews in (7, 18, 43, 50, 61–66)].

More specifically, numerous *in vivo* or *in vitro* experimental-laboratory studies have shown genetic damage and related effects induced by man-made ELF or WC EMFs on a variety of organisms/cell types under various experimental conditions, especially in recent years. Representative such studies are (15, 16, 33–38, 42, 67–126). If we add studies that found induction of OS and/or cell senescence, the list becomes much longer (62–64, 127–133).

Several of these studies have found OS, and/or DNA damage with consequent cell death in reproductive cells of various animals, resulting in decreased reproduction or embryonic death. In particular, effects of WC EMFs on the DNA of reproductive cells reported by several studies on a variety of animals display a remarkable similarity (68, 71, 72, 74, 75, 97–99, 107, 115, 117, 125, 130). The genetic damage found in reproductive cells explains other findings that connect WC EMF exposures with insect, bird, and mammalian (including human) infertility (121, 134–144), miscarriages (145), or declines in bird and insect populations (especially bees) during the past 20 years (146–150). Significant decrease in reproduction (reduced egg laying, reduced development of reproductive cells, or embryonic death) after exposure to MT radiation, was identically observed in fruit flies (97, 98, 141, 142), chicken or quail embryos (71, 125, 151), bovine oocytes (137), birds (147, 148, 150), and bees (143). Similar effects are reported for amphibians (152, 153), rats and mice (107, 121, 135, 136, 138), and human sperm (decreased number and motility of spermatozoa) (134, 144). These remarkably similar findings in various animals and humans by different research groups can be explained by the cell death in reproductive cells or embryonic death after DNA damage observed in mouse or rat sperm cells (68, 107), fruit fly ovarian cells (72, 97–99), human sperm cells (74, 75), and quail embryos (71, 125).

It is again remarkable that the effects of purely ELF EMFs on reproductive cells and reproduction are very similar to those of WC EMFs (31, 33, 36–38, 42, 45, 46), further implicating ELF EMFs as a key bioactive agent.

Apart from the laboratory findings on genetic damage and infertility, epidemiological studies increasingly link man-made ELF or WC EMF exposures with health problems, genetic damage, and cancer in human populations. More specifically, ELF EMFs from power lines and high-voltage transformers (50–60 Hz) are linked to childhood leukemia and other cancer types (154–167) for magnetic field intensities down to 2 mG (0.2 μT) (159, 161), or distances from power lines up to 600 m (157), and electric field intensities down to 10 V/m (155). WC EMFs from various antennas, especially radio broadcasting and MT antennas, have been linked to various forms of cancer (168–171) and genetic damage (113, 172, 173). During the past 15–20 years epidemiological studies find an increasing association between mobile or cordless phone use and brain tumors in humans (174–185). For a review of EMF carcinogenicity studies see Yakymenko and Tsibulin (171).

Moreover, during the past 25 years, other epidemiological studies find association between exposure to MT/WC antennas/devices with reported symptoms of un-wellness referred to as "microwave syndrome," or "electro-hypersensitivity" (EHS). The symptoms include headaches, fatigue, sleep disorders, and various other adverse effects (169, 186–196). A high percentage (~80%) of EHS self-reporting patients were found with increased OS in their peripheral blood (197). EHS symptoms have been reported to increase dramatically among people exposed to 5G WC antennas, and the ambient RF EMF levels in cities have also been found to increase significantly during the past 2 years, after the beginning of 5G rollout (198, 199).

Cancer in experimental animals after chronic exposure to MT/WC EMFs has also been reported (200, 201). A study of the US National Toxicology Program (NTP) found that exposure of rats to simulated 2G or 3G MT emissions (2 years, 9 h per day) induced brain cancer (glioma) and heart cancer (malignant schwannoma) for both lower and higher radiation levels than the officially accepted limits (202). The study also found significantly increased DNA damage (strand breaks) in the brains of exposed animals (124) confirming the tight link between DNA damage and carcinogenesis. An Italian life-span exposure study of rats to a simulated 2G MT EMF also found induction of heart schwannomas and brain glial tumors, confirming the results of the NTP study (203).

Other studies have reported no effects of ELF or RF/WC EMFs in all of the above end points [see reviews in (3, 18, 42, 43, 61–65, 141, 171, 204–213)], especially studies that employed simulated MT/WC exposures from generators with invariable parameters and no modulation. By contrast, more than 95% of the studies that employed real-life MT/WC exposures, from commercially available devices (mobile/cordless phones, Wi-Fi, etc.) with high signal variability, find effects (3, 7, 206, 209, 210, 214–216).

Regardless of real-life or simulated exposures, the majority of experimental studies (approximately 70%) either with "RF" (combined with ELF) or purely ELF EMFs do find effects (62–64, 206, 208). Jagetia (64) did an extensive review of laboratory studies addressing genotoxic effects of either ELF or RF/WC EMFs in a variety of biological systems, and found that among 207 studies, 144 (69.6%) found statistically significant genotoxic effects. The vast majority of reported effects were non-thermal, and the vast majority of employed EMFs contained ELF/ULF components.

The recorded human and animal carcinogenicity, the DNA/genetic damage, the OS findings, and the reproductive declines due to DNA damage in ovarian or sperm cells or embryonic death, all point toward the same direction: Man-made EMFs induce OS and DNA damage, infertility, cancer, and other related pathologies. The reason why the same effects are observed in a wide variety of animals such as mammals, birds, insects, etc., and humans, is that all biological and health effects initiate in cells and all cells are essentially identical in all animals, humans, and even plants. They have identical membranes, ions, ion channels and pumps, biomolecules such as DNA, RNA, proteins, etc., water, ROS, identical cellular organelles such as nuclei, mitochondria, ribosomes, endoplasmic reticulum, etc., and very similar metabolic processes and regulatory mechanisms. These similarities at the cellular level between all animals and humans are much more fundamental than differences in volume, mass, shape, macroscopic functions, intelligence, etc. As a result, any effect induced by EMFs in animal cells such as OS, DNA damage, etc., is expected to be induced also in the human cells, and vice-versa (7, 66).

The exposure levels in the vast majority of all the aforementioned studies were significantly below the officially accepted exposure limits for ELF and RF EMFs, which are recommended by a private organization called the International Commission on Non-Ionizing Radiation Protection (ICNIRP) to prevent discharges on humans in the case of ELF and acute heating of living tissues in the case of RF/WC EMFs. It is remarkable that this organization arbitrarily ignores the overwhelming evidence of non-thermal effects which constitute the vast majority of effects of anthropogenic EMFs, and yet, governments adopt its recommendations instead of following the Precautionary Principle which dictates the obvious, that no new technology should be applied unless those who promote it have proven its safety beyond any doubt (50, 217–226).

The International Agency for Research on Cancer (IARC) branch of the World Health Organization (WHO), has, since long time, classified both ELF and "RF" (in fact WC) EMFs as possibly carcinogenic to humans (Group 2B) (204, 205, 227). Based on additional scientific evidence after the 2011 IARC classification for "RF" EMFs, several studies have argued that "RF"/WC EMFs should be re-evaluated and classified as probably carcinogenic (Group 2A) or carcinogenic (Group 1) to humans (50, 63, 64, 66, 118–120, 171, 179, 182, 183, 218, 219). Moreover, studies have asked for the urgent application of the Precautionary Principle, stricter exposure limits, especially for WC EMFs, and a moratorium on 5G rollout (50, 215, 217, 218, 225, 228).

1.3 Ionization in living tissue by "non-ionizing" EMFs

As indicated by the long list of laboratory and epidemiological studies, man-made EMF exposures are linked to OS, genetic damage, infertility, EHS, and cancer. Damage to DNA or other biological molecules involves breakage of chemical bonds and chemical alterations, in other words ionization. Man-made EMFs with frequencies up to the low limit of infrared ($0–3 \times 10^{11}$ Hz) examined here cannot directly break chemical bonds and cause ionization, except for very strong field intensities ($\geq 10^6$ V/m) (229, 230). Such field intensities are rarely present in the environment, apart from very close proximity to high-voltage power lines and transformers, or very close to atmospheric discharges (lightning). How are then man-made EMFs at environmental intensities capable of ionizing DNA and other biological molecules? What is the unique property that makes man-made EMFs capable of inducing adverse biological/health effects in contrast to natural EMFs including light? It has been shown that this unique property is polarization and coherence combined with low frequency (ULF/ELF) variability (2, 3, 5, 7).

In the present work we provide an updated description of how man-made EMFs at non-thermal levels are capable of inducing dysfunction of Voltage-Gated Ion Channels (VGICs) in cell membranes, triggering ROS overproduction and OS, which in turn is responsible for most, if not all, known adverse biological/health effects including DNA damage and related pathologies. Thus, ionization of biological molecules occurs indirectly after man-made EMF exposure, mediated by the produced ROS in the cells (2, 210).

2 Anthropogenic ELF or WC EMFs and OS: Experimental evidence

Yakymenko et al. (62) reviewed 100 published experimental studies that examined OS in living cells from a wide variety of organisms (humans, rats, mice, rabbits, quail embryos, plants etc.) exposed *in vitro* or *in vivo* to RF/WC EMFs. From those studies, 93 found increased OS expressed as activation of key pathways generating ROS overproduction, peroxidation, oxidative damage of DNA, changes in activity of antioxidant enzymes, etc. In a more recent update, Yakymenko and Tsibulin (63) found that among 131 published peer-reviewed studies looking for oxidative effects of RF/WC EMFs at non-thermal intensities, in most cases pulsed/modulated by ELF EMFs, 124 (95%) confirmed statistically significant oxidative effects on various types of biological systems. And among 39 published studies on oxidative effects of purely ELF EMFs, 36 of them (92%) also found significant oxidative effects induced by the exposure. Therefore, it is well-documented that anthropogenic EMF exposures cause ROS overproduction and OS in living cells, which in turn is responsible for the observed DNA damage, infertility, cancer, and other related pathologies.

Even though ROS at sub-toxic levels in the cells act as signaling molecules involved in various physiological cellular processes, they can also damage biological molecules (such as lipids, proteins, and nucleic acids) causing various diseases when they are in excess (231–234). Most ROS are free radicals. Free radicals are extremely unstable and reactive molecules containing an unpaired electron denoted by a dot (•) in their chemical formula. They possess a very strong tendency to chemically react with other molecules and/or with each other in order to couple their unpaired electron, balance electron spins, and become stable. This extreme reactivity is the reason why they have extremely short lifetimes. Most ROS react rapidly with surrounding biomolecules, causing chemical alterations (235, 236).

Two important initial free radical ROS found in cells after exposure to man-made EMFs are the superoxide anion ($O_2\bullet^-$) and the nitric oxide (NO•) (62, 63, 125). The superoxide anion free radical may be converted into hydroxyl radical (OH•), or react with nitric oxide to form peroxynitrite ($ONOO^-$). Both products (especially the hydroxyl radical) are very reactive ROS with biological molecules, especially DNA (62, 125, 237, 238).

3 Biochemistry of ROS

3.1 ROS sources in the cells: Identity and function: Dependence on ion concentrations

3.1.1 Mitochondria

A major source of ROS in all cells is the Electron Transport Chain (ETC) in the inner membrane of the mitochondria (62, 65, 234, 235, 239), likely contributing 50–80%, or even 90% of total cellular ROS production under normal conditions (240). Electron leakage from Complexes I and III of the ETC is a significant source of ROS, especially superoxide anion free radical ($O_2\bullet^-$) after adherence to molecular oxygen (241):

$$O_2 + e^- \rightarrow O_2\bullet^- \quad (1)$$

Certain cell types such as neurons or spermatozoa have high energy demands and thus high mitochondrial activity, making them particularly susceptible to OS from mitochondrial ROS production (65, 242).

The large amounts of energy (in the form of Adenosine Triphosphate-ATP) required for the maintenance of a cell's aerobic life are generated predominantly by oxidative phosphorylation in the mitochondria at the expense of molecular oxygen, which is reduced to water by 2 electrons per water molecule terminating in complex IV of the ETC [$2H^+ + 1/2O_2 + 2e^- \rightarrow H_2O$] (65). However, a fraction of the electrons will 'leak' from the ETC and partially reduce oxygen (Equation 1). The result is that a small amount (~2%) of oxygen during this process is converted to superoxide anion radical, hydrogen peroxide and related ROS. Cells and tissues reliant on oxidative phosphorylation have evolved effective antioxidant measures to keep these modest ROS levels in check and inhibit OS. Nevertheless, perturbation of electron flow and/or the homeostasis of the mitochondrial environment can dramatically elevate the risk of OS. This is exemplified in spermatozoa, where minimal cytoplasm and abundant substrates for oxidative chemistry offer a platform for run-away levels of ROS with minimal perturbation of their mitochondrial environment (65, 243). Electron leakage from the ETC in spermatozoa under WC EMF exposure was recorded to be sourced from complex III, as this was tested in parallel with the use of complex III-inhibitors (115). See Miller et al. (65) for a more detailed view on mitochondrial ETC and ROS production.

When considering the mitochondrial origins of OS, Ca^{2+} plays a key role. Physiological increases in mitochondrial Ca^{2+} can stimulate ATP production when energy demands are high, however this can also result in elevated ROS generation. Excessive Ca^{2+} accumulation can lead to mitochondrial dysfunction and a drop of ATP production, but importantly, further elevates ROS production and apoptotic factors (244). Ca^{2+} can act upon the mitochondria through its regulatory activity on key mitochondrial specific dehydrogenases, such as pyruvate dehydrogenase, which is an intrinsic mediator of electron flow through the ETC and influences ROS production (245). Therefore, careful control of Ca^{2+} levels in the mitochondria is a key factor in ROS homestasis, with any dysfunction of Ca^{2+} channels induced by EMFs potentially leading to ROS overproduction.

Voltage-gated anion channels in the outer membrane of the mitochondria regulate Ca^{2+} entry into the intermembrane space and the matrix. While increased levels of Ca^{2+} in the mitochondria stimulate $O_2\bullet^-$ synthesis by the ETC, the presence of the other "initial" ROS, NO•, inhibits complex IV of the ETC causing additional electron leakage and increased $O_2\bullet^-$ production (235, 244). Thus, the two important primary ROS (NO• and $O_2\bullet^-$) act in synergy in the mitochondria, and increased levels of NO• stimulate further production of $O_2\bullet^-$.

ROS overproduction in the mitochondria may damage DNA both in the mitochondria and the nucleus, and may initiate a signaling cascade leading to apoptosis. In turn, excessive apoptosis induced by increased ROS levels, has been linked to inflammatory diseases and cancer (246).

3.1.2 NADPH/NADH oxidases (NOXs)

These plasma membrane enzymes, found in abundance in all cells, normally generate ROS for the elimination of invading microorganisms. NAD(P)H oxidase is an enzyme exhibiting different affinities for its two substrates; Nicotinamide Adenine Dinucleotide Phosphate (NADPH), and Nicotinamide Adenine Dinucleotide (NADH), with the NADPH substrate being the most common (247–251). The NOXs catalyze the production of superoxide anion free radical by transferring electrons to oxygen from NAD(P)H according to the reaction:

$$NAD(P)H + 2O_2 \rightarrow NAD(P)^+ + 2O_2\bullet^- + H^+ \quad (2)$$

Thus, they also generate an ETC for the reduction of extracellular O_2 to $O_2\bullet^-$. The activity of NOX is intimately connected with H^+ channels and the enzyme may even act as a H^+ VGIC itself, due to its $gp91^{phox}$ transmembrane subunit (252–254).

NOXs are also activated by cytosolic Ca^{2+} and possess a Ca^{2+}-binding site, apart from their H^+ voltage-gated channel ($gp91^{phox}$ domain) (251). Thus, perturbation of intracellular concentrations of either H^+ or Ca^{2+}, after irregular gating of their VGICs, can affect NOX function and trigger ROS (over)production.

NOXs may contribute 10–30% of total ROS production in neurons under basal conditions. However, their contribution can increase significantly during neuronal activation or inflammation. NOXs, particularly NOX2 and NOX4, are expressed in neurons and play roles in synaptic plasticity, neuronal signaling, and neuroinflammation. Their activity can be upregulated in response to various stimuli, leading to increased ROS production (255).

Some NOX isoforms, such as NOX2 in phagocytes, are directly activated by Ca^{2+} through interactions with regulatory subunits like p47phox and p67phox, and increased intracellular Ca^{2+} levels can promote ROS production. Ca^{2+} can also indirectly regulate NOX

activity through various signaling pathways, such as those involving protein kinase C and other kinases (256).

The NOXs have been identified as a key target for man-made EMFs. Friedman et al. (257) found rapid ROS production by the NADH oxidase in cultured cells after a few min exposure to simulated mobile phone EMF.

A common function in the NOXs and the mitochondria is the generated ETC. In both cases, the primary ROS produced is superoxide anion radical ($O_2\bullet^-$), which may finally convert to hydroxyl radical (OH•), or peroxynitrite ($ONOO^-$) as shown below (Equations 3–7).

3.1.3 Nitric oxide synthases (NOS)

These are specific enzymes found in various locations in all animal and plant cells, and as denoted by their name, produce nitric oxide free radicals (NO•). Several NOS enzymes have been well described, such as the neuronal NOS (nNOS), or the endothelial NOS (eNOS) which are plasma membrane enzymes. Their activation seems to be dependent on intracellular calcium levels and calmodulin. Increased levels of intracellular Ca^{2+} stimulate NO• synthesis by the NOS. NO• is ubiquitous in cells and tissues in all vertebrates as an intercellular messenger and certain studies suggest that it is not particularly toxic by itself, but it may easily be converted to peroxynitrite which is particularly toxic (237, 258). Increases in Ca^{2+} and NO• levels in cells have been found to be triggered very rapidly (within a few seconds) by EMF exposure (259), with the induction of DNA damage by peroxynitrite blocked by NOS inhibitors (260) and antioxidants (238, 261, 262). While nNOS and eNOS, are Ca^{2+}-dependent enzymes activated by increased intracellular Ca^{2+} levels, and promoting NO• production, under certain conditions NOS can become "uncoupled" due to substrate depletion or cofactor deficiency, triggering the cell machinery to produce $O_2\bullet^-$ instead of NO• by other ROS sourses/enzymes (263).

3.1.4 Xanthine oxidase (XO)

Xanthine Oxidase (XO) is another important source of ROS in the cytoplasm of living cells. XO catalyzes the oxidation of hypoxanthine to xanthine and then to uric acid, producing superoxide anion radical ($O_2\bullet^-$) and hydrogen peroxide (H_2O_2) as byproducts. XO is involved in purine metabolism and can be a significant source of ROS under certain conditions, such as ischemia–reperfusion injury (264).

3.1.5 Other ROS-generating/promoting enzymes

Such enzymes in cells are, e.g., cytochrome P450 (CYP), lipoxygenases, cyclooxygenases, myeloperoxidases and others (240). They may contribute to ROS generation differently under different physiological conditions. For example, CYP is localized in the endoplasmic reticulum and is crucial for the metabolism of various endogenous and exogenous compounds, including drugs, steroids, and fatty acids. CYP reactions can generate ROS as byproducts, particularly during the catalytic cycle when oxygen is activated (265).

The ionic balance within a cell (also called electrochemical balance) is most crucial for ROS production, and both ion channels and pumps can trigger ROS production by the above described ROS sources. The ion pumps (active ion transporters) such as the Na^+/K^+ pump (ATPase), in coordination with the ion channels (passive ion transporters) determine the membrane voltage, the electrochemical balance, the cell's homeostasis, the redox status (concentrations of reducing and oxidizing molecules), and the cell's volume among other functions. Ca^{2+} and K^+ channels are involved in cell proliferation, apoptosis, and carcinogenesis (266, 267). In addition, they are both involved in iron entry into the cells (268–270). Iron catalyzes the production of OH• via the Fenton reaction and thus, impaired function of these channels can promote cellular toxicity. Dysfunction of Na^+, K^+, Mg^{2+}, and Ca^{2+} VGICs will affect the function of the Na^+/K^+ pump (ATPase), and Ca^{2+} pumps in the plasma membranes of all cells.

In addition to its role as an ion pump, Na^+/K^+-ATPase operates as a signal regulator, transducing signals from the plasma membrane to the intracellular organelles and acting as a normalizer of the Na^+/K^+ balance in cells after, e.g., VGIC dysfunction (231, 234, 271). It has long been shown that the activity of the Na^+/K^+-ATPase is affected by ELF EMFs (44, 272, 273), and that changes in its activity are linked to ROS production by the mitochondria and in turn, increased mitochondrial ROS production stimulates the signaling function of the enzyme forming a positive amplification feedback loop (274, 275). Thus, changes in the activity of the Na^+/K^+-ATPase due to EMF-induced dysfunction of VGICs can stimulate ROS production by the mitochondria and the process can be amplified by increasing ROS levels (2, 210).

3.2 ROS action on DNA and other biological molecules

DNA damage induced by OS/ROS leading to mutations and disease has been well documented since long time. The effects of ROS on DNA commonly result in altering the nucleotide bases which directly affects their paring elevating mutational load, altering a sugar (deoxyribose), breaking a covalent bond between deoxyribose and nucleotide base, and causing single- and double-strand breaks, further increasing the repair burden on the affected cells and tissues (2, 210, 243, 276–279).

We have described the evidence regarding the generation of primary ROS, NO• and $O_2\bullet^-$, by the ROS sources in the cells after anthropogenic ELF or WC EMF exposure (section 2). These initial ROS are converted to other even more potent ROS, hydroxyl radical and peroxynitrite, which we call "final" ROS, and are those that mainly damage DNA and other biological molecules.

3.2.1 Peroxynitrite

Increased concentrations of NO• and $O_2\bullet^-$ within a cell lead to peroxynitrite ($ONOO^-$) overproduction after reaction among the two initial ROS, as follows:

$$NO\bullet + O_2\bullet^- \rightarrow ONOO^- \quad (3)$$

Peroxynitrite is a strong non-free radical ROS which can damage critical molecules including DNA (280). Both nitric oxide and peroxynitrite can diffuse anywhere within the cell and, thus, act directly on DNA or other molecules. The effects of peroxynitrite on DNA include base and sugar oxidative modifications, and DNA single-strand breaks (258, 281). Of the four DNA bases, guanine is the most vulnerable to peroxynitrite (282). DNA single-strand breaks caused by peroxynitrite is a

well-documented effect which can be prevented by use of calcium channel blockers and antioxidants (238, 258, 261, 262, 283). Pall (238) noted a connection between EMF-induced dysfunction of Voltage-Gated Calcium Channels (VGCCs) and NO•/$ONOO^-$ overproduction. Peroxynitrite can also decompose easily in the presence of H^+ to form OH• and NO_2• (284, 285):

$$ONOO^- + H^+ \rightarrow OH\bullet + NO_2\bullet \quad (4)$$

3.2.2 Hydroxyl radical

The superoxide anion radical ($O_2\bullet^-$) produced by the mitochondria or the NOXs, is catalyzed by superoxide dismutase (*SOD*) in the cytosol or the mitochondria converting to hydrogen peroxide (H_2O_2) (248, 280, 286):

$$2O_2\bullet^- + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2 \quad (5)$$

H_2O_2 can move to any cellular site, including the nucleus, where it can be converted to the most potent hydroxyl radical (OH•) which can damage any biological molecule, including DNA (287–291).

OH• is considered the most potent oxidant of DNA. It is mainly produced by iron-catalyzed conversion of H_2O_2 via the Fenton reaction (292): Fe^{2+} is oxidized by H_2O_2 to Fe^{3+}, producing a OH• radical and a hydroxide ion (OH^-). Fe^{3+} is then reduced back to Fe^{2+} by another H_2O_2 molecule, producing a hydroperoxyl radical (HOO•) and a proton. The net effect is the conversion of two hydrogen peroxide molecules to produce OH• and HOO•, with water (H^+ + OH^-) as a byproduct (2, 210):

$$2\,H_2O_2 \rightarrow OH\bullet + HOO\bullet + H_2O \quad (6)$$

Another way for OH• production is the Haber-Weiss reaction (293):

$$O_2\bullet^- + H_2O_2 \rightarrow O_2 + OH\bullet + OH^- \quad (7)$$

The OH• radical can break biological macromolecules (R-R or R-H) in its immediate environment or subtract atoms from them (such as the various hydrogen atoms of the deoxyribose molecule) by breakage of covalent bonds. This results in chemical alterations in the macromolecules and production of new free radicals such as R• or RO• (2, 210, 294, 295).

$$R-R + OH\bullet \rightarrow ROH + R\bullet \quad (8)$$

$$RH + OH\bullet \rightarrow R\bullet + H_2O \quad (9)$$

$$RH + OH\bullet \rightarrow RO\bullet + H_2 \quad (10)$$

The new free radicals will further react with other molecules and with each other resulting in additional chemical alterations.

A more specific example is the action of OH• on DNA that results in the breakage of the DNA chain (single- or double-strand breaks). The backbone of each strand of the DNA is formed by phosphodiester bonds between two successive deoxyribose (DOX) molecules and a phosphate (–PO_4–) between them. For a strand breakage, the phosphodiester bond needs to break. The double-strand breaks (breakage of both strands of the double helix at the same point) are the most severe and in most cases irreparable damages that lead to DNA fragmentation, mutations, cell death etc. The breakage of the phosphodiester bond by two hydroxyl radicals can be written as:

$$\left[-(b)DOX_{i(3')} - PO_4 -_{(5')} DOX_{i+1}(b)-\right] + 2OH\bullet \rightarrow \left[-(b)DOX_{i(3')} - OH\right] + PO_3 + \left[HO -_{(5')} DOX_{i+1}(O-b)-\right] \quad (11)$$

By (b) we denote the DNA bases connected to the DOX_i and DOX_{i+1} molecules. (3′) and (5′) are the carbon atoms in successive deoxyribose molecules that form the phosphodiester bond with the phosphate. In the products of the reaction, PO_3 is separated from the DNA molecule and is not anymore part of the phosphodiester bond that kept the strand intact. The second base is oxidized by the hydroxyl radical as well (to form O-b) in addition to the breakage of the strand (296). The breakage forms OH at the terminals of the broken strands. The TUNEL (Terminal deoxynucleotide transferase dUTP Nick End Labeling) assay used in biology to detect fragmented DNA, specifically detects the free OH terminals of the broken strands (42, 97, 98).

4 Anthropogenic EMFs and VGICs

4.1 VGICs: Most sensitive electromagnetic sensors in living organisms

Previous studies have hypothesized the existence of specific electro/magneto-sensor organs/cells in animals/humans in order to explain the biological effects of EMFs [see review in (297)]. This is not necessary, as all cells in all animals including humans and even plants are equipped with the most sensitive EMF-sensors which are no other than the VGICs, the most abundant class of ion channels in all cell membranes (231, 234, 271, 297, 298).

Normally VGICs convert between open and closed states by membrane voltage changes $dV \geq 30$ mV which exert forces on their voltage-sensors. More specifically VGICs respond to changes between ~30 and ~100 mV. The voltage sensors of the VGICs are four symmetrically arranged, transmembrane, positively charged parallel α-helices (subunits), each one named S4. They occupy the 4th position in a group of 6 parallel α-helices (S1-S6), and are the closest helices to the pore apart from the S5-S6 helices which form the pore walls. The channel consists of four identical such groups (main units I-IV) in symmetrical positions around the pore of the channel (Figure 2). The sensors are positive Lys and Arg amino-acids in the S4 helices. The effective (net) charge on each S4 has been calculated to be $q = 1.7q_e$, where q_e is the elementary charge. The positive charges of the S4 sensors are paired with negative charges from adjacent helices so that the net charge on the walls of the pore is zero. The ions pass dehydrated

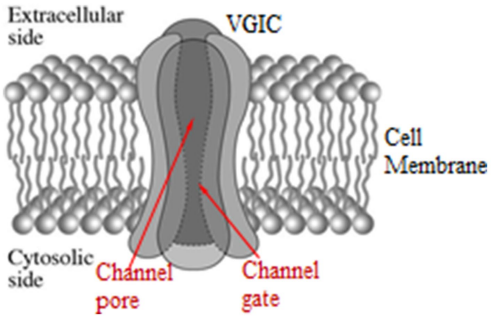


FIGURE 2
Schematic representation of a VGIC with its four main units, the pore, and the gate in opened state. Each main unit consists of six parallel α-helices (S1–S6). The voltage-sensors of the VGIC are the four S4 helices, one in each main unit, in symmetrical positions around the pore [adapted from Panagopoulos et al. (297)].

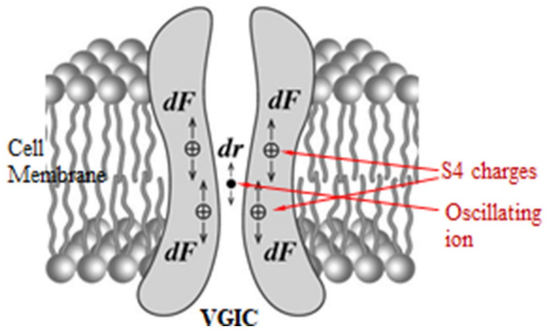


FIGURE 3
Forces *dF* exerted on the S4 positive charges in a VGIC due to the displacement *dr* of an oscillating ion in the channel pore [adapted from Panagopoulos et al. (297)].

and in single file through the channel gate, the narrowest part of the pore (Figure 2). At least four dehydrated mobile ions are very close to the S4 sensors at a distance of less than 1 nm, as, except for the ion(s) that may be passing through the gate any moment or is just outside the gate ready to pass, at least three more are bound in specific ion-binding sites very close to the gate (234, 297, 299–304).

4.2 Anthropogenic EMFs and VGIC dysfunction: The IFO-VGIC mechanism

A biophysical mechanism for EMF-induced biological effects has been described in Panagopoulos et al. (2, 5, 297, 305, 306), and Panagopoulos (302). It explains, in standard physics and biology, how polarized, coherent and slow-varying (ULF/ELF/VLF) EMFs, even at very low field intensities, can cause irregular gating (opening/closing) of VGICs in cell membranes with consequent disruption of the cell's electrochemical balance, redox state and homeostasis. As ELF/ULF/VLF EMFs are basic components of the WC EMFs, this mechanism accounts for the biological effects of the vast majority of all man-made (polarized, coherent, and varying) EMFs.

While VGICs are normally gated by ~30–100 mV voltage changes in the very strong transmembrane field, in other words respond to field changes between 3×10^6 and 10^7 V/m, they may also respond to very weak polarized, coherent, and slow-varying EMFs down to ~10^{-5} V/m via the forced-oscillation such EMFs induce on mobile ions in close proximity (<1 nm) to the sensors (ion forced-oscillation: IFO). This occurs because the force exerted on the S4 sensors by oscillating ions in close proximity, depending upon the inverse third power of the distance between charges (see Equation 12 below), is much greater than a direct force from an externally applied EMF which depends upon the first power of the applied field (2, 5, 297). The aforementioned (at least) four ions close to the pore gate, once forced to oscillate in parallel and in phase, exert constructive coordinated forces on the S4 sensors able to gate the channel (Figure 3).

Forces exerted by an external polarized EMF on any mobile ion within any VGIC, cause a displacement *dr* of the ion from its "initial" position which in turn exerts an additional Coulomb force *dF* on the S4 voltage-sensors of the VGIC which can result in the opening/closing (gating) of the channel (2, 5, 297, 305, 306) (Figure 3). This additional Coulomb force on each S4 sensor due to the ion displacement *dr* is given by the equation:

$$dF = -\frac{q \cdot z q_e}{2\pi\varepsilon\varepsilon_o r^3} dr \tag{12}$$

with $q = 1.7\, q_e$ the effective (net) charge of the S4 sensor, zq_e the mobile ion charge with z the ion valence (e.g., $z = 1$ for K^+, Na^+ or $z = 2$ for Ca^{2+} ions), $q_e = 1.6 \times 10^{-19}$C the elementary charge, $\varepsilon_o = 8.854 \times 10^{-12}$ $N^{-1}m^{-2}C^2$ the vacuum permittivity, $\varepsilon \sim 4$ the relative permittivity of the ion channel, and $r = 1$ nm the "initial" distance between the two charges (2, 299, 305–308).

In the simplest case of a harmonically oscillating applied EMF, the maximal ion displacement in one direction during its oscillation is $2A$ (A the amplitude of the forced oscillation). By solving the corresponding differential equation [see (302, 305)] we get that for an applied electric field,

$$A = \frac{E_o z q_e}{\beta\omega} \tag{13}$$

where E_o is the intensity amplitude (maximal value) of the applied field, $\omega = 2\pi\nu$ (ν the frequency of the applied field), and β the damping coefficient during the ion oscillation (found to be within channels $\beta = \frac{E_m z q_e}{u_o} \cong 6.4z \times 10^{-12}$kg/s, with $E_m \sim 10^7$ V/m the transmembrane electric field, and $u_o = 0.25$ m/s the ion maximal velocity through an open channel).

When the VGIC is gated physiologically by membrane voltage changes $dV \geq 30$ mV, the minimum force on each voltage sensor that causes gating is calculated to be $dF = 8.16 \times 10^{-13}$ N, which, according to Equation 12, corresponds to a minimum coordinated displacement *dr* of four *z*-valence ions within the channel at ~1 nm distance from the sensors (2, 297), $dr = 10^{-12}/z$ (in m), and thus in order for an applied electric field to be able to gate the VGIC, the max ion displacement ($2A$) must satisfy the condition:

$$2\frac{E_o z q_e}{\beta\omega} \geq 10^{-12}/z \quad (14)$$

For double-valence cations ($z = 2$) (e.g., Ca^{+2}), this condition finally becomes:

$$E_o \geq 0.6\,\nu \times 10^{-4} \qquad (\nu \text{ in Hz}, E_o \text{ in V/m}) \quad (15)$$

This is the condition for electric fields in order to be bioactive with respect to field frequencies, and is represented in logarithmic scales ($\log E_o$, $\log\nu$) by the area above the line (including the line) in Figure 4 ("bioactive region"). The intensity-frequency combinations of all known anthropogenic EMF sources linked to adverse biological/health effects are within the predicted bioactive region. As the frequency of the applied EMF increases from ULF/ELF to VLF/LF (Low Frequency: 30–300 kHz) the required minimum field intensity in order to be able to induce effects increases considerably, and purely RF/MW EMFs need to have very high intensities (hundreds or thousands of V/m) in order to be bioactive.

The maximal ion displacement ($2A$) expresses the potential of the applied EMF to cause VGIC gating and initiate biological effects, in other words it represents the biological activity (or bioactivity) of the applied EMF:

$$EMF\ bioactivity = 2\frac{E_o z q_e}{\beta\omega} \quad (16)$$

Thus, the IFO-VGIC mechanism finds that the biological activity of an EMF is proportional to its maximum intensity and inversely proportional to its frequency, meaning that the reported effects in the literature are induced by low-frequency (ULF/ELF/VLF), and not high frequency (purely RF/MW), EMFs. Moreover, it finds that pulsing EMFs are significantly more bioactive than corresponding continuous-wave (non-pulsing) EMFs (see analysis in (2, 297, 302)).

According to the IFO-VGIC mechanism, VGICs respond to changes of polarized, coherent and slow-varying electric fields down to ~10^{-5}–10^{-4} V/m, which is in impressive agreement with the threshold intensities of ELF man-made EMFs reported to induce biological effects in cell/tissue cultures (309, 310), and be sensed by electrosensitive animals (311, 312).

Apart from the electric fields, in fast moving animals/humans, the magnetic fields become increasingly bioactive with increasing velocities, and the same mechanism has explained animal orientation and navigation in the GMF (297).

It is known that living organisms are not particularly affected by static electric or magnetic fields but mostly by oscillating/varying (and polarized) ones. This is consistent with the IFO-VGIC mechanism, as VGICs are not gated by the normal static voltage/electric field across the cell membrane, but only by membrane voltage changes of the order of 30% in this voltage/field that cause membrane depolarization. In other words, VGICs do not respond simply to the presence of an invariable (static) electric field, otherwise they would open/close chaotically all the time and no life could be maintained. The same holds for the static magnetic fields, which can become bioactive with a variable animal velocity (297). This is the reason why the GMF and the GEF are not particularly bioactive under normal conditions but they become bioactive when ~20% changes in their normal intensities occur during magnetic storms (3, 6, 7, 297).

Thus, the IFO-VGIC mechanism predicts that polarized/coherent and slow-varying EMFs cause VGIC dysfunction (irregular gating), and this is today verified by many experimental studies [see (313–317), and reviews (44, 210, 238, 298, 318)].

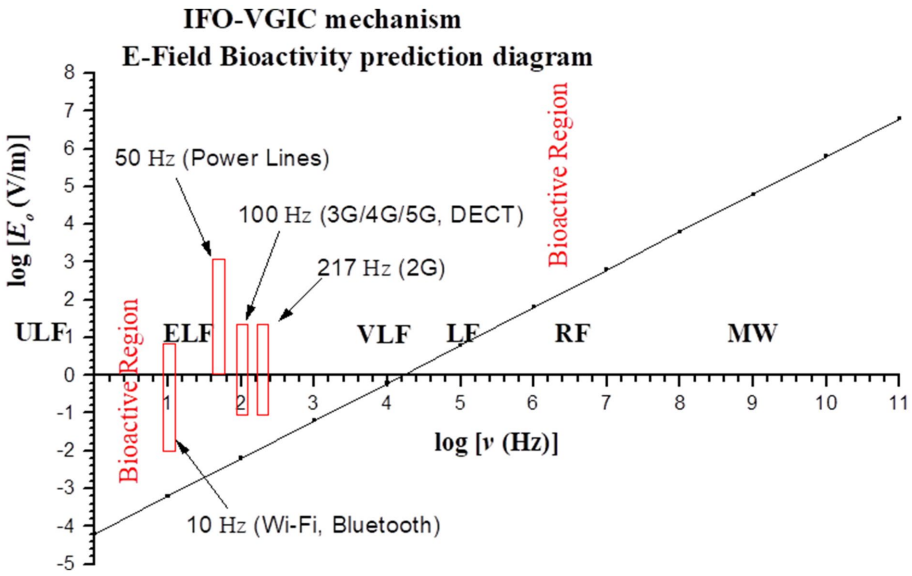


FIGURE 4
Graph (in logarithmic scales) showing the bioactive combinations of EMF intensity and frequency (above line) as predicted by the IFO-VGIC mechanism. The intensity-frequency combinations of all known anthropogenic EMF sources linked to adverse bioeffects are within the predicted bioactive region (2, 302).

5 VGIC dysfunction leading to OS: Connecting the dots for a comprehensive mechanism of EMF-induced biological and health effects

How can the initial ROS ($O_2\bullet^-$ and NO•) generated after EMF exposure be produced by VGIC dysfunction? This was a missing link until recently when we specifically looked for such evidence (2, 210). We realized that even though plenty of data connecting impaired ion channel function and induction of cell death or cancer had been available for a long time (266, 267), and even though most ion channels, especially cation channels, are VGICs, the connection between VGIC dysfunction induced by EMF exposure and OS (2, 210, 238, 319–322) leading to DNA/cellular damage, had escaped the necessary attention.

Many studies have found a connection between Ca^{2+}, K^+, Na^+, and Cl^- VGIC dysfunction with OS and related pathologies (238, 319, 321, 322). It is repeatedly shown that VGIC dysfunction induced by anthropogenic EMFs can trigger immediate ROS generation in the cells with this effect significantly diminished by the use of specific ion channel blockers (238, 259, 314, 316). Recent research further confirms the connection between VGIC dysfunction and ROS (over)production. For example, ROS overproduction through the activation of NADPH oxidase by extracellular tau-protein in co-cultures of neurons and astrocytes was reduced in the presence of nifedipine, inhibitor of Ca^{2+} VGIC (323). Epithelial cell death associated with elevation in ROS was prevented by lidocaine, a well-known Na^+ VGIC inhibitor with antioxidant effects (324). Induced ROS production in murine microglia was inhibited in a dose-dependent manner by K^+ VGIC blockage, and to a more limited degree, by Cl^- channel blockage (325).

Various pathological conditions, including neurodegenerative diseases, termed "channelopathies", were discovered to be caused by ion channel dysfunction. Impairment of either voltage- or ligand-gated ion channels has been identified as a cause of neurological diseases. The ion channels involved include Ca^{2+}, K^+, and Na^+ VGICs (318, 326). Multiple studies have documented the connection between Ca^{2+}, K^+, Na^+, and Cl^- channel dysfunction and the development of OS-related pathologies (321). Ion channel dysfunction leading to OS is also a common cause of degenerative Central Nervous System (CNS) diseases of various genetic etiologies, and is a common factor in neurological disorders. The role of ion channels in neurodegenerative disorders associated with OS has now been recognized, as the ion channels undergo functional adjustments in such conditions (318, 327).

It is evident that the function of ion pumps and channels controls the intracellular concentrations of mobile ions, and in turn the function of the cellular systems/enzymes that produce ROS (2, 210). Any dysfunction in ion channels will affect the otherwise carefully controlled intracellular ionic concentrations, disrupting the cell's electrochemical balance and homeostasis, including the intracellular redox status which is an index of the ROS content in the cell. From the evidence highlighted here, it follows that disturbance of ion homeostasis can trigger OS by ROS overproduction and subsequent DNA damage. Inversely, the intracellular redox status can alter the gating properties of ion channels and trigger opening or closing of Ca^{2+}, Na^+, and K^+ channels in order to reinstate homeostasis (318, 331). Ion channels are thus gate keepers of redox status, and the cell's electrochemical balance and homeostasis (305, 328).

For example, Ca^{2+} is a critical signaling factor, regulating many cell functions including cell proliferation, differentiation, and apoptosis (233, 244, 267, 329). Alterations in intracellular Ca^{2+} levels are decoded by Ca^{2+}-sensors, which initiate signaling for various physiological processes (330). Alterations in Ca^{2+} homoeostasis and signaling are often associated with various pathological conditions, including cancer. The ROS regulatory system is closely linked to the Ca^{2+} signaling system which operates by changes in intracellular Ca^{2+} concentrations. Dysfunction of Ca^{2+} channels in the plasma or the mitochondrial membrane will disrupt the signaling system and increase ROS levels in any cell, potentiating harmful effects including cytotoxicity and resulting in pathogenesis of various disorders (44, 244, 321, 322, 328, 330, 331). Inversely, ROS can significantly affect calcium concentration in the cell by modifying the function of Ca^{2+} channels (233).

Increased levels of intracellular Ca^{2+} in some cases are associated with increased apoptosis, probably due to activation of Ca^{2+} dependent DNase I (332). This may be an alternative pathway for DNA damage and related pathologies. Changes in normal Ca^{2+} levels in the mitochondria can induce release of cytochrome C, a mitochondrial protein which is a signaling molecule for apoptosis in the cytoplasm, which then goes on to initiate apoptosis in the cell, and activation of nucleases which will cause DNA damage (330).

The effect of man-made EMFs, especially ELF, or RF pulsed or amplitude-modulated by ELF signals, on calcium concentrations in exposed cells and the unique role of the calcium VGICs or VGCCs in EMF-induced bioeffects have been well-documented for long time (8–10, 18, 22, 44, 238, 298, 314–316, 333–341), and explained by the IFO-VGIC mechanism (2, 5, 297, 305, 306). Dysfunction of VGCCs will cause alterations in the intracellular calcium concentrations, impairment of the Ca^{2+} signaling system and consequent ROS overproduction.

Walleczek (44) reviewed many studies showing effects of ELF EMFs on cells of the immune system revealing the critical role of intracellular calcium. But until that time, the site of interaction of EMFs with cells was unknown, even though the facts were pointing toward the calcium ion channels in the cell membranes as a most reasonable explanation. At the same time, Liburdy (315) in a series of pioneering experiments showed that calcium influx in lymphocytes which occurred within minutes after the onset of ELF EMF exposures, was due to an effect on the calcium channels in the cell plasma membranes (most of which are voltage-gated), and not due to release from intracellular stores.

Apart from the effect of EMFs on Ca^{2+}, Na^+, K^+, etc. VGICs, proton (H^+) VGICs will be similarly affected (342, 343). This in turn will disturb the function of NOXs triggering ROS generation (section 3.1.2). Thus, not only VGCCs, but all VGICs are the sites where the effects of man-made EMFs on cells take place (2, 210).

Besides many other adverse effects, ROS can also affect ion channels themselves. For example, many ion channels contain cysteine residues with highly reactive thiol (SH) groups. These are particularly susceptible to oxidation by ROS. Oxidation of cysteine residues can lead to formation of disulfide bonds. This can alter the channel

conformation and affect channel gating. Another effect of ROS on VGICs can be the formation of sulfenic, sulfinic, or sulfonic acids: These modifications can change the channel's structure and function, potentially leading to channel inactivation or altered ion permeability (318). Oxidation of K^+ channels by ROS is a common event in the aging brain (344). Therefore, ion channel dysfunction leads to ROS overproduction, and ROS further amplify ion channel dysfunction. Obviously, we have a vicious circle here, where VGIC dysfunction leads to OS in cells, and this in turn disrupts the ion channels even more, leading to even more pronounced OS.

The balance of the various mobile ions in a cell is closely linked to and, in fact, determines the cell's homeostasis. ROS production in all cells initiates after imbalance of ion concentrations. Dysfunction of ion channels or pumps due to any reason, including EMF-exposure, can readily cause ionic imbalance, ROS overproduction and OS. Figure 5 shows the biochemical processes related with OS, and initiated after EMF-induced dysfunction of VGICs and imbalance of ion concentrations.

It is thus well documented that ion channel dysfunction causes OS, and here we make the case that the OS found after anthropogenic and especially WC EMF exposure is induced after VGIC dysfunction. We have a clear sequence of events starting from irregular gating of VGICs by man-made EMFs up to OS, cell/DNA damage and related pathologies including infertility and carcinogenesis. Therefore, a comprehensive mechanism of EMF-induced bioeffects can be clearly delineated, with a biophysical stage causing VGIC dysfunction and ionic imbalance, and a subsequent biochemical stage resulting in OS-related pathogenesis. Figure 6 shows a schematic representation of the described comprehensive mechanism initiated by EMF-induced dysfunction of VGICs, and resulting in OS and cellular damage.

6 Discussion

We have reviewed experimental and epidemiological studies referring to the biological and health impacts of anthropogenic ELF and WC EMF exposures. We find once again that it is well documented that both purely ELF and WC/RF (containing ELF) man-made EMFs induce OS and genetic damage, which can lead to related pathologies, such as infertility and cancer in both humans and animals.

We have documented that all anthropogenic EMFs referred to as "RF," especially WC EMFs, apart from their RF emissions (carrier waves), emit ELF/ULF/VLF EMFs in the form of modulation, pulsation, and variability, and thus, in fact, are a combination of RF and ELF/ULF/VLF EMFs.

Some authors confuse "pulsation" with exposure intermittence. Zahumenska et al. (373) applied an intermittent exposure (6 × 10 min) to a continuous-wave LF EMF (87–207 kHz), with 10-min pauses between exposure periods, and claimed they studied effects of pulsed EMF, finding no significant difference from the absence of effects with an uninterrupted exposure (1 × 60 min). This is not the case. In a "pulsing field" the on/off pulsations are inherent in the signal and occur at ELF/VLF rates usually of the order of hundreds/thousands pulsations per second, whereas in the "intermittent" exposure as in this case, the field/signal is interrupted externally by a timer, or even manually by use of a switch. While pulsed EMFs are, in almost all cases, found to produce significantly greater effects than continuous-wave (non-pulsed) EMFs, an intermittent exposure to any EMF may produce smaller effects than an uninterrupted exposure to the same EMF when the intermittence interval is long enough (e.g., ≥10 min) to allow the exposed organism repair damages and/or

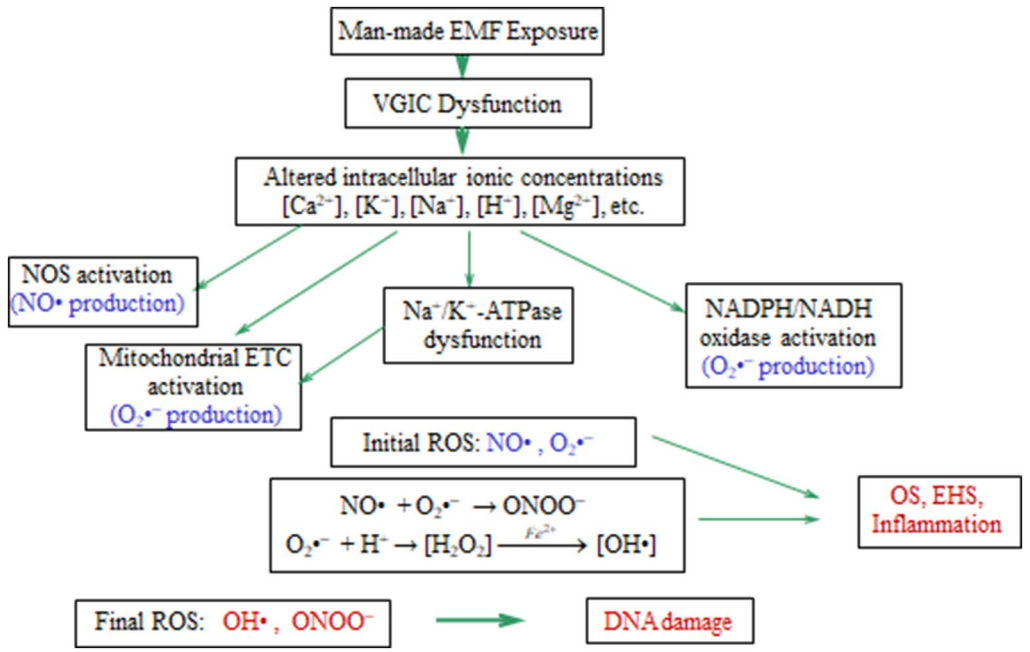


FIGURE 5
Schematic diagram of the OS processes initiated in living cells after anthropogenic EMF exposure and dysfunction of VGICs. Genetic/cell damage is executed by the generated "final" ROS [adapted from Panagopoulos et al. (210)].

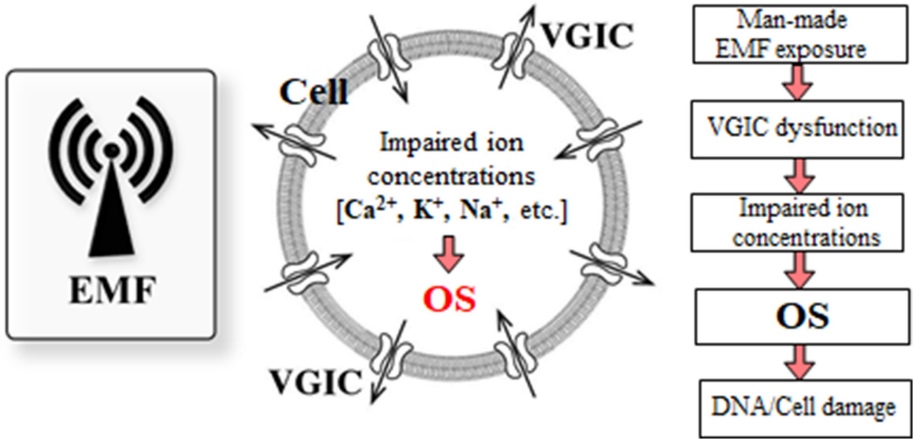


FIGURE 6
Comprehensive mechanism of anthropogenic EMF-induced bioeffects.

adapt to the stressor (72). By confusing pulsation with intermittence one may draw completely misleading conclusions. Zahumenska et al. (373) actually found no effect by use of a continuous-wave LF EMF, which was expected, but they claimed the found no effect with a "pulsed" EMF. A definition of the various physical parameters of EMFs can be found in Panagopoulos and Margaritis (345) and Panagopoulos et al. (3).

We have explained that all man-made EMFs are fully polarized and coherent, with low-frequency (ELF/ULF/VLF) intensity variations in the vast majority of cases, meaning they possess net electric and magnetic fields oscillating (at ELF/ULF/VLF rates) in single directions and in phase. This condition induces parallel and coherent low-frequency forced oscillations of mobile ions and other charged/polar molecules in living tissues. The IFO-VGIC mechanism has described how such oscillations induce dysfunction of VGICs in the membranes of all cells resulting in altered intracellular ionic concentrations (2, 5, 297, 305, 306).

According to the IFO-VGIC mechanism, the non-thermal biological/health effects reported in the literature, are induced specifically by the low-frequency (ULF/ELF/VLF), and not the high-frequency (purely RF/MW), EMFs. This explains why, in the absence of low-frequency modulation/pulsation/variability, the non-thermal effects, attributed before to "RF" EMFs, disappear. It follows that purely RF/MW EMFs can only induce heating of biological tissues at adequately high intensities and frequencies approaching infrared (2, 3). An overview of VGIC structure and function, and the IFO-VGIC mechanism has been provided in section 4.

It is important to note that VGICs are not gated by direct forces on their S4 sensors by externally applied EMFs. That would require applied fields of the order of the transmembrane fields (~10^7 V/m) (56). The reason why even very weak (down to 10^{-5}–10^{-4} V/m) ULF/ELF anthropogenic fields can gate VGICs is that due to their polarized and coherent character combined with low frequency variability, they can induce parallel and coordinated low frequency forced oscillations of mobile ions within the channels. And the forces exerted on the S4 sensors by several oscillating ions in close proximity (≤1 nm), depending upon the inverse third power of the distance (Equation 12), are much greater than direct forces from externally applied EMFs. In other words, due to the IFO phenomenon in close proximity to the VGIC-sensors, the forces are enormously amplified. This is a key point in understanding the IFO-VGIC mechanism.

It is thus, polarization and coherence combined with low frequency variability that make anthropogenic EMFs able to irregularly gate (open or close) VGICs, the most sensitive EMF sensors and the most abundant class of ion channels in all cell membranes of all living organisms. This causes perturbation of ionic concentrations in the cells which in turn triggers (over)production of ROS. ROS can readily cause ionization/chemical alterations in living tissue, i.e., breakage of chemical bonds, and DNA damage.

We described biochemical processes initiated in living cells by dysfunction of VGICs due to man-made EMF-exposure, leading to altered intracellular concentrations of critical ions such as Ca^{2+}, Na^+, K^+, H^+, etc., and disruption of the cell's electrochemical balance, redox state, and homeostasis. This leads to immediate production of the two initial ROS, superoxide anion ($O_2\bullet^-$) and nitric oxide (NO•), which can then be easily converted to the powerful "final" ROS peroxynitrite ($ONOO^-$) and/or hydroxyl radical (OH•), which can damage DNA or any other biological molecule.

It is remarkable that the same "final" ROS that ultimately cause biological damage in the case of EMFs ("non-ionizing" radiations), hydroxyl radical and peroxynitrite, are also found in the case of exposure to ionizing radiations. It is estimated that about 2/3 of the DNA damages caused by ionizing radiation are due to OH• (276, 294, 295, 346–348). This provides an answer to claims that "non-ionizing" anthropogenic EMFs cannot possibly cause biological damage. It comes that the same ROS that actually execute the biological damage in most cases, are produced by either ionizing radiation or "non-ionizing" EMFs/EMR. This is related with the fact that in most cases the action of radiation in biological tissue is indirect. The external agent causes impairment of cell homeostasis and in response, the cell generates ROS which execute the damage.

ROS sources in cells are the ETC in the mitochondria, the ETC in the NOXs in the plasma membrane, the NOS enzymes at various locations in the cell, and various other secondary sources (described in section 3.1). All ROS sources/promoters are affected by the intracellular concentrations of cations like Ca^{2+}, K^+, Na^+, H^+, with most cation

channels being voltage-gated (VGICs) (231, 234, 271). Therefore, all ROS sources in cells can be affected by man-made EMFs. It is remarkable that in all cases reported so far in the literature, anthropogenic EMF exposures increase and not decrease ROS/OS in cells. This is an additional indication that the cells perceive anthropogenic EMFs as a disturbance.

Even though many of the details of the ion signaling that triggers ROS generation by the above sources are still unexplored, we do know that the triggering involves changes in the intracellular ionic concentrations. Since man-made EMFs have the ability to cause dysfunction of VGICs, the basic parts of the entire process leading to DNA damage and related pathologies are already identified, and the dots are already connected revealing the complete EMF-induced bioeffects mechanism.

Several questions still need to be addressed. For example, we did not discuss the state of the antioxidant system (AOS) under the condition of chronic OS due to long-term EMF exposure. As the production of ROS at physiological levels is an essential part in any cell's life, the role of the AOS is to limit the level of ROS under the OS threshold where damage would ensue. Moreover, the AOS controls the activity of repair enzymes. Cells/organisms with compromised antioxidant capacity or high energy demands are particularly vulnerable to OS, and, subsequently, to man-made EMFs. Many studies have revealed significant changes in activity of key antioxidant enzymes under modulated and/or pulsed RF/WC EMF exposure [see reviews in (62–64)]. And while in many cases the changes in activities of antioxidant enzymes may be induced by ROS overproduction in the exposed cells, they may also be affected by ionic imbalances related to VGIC dysfunction. For example, Ca^{2+} can influence the activity of transcription factors like NF-κB and Nrf2, which regulate the expression of antioxidant genes (349). Further, disruption of Na^+/K^+ gradients can indirectly affect Ca^{2+} homeostasis through the Na^+/Ca^{2+} exchanger, which can operate in both directions depending on the ion gradients (350).

When overproduction of ROS in a cell exceeds the capacity of its AOS, the cell/organism is under OS. A sustained or repeated such condition leads to DNA/cellular damage. Intracellular ions, particularly Ca^{2+}, affect the activity of AOS and DNA repair enzymes. For example, some DNA repair pathways are Ca^{2+}-dependent. Disruption of Ca^{2+} homeostasis can therefore impair DNA repair capacity, making cells more susceptible to DNA damage (351). Unrepaired/misrepaired DNA lesions such as strand breaks, covalent bond breakage, or nucleotide base and sugar damages, can lead to cell senescence, cell death, or mutations, and related pathologies such as aging, infertility, neurodegenerative diseases, and cancer (2, 61, 210, 233, 280, 290).

The processes initiated in living cells due to VGIC dysfunction in their cell membranes resulting in OS, genetic damage, and related pathologies provide an explanation for the plethora of biological and health effects reviewed in the Introduction (section 1.2). Moreover, the dysfunction of VGICs caused by man-made EMF exposure and leading to OS can also explain EHS, as EHS is accompanied by OS (197, 352), and in fact it is likely due to chronic OS. The pathophysiological changes in the CNS observed to accompany EHS [see (190)] can be explained by the fact that neurons have higher percentages of VGICs, as VGICs (specifically Na^+ and K^+ VGICs) are the mediators for the transmission of the nerve impulses (231, 271).

Several studies have found that ELF EMFs induce epigenetic changes in cells, commonly resulting in altered gene expression. Such changes include methylation/de-methylation of genes via activation/deactivation of methyltransferase enzymes, post-translational modification of histone proteins, and alteration of microRNA expression (353–355). Epigenetic changes can induce significant alterations in cell function and consequently the health of an organism. Since ROS affect cell signaling (232) related also with epigenetic changes (320, 354), the reported epigenetic effects induced by anthropogenic ELF EMFs can be due to ROS signaling, and the presented mechanism of EMF-induced ROS (over)production provides an explanation for this. For example, EMF-induced ROS may interfere with DNA or histone methyltransferases and histone deacetylases, resulting in modifications of the epigenome at various regions, including the promoter regions of tumor suppressor genes, resulting in their silencing/inactivation, and leading to cancer promotion (356, 357).

Like us, Blank and Goodman (57, 58) also noted that both ELF and "RF" (actually WC) EMFs produce similar effects, especially in inducing synthesis of stress proteins in cells very rapidly (within a few min). For us, an apparent explanation of the common ELF and RF/WC EMF effects that escaped attention, is that "RF" EMFs affect cells not by their carrier (RF) components, but by their ELF components of pulsing and modulation. As this study shows, actually only the ELF EMFs are those that induce the non-thermal biological effects, and they do not act directly on DNA, but indirectly through VGIC dysfunction and consequent induction of OS (2, 210). Further, it follows that purely RF EMFs can only induce heating at adequately high intensities and frequencies (3).

As documented here, anthropogenic EMFs at environmentally existing levels can ionize living tissue through the action of the generated ROS/OS. It is through the action of ROS the damage found in the DNA after anthropogenic and especially WC EMF exposures. There is a tight link between anthropogenic EMF-exposures, VGIC dysfunction, OS, and DNA/cellular damage.

For cells with irreparably damaged genomic DNA, possible outcomes are, cell senescence or cell death (which may result in aging, organic/neurodegenerative diseases, and/or reproductive difficulties), cancer, or mutated offspring (Figure 7), depending on cell type, the specific biological/environmental conditions, and the state of the organism (2, 210). Thus, DNA damage induced by OS explains the pathologies linked to chronic exposure to anthropogenic EMFs, such as infertility and cancer.

Man-made EMFs, and especially the most detrimental ones from WC antennas/devices and high-voltage electric power lines, have become a new reality in modern life exposing billions of people on a daily basis (7, 50). Even though they are significantly less cytotoxic than radioactivity or certain toxic chemicals, they represent an evolutionary novel and most persistent daily cytotoxic agent, against which, existing repair mechanisms may not be efficient enough. Especially in individuals who are already genetically or epigenetically compromised.

Therapeutic effects of man-made EMFs have also been reported in the literature, especially of pulsing ELF EMFs and specifically in bone fracture healing (238, 358–363). Altered intracellular calcium levels have also been reported to accompany such effects, and the same biophysical mechanism of induced VGIC gating seems to be involved in both the detrimental and therapeutic effects of man-made EMFs (238, 359, 363). Several authors speak of therapeutic effects of pulsing ELF EMFs without specifying or discussing which parameter of the EMF exposure might be the therapeutic one (364–366). This might lead to the false impression that any EMF with ELF/ULF pulsations may

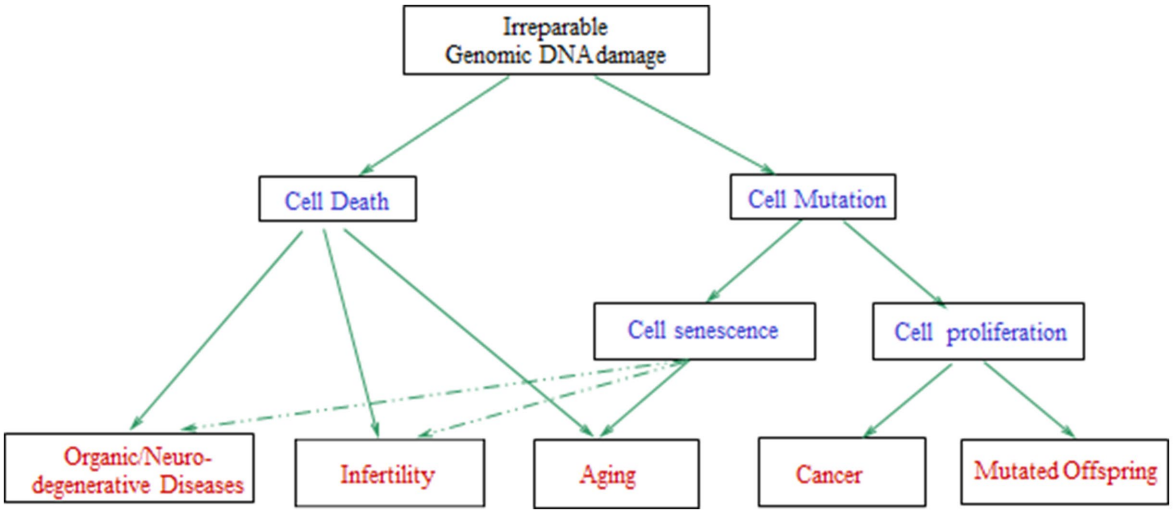


FIGURE 7
Schematic diagram with the possible consequences of irreparable genomic DNA damage in the cells of a living organism. The arrows with dashed lines mean that the effects can be induced in a lesser degree [adapted from Panagopoulos et al. (210)].

be therapeutic, which, of course, is not the case, as, e.g., all WC EMFs consist of such pulsations, and yet are the most detrimental. Some other authors suggest that there are specific "beneficial" or "detrimental" frequencies in the ELF range (367) without considering the IFO-VGIC mechanism published for almost 25 years (and already referenced by more than a thousand other publications), which clearly shows according to generally accepted mathematics, physics, and biology, that the bioactivity of polarized, coherent, and oscillating EMFs, is proportional to field intensity and inversely proportional to field frequency, which makes all ULF/ELF frequencies very bioactive rather than only some specific ones (2, 5, 297, 305, 306). Thus, the basis of EMF bioactivity is not some specific frequencies, but polarization and coherence combined with low frequency variability (at any ULF/ELF frequency), with the lower the frequency the more bioactive the field (Equation 16). Once an EMF is polarized, coherent, and slow varying, we cannot exclude the possibility of resonance phenomena taking place at specific physiological ULF/ELF frequencies. However, we would not expect such phenomena, if they occur, to be particularly intense, especially under actual damping conditions within cells and ion channels (368).

In our opinion, a condition for an applied EMF in order to have a therapeutic action is, to simulate natural EMFs or physiological endogenous cellular signals. Once we know that the most bioactive polarized and coherent EMFs are the ULF/ELF ones, the critical issue for an applied ULF/ELF EMF is whether its included frequencies (and other parameters such as waveform, polarity, etc.) reinforce or cancel the endogenous physiological electrical activity of the cells which is responsible for the specific therapeutic action (49, 210, 369). The basic frequency of the natural atmospheric "Schumann" electromagnetic resonances (7.83 Hz) and its harmonics are detected in the human/animal brain activity, and the physical parameters of electromagnetic brain activity and atmospheric lightning display remarkable similarities (369–371). Thus, we have suggested (210) that the therapeutic effects of pulsed EMFs are expected to be optimal at pulsing frequencies coinciding with the Schumann frequencies, or the endogenous ionic oscillations in cells (49). Indeed, Yan et al. (372) found that pulses at an ELF repetition rate coinciding with the basic Schumann frequency 7.83 Hz inhibit proliferation and induce apoptosis of cancer cells while this does not occur with normal cells. This needs to be further verified and certainly, there are important limitations: All anthropogenic EMFs are fully polarized and coherent something that does not occur with the natural EMFs which are only partially polarized on certain occasions (5). This seems to be the reason why the vast majority of effects of anthropogenic EMFs are detrimental, whereas the vast majority of natural EMFs can be beneficial.

In conclusion, the IFO-VGIC mechanism that explains VGIC dysfunction, and the subsequent OS, provide a comprehensive biophysical/biochemical mechanism explaining the plethora of experimental and epidemiological findings connecting anthropogenic EMF exposures with OS, DNA/cellular damage and related pathologies such as poor health, EHS, infertility, organic/neurodegenerative diseases, cancer, etc. Even though the mechanistic details of how exactly the ionic perturbations stimulate ROS production by their sources need to be further explored, the basic scheme of the complete EMF-bioeffects mechanism is revealed already. The long existing experimental and epidemiological findings connecting exposure to man-made EMFs and DNA damage, infertility, and cancer, are now explained by the presented comprehensive mechanism. We hope this provides a better understanding of the involved science, a basis for future research, and the establishment of biologically relevant EMF exposure guidelines for effective protection of public health and the environment.

Author contributions

DP: Conceptualization, Writing – original draft. IY: Writing – review & editing. GI: Writing – review & editing. GC: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by the Special Account for Research Grants of the National Kapodistrian University of Athens (grant number 16599).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Misek J, Jakus J, Hamza Sladicekova K, Zastko L, Veternik M, Jakusova V, et al. Extremely low frequency magnetic fields emitted by cell phones. *Front Phys*. (2023) 11:1094921. doi: 10.3389/fphy.2023.1094921

2. Panagopoulos DJ, Karabarbounis A, Yakymenko I, Chrousos GP. Human-made electromagnetic fields: ion forced-oscillation and voltage-gated ion channel dysfunction, oxidative stress and DNA damage. *Int J Oncol*. (2021) 59:92. doi: 10.3892/ijo.2021.5272

3. Panagopoulos DJ, Karabarbounis A, Lioliousis C. Defining wireless communication (WC) electromagnetic fields (EMFs): A. Polarization is a principal property of all man-made EMFs; B. Modulation, pulsation, and variability are inherent parameters of WC EMFs; C. Most man-made EMF exposures are non-thermal; D. Measuring incident EMFs is more relevant than specific absorption rate (SAR); E. All man-made EMFs emit continuous waves, not photons; F. Differences from natural EMFs. Interaction with matter In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: Biological and health effects. Boca Raton: CRC Press (2022)

4. Pedersen GF. Amplitude modulated RF fields stemming from a GSM/DCS-1800 phone. *Wirel Netw*. (1997) 3:489–98. doi: 10.1023/A:1019158712657

5. Panagopoulos DJ, Johansson O, Carlo GL. Polarization: a key difference between man-made and natural electromagnetic fields, in regard to biological activity. *Sci Rep*. (2015) 5:14914. doi: 10.1038/srep14914

6. Dubrov AP. The geomagnetic field and life. New York: Plenum Press (1978).

7. Panagopoulos DJ. Comparing DNA damage induced by Mobile telephony and other types of man-made electromagnetic fields. *Mutation Res Rev*. (2019) 781:53–62. doi: 10.1016/j.mrrev.2019.03.003

8. Bawin SM, Kaczmarek LK, Adey WR. Effects of modulated VHF fields, on the central nervous system. *Ann NY Acad Sci*. (1975) 247:74–81.

9. Bawin SM, Adey WR, Sabbot IM. Ionic factors in release of $^{45}Ca^{2+}$ from chick cerebral tissue by electromagnetic fields. *Proc Natl Acad Sci USA*. (1978) 75:6314–8.

10. Blackman CF, Benane SG, Elder JA, House DE, Lampe JA, Faulk JM. Induction of calcium-ion efflux from brain tissue by radiofrequency radiation: effect of sample number and modulation frequency on the power-density window. *Bioelectromagnetics*. (1980) 1:35–43. doi: 10.1002/bem.2250010104

11. Blackman CF, Benane SG, Kinney LS, Joines WT, House DE. Effects of ELF fields on calcium-ion efflux from brain tissue in vitro. *Radiat Res*. (1982) 92:510–20.

12. Bolshakov MA, Alekseev SI. Bursting responses of Lymnea neurons to microwave radiation. *Bioelectromagnetics*. (1992) 13:119–29. doi: 10.1002/bem.2250130206

13. Byus CV, Lundak RL, Fletcher RM, Adey WR. Alterations in protein kinase activity following exposure of cultured lymphocytes to modulated microwave fields. *Bioelectromagnetics*. (1984) 5:341–51. doi: 10.1002/bem.2250050307

14. Byus CV, Kartum K, Pieper SE, Adey WR. Ornithine decarboxylase activity in liver cells is enhanced by low-level amplitude modulated microwave fields. *Cancer Res*. (1988) 48:4222–6.

15. Campisi A, Gulino M, Acquaviva R, Bellia P, Raciti G, Grasso R, et al. Reactive oxygen species levels and DNA fragmentation on astrocytes in primary culture after acute exposure to low intensity microwave electromagnetic field. *Neurosci Lett*. (2010) 473:52–5. doi: 10.1016/j.neulet.2010.02.018

16. Franzellitti S, Valbonesi P, Ciancaglini N, Biondi C, Contin A, Bersani F, et al. Transient DNA damage induced by high-frequency electromagnetic fields (GSM 1.8 GHz) in the human trophoblast HTR-8/SVneo cell line evaluated with the alkaline comet assay. *Mutat Res*. (2010) 683:35–42. doi: 10.1016/j.mrfmmm.2009.10.004

17. Frei M, Jauchem J, Heinmets F. Physiological effects of 2.8 GHz radio-frequency radiation: a comparison of pulsed and continuous-wave radiation. *J Microw Power Electromagn Energy*. (1988) 23:2.

18. Goodman EM, Greenebaum B, Marron MT. Effects of electro- magnetic fields on molecules and cells. *Int Rev Cytologia*. (1995) 158:279–338.

19. Hinrikus H, Bachmann M, Lass J, Tomson R, Tuulik V. Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms. *Int J Radiat Biol*. (2008) 84:69–79. doi: 10.1080/09553000701691679

20. Höytö A, Luukkonen J, Juutilainen J, Naarala J. Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants. *Radiat Res*. (2008) 170:235–43. doi: 10.1667/RR1322.1

21. Huber R, Treyer V, Borbely AA, Schuderer J, Gottselig JM, Landolt HP, et al. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. *J Sleep Res*. (2002) 11:289–95. doi: 10.1046/j.1365-2869.2002.00314.x

22. Lin-Liu S, Adey WR. Low frequency amplitude modulated microwave fields change calcium efflux rates from synaptosomes. *Bioelectromagnetics*. (1982) 3:309–22. doi: 10.1002/bem.2250030303

23. Litovitz TA, Krause D, Penafiel M, Elson EC, Mullins JM. The role of coherence time in the effect of microwaves on ornithine decarboxylase activity. *Bioelectromagnetics*. (1993) 14:395–403. doi: 10.1002/bem.2250140502

24. Mohammed HS, Fahmy HM, Radwan NM, Elsayed AA. Non-thermal continuous and modulated electromagnetic radiation fields effects on sleep EEG of rats. *J Adv Res*. (2013) 4:181–7. doi: 10.1016/j.jare.2012.05.005

25. Penafiel LM, Litovitz T, Krause D, Desta A, Mullins MJ. Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells. *Bioelectromagnetics*. (1997) 18:132–41. doi: 10.1002/(SICI)1521-186X(1997)18:2<132::AID-BEM6>3.0.CO;2-3

26. Somosy Z, Thuroczy G, Kubasova T, Kovacs J, Szabo LD. Effects of modulated and continuous microwave irradiation on the morphology and cell surface negative charge of 3T3 fibroblasts. *Scanning Microsc*. (1991) 5:1145–55.

27. Thuroczy G, Kubinyi G, Bodo M, Bakos J, Szabo LD. Simultaneous response of brain electrical activity (EEG) and cerebral circulation (REG) to microwave exposure in rats. *Rev Environ Health*. (1994) 10:135–48. doi: 10.1515/REVEH.1994.10.2.135

28. Van der Meer JN, Eisma YB, Meester R, Jacobs M, Nederveen AJ. Effects of mobile phone electromagnetic fields on brain waves in healthy volunteers. *Sci Rep*. (2023) 13:21758. doi: 10.1038/s41598-023-48561-z

29. Veyret B, Bouthet C, Deschaux P, de Seze R, Geffard M, Joussot-Dubien J, et al. Antibody responses of mice exposed to low-power microwaves under combined, pulse-and-amplitude modulation. *Bioelectromagnetics*. (1991) 12:47–56. doi: 10.1002/bem.2250120107

30. Mohammed HS. Effects of wireless communication electromagnetic fields on human and animal brain activity In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press (2022)

31. Aydin M, Turk G, Yuksel M, Cevik A, Apaydin A, Yilmaz S. Effect of electromagnetic field on the sperm characteristics and histopathological status of testis in rats. *Med Weter*. (2007) 63:178–83.

32. Azanza MJ, Perez Bruzon RN, Lederer D, et al. Reversibility of the effects induced on the spontaneous bioelectric activity of neurons under exposure to 8.3 and 217.0 Hz low intensity magnetic fields. 2nd Int. Workshop Biol Effects of EMFs, Rhodes, Greece. (2002). p. 651–659.

33. Hong R, Zhang Y, Liu Y, Weng EQ. Effects of extremely low frequency electromagnetic fields on DNA of testicular cells and sperm chromatin structure in mice. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. (2005) 23:414–7.

34. Ivancsits S, Diem E, Pilger A, Rüdiger HW, Jahn O. Induction of DNA strand breaks by intermittent exposure to extremely-low-frequency electromagnetic fields in

human diploid fibroblasts. *Mutat Res*. (2002) 519:1–13. doi: 10.1016/S1383-5718(02)00109-2

35. Ivancsits S, Diem E, Jahn O, Rüdiger HW. Intermittent extremely low frequency electromagnetic fields cause DNA damage in a dose-dependent way. *Int Arch Occup Environ Health*. (2003) 76:431–6. doi: 10.1007/s00420-003-0446-5

36. Lee JS, Ahn SS, Jung KC, Kim YW, Lee SK. Effects of 60 Hz electromagnetic field exposure on testicular germ cell apoptosis in mice. *Asian J Androl*. (2004) 6:29–34.

37. Lee SK, Park S, Gimm YM, Kim YW. Extremely low frequency magnetic fields induce spermatogenic germ cell apoptosis: possible mechanism. *Biomed Res Int*. (2014) 2014:567183:1–8. doi: 10.1155/2014/567183

38. Ma TH, Chu KC. Effect of the extremely low frequency (ELF) electromagnetic field (EMF) on developing embryos of the fruit fly (Drosophila melanogaster L.). *Mutat Res*. (1993) 303:35–9. doi: 10.1016/0165-7992(93)90006-H

39. Moghadam MK, Firoozabadi SM, Janahmadi M. 50 Hz alternating extremely low frequency magnetic fields affect excitability, firing and action potential shape through interaction with ionic channels in snail neurones. *Environmentalist*. (2008) 28:341–7. doi: 10.1007/s10669-007-9143-3

40. Moghadam MK, Firoozabadi SM, Janahmadi M. Reduction of F1 neuronal excitability by exposure to 217 Hz magnetic fields from GSM 900 mobile phone. *Cell J*. (2009) 11:176–83.

41. Moghadam MK, Firoozabadi M, Janahmadi M. Effects of weak environmental magnetic fields on the spontaneous bioelectrical activity of snail neurons. *J Membr Biol*. (2011) 240:63–71. doi: 10.1007/s00232-011-9344-z

42. Panagopoulos DJ, Karabarbounis A, Liolioussi C. ELF alternating magnetic field decreases reproduction by DNA damage induction. *Cell Biochem Biophys*. (2013) 67:703–16. doi: 10.1007/s12013-013-9560-5

43. Santini MT, Ferrante A, Rainaldi G, Indovina P, Indovina PL. Extremely low frequency (ELF) magnetic fields and apoptosis: a review. *Int J Radiat Biol*. (2005) 81:1–11. doi: 10.1080/09553000400029502

44. Walleczek J. Electromagnetic field effects on cells of the immune system: the role of calcium signaling. *FASEB J*. (1992) 6:3177–85. doi: 10.1096/fasebj.6.13.1397839

45. Górski R, Kotwicka M, Skibińska I, Jendraszak M, Wosiński S. Effect of low-frequency electric field screening on motility of human sperm. *Ann Agric Environ Med*. (2020) 27:427–34. doi: 10.26444/aaem/116019

46. Karbalay-Doust S, Darabyan M, Sisakht M, Haddadi G, Sotoudeh N, Haghani M, et al. Extremely low frequency-electromagnetic fields (ELF-EMF) can decrease spermatocyte count and motility and change testicular tissue. *J Biomed Phys Eng*. (2023) 13:135–46. doi: 10.31661/jbpe.v0i0.2011-1234

47. Mahna A, Firoozabadi SM, Atashi A. Cell phone and breast cancer: the cell phone-generated pulsed 217Hz ELF magnetic field increases angiogenesis. *Iran J Med Phys*. (2021) 18:421–9. doi: 10.22038/IJMP.2020.52303.1859

48. Mansourian M, Firoozabadi M, Hassan ZM. The role of 217-Hz ELF magnetic fields emitted from GSM mobile phones on electrochemotherapy mechanisms. *Electromagn Biol Med*. (2020) 39:239–49. doi: 10.1080/15368378.2020.1762635

49. Panagopoulos DJ. Electromagnetic interaction between environmental fields and living systems determines health and well-being In: Electromagnetic fields: principles, engineering applications and biophysical effects. K Myung-Hee and Y Sang-Ook (editors). New York, USA: Nova Science Publishers (2013)

50. Panagopoulos DJ. Electromagnetic fields of wireless communications: biological and health effects. *1st* ed. Boca Raton: CRC Press (2023).

51. Persinger MA. ELF and VLF electromagnetic fields. New York: Plenum Press (1974).

52. Wever R. The circadian system of man: results of experiments under temporal isolation. New York: Springer-Verlag (1979).

53. Panagopoulos DJ. Man-made electromagnetic radiation is not quantized In: A Reimer, editor. Horizons in world physics, vol. *296*. New York: Nova Science Publishers (2018). 1–57.

54. Puranen L, Jokela K. Radiation hazard assessment of pulsed microwave radars. *J Microw Power Electromagn Energy*. (1996) 31:165–77. doi: 10.1080/08327823.1996.11688307

55. Pirard W, Vatovez B. Study of pulsed character of radiation emitted by wireless telecommunication systems. Liège, Belgium: Institut scientifique de service public. (Available in: https://www.issep.be/wp-content/uploads/7IWSBEEMF_B-Vatovez_W-Pirard.pdf)

56. Panagopoulos DJ. Comments on Pall's "millimeter (MM) wave and microwave frequency radiation produce deeply penetrating effects: the biology and the physics". *Rev Environ Health*. (2021) 37:295–7. doi: 10.1515/reveh-2021-0090

57. Blank M, Goodman R. Electromagnetic fields stress living cells. *Pathophysiology*. (2009) 16:71–8. doi: 10.1016/j.pathophys.2009.01.006

58. Blank M, Goodman R. DNA is a fractal antenna in electromagnetic fields. *Int J Radiat Biol*. (2011) 87:409–15. doi: 10.3109/09553002.2011.538130

59. Henshaw DL, Philips A. A mechanistic understanding of human magnetoreception validates the phenomenon of electromagnetic hypersensitivity (EHS). *Int J Radiat Biol*. (2024):1–19.

60. Roux D, Vian A, Girard S, Bonnet P, Paladian F, Davies E, et al. Electromagnetic fields (900MHz) evoke consistent molecular responses in tomato plants. *Physiol Plant*. (2006) 128:283–8. doi: 10.1111/j.1399-3054.2006.00740.x

61. Phillips JL, Singh NP, Lai H. Electromagnetic fields and DNA damage. *Pathophysiology*. (2009) 16:79–88. doi: 10.1016/j.pathophys.2008.11.005

62. Yakymenko I, Tsybulin O, Sidorik E, Henshel D, Kyrylenko O, Kyrylenko S. Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. *Electromagn Biol Med*. (2016) 35:186–202. doi: 10.3109/15368378.2015.1043557

63. Yakymenko I, Tsybulin O. Oxidative stress induced by wireless communication electromagnetic fields In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press (2022)

64. Jagetia GC. Genotoxic effects of wireless communication electromagnetic fields In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press, Taylor and Francis (2022)

65. Miller K, Harrison K, Martin JH, Nixon B, De Iuliis GN. The impacts of wireless communication electromagnetic fields on human reproductive biology In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC press, Taylor and Francis (2022)

66. Panagopoulos DJ. DNA and chromosome damage in human and animal cells induced by mobile telephony electromagnetic fields and other stressors In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press (2022)

67. Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, et al. Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. *Fertil Steril*. (2009) 92:1318–25. doi: 10.1016/j.fertnstert.2008.08.022

68. Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM, King BV. Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline. *Int J Androl*. (2005) 28:171–9. doi: 10.1111/j.1365-2605.2005.00531.x

69. Banerjee S, Singh NN, Sreedhar G, Mukherjee S. Analysis of the genotoxic effects of Mobile phone radiation using buccal micronucleus assay: a comparative evaluation. *J Clin Diagn Res*. (2016) 10:ZC82–5. doi: 10.7860/JCDR/2016/17592.7505

70. Belyaev IY, Hillert L, Protopopova M, Tamm C, Malmgren LOG, Persson BRR, et al. 915 MHz microwaves and 50 Hz magnetic field affect chromatin conformation and 53BP1 foci in human lymphocytes from hypersensitive and healthy persons. *Bioelectromagnetics*. (2005) 26:173–84. doi: 10.1002/bem.20103

71. Burlaka A, Tsybulin O, Sidorik E, Lukin S, Polishuk V, Tsehmistrenko S, et al. Overproduction of free radical species in embryonic cells exposed to low intensity radiofrequency radiation. *Exp Oncol*. (2013) 35:219–25.

72. Chavdoula ED, Panagopoulos DJ, Margaritis LH. Comparison of biological effects between continuous and intermittent exposure to GSM-900 MHz mobile phone radiation. Detection of apoptotic cell death features. *Mutation Res*. (2010) 700:51–61. doi: 10.1016/j.mrgentox.2010.05.008

73. Daroit NB, Visioli F, Magnusson AS, Vieira GR, Rados PV. Cell phone radiation effects on cytogenetic abnormalities of oral mucosal cells. *Braz Oral Res*. (2015) 29:1–8. doi: 10.1590/1807-3107BOR-2015.vol29.0114

74. De Iuliis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. *PLoS One*. (2009) 4:e6446. doi: 10.1371/journal.pone.0006446

75. De Iuliis GN, Thomson LK, Mitchell LA, Finnie JM, Koppers AJ, et al. DNA damage in human spermatozoa is highly correlated with the efficiency of chromatin remodeling and the formation of 8-hydroxy-2′-deoxyguanosine, a marker of oxidative stress. *Biol Reprod*. (2009) 81:517–24. doi: 10.1095/biolreprod.109.076836

76. Delgado JMR. Biological effects of extremely low frequency electromagnetic fields. *J Bioelectr*. (1985) 4:75–92. doi: 10.3109/15368378509040362

77. Diem E, Schwarz C, Adlkofer F, Jahn O, Rudiger H. Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro. *Mutat Res*. (2005) 583:178–83. doi: 10.1016/j.mrgentox.2005.03.006

78. Ferreira AR, Knakievicz T, de Bittencourt Pasquali MA, Gelain DP, Dal-Pizzol F, Fernández CER, et al. Ultra high frequency-electromagnetic field irradiation during pregnancy leads to an increase in erythrocytes micronuclei incidence in rat offspring. *Life Sci*. (2006) 80:43–8050. doi: 10.1016/j.lfs.2006.08.018

79. Garaj-Vrhovac V, Horvat D, Koren Z. The effect of microwave radiation on the cell genome. *Mutat Res*. (1990) 243:87–93. doi: 10.1016/0165-7992(90)90028-I

80. Garaj-Vrhovac V, Horvat D, Koren Z. The relationship between colony-forming ability, chromosome aberrations and incidence of micronuclei in V79 Chinese hamster cells exposed to microwave radiation. *Mutat Res*. (1991) 263:143–9. doi: 10.1016/0165-7992(91)90054-8

81. Garaj-Vrhovac V, Fucić A, Horvat D. The correlation between the frequency of micronuclei and specific chromosome aberrations in human lymphocytes exposed to microwave radiation in vitro. *Mutat Res*. (1992) 281:181–6. doi: 10.1016/0165-7992(92)90006-4

82. Guler G, Tomruk A, Ozgur E, Seyhan N. The effect of radiofrequency radiation on DNA and lipid damage in non-pregnant and pregnant rabbits and their newborns. *Gen Physiol Biophys*. (2010) 29:59–60. doi: 10.4149/gpb_2010_01_59

83. Ji S, Oh E, Sul D, Choi JW, Park H, Lee E. DNA damage of lymphocytes in volunteers after 4 hours use of Mobile phone. *J Prev Med Public Health*. (2004) 37:373–80.

84. Koana T, Okada MO, Takashima Y, Ikehata M, Miyakoshi J. Involvement of eddy currents in the mutagenicity of ELF magnetic fields. *Mutat Res*. (2001) 476:55–62. doi: 10.1016/S0027-5107(01)00082-3

85. Lai H, Singh NP. Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. *Bioelectromagnetics*. (1995) 16:207–10. doi: 10.1002/bem.2250160309

86. Lai H, Singh NP. Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. *Int J Radiat Biol*. (1996) 69:513–21. doi: 10.1080/095530096145814

87. Lai H, Singh NP. Acute exposure to a 60 Hz magnetic field increases DNA strand breaks in rat brain cells. *Bioelectromagnetics*. (1997) 18:156–65. doi: 10.1002/(SICI)1521-186X(1997)18:2<156::AID-BEM8>3.0.CO;2-1

88. Lee KS, Choi JS, Hong SY, Son TH, Yu K. Mobile phone electromagnetic radiation activates MAPK signaling and regulates viability in Drosophila. *Bioelectromagnetics*. (2008) 29:371–9. doi: 10.1002/bem.20395

89. Liu C, Gao P, Xu SC, Wang Y, Chen CH, He MD, et al. Mobile phone radiation induces mode-dependent DNA damage in a mouse spermatocyte-derived cell line: a protective role of melatonin. *Int J Radiat Biol*. (2013) 89:993–1001. doi: 10.3109/09553002.2013.811309

90. Lixia S, Yao K, Kaijun W, Deqiang L, Huajun H, Xiangwei G, et al. Effects of 1.8 GHz radiofrequency field on DNA damage and expression of heat shock protein 70 in human lens epithelial cells. *Mutat Res*. (2006) 602:135–42. doi: 10.1016/j.mrfmmm.2006.08.010

91. Luukkonen J, Hakulinen P, Mäki-Paakkanen J, Juutilainen J, Naarala J. Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872 MHz radiofrequency radiation. *Mutat Res*. (2009) 662:54–8. doi: 10.1016/j.mrfmmm.2008.12.005

92. Mailankot M, Kunnath AP, Jayalekshmi H, Koduru B, Valsalan R. Radio frequency electromagnetic radiation (RF-EMR) from GSM (0.9/1.8GHz) mobile phones induces oxidative stress and reduces sperm motility in rats. *Clinics*. (2009) 64:561–5. doi: 10.1590/S1807-59322009000600011

93. Markova E, Hillert L, Malmgren L, Persson BR, Belyaev IY. Microwaves from GSM mobile telephones affect 53BP1 and gamma-H2AX foci in human lymphocytes from hypersensitive and healthy persons. *Environ Health Perspect*. (2005) 113:1172–7. doi: 10.1289/ehp.7561

94. Mausset-Bonnefont AL, et al. Acute exposure to GSM 900-MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. *Neurobiol Dis*. (2004) 17:445–54. doi: 10.1016/j.nbd.2004.07.004

95. Mihai CT, Rotinberg P, Brinza F, Vochita G. Extremely low-frequency electromagneticfields cause DNA strand breaks in normal cells. *J Environ Health Sci Eng*. (2014) 12:15. doi: 10.1186/2052-336X-12-15

96. Nikolova T, Czyz J, Rolletschek A, Blyszczuk P, Fuchs J, Jovtchev G, et al. Electromagnetic fields affect transcript levels of apoptosis-related genes in embryonic stem cell-derived neural progenitor cells. *FASEB J*. (2005) 19:1686–8. doi: 10.1096/fj.04-3549fje

97. Panagopoulos DJ, Chavdoula ED, Nezis IP, Margaritis LH. Cell death induced by GSM 900MHz and DCS 1800MHz Mobile telephony radiation. *Mutat Res*. (2007) 626:69–78. doi: 10.1016/j.mrgentox.2006.08.008

98. Panagopoulos DJ, Chavdoula ED, Margaritis LH. Bioeffects of Mobile telephony radiation in relation to its intensity or distance from the antenna. *Int J Radiat Biol*. (2010) 86:345–57. doi: 10.3109/09553000903567961

99. Panagopoulos DJ. Effect of microwave exposure on the ovarian development of Drosophila melanogaster. *Cell Biochem Biophys*. (2012) 63:121–32. doi: 10.1007/s12013-012-9347-0

100. Pesnya DS, Romanovsky AV. Comparison of cytotoxic and genotoxic effects of plutonium-239 alpha particles and mobile phone GSM 900 radiation in the Allium cepa test. *Mutat Res*. (2013) 750:27–33. doi: 10.1016/j.mrgentox.2012.08.010

101. Sarkar S, Ali S, Behari J. Effect of low power microwave on the mouse genome: a direct DNA analysis. *Mutat Res*. (1994) 320:141–7. doi: 10.1016/0165-1218(94)90066-3

102. Sokolovic D, et al. Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from Mobile phones in rat brain. *J Radiat Res*. (2008) 49:579–86. doi: 10.1269/jrr.07077

103. Svedenstal BM, Johanson KJ, Mild KH. DNA damage induced in brain cells of CBA mice exposed to magnetic fields. *In Vivo*. (1999) 13:551–2.

104. Tomruk A, Guler G, Dincel AS. The influence of 1800 MHz GSM-like signals on hepatic oxidative DNA and lipid damage in nonpregnant, pregnant, and newly born rabbits. *Cell Biochem Biophys*. (2010) 56:39–47. doi: 10.1007/s12013-009-9068-1

105. Winker R, Ivancsits S, Pilger A, Adlkofer F, Rüdiger HW. Chromosomal damage in human diploid fibroblasts by intermittent exposure to extremely low-frequency electromagnetic fields. *Mutat Res*. (2005) 585:43–9. doi: 10.1016/j.mrgentox.2005.04.013

106. Yadav AS, Sharma MK. Increased frequency of micronucleated exfoliated cells among humans exposed in vivo to mobile telephone radiations. *Mutat Res*. (2008) 650:175–80. doi: 10.1016/j.mrgentox.2007.11.005

107. Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS. Effects of cellular phone emissions on sperm motility in rats. *Fertil Steril*. (2007) 88:957–64. doi: 10.1016/j.fertnstert.2006.12.022

108. Yao K, et al. Electromagnetic noise inhibits radiofrequency radiation-induced DNA damage and reactive oxygen species increase in human lens epithelial cells. *Mol Vis*. (2008) 19:964–9.

109. Zhang DY, Xu ZP, Chiang H, Lu DQ, Zeng QL. Effects of GSM 1800 MHz radiofrequency electromagnetic fields on DNA damage in Chinese hamster lung cells. *Zhonghua Yu Fang Yi Xue Za Zhi*. (2006) 40:149–52.

110. Zhang G, Yan H, Chen Q, Liu K, Ling X, Sun L, et al. Effects of cell phone use on semen parameters: results from the MARHCS cohort study in Chongqing, China. *Environ Int*. (2016) 91:116–21. doi: 10.1016/j.envint.2016.02.028

111. D'Silva MH, Swer RT, Anbalagan J, Rajesh B. Effect of radiofrequency radiation emitted from 2G and 3G cell phone on developing liver of Chick embryo - a comparative study. *J Clin Diagn Res*. (2017) 11:5–9. doi: 10.7860/JCDR/2017/26360.10275

112. D'Silva MH, Swer RT, Anbalagan J, Bhargavan R. Assessment of DNA damage in chick embryo brains exposed to 2G and 3G cell phone radiation using alkaline comet assay technique. *J Clin Diagn Res*. (2021) 15:AC01–4. doi: 10.7860/JCDR/2021/47115.14441

113. Gulati S, Mosgoeller W, Moldan D, Kosik P, Durdik M, Jakl L, et al. Evaluation of oxidative stress and genetic instability among residents near mobile phone base stations in Germany. *Ecotoxicol Environ Saf*. (2024) 279:116486. doi: 10.1016/j.ecoenv.2024.116486

114. Gunes M, Ates K, Yalcin B, Akkurt S, Ozen S, Kaya B. An evaluation of the genotoxic effects of electromagnetic radiation at 900 MHz, 1800 MHz, and 2100 MHz frequencies with a SMART assay in Drosophila melanogaster. *Electromagn Biol Med*. (2021) 40:254–63. doi: 10.1080/15368378.2021.1878210

115. Houston BJ, Nixon B, King BV, Aitken RJ, De Iuliis GN. Probing the origins of 1,800 MHz radio frequency electromagnetic radiation induced damage in mouse immortalized germ cells and spermatozoa in vitro. *Front Public Health*. (2018) 6:270. doi: 10.3389/fpubh.2018.00270

116. Kesari KK, Agarwal A, Henkel R. Radiations and male fertility. *Reprod Biol Endocrinol*. (2018) 16:118. doi: 10.1186/s12958-018-0431-1

117. Keskin I, Karabulut S, Kaplan AA, Alagöz M, Akdeniz M, Tüfekci KK, et al. Preliminary study on the impact of 900 MHz radiation on human sperm: an in vitro molecular approach. *Reprod Toxicol*. (2024) 130:108744. doi: 10.1016/j.reprotox.2024.108744

118. Panagopoulos DJ. Chromosome damage in human cells induced by UMTS Mobile telephony radiation. *Gen Physiol Biophys*. (2019) 38:445–54. doi: 10.4149/gpb_2019032

119. Panagopoulos DJ. Comparing chromosome damage induced by Mobile telephony radiation and a high caffeine dose. Effect of combination and exposure duration. *Gen Physiol Biophys*. (2020) 39:531–44. doi: 10.4149/gpb_2020036

120. Panagopoulos DJ. Mobile telephony radiation exerts genotoxic action and significantly enhances the effects of gamma radiation in human cells. *Gen Physiol Biophys*. (2024) 43:103–20. doi: 10.4149/gpb_2023036

121. Shahin S, Singh SP, Chaturvedi CM. Mobile phone (1800MHz) radiation impairs female reproduction in mice, Mus musculus, through stress induced inhibition of ovarian and uterine activity. *Reprod Toxicol*. (2017) 73:41–60. doi: 10.1016/j.reprotox.2017.08.001

122. Sharma A, Shrivastava S, Shukla S. Exposure of radiofrequency electromagnetic radiation on biochemical and pathological alterations. *Neurol India*. (2020) 68:1092–100. doi: 10.4103/0028-3886.294554

123. Singh KV, Prakash C, Nirala JP, Nanda RK, Rajamani P. Acute radiofrequency electromagnetic radiation exposure impairs neurogenesis and causes neuronal DNA damage in the young rat brain. *Neurotoxicology*. (2023) 94:46–58. doi: 10.1016/j.neuro.2022.11.001

124. Smith-Roe SL, Wyde ME, Stout MD, Winters JW, Hobbs CA, Shepard KG, et al. Evaluation of the genotoxicity of cell phone radiofrequency radiation in male and female rats and mice following subchronic exposure. *Environ Mol Mutagen*. (2019) 1:276–90.

125. Yakymenko I, Burlaka A, Tsybulin I, Brieieva I, Buchynska L, Tsehmistrenko S, et al. Oxidative and mutagenic effects of low intensity GSM 1800 MHz microwave radiation. *Exp Oncol*. (2018) 40:282–7. doi: 10.31768/2312-8852.2018.40

126. Yuan LQ, Wang C, Lu DF, Zhao XD, Tan LH, Chen X. Induction of apoptosis and ferroptosis by a tumor suppressing magnetic field through ROS-mediated DNA damage. *Aging*. (2020) 12:3662–81. doi: 10.18632/aging.102836

127. Cappucci U, Casale AM, Proietti M, Marinelli F, Giuliani L, Piacentini L. WiFi related radiofrequency electromagnetic fields promote transposable element dysregulation and genomic instability in Drosophila melanogaster. *Cells*. (2022) 11:4036. doi: 10.3390/cells11244036

128. Choi J, Min K, Jeon S, Kim N, Pack JK, Song K. Continuous exposure to 1.7 GHz LTE electromagnetic fields increases intracellular reactive oxygen species to decrease human cell proliferation and induce senescence. *Sci Rep*. (2020) 10:9238. doi: 10.1038/s41598-020-65732-4

129. Kim JH, Jeon S, Choi HD, Lee JH, Bae JS, Kim N, et al. Exposure to long-term evolution radiofrequency electromagnetic fields decreases neuroblastoma cell proliferation via Akt/mTOR-mediated cellular senescence. *J Toxic Environ Health A*. (2021) 84:846–57. doi: 10.1080/15287394.2021.1944944

130. Shahin S, Singh VP, Shukla RK, Dhawan A, Gangwar RK, Singh SP, et al. 2.45 GHz microwave irradiation-induced oxidative stress affects implantation or pregnancy in mice, Mus musculus. *Appl Biochem Biotechnol*. (2013) 169:1727–51. doi: 10.1007/s12010-012-0079-9

131. Czerwiński M, Vian A, Woodcock BA, Goliński P, Virto LR, Januszkiewicz Ł. Do electromagnetic fields used in telecommunications affect wild plant species? A control impact study conducted in the field. *Ecol Indic*. (2023) 150:110267. doi: 10.1016/j.ecolind.2023.110267

132. Deena K, Maadurshni GB, Manivannan J, Sivasamy R. Short-term exposure of 2.4 GHz electromagnetic radiation on cellular ROS generation and apoptosis in SH-SY5Y cell line and impact on developing chick embryo brain tissue. *Mol Biol Rep*. (2025) 52:144. doi: 10.1007/s11033-025-10217-8

133. Özen G, Kahvecioğlu D, Bulut İ, Erel Ö, Neşelioğlu S, Üstün Y, et al. Effect of Mobile phone usage during pregnancy on total oxidant and antioxidant levels in cord blood. *J Behcet Uz Children's Hosp*. (2023) 13:177–84. doi: 10.4274/jbuch.galenos.2023

134. Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. *Fertil Steril*. (2008) 89:124–8. doi: 10.1016/j.fertnstert.2007.01.166

135. Bakacak M, Bostancı MS, Attar R, Yıldırım ÖK, Yıldırım G, Bakacak Z, et al. The effects of electromagnetic fields on the number of ovarian primordial follicles: an experimental study. *Kaohsiung J Med Sci*. (2015) 31:287–92. doi: 10.1016/j.kjms.2015.03.004

136. Gul A, Celebi H, Uğraş S. The effects of microwave emitted by cellular phones on ovarian follicles in rats. *Arch Gynecol Obstet*. (2009) 280:729–33. doi: 10.1007/s00404-009-0972-9

137. Guzey YZ, Onal AG. Effects of chronic exposure to 2G/3G cell phone radiation on in vitro maturation of bovine oocytes. *Indian J Anim Res*. (2018) 52:523–6.

138. Gye MC, Park CJ. Effect of electromagnetic field exposure on the reproductive system. *Clin Exp Reprod Med*. (2012) 39:1–9. doi: 10.5653/cerm.2012.39.1.1

139. La Vignera S, Condorelli RA, Vicardi E, D'Agata R, Calogero AE. Effects of the exposure to Mobile phones on male reproduction: a review of the literature. *J Androl*. (2012) 33:350–6. doi: 10.2164/jandrol.111.014373

140. Magras IN, Xenos TD. RF radiation-induced changes in the prenatal development of mice. *Bioelectromagnetics*. (1997) 18:455–61. doi: 10.1002/(SICI)1521-186X(1997)18:6<455::AID-BEM8>3.0.CO;2-1

141. Panagopoulos DJ, Karabarbounis A, Margaritis LH. Effect of GSM 900-MHz Mobile phone radiation on the reproductive capacity of Drosophila melanogaster. *Electromagn Biol Med*. (2004) 23:29–43. doi: 10.1081/JBC-120039350

142. Panagopoulos DJ, Chavdoula ED, Karabarbounis A, Margaritis LH. Comparison of bioactivity between GSM 900 MHz and DCS 1800 MHz Mobile telephony radiation. *Electromagn Biol Med*. (2007) 26:33–44. doi: 10.1080/15368370701205644

143. Sharma VP, Kumar NR. Changes in honeybee behaviour and biology under the influence of cellphone radiations. *Curr Sci*. (2010) 98:1376–8.

144. Wdowiak A, Wdowiak L, Wiktor H. Evaluation of the effect of using mobile phones on male fertility. *Ann Agric Environ Med*. (2007) 14:169–72.

145. Irani M, Aradmehr M, Ghorbani M, Baghani R. Electromagnetic field exposure and abortion in pregnant women: a systematic review and meta-analysis. *Malays J Med Sci*. (2023) 30:70–80. doi: 10.21315/mjms2023.30.5.6

146. Bacandritsos N, Granato A, Budge G, Papanastasiou I, Roinioti E, Caldon M, et al. Sudden deaths and colony population decline in Greek honey bee colonies. *J Invertebr Pathol*. (2010) 105:335–40. doi: 10.1016/j.jip.2010.08.004

147. Balmori A. Possible effects of electromagnetic fields from phone masts on a population of White stork (Ciconia ciconia). *Electromagn Biol Med*. (2005) 24:109–19. doi: 10.1080/15368370500205472

148. Balmori A, Hallberg O. The urban decline of the house sparrow (Passer domesticus): a possible link with electromagnetic radiation. *Electromagn Biol Med*. (2007) 26:141–51. doi: 10.1080/15368370701410558

149. Cucurachi S, Tamis WLM, Vijver MG, Peijnenburg WJGM, Bolte JFB, de Snoo GR. A review of the ecological effects of radiofrequency electromagnetic fields (RF-EMF). *Environ Int*. (2013) 51:116–40. doi: 10.1016/j.envint.2012.10.009

150. Everaert J, Bauwens D. A possible effect of electromagnetic radiation from mobile phone base stations on the number of breeding house sparrows (Passer domesticus). *Electromagn Biol Med*. (2007) 26:63–72. doi: 10.1080/15368370701205693

151. Batellier F, Couty I, Picard D, Brillard JP. Effects of exposing chicken eggs to a cell phone in "call" position over the entire incubation period. *Theriogenology*. (2008) 69:737–45. doi: 10.1016/j.theriogenology.2007.12.006

152. Balmori A. The incidence of electromagnetic pollution on the amphibian decline: is this an important piece of the puzzle? *Toxicol Environ Chem*. (2006) 88:287–99. doi: 10.1080/02772240600687200

153. Balmori A. Mobile phone mast effects on common frog (Rana temporaria) tadpoles: the city turned into a laboratory. *Electromagn Biol Med*. (2010) 29:31–5. doi: 10.3109/15368371003685363

154. Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, et al. A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer*. (2000) 83:692–8. doi: 10.1054/bjoc.2000.1376

155. Coghill RW, Steward J, Philips A. Extra low frequency electric and magnetic fields in the bed place of children diagnosed with leukaemia: a case-control study. *Eur J Cancer Prev*. (1996) 5:153–8. doi: 10.1097/00008469-199606000-00002

156. Coleman MP, Bell CM, Taylor HL, Primic-Zakelj M. Leukaemia and residence near electricity transmission equipment: a case-control study. *Br J Cancer*. (1989) 60:793–8. doi: 10.1038/bjc.1989.362

157. Draper G, Vincent T, Kroll ME, Swanson J. Childhood cancer in relation to distance from high voltage power lines in England and Wales: a case-control study. *BMJ*. (2005) 330:1290. doi: 10.1136/bmj.330.7503.1290

158. Feychting M, Ahlbom A. Magnetic fields and cancer in children residing near Swedish high - voltage power lines. *Am J Epidemiol*. (1993) 138:467–81. doi: 10.1093/oxfordjournals.aje.a116881

159. Feychting M, Ahlbom A. Magnetic fields, leukemia and central nervous system tumors in Swedish adults residing near high - voltage power lines. *Epidemiology*. (1994) 5:501–9.

160. Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood leukemia-EMF study group. *Epidemiology*. (2000) 11:624–34. doi: 10.1097/00001648-200011000-00003

161. Kheifets L, Ahlbom A, Crespi CM, Draper G, Hagihara J, Lowenthal RM, et al. Pooled analysis of recent studies on magnetic fields and childhood leukaemia. *Br J Cancer*. (2010) 103:1128–35.

162. Miller A, To T, Agnew DA, et al. Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers. *Am J Epidemiol*. (1996) 144:150–60. doi: 10.1093/oxfordjournals.aje.a008902

163. Savitz DA, Wachtel H, Barnes F, John EM, Tvrdik JG. Case-control study of childhood cancer and exposure to 60Hz magnetic fields. *Am J Epidemiol*. (1988) 128:21–38. doi: 10.1093/oxfordjournals.aje.a114943

164. Villeneuve PJ, Agnew DA, Miller AB, Corey PN. Non-Hodgkin's lymphoma among electric utility workers in Ontario: the evaluation of alternate indices of exposure to 60 Hz electric and magnetic fields. *Occup Environ Med*. (2000) 57:249–57. doi: 10.1136/oem.57.4.249

165. Villeneuve PJ, Agnew DA, Miller AB, Corey PN, Purdham JT. Leukemia in electric utility workers: the evaluation of alternative indices of exposure to 60 Hz electric and magnetic fields. *Am J Ind Med*. (2000) 37:607–17. doi: 10.1002/(SICI)1097-0274(200006)37:6<607::AID-AJIM5>3.0.CO;2-L

166. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. *Am J Epidemiol*. (1979) 109:273–84. doi: 10.1093/oxfordjournals.aje.a112681

167. Wertheimer N, Leeper E. Adult cancer related to electrical wires near the home. *Int J Epidemiol*. (1982) 11:345–55. doi: 10.1093/ije/11.4.345

168. Hallberg O, Johansson O. Melanoma incidence and frequency modulation (FM) broadcasting. *Arch Environ Health*. (2002) 57:32–40. doi: 10.1080/00039890209602914

169. López I, Félix N, Rivera M, Alonso A, Maestú C. What is the radiation before 5G? A correlation study between measurements in situ and in real time and epidemiological indicators in Vallecas, Madrid. *Environ Res*. (2021) 194:110734. doi: 10.1016/j.envres.2021.110734

170. Yakymenko I, Sidorik E, Kyrylenko S, Chekhun V. Long-term exposure to microwave radiation provokes cancer growth: evidences from radars and mobile communication systems. *Exp Oncol*. (2011) 33:62–70.

171. Yakymenko I, Tsybulin O. Carcinogenic effects of non-thermal exposure to wireless communication electromagnetic fields In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press (2022)

172. Gulati S, Yadav A, Kumar N, Kanupriya, Aggarwal NK, Kumar R, et al. Effect of GSTM1 and GSTT1 polymorphisms on genetic damage in humans populations exposed to radiation from Mobile towers. *Arch Environ Contam Toxicol*. (2016) 70:615–25. doi: 10.1007/s00244-015-0195-y

173. Zothansiama, Zosangzuali M, Lalramdinpuii M, Jagetia GC. Impact of radiofrequency radiation on DNA damage and antioxidants in peripheral blood lymphocytes of humans residing in the vicinity of mobile phone base stations. *Electromagn Biol Med*. (2017) 36:295–305. doi: 10.1080/15368378.2017.1350584

174. Carlberg M, Hardell L. Evaluation of Mobile phone and cordless phone use and glioma risk using the Bradford Hill viewpoints from 1965 on association or causation. *Biomed Res Int*. (2017) 2017:9218486–17. doi: 10.1155/2017/9218486

175. Hardell L, Carlberg M, Söderqvist F, Mild KH, Morgan LL. Long-term use of cellular phones and brain tumours: increased risk associated with use for > or =10 years. *Occup Environ Med*. (2007) 64:626–32. doi: 10.1136/oem.2006.029751

176. Hardell L, Carlberg M. Mobile phones, cordless phones and the risk for brain tumours. *Int J Oncol*. (2009) 35:5–17. doi: 10.3892/ijo_00000307

177. Hardell L, Carlberg M, Hansson MK. Epidemiological evidence for an association between use of wireless phones and tumor diseases. *Pathophysiology*. (2009) 16:113–22. doi: 10.1016/j.pathophys.2009.01.003

178. Hardell L, Carlberg M, Söderqvist F, Mild KH. Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. *Int J Oncol*. (2013) 43:1833–45. doi: 10.3892/ijo.2013.2111

179. Hardell L, Carlberg M, Hansson Mild K. Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. *Pathophysiology*. (2013) 20:85–110. doi: 10.1016/j.pathophys.2012.11.001

180. Hardell L. Effects of Mobile phones on Children's and Adolescents' health: a commentary. *Child Dev*. (2018) 89:137–40. doi: 10.1111/cdev.12831

181. Khurana VG, Teo C, Kundi M, Hardell L, Carlberg M. Cell phones and brain tumors: a review including the long-term epidemiologic data. *Surg Neurol*. (2009) 72:205–14. doi: 10.1016/j.surneu.2009.01.019

182. Miller AB, Morgan LL, Udasin I, Davis DL. Cancer epidemiology update, following the 2011 IARC evaluation of radiofrequency electromagnetic fields (monograph 102). *Environ Res*. (2018) 167:673–83. doi: 10.1016/j.envres.2018.06.043

183. Miller AB, Sears ME, Morgan LL, Davis DL, Hardell L, Oremus M, et al. Risks to health and well-being from radio-frequency radiation emitted by cell phones and other wireless devices. *Front Public Health*. (2019) 7:223. doi: 10.3389/fpubh.2019.00223

184. Momoli F, Siemiatycki J, McBride ML, Parent MÉ, Richardson L, Bedard D, et al. Probabilistic multiple-bias modeling applied to the Canadian data from the interphone study of mobile phone use and risk of glioma, meningioma, acoustic neuroma, and parotid gland tumors. *Am J Epidemiol*. (2017) 186:885–93. doi: 10.1093/aje/kwx157

185. Wang Y, Guo X. Meta-analysis of association between mobile phone use and glioma risk. *J Cancer Res Ther*. (2016) 12:298–C300. doi: 10.4103/0973-1482.200759

186. Navarro A, et al. The microwave syndrome: a preliminary study in Spain. *Electromagn Biol Med*. (2003) 22:161–9. doi: 10.1081/JBC-120024625

187. Santini R, Santini P, Danze JM, Le Ruz P, Seigne M. Study of the health of people living in the vicinity of mobile phone base stations: I. Influences of distance and sex. *Pathol Biol*. (2002) 50:369–73. doi: 10.1016/S0369-8114(02)00311-5

188. Salama OE, Abou El Naga RM. Cellular phones: are they detrimental? *J Egypt Public Health Assoc*. (2004) 79:197–223.

189. Abdel-Rassoul G, El-Fateh OA, Salem MA, Michael A, Farahat F, El-Batanouny M, et al. Neurobehavioral effects among inhabitants around mobile phone base stations. *Neurotoxicology*. (2007) 28:434–40. doi: 10.1016/j.neuro.2006.07.012

190. Belpomme D, Irigaray P. Electrohypersensitivity as a worldwide man-made electromagnetic pathology: a review of the medical evidence In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press (2022)

191. Blettner M, Schlehofer B, Breckenkamp J, Kowall B, Schmiedel S, Reis U, et al. Mobile phone base stations and adverse health effects: phase 1 of a population-based, cross-sectional study in Germany. *Occup Environ Med*. (2009) 66:118–23. doi: 10.1136/oem.2007.037721

192. Davis D, Birnbaum L, Ben-Ishai P, Taylor H, Sears M, Butler T, et al. Wireless technologies, non-ionizing electromagnetic fields and children: identifying and reducing health risks. *Curr Probl Pediatr Adolesc Health Care*. (2023) 53:101374. doi: 10.1016/j.cppeds.2023.101374

193. Greco F, Garnier O, Macioce V, Picot MC. Prevalence of migraine disease in Electrohypersensitive patients. *J Clin Med*. (2023) 12:4092. doi: 10.3390/jcm12124092

194. Hutter H-P, Moshammer H, Wallner P, Kundi M. Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. *Occup Environ Med*. (2006) 63:307–13. doi: 10.1136/oem.2005.020784

195. Kundi M, Hutter HP. Mobile phone base stations-effects on wellbeing and health. *Pathophysiology*. (2009) 16:123–35. doi: 10.1016/j.pathophys.2009.01.008

196. Viel JF, Clerc S, Barrera C, Rymzhanova R, Moissonnier M, Hours M, et al. Residential exposure to radiofrequency fields from mobile phone base stations, and broadcast transmitters: a population-based survey with personal meter. *Occup Environ Med*. (2009) 66:550–6. doi: 10.1136/oem.2008.044180

197. Irigaray P, Caccamo D, Belpomme D. Oxidative stress in electrohypersensitivity self-reporting patients: results of a prospective in vivo investigation with comprehensive molecular analysis. *Int J Mol Med*. (2018) 42:1885–98. doi: 10.3892/ijmm.2018.3774

198. Hardell L, Nilsson M. Summary of seven Swedish case reports on the microwave syndrome associated with 5G radiofrequency radiation. *Rev Environ Health*. (2024) 40:147–57. doi: 10.1515/reveh-2024-0017

199. Hardell L, Koppel T. Spots with extremely high radiofrequency radiation after deployment of 5G base stations in Stockholm, Sweden. *Ann Clin Med Case Rep*. (2024) V14:1–8.

200. Lerchl A, Klose M, Grote K, Wilhelm AFX, Spathmann O, Fiedler T, et al. Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans. *Biochem Biophys Res Commun*. (2015) 459:585–90. doi: 10.1016/j.bbrc.2015.02.151

201. Tillmann T, Ernst H, Streckert J, Zhou Y, Taugner F, Hansen V, et al. Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model. *Int J Radiat Biol*. (2010) 86:529–41. doi: 10.3109/09553001003734501

202. NTP. Toxicology and carcinogenesis studies in Hsd: Sprague Dawley SD rats exposed to whole-body radio frequency radiation at a frequency (900 MHz) and modulations (GSM and CDMA) used by cell phones. USA: NTP TR 595, Department of Health and Human Services (2018).

203. Falcioni L, Bua L, Tibaldi E, Lauriola M, de Angelis L, Gnudi F, et al. Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8GHz GSM base station environmental emission. *Environ Res*. (2018) 165:496–503. doi: 10.1016/j.envres.2018.01.037

204. IARC. Non-ionizing radiation, part 1: static and extremely low-frequency (ELF) electric and magnetic fields, vol. *80*. Lyon, France: International Agency for Research on Cancer. (2002).

205. IARC. Non-ionizing radiation, part 2: radiofrequency electromagnetic fields, vol. *102*. Lyon, France: International Agency for Research on Cancer. (2013).

206. Leach V, Weller S, Redmayne M. A novel database of bio-effects from non-ionizing radiation. *Rev Environ Health*. (2018) 33:273–80. doi: 10.1515/reveh-2018-0017

207. Lerchl A, Klose M, Drees K. No increased DNA damage observed in the brain, liver, and lung of fetal mice treated with Ethylnitrosourea and exposed to UMTS radiofrequency electromagnetic fields. *Bioelectromagnetics*. (2020) 41:611–6. doi: 10.1002/bem.22301

208. Manna D, Ghosh R. Effect of radiofrequency radiation in cultured mammalian cells: a review. *Electromagn Biol Med*. (2016) 35:265–301. doi: 10.3109/15368378.2015.1092158

209. Panagopoulos DJ, Johansson O, Carlo GL. Real versus simulated Mobile phone exposures in experimental studies. *Biomed Res Int*. (2015) 2015:607053. doi: 10.1155/2015/607053

210. Panagopoulos DJ, Yakymenko I, Chrousos GP. Electromagnetic field-induced dysfunction of voltage-gated ion channels, oxidative stress, DNA damage, and related pathologies In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press (2022)

211. Schuermann D, Ziemann C, Barekati Z, Capstick M, Oertel A, Focke F, et al. Assessment of Genotoxicity in human cells exposed to modulated electromagnetic fields of wireless communication devices. *Genes*. (2020) 11:347. doi: 10.3390/genes11040347

212. Verschaeve L. Misleading scientific papers on health effects from wireless communication devices In: CD Geddes, editor. Microwave effects on DNA and proteins. Cham, Switzerland: Springer. (2017)

213. Wood A, Mate R, Karipidis K. Meta-analysis of in vitro and in vivo studies of the biological effects of low-level millimetre waves. *J Expo Sci Environ Epidemiol*. (2021) 31:606–13. doi: 10.1038/s41370-021-00307-7

214. McCredden JE, Cook N, Weller S, Leach V. Wireless technology is an environmental stressor requiring new understanding and approaches in health care. *Front Public Health*. (2022) 10:986315. doi: 10.3389/fpubh.2022.986315

215. McCredden JE, Weller S, Leach V. The assumption of safety is being used to justify the rollout of 5G technologies. *Front Public Health*. (2023) 11:1058454. doi: 10.3389/fpubh.2023.1058454

216. Panagopoulos DJ. Mobile telephony radiation effects on insect ovarian cells. The necessity for real exposures bioactivity assessment. The key role of polarization, and the ion forced-oscillation mechanism In: CD Geddes, editor. Microwave effects on DNA and proteins. Cham, Switzerland: Springer (2017) 1–48.

217. Frank JW. Electromagnetic fields, 5G and health: what about the precautionary principle? *J Epidemiol Community Health*. (2021) 75:562–6. doi: 10.1136/jech-2019-213595

218. Hardell L, Nyberg R. Appeals that matter or not on a moratorium on the deployment of the fifth generation, 5G, for microwave radiation. *Mol Clin Oncol*. (2020) 12:247–57. doi: 10.3892/mco.2020.1984

219. Hardell L, Carlberg M. Health risks from radiofrequency radiation, including 5G, should be assessed by experts with no conflicts of interest. *Oncol Lett*. (2020) 20:15. doi: 10.3892/ol.2020.11876

220. Hardell L, Carlberg M. Lost opportunities for cancer prevention: historical evidence on early warnings with emphasis on radiofrequency radiation. *Rev Environ Health*. (2021) 36:585–97. doi: 10.1515/reveh-2020-0168

221. Harremoes P, Gee D, MacGarvin M, Stirling A, Keys J, Wynne B, et al. The precautionary principle in the 20th century: late lessons from early warnings. London: Routledge (2013).

222. ICNIRP. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). *Health Phys*. (1998) 74:494–521.

223. ICNIRP. Guidelines for limiting exposure to time-varying electric and magnetic fields (1Hz to 100 kHz). *Health Phys*. (2010) 99:818–36.

224. ICNIRP. Guidelines for limiting exposure to electromagnetic fields (100 kHz to 300 GHz). *Health Phys*. (2020) 118:483–524.

225. Ishai PB, Baldwin HZ, Birnbaum LS, Butler T, Chamberlin K, Davis DL, et al. Applying the precautionary principle to wireless technology: policy dilemmas and systemic risks. *Environ Sci Policy Sustain Dev*. (2024) 66:5–18. doi: 10.1080/00139157.2024.2293631

226. Read R, O'Riordan T. The precautionary principle under fire. *Environ Sci Policy Sustain Dev*. (2017) 59:4–15. doi: 10.1080/00139157.2017.1350005

227. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al. WHO International Agency for Research on Cancer monograph working group: carcinogenicity of radiofrequency electromagnetic fields. *Lancet Oncol*. (2011) 12:624–6. doi: 10.1016/S1470-2045(11)70147-4

228. Nyberg NR, McCredden JE, Weller SG, Hardell L. The European Union prioritises economics over health in the rollout of radiofrequency technologies. *Rev Environ Health*. (2024) 39:47–64. doi: 10.1515/reveh-2022-0106

229. Francis G. Ionization phenomena in gases. London: Butterworths Scientific Publications (1960).

230. Gomer R. Field emission and field ionization. USA: Harvard University Press (1961).

231. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Molecular biology of the cell. New York, USA: Garland Publishing, Inc (1994).

232. Finkel T. Signal transduction by reactive oxygen species. *J Cell Biol*. (2011) 194:7–15. doi: 10.1083/jcb.201102095

233. Görlach A, Bertram K, Hudecova S, Krizanova O. Calcium and ROS: a mutual interplay. *Redox Biol*. (2015) 6:260–71. doi: 10.1016/j.redox.2015.08.010

234. Stryer L. Biochemistry. New York: Freeman (1995).

235. Inoue M, Sato EF, Nishikawa M, Park AM, Kira Y, Imada I, et al. Mitochondrial generation of reactive oxygen species and its role in aerobic life. *Curr Med Chem*. (2003) 10:2495–505. doi: 10.2174/0929867033456477

236. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. *Chem Biol Interact*. (2014) 224:164–75. doi: 10.1016/j.cbi.2014.10.016

237. Ischiropoulos H, Zhu L, Beckman JS. Peroxynitrite formation from macrophage-derived nitric oxide. *Arch Biochem Biophys*. (1992) 298:446–51. doi: 10.1016/0003-9861(92)90433-W

238. Pall ML. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med*. (2013) 17:958–65. doi: 10.1111/jcmm.12088

239. Schuermann D, Mevissen M. Manmade electromagnetic fields and oxidative stress—biological effects and consequences for health. *Int J Mol Sci*. (2021) 22:3772. doi: 10.3390/ijms22073772

240. Checa J, Aran JM. Reactive oxygen species: drivers of physiological and pathological processes. *J Inflamm Res*. (2020) 13:1057–73. doi: 10.2147/JIR.S275595

241. Andrés CMC, Pérez de la Lastra JM, Andrés Juan C, Plou FJ, Pérez-Lebeña E. Superoxide anion chemistry—its role at the core of the innate immunity. *Int J Mol Sci*. (2023) 24:1841. doi: 10.3390/ijms24031841

242. Koppers AJ, De Iuliis GN, Finnie JM, McLaughlin EA, Aitken RJ. Significance of mitochondrial reactive oxygen species in the generation of oxidative stress in spermatozoa. *J Clin Endocrinol Metabol*. (2008) 93:3199–207. doi: 10.1210/jc.2007-2616

243. Gibb Z, Griffin RA, Aitken RJ, De Iuliis GN. Functions and effects of reactive oxygen species in male fertility. *Anim Reprod Sci*. (2020) 220:106456. doi: 10.1016/j.anireprosci.2020.106456

244. Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. *Am J Physiol Cell Physiol*. (2004) 287:C817–33. doi: 10.1152/ajpcell.00139.2004

245. Bertero E, Maack C. Calcium signaling and reactive oxygen species in mitochondria. *Circ Res*. (2018) 122:1460–78. doi: 10.1161/CIRCRESAHA.118.310082

246. Lowe SW, Lin AW. Apoptosis in cancer. *Carcinogenesis*. (2000) 21:485–95. doi: 10.1093/carcin/21.3.485

247. Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiol Rev*. (2007) 87:245–313. doi: 10.1152/physrev.00044.2005

248. Gamaley I, Augsten K, Berg H. Electrostimulation of macrophage NADPH oxidase by modulated high-frequency electromagnetic fields. *Bioelectrochem Bioenerg*. (1995) 38:415–8. doi: 10.1016/0302-4598(95)01836-4

249. Iverson D, De Chatelet LR, Spitznagel JK, Wang P. Comparison of NADH and NADPH oxidase activities in granules isolated from human polymorphonuclear leukocytes with a fluorometric assay. *J Clin Invest*. (1977) 59:282–90. doi: 10.1172/JCI108639

250. Li JM, Shah AM. Differential NADPH- versus NADH-dependent superoxide production by phagocyte-type endothelial cell NADPH oxidase. *Cardiovasc Res*. (2001) 52:477–86. doi: 10.1016/s0008-6363(01)00407-2

251. Panday A, Sahoo MK, Osorio D, Batra S. NADPH oxidases: an overview from structure to innate immunity-associated pathologies. *Cell Mol Immunol*. (2015) 12:5–23. doi: 10.1038/cmi.2014.89

252. Cross AR, Segal AW. The NADPH oxidase of professional phagocytes—prototype of the NOX electron transport chain systems. *Biochim Biophys Acta*. (2004) 1657:1–22. doi: 10.1016/j.bbabio.2004.03.008

253. Henderson LM. NADPH oxidase subunit gp91phox: a proton pathway. *Protoplasma*. (2001) 217:37–42. doi: 10.1007/BF01289411

254. Musset B, Cherny VV, Morgan D, De Coursey TE. The intimate and mysterious relationship between proton channels and NADPH oxidase. *FEBS Lett*. (2009) 583:7–12. doi: 10.1016/j.febslet.2008.12.005

255. André-Lévigne D, Modarressi A, Pepper MS, et al. Reactive oxygen species and NOX enzymes are emerging as key players in cutaneous wound repair. *Int J Mol Sci*. (2017) 18:2149. doi: 10.3390/ijms18102149

256. Fang J, Sheng R, Qin Z-H. NADPH oxidases in the central nervous system: regional and cellular localization and the possible link to brain diseases. *Antioxid Redox Signal*. (2021) 35:951–73. doi: 10.1089/ars.2021.0040

257. Friedman J, Kraus S, Hauptman Y, Schiff Y, Seger R. Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. *Biochem J*. (2007) 405:559–68. doi: 10.1042/BJ20061653

258. Pacher P, Beckman JS, Liaudet L. Nitric oxide and Peroxynitrite in health and disease. *Physiol Rev*. (2007) 87:315–424. doi: 10.1152/physrev.00029.2006

259. Pilla AA. Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. *Biochem Biophys Res Commun*. (2012) 426:330–3. doi: 10.1016/j.bbrc.2012.08.078

260. Lai H, Singh NP. Magnetic-field-induced DNA strand breaks in brain cells of the rat. *Environ Health Perspect*. (2004) 112:687–94. doi: 10.1289/ehp.6355

261. Moon HK, Yang ES, Park JW. Protection of peroxynitrite-induced DNA damage by dietary antioxidants. *Arch Pharm Res*. (2006) 29:213–7. doi: 10.1007/BF02969396

262. Sakihama Y, Maeda M, Hashimoto M, Tahara S, Hashidoko Y. Beetroot betalain inhibits peroxynitrite- mediated tyrosine nitration and DNA strand damage. *Free Radic Res*. (2012) 46:93–9. doi: 10.3109/10715762.2011.641157

263. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J*. (2012) 33:829–37. doi: 10.1093/eurheartj/ehr304

264. Bortolotti M, Polito L, Battelli MG, Bolognesi A. Xanthine oxidoreductase: one enzyme for multiple physiological tasks. *Redox Biol*. (2021) 41:101882. doi: 10.1016/j.redox.2021.101882

265. Manikandan P, Nagini S. Cytochrome P450 structure, function and clinical significance: a review. *Curr Drug Targets*. (2018) 19:38–54. doi: 10.2174/1389450118666170125144557

266. Becchetti A. Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer. *Am J Phys Cell Phys*. (2011) 301:C255–65.

267. Lang F, Föller M, Lang KS, Lang PA, Ritter M, Gulbins E, et al. Ion channels in cell proliferation and apoptotic cell death. *J Membr Biol*. (2005) 205:147–57. doi: 10.1007/s00232-005-0780-5

268. Chattipakorn N, Kumfu S, Fucharoen S, Chattipakorn S. Calcium channels and iron uptake into the heart. *World J Cardiol*. (2011) 3:215–8. doi: 10.4330/wjc.v3.i7.215

269. Gaasch JA, Geldenhuys WJ, Lockman PR, Allen DD, Van der Schyf CJ. Voltage-gated calcium channels provide an alternate route for Iron uptake in neuronal cell cultures. *Neurochem Res*. (2007) 32:1686–93. doi: 10.1007/s11064-007-9313-1

270. Salsbury G, Cambridge EL, McIntyre Z, Arends MJ, Karp NA, Isherwood C, et al. Disruption of the potassium channel regulatory subunit KCNE2 causes iron-deficient anemia. *Exp Hematol*. (2014) 42:1053–1058.e1. doi: 10.1016/j.exphem.2014.07.269

271. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Membrane transport of small molecules and the electrical properties of membranes-molecular biology of the cell. New York, USA: Garland Science (2002).

272. Blank M, Soo L. Ion activation of the Na, K-ATPase in alternating currents. *Bioelectrochem Bioenerg*. (1990) 24:51–61. doi: 10.1016/0302-4598(80)85006-9

273. Serpersu EH, Tsong TY. Activation of electrogenic Rb transport of (Na/K)-ATPase by an electric field. *J Biol Chem*. (1984) 259:7155–62. doi: 10.1016/S0021-9258(17)39851-4

274. Pratt RD, Brickman CR, Cottrill CL, Shapiro JI, Liu J. The Na/K-ATPase signaling: from specific ligands to general reactive oxygen species. *Int J Mol Sci*. (2018) 19:2600. doi: 10.3390/ijms19092600

275. Zhang L, Zhang Z, Guo H, Wang Y. Na^+/K^+-ATPase-mediated signal transduction and Na+/K+-ATPase regulation. *Fundam Clin Pharmacol*. (2008) 22:615–21. doi: 10.1111/j.1472-8206.2008.00620.x

276. Prasad KN. Handbook of radiobiology. *2nd* ed. Boca Raton: CRC Press (1995).

277. Barzilai A, Yamamoto K. DNA damage responses to oxidative stress. *DNA Repair*. (2004) 3:1109–15. doi: 10.1016/j.dnarep.2004.03.002

278. Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB J*. (2003) 17:1195–214. doi: 10.1096/fj.02-0752rev

279. Sillar JR, Germon ZP, De Iuliis GN, Dun MD. The role of reactive oxygen species in acute myeloid leukaemia. *Int J Mol Sci*. (2019) 20:6003. doi: 10.3390/ijms20236003

280. Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol*. (2007) 39:44–84. doi: 10.1016/j.biocel.2006.07.001

281. Burney S, Caulfield JL, Niles JC, Wishnok JS, Tannenbaum SR. The chemistry of DNA damage from nitric oxide and peroxynitrite. *Mutat Res*. (1999) 424:37–49. doi: 10.1016/S0027-5107(99)00006-8

282. Yu H, Venkatarangan L, Wishnok JS, Tannenbaum SR. Quantitation of four guanine oxidation products from reaction of DNA with varying doses of Peroxynitrite. *Chem Res Toxicol*. (2005) 18:1849–57. doi: 10.1021/tx050146h

283. Szabo G, Baehrle S. Role of nitrosative stress and poly(ADP-ribose) polymerase activation in myocardial reperfusion injury. *Curr Vasc Pharmacol*. (2005) 3:215–20. doi: 10.2174/1570161054368599

284. Lymar SV, Khairutdinov RF, Hurst JK. Hydroxyl radical formation by O-O bond homolysis in peroxynitrous acid. *Inorg Chem*. (2003) 42:5259–66. doi: 10.1021/ic030104l

285. Pérez de la Lastra JM, Juan CA, Plou FJ, Pérez-Lebeña E. The nitration of proteins, lipids and DNA by peroxynitrite derivatives-chemistry involved and biological relevance. *Stress*. (2022) 2:53–64. doi: 10.3390/stresses2010005

286. De Coursey T, Morgan D, Cherny V. The voltage dependence of NADPH oxidase reveals why phagocytes need proton channels. *Nature*. (2003) 422:531–4. doi: 10.1038/nature01523

287. Balasubramanian B, Pogozelski WK, Tullius TD. DNA strand breaking by hydroxyl radical is governed by the accessible surface area of the hydrogen atom of the DNA backbone. *PNAS*. (1998) 95:9738–43. doi: 10.1073/pnas.95.17.9738

288. Cadet J, Delatour T, Douki T, Gasparutto D, Pouget JP, Ravanat JL, et al. Hydroxyl radicals and DNA base damage. *Mutat Res*. (1999) 424:9–21. doi: 10.1016/S0027-5107(99)00004-4

289. Cadet J, Wagner JR. DNA base damage by reactive oxygen species, oxidizing agents, and UV radiation. *Cold Spring Harb Perspect Biol*. (2013) 5:a012559. doi: 10.1101/cshperspect.a012559

290. Halliwell B. Biochemistry of oxidative stress. *Biochem Soc Trans*. (2007) 35:1147–50. doi: 10.1042/BST0351147

291. Tsunoda M, Sakaue T, Naito S, Sunami T, Abe N, Ueno Y, et al. Insights into the structures of DNA damaged by hydroxyl radical: crystal structures of DNA duplexes containing 5-formyluracil. *J Nucleic Acids*. (2010) 2010:107289. doi: 10.4061/2010/107289

292. Fenton HJH. Oxidation of tartaric acid in presence of iron. *J Chem Soc Trans*. (1894) 65:899–910. doi: 10.1039/CT8946500899

293. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact*. (2006) 160:1–40. doi: 10.1016/j.cbi.2005.12.009

294. Casarett AP. Radiation biology. New Jersey: Prentice-Hall Inc (1968).

295. Coggle JE. Biological effects of radiation. London: Taylor & Francis (1983).

296. Abolfath RM, Van Duin ACT, Brabec T. Reactive molecular dynamics study on the first steps of DNA damage by free hydroxyl radicals. *Chem A Eur J*. (2011) 115:11045–9. doi: 10.1021/jp204894m

297. Panagopoulos DJ, Karabarbounis A, Chrousos GP. Biophysical mechanism of animal magnetoreception, orientation and navigation. *Sci Rep*. (2024) 14:30053. doi: 10.1038/s41598-024-77883-9

298. Bertagna F, Lewis R, Silva SRP, McFadden J, Jeevaratnam K. Effects of electromagnetic fields on neuronal ion channels: a systematic review. *Ann N Y Acad Sci*. (2021) 1499:82–103. doi: 10.1111/nyas.14597

299. Liman ER, Hess P, Weaver F, Koren G. Voltage sensing residues in the S4 region of a mammalian K^+ channel. *Nature*. (1991) 353:752–6. doi: 10.1038/353752a0

300. Miller C. An overview of the potassium channel family. *Genome Biol*. (2000) 1:reviews0004.1. doi: 10.1186/gb-2000-1-4-reviews0004

301. Noda M, Ikeda T, Kayano T, Suzuki H, Takeshima H, Kurasaki M, et al. Existence of distinct sodium channel messenger RNAs in rat brain. *Nature*. (1986) 320:188–92. doi: 10.1038/320188a0

302. Panagopoulos DJ. Mechanism of ion forced-oscillation and voltage-gated ion channel dysfunction by polarized and coherent electromagnetic fields In: DJ Panagopoulos, editor. Electromagnetic fields of wireless communications: biological and health effects. Boca Raton: CRC Press, Taylor and Francis (2022)

303. Sandipan C, Baron C. Basic mechanisms of voltage sensing In: J Zheng and MC Trudeau, editors. Handbook of ion channels. Boca Raton: CRC Press (2015)

304. Zhang XC, Yang H, Liu Z, Sun F. Thermodynamics of voltage-gated ion channels. *Biophys Rep*. (2018) 4:300–19. doi: 10.1007/s41048-018-0074-y

305. Panagopoulos DJ, Messini N, Karabarbounis A, Filippetis AL, Margaritis LH. A mechanism for action of oscillating electric fields on cells. *Biochem Biophys Res Commun*. (2000) 272:634–40. doi: 10.1006/bbrc.2000.2746

306. Panagopoulos DJ, Karabarbounis A, Margaritis LH. Mechanism for action of electromagnetic fields on cells. *Biochem Biophys Res Commun*. (2002) 298:95–102. doi: 10.1016/S0006-291X(02)02393-8

307. Balcavage WX, Alvager T, Swez J, Goff CW, Fox MT, Abdullyava S, et al. A mechanism for action of extremely low frequency electromagnetic fields on biological systems. *Biochem Biophys Res Commun*. (1996) 222:374–8. doi: 10.1006/bbrc.1996.0751

308. Honig BH, Hubbell WL, Flewelling RF. Electrostatic interactions in membranes and proteins. *Ann Rev Biophys Biophys Chem*. (1986) 15:163–93. doi: 10.1146/annurev.bb.15.060186.001115

309. Cleary SF, Liu LM, Graham R, Diegelmann RF. Modulation of tendon fibroplasia by exogenous electric currents. *Bioelectromagnetics*. (1988) 9:183–94. doi: 10.1002/bem.2250090210

310. McLeod KJ, Lee RC, Ehrlich HP. Frequency dependence of electric field modulation of fibroblast protein synthesis. *Science*. (1987) 236:1465–9. doi: 10.1126/science.3589667

311. England SJ, Robert D. The ecology of electricity and electroreception. *Biol Rev*. (2022) 97:383–413. doi: 10.1111/brv.12804

312. Johnsen S, Lohmann KJ. Magnetoreception in animals. *Phys Today*. (2008) 61:29–35. doi: 10.1063/1.2897947

313. Cecchetto C, Maschietto M, Boccaccio P, Vassanelli S. Electromagnetic field affects the voltage-dependent potassium channel Kv1.3. *Electromagn Biol Med*. (2020) 39:316–22. doi: 10.1080/15368378.2020.1799386

314. El-Swefy S, Soliman H, Huessein M. Calcium channel blockade alleviates brain injury induced by long-term exposure to an electromagnetic field. *J Appl Biomed*. (2008) 6:153–63. doi: 10.32725/jab.2008.019

315. Liburdy RP. Calcium signaling in lymphocytes and ELF fields. *FEBS Lett*. (1992) 301:53–9. doi: 10.1016/0014-5793(92)80209-Y

316. Piacentini R, Ripoli C, Mezzogori D, Azzena GB, Grassi C. Extremely low-frequency electromagnetic fields promote in vitro neurogenesis via upregulation of Ca_v1-channel activity. *J Cell Physiol*. (2008) 215:129–39. doi: 10.1002/jcp.21293

317. Zheng Y, Xia P, Dong L, Tian L, Xiong C. Effects of modulation on sodium and potassium channel currents by extremely low frequency electromagnetic fields stimulation on hippocampal CA1 pyramidal cells. *Electromagn Biol Med*. (2021) 40:274–85. doi: 10.1080/15368378.2021.1885433

318. Orfali R, Alwatban AZ, Orfali RS, Lau L, Chea N, Alotaibi AM, et al. Oxidative stress and ion channels in neurodegenerative diseases. *Front Physiol*. (2024) 15:1320086. doi: 10.3389/fphys.2024.1320086

319. Batcioglu K, Uyumlu AB, Satilmis B, Yildirim B, Yucel N, Demirtas H, et al. Oxidative stress in the in vivo DMBA rat model of breast cancer: suppression by a voltage-gated Sodium Channel inhibitor (RS100642). *Basic Clin Pharmacol Toxicol*. (2012) 111:137–41. doi: 10.1111/j.1742-7843.2012.00880.x

320. Afanas'ev I. New nucleophilic mechanisms of ROS-dependent epigenetic modifications: comparison of aging and cancer. *Aging Dis*. (2014) 5:52–62. doi: 10.14336/AD.2014.050052

321. Ramírez A, Vázquez-Sánchez AY, Carrión-Robalino N, Camacho J. Ion channels and oxidative stress as a potential link for the diagnosis or treatment of liver diseases. *Oxidative Med Cell Longev*. (2016) 2016:3928714. doi: 10.1155/2016/3928714

322. O'Hare Doig RL, Chiha W, Giacci MK, Yates NJ, Bartlett CA, Smith NM, et al. Specific ion channels contribute to key elements of pathology during secondary degeneration following neurotrauma. *BMC Neurosci*. (2017) 18:62. doi: 10.1186/s12868-017-0380-1

323. Esteras N, Kundel F, Amodeo GF, Pavlov EV, Klenerman D, Abramov AY. Insoluble tau aggregates induce neuronal death through modification of membrane ion conductance, activation of voltage-gated calcium channels and NADPH oxidase. *FEBS J*. (2021) 288:127–41. doi: 10.1111/febs.15340

324. Fouda MA, Ghovanloo MR, Ruben PC. Cannabidiol protects against high glucose-induced oxidative stress and cytotoxicity in cardiac voltage-gated sodium channels. *Br J Pharmacol*. (2020) 177:2932–46. doi: 10.1111/bph.15020

325. Thomas MP, Chartrand K, Reynolds A, Vitvitsky V, Banerjee R, Gendelman HE. Ion channel blockade attenuates aggregated alpha synuclein induction of microglial reactive oxygen species: relevance for the pathogenesis of Parkinson's disease. *J Neurochem*. (2007) 100:503–19. doi: 10.1111/j.1471-4159.2006.04315.x

326. Li M, Lester HA. Ion Channel diseases of the central nervous system. *CNS Drug Rev*. (2001) 7:214–40. doi: 10.1111/j.1527-3458.2001.tb00196.x

327. Huang H, Shakkottai VG. Targeting ion channels and Purkinje neuron intrinsic membrane excitability as a therapeutic strategy for cerebellar Ataxia. *Life*. (2023) 13:1350. doi: 10.3390/life13061350

328. Kourie JI. Interaction of reactive oxygen species with ion transport mechanisms. *Am J Phys*. (1998) 275:C1–C24.

329. Lombardi AA, Gibb AA, Arif E, Kolmetzky DW, Tomar D, Luongo TS, et al. Mitochondrial calcium exchange links metabolism with the epigenome to control cellular differentiation. *Nat Commun*. (2019) 10:1–17. doi: 10.1038/s41467-019-12103-x

330. Patergnani S, Danese A, Bouhamida E, Aguiari G, Previati M, Pinton P, et al. Various aspects of calcium signaling in the regulation of apoptosis, autophagy, cell proliferation, and cancer. *Int J Mol Sci*. (2020) 21:8323. doi: 10.3390/ijms21218323

331. Akbarali HI. Oxidative stress and ion channels In: I Lahers, editor. Systems biology of free radicals and antioxidants. Berlin, Heidelberg: Springer. (2014) 355–73.

332. Nitahara JA, Cheng W, Liu Y, Li B, Leri A, Li P, et al. Intracellular calcium, DNase activity and myocyte apoptosis in aging Fischer 344 rats. *J Mol Cell Cardiol*. (1998) 30:519–35. doi: 10.1006/jmcc.1997.0616

333. Bawin SM, Adey WR. Sensitivity of calcium binding in cerebral tissue to weak environmental electric fields oscillating at low frequency. *Proc Natl Acad Sci USA*. (1976) 73:1999–2003.

334. Barbier E, Vetret B, Dufy B. Stimulation of Ca2+ influx in rat pituitary cells under exposure to a 50 Hz magnetic field. *Bioelectromagnetics*. (1996) 17:303–11. doi: 10.1002/(SICI)1521-186X(1996)17:4<303::AID-BEM6>3.0.CO;2-7

335. Dutta SK, Subramaniam A, Ghosh B, Parshad R. Microwave radiation - induced calcium ion efflux from human neuroblastoma cells in culture. *Bioelectromagnetics*. (1984) 5:71–8. doi: 10.1002/bem.2250050108

336. Gobba F, Malagoli D, Ottaviani E. Effects of 50 Hz magnetic fields on fMLP-induced shape changes in invertebrate immunocytes: the role of calcium ion channels. *Bioelectromagnetics*. (2003) 24:277–82. doi: 10.1002/bem.10102

337. Grassi C, D'Ascenzo M, Torsello A, Martinotti G, Wolf F, Cittadini A, et al. Effects of 50 Hz electromagnetic fields on voltage-gated Ca^{2+} channels and their role in modulation of neuroendocrine cell proliferation and death. *Cell Calcium*. (2004) 35:307–15. doi: 10.1016/j.ceca.2003.09.001

338. Jeong JH, Kum C, Choi HJ, Park ES, Sohn UD. Extremely low frequency magnetic field induces hyperalgesia in mice modulated by nitric oxide synthesis. *Life Sci*. (2006) 78:1407–12. doi: 10.1016/j.lfs.2005.07.006

339. Lisi A, Ledda M, Rosola E, Pozzi D, Emilia ED', Giuliani L, et al. Extremely low frequency electromagnetic field exposure promotes differentiation of pituitary corticotrope-derived AtT20 D16V cells. *Bioelectromagnetics*. (2006) 27:641–51. doi: 10.1002/bem.20255

340. Marchionni I, Paffi A, Pellegrino M, Liberti M, Apollonio F, Abeti R, et al. Comparison between low-level 50 Hz and 900 MHz electromagnetic stimulation on single channel ionic currents and on firing frequency in dorsal root ganglion isolated neurons. *Biochim Biophys Acta*. (2006) 1758:597–605. doi: 10.1016/j.bbamem.2006.03.014

341. Morgado-Valle C, Verdugo-Dıaz L, Garcıa DE, et al. The role of voltage-gated Ca^{2+} channels in neurite growth of cultured chromaffin cells induced by extremely low frequency (ELF) magnetic field stimulation. *Cell Tissue Res*. (1998) 291:217–30. doi: 10.1007/s004410050992

342. De Coursey TE. Interactions between NADPH oxidase and voltage-gated proton channels: why electron transport depends on proton transport. *FEBS Lett*. (2003) 555:57–61. doi: 10.1016/S0014-5793(03)01103-7

343. Seredenina T, Demaurex N, Krause KH. Voltage-gated proton channels as novel drug targets: from NADPH oxidase regulation to sperm biology. *Antioxid Redox Sign*. (2015) 23:490–513. doi: 10.1089/ars.2013.5806

344. Sesti F, Liu S, Cai SQ. Oxidation of potassium channels by ROS: a general mechanism of aging and neurodegeneration? *Trends Cell Biol*. (2010) 20:45–51. doi: 10.1016/j.tcb.2009.09.008

345. Panagopoulos DJ, Margaritis LH. Theoretical considerations for the biological effects of electromagnetic fields In: P Stavroulakis, editor. Biological effects of electromagnetic fields: Springer (2003). 5–33.

346. Hall EJ, Giaccia AJ. Radiobiology for the radiologist. Philadelphia: Lippincott Williams & Wilkins (2006).

347. Nias AHW. An introduction to radiobiology. Chichester: J. Wiley & Sons (1998).

348. Reisz JA, Bansal N, Qian J, Zhao W, Furdui CM. Effects of ionizing radiation on biological molecules—mechanisms of damage and emerging methods of detection. *Antioxid Redox Signal*. (2014) 21:260–92. doi: 10.1089/ars.2013.5489

349. Kiselyov K, Muallem S. ROS and intracellular ion channels. *Cell Calcium*. (2016) 60:108–14. doi: 10.1016/j.ceca.2016.03.004

350. Blaustein MP, Lederer WJ. Sodium/calcium exchange: its physiological implications. *Physiol Rev*. (1999) 79:763–854. doi: 10.1152/physrev.1999.79.3.763

351. Maliszewska-Olejniczak K, Bednarczyk P. Novel insights into the role of ion channels in cellular DNA damage response. *Mutation Res*. (2024) 793:108488. doi: 10.1016/j.mrrev.2024.108488

352. De Luca C, Thai JC, Raskovic D, et al. Metabolic and genetic screening of electromagnetic hypersensitive subjects as a feasible tool for diagnostics and intervention. *Mediat Inflamm*. (2014) 2014:924184

353. Baek S, Quan X, Kim S, Lengner C, Park JK, Kim J. Electromagnetic fields mediate efficient cell reprogramming into a pluripotent state. *ACS Nano*. (2014) 8:10125–38. doi: 10.1021/nn502923s

354. Giorgi G, Del Re B. Epigenetic dysregulation in various types of cells exposed to extremely low-frequency magnetic fields. *Cell Tissue Res*. (2021) 386:1–15. doi: 10.1007/s00441-021-03489-6

355. Liu Y, Liu WB, Liu KJ, Ao L, Zhong JL, Cao J, et al. Effect of 50 Hz extremely low frequency electromagnetic fields on the DNA methylation and DNA methyltransferases in mouse spermatocyte-derived cell line GC-2. *Biomed Res Int*. (2015) 2015:237183:1–10. doi: 10.1155/2015/237183

356. Kaur RP, Kaur P, Munshi A. Epigenetic instability caused by oxidative stress triggers tumorigenesis In: S Chakraborti, BK Ray and S Roychoudhury, editors. Handbook of oxidative stress in cancer: Mechanistic aspects. Singapore: Springer (2022). 1639–55.

357. Nishida N, Kudo M. Oxidative stress and epigenetic instability in human hepatocarcinogenesis. *Dig Dis*. (2013) 31:447–53. doi: 10.1159/000355243

358. Chalidis B, Sachinis N, Assiotis A, Maccauro G, Graziani F. Stimulation of bone formation and fracture healing with pulsed electromagnetic fields: biologic responses and clinical implications. *Int J Immunopathol Pharmacol*. (2011) 24:17–20. doi: 10.1177/03946320110241S204

359. Daish C, Blanchard R, Fox K, Pivonka P, Pirogova E. The application of pulsed electromagnetic fields (PEMFs) for bone fracture repair: past and perspective findings. *Ann Biomed Eng*. (2018) 46:525–42. doi: 10.1007/s10439-018-1982-1

360. Pilla AA. State of the art in electromagnetic therapeutics In: M Blank, editor. Electricity and magnetism in biology and medicine. San Francisco: San Francisco Press Inc (1993). 17–22.

361. Pilla AA. Weak time-varying and static magnetic fields: from mechanisms to therapeutic applications In: P Stavroulakis, editor. Biological effects of electromagnetic fields. Berlin: Springer (2003). 34–75.

362. Ryabi JT. Clinical effects of electromagnetic fields on fracture healing. *Clin Orthop Relat Res*. (1998) 355S:S205–15. doi: 10.1097/00003086-199810001-00021

363. Wade B. A review of pulsed electromagnetic field (PEMF) mechanisms at a cellular level: a rationale for clinical use. *Am J Health Res*. (2013) 1:51–5. doi: 10.11648/j.ajhr.20130103.13

364. Funk RH. Coupling of pulsed electromagnetic fields (PEMF) therapy to molecular grounds of the cell. *Am J Transl Res*. (2018) 10:1260–72.

365. Maziarz A, Kocan B, Bester M, Budzik S, Cholewa M, Ochiya T, et al. How electromagnetic fields can influence adult stem cells: positive and negative impacts. *Stem Cell Res Ther*. (2016) 7:1–12. doi: 10.1186/s13287-016-0312-5

366. Pantelis P, Theocharous G, Veroutis D, Vagena IA, Polyzou A, Thanos DF, et al. Pulsed electromagnetic fields (PEMFs) trigger cell death and senescence in Cancer cells. *Int J Mol Sci*. (2024) 25:2473. doi: 10.3390/ijms25052473

367. Meijer DK, Geesink HJ. Favourable and unfavourable EMF frequency patterns in cancer: perspectives for improved therapy and prevention. *J Cancer Ther*. (2018) 9:188–230. doi: 10.4236/jct.2018.93019

368. Panagopoulos DJ, Karabarbounis A. Comments on behavior of charged particles in a biological cell exposed to AC-DC electromagnetic fields, and on comparison between two models of interaction between electric and magnetic fields and proteins in cell membranes. *Environ Eng Sci*. (2011) 28:749–51. doi: 10.1089/ees.2011.2810.com

369. Panagopoulos DJ, Chrousos GP. Shielding methods and products against man-made electromagnetic fields: protection versus risk. *Sci Total Environ*. (2019) 667:255–62. doi: 10.1016/j.scitotenv.2019.02.344

370. Persinger MA. Brain electromagnetic activity and lightning: potentially congruent scale - invariant quantitative properties. *Front Integr Neurosci*. (2012) 6:1–7. doi: 10.3389/fnint.2012.00019

371. Persinger MA. Schumann resonance frequencies found within quantitative electro-encephalographic activity: implications for earth-brain interactions. *Int Lett Chem Phys Astron*. (2014) 30:24–32. doi: 10.56431/p-ly2br0

372. Yan X, Liu X, Zhang S, Liu Z, Ren L. Study of the inhibition of Schumann resonance-inspired electromagnetic field on cancer cell proliferation. *J Bionic Eng*. (2025) 22:341–53.

373. Zahumenska R, Badurova B, Pavelek M, Sojka P, Pavlisova T. Comparison of pulsed and continuous electromagnetic field generated by WPT system on human dermal and neural cells. *Scientific Reports*. (2024) 14:5514.

Glossary

AOS - Antioxidant System

ATP - Adenosine Triphosphate

CNS - Central Nervous System

CYP - Cytochrome P450

DECT - Digitally Enhanced Cordless Telecommunications

DOX - Deoxyribose

EHS - Electro-hypersensitivity

ELF - Extremely Low Frequency

EMF - Electromagnetic Field

EMR - Electromagnetic Radiation

ETC - Electron Transport Chain

GEF - geoelectric field

GMF - geomagnetic field

GSM - Global System for Mobile telecommunications

IFO - Ion Forced Oscillation

LF - Low Frequency

MT - Mobile Telephony

MW - Microwave

NADH - Nicotinamide Adenine Dinucleotide

NADPH - Nicotinamide Adenine Dinucleotide Phosphate

NOS - Nitric Oxide Synthase

NOX - NADH/NADPH Oxidase

OS - Oxidative Stress

RF - Radio Frequency

ROS - Reactive Oxygen Species

SOD - Superoxide Dismutase

VGCC - Voltage-Gated Calcium Channel

VGIC - Voltage-Gated Ion Channel

VLF - Very Low Frequency

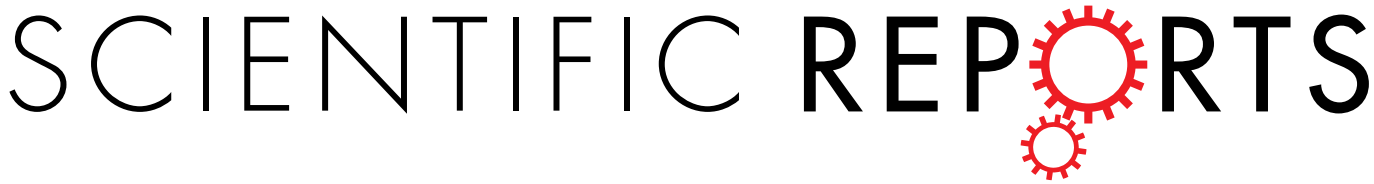
WC - Wireless Communication

Wi-Fi - Wireless Fidelity

ULF - Ultra Low Frequency

XO - Xanthine Oxidase

2G, 3G, 4G, 5G - Second, Third, Fourth, Fifth Generation of MT/WC



OPEN

Polarization: A Key Difference between Man-made and Natural Electromagnetic Fields, in regard to Biological Activity

Received: 24 February 2015
Accepted: 07 September 2015
Published: 12 October 2015

Dimitris J. Panagopoulos[1,2,3], Olle Johansson[4] & George L. Carlo[5]

In the present study we analyze the role of polarization in the biological activity of Electromagnetic Fields (EMFs)/Electromagnetic Radiation (EMR). All types of man-made EMFs/EMR - in contrast to natural EMFs/EMR - are polarized. Polarized EMFs/EMR can have increased biological activity, due to: 1) Ability to produce constructive interference effects and amplify their intensities at many locations. 2) Ability to force all charged/polar molecules and especially free ions within and around all living cells to oscillate on parallel planes and in phase with the applied polarized field. Such ionic forced-oscillations exert additive electrostatic forces on the sensors of cell membrane electro-sensitive ion channels, resulting in their irregular gating and consequent disruption of the cell's electrochemical balance. These features render man-made EMFs/EMR more bioactive than natural non-ionizing EMFs/EMR. This explains the increasing number of biological effects discovered during the past few decades to be induced by man-made EMFs, in contrast to natural EMFs in the terrestrial environment which have always been present throughout evolution, although human exposure to the latter ones is normally of significantly higher intensities/energy and longer durations. Thus, polarization seems to be a trigger that significantly increases the probability for the initiation of biological/health effects.

Man-Made EMR is more Active biologically than Natural Non-Ionizing EMR. A large and increasing number of studies during the past few decades have indicated a variety of adverse biological effects to be triggered by exposure to man-made EMFs, especially of radio frequency (RF)/microwaves, and extremely low frequency (ELF). The recorded biological effects range from alterations in the synthesis rates and intracellular concentrations of different biomolecules, to DNA and protein damage, which may result in cell death, reproductive declines, or even cancer[1–7]. Under the weight of this evidence the International Agency for Research on Cancer (IARC) has classified both ELF magnetic fields and RF EMFs as possibly carcinogenic to humans[8,9]. The intensities of radiation and durations of exposure in all these studies were significantly smaller than those of corresponding exposures from natural EMFs in the terrestrial environment. Moreover, the field intensities applied in the studies were several orders of magnitude smaller than physiological fields in cell membranes, or fields generated by nerve and muscle excitations[10,11].

Solar EMR intensity incident upon a human body ranges normally between 8 and 24 mW/cm^2 (depending on season, atmospheric conditions, geographical location, etc) while corresponding intensity from a digital mobile phone handset upon a human head during "talk" emission is normally less than

[1]National Center for Scientific Research "Demokritos", Athens, Greece. [2]Department of Biology, University of Athens, Greece. [3]Radiation and Environmental Biophysics Research Centre, Greece. [4]Experimental Dermatology Unit, Department of Neuroscience, Karolinska Institute, Stockholm, Sweden. [5]The Science and Public Policy Institute, Institute for Healthful Adaptation, Washington, DC, USA. Correspondence and requests for materials should be addressed to D.J.P. (email: dpanagop@biol.uoa.gr)

0.2 mW/cm^2 (Refs. 6,12,13). Similarly, terrestrial electric and magnetic fields, or infrared radiation from every human body at normal temperature, have significantly larger incident intensities and exposure durations on any human than most artificial EMF sources[14–16]. Why is then the first beneficial while the latter seem to be detrimental? In the present study we shall attempt to explain theoretically that the increased adverse biological action of man-made EMFs is due to the fact that they are polarized in contrast to the natural ones.

Man-Made EMR is Polarized, while Natural EMR is not. A field/wave is called linearly polarized when it oscillates on a certain plane which is called the "polarization plane". A combination of linearly polarized fields/waves can give circularly or elliptically polarized fields/waves.

Natural EMR/EMFs (cosmic microwaves, infrared, visible light, ultraviolet, gamma rays) and several forms of artificially triggered electromagnetic emissions (such as from light bulbs with thermal filaments, gas discharge lamps, x-rays, lasers, etc.) are not polarized. They are produced by large numbers of molecular, atomic, or nuclear transitions of random orientation and random phase difference between them (except for the lasers which are coherent). These are de-excitations of molecules, atoms, or atomic nuclei[17]. Each photon they consist of oscillates on a distinct random plane, and therefore it has a different polarization. Moreover the different photons are not produced simultaneously but they have random phase differences among them.

In contrast, man-made electromagnetic waves are produced by electromagnetic oscillation circuits ("Thomson" circuits), forcing free electrons to oscillate back and forth along a metal wire (electric circuit). Thus, they are not produced by excitations/de-excitations of molecules, atoms, or nuclei, and because the electronic oscillations take place in specific directions/orientations they are polarized (most usually linearly polarized). The plane of polarization is determined by the geometry of the circuit. [Lasers are coherent light emissions, not necessarily polarized, and condensed within a narrow beam with high intensity, but they may also be polarized]. Superposition of two fields of identical frequency and linear polarizations, equal amplitudes, and a phase difference 90° between them, or superposition of three such fields with a phase difference 120° between each two of them, and with specific geometrical arrangement, results in a circularly polarized field of the same frequency. The above combinations with unequal amplitudes results in elliptically polarized field of the same frequency[18]. Circularly and elliptically polarized 50–60 Hz electric and magnetic fields are formed around 3-phase electric power transmission lines. These fields are accused for an association with cancer[7,8].

Oscillating polarized EMFs/EMR (in contrast to unpolarized) have the ability to induce coherent forced-oscillations on charged/polar molecules within a medium. In case that the medium is biological tissue, the result is that all charged molecules will be forced to oscillate in phase with the field and on planes parallel to its polarization[19,20]. Several oscillating electromagnetic fields of the same polarization - such as the fields from different antennas vertically oriented - may also produce constructive interference effects and thus, amplify at certain locations the local field intensity, and the amplitude of oscillation of any charged particle within the medium (and within living tissue). At such locations, living tissue becomes more susceptible to the initiation of biological effects[21].

Only coherent polarized fields/waves of the same polarization and frequency are able to produce standing interference effects (fringes of maximum and minimum intensity)[22]. When the polarization is fixed (e.g. vertically oriented antennas) but there are differences in coherence and/or frequency between the sources, the interference effects are not standing at fixed locations, but change with time creating transient peaks at changing locations.

Natural light from two or more different sources does not produce interference effects, except under the specific conditions of the Young experiment, where the light from a single source passes through two identical slits which - in turn - become two identical-coherent secondary sources[18,23].

Unpolarized electromagnetic radiation can become polarized when it passes through anisotropic media, as are certain crystals. In fluids (gases and liquids) the molecules are randomly oriented, and macroscopically are considered isotropic inducing no polarization in the electromagnetic waves transmitted through them. Unpolarized natural light can become partly polarized to a small average degree after diffraction on atmospheric molecules, or reflection on water, mirrors, metallic surfaces, etc.[18]. Thus, living creatures exposed to natural radiation since the beginning of life on Earth, although have been exposed to partially polarized light at a small average degree under certain circumstances[24,25], have never been exposed to totally polarized radiation as is EMR/EMFs of modern human technology.

Field Intensity versus Wave Intensity of electromagnetic waves. A plane harmonic electromagnetic wave in the vacuum or the air has electric and magnetic field intensity components, given by the equations:

$$E = E_0 \sin(k_w r - \omega t) \quad (1)$$

$$B = B_0 \sin(k_w r - \omega t) \quad (2)$$

r is the distance from the source, t is the time, $\omega = 2\pi\nu = k_w \cdot c$, is the circular frequency of the wave (ν the frequency), and $k_w (= 2\pi/\lambda)$ is the wave number (λ the wavelength).

The velocity of the electromagnetic wave (and of any wave), is:

$$c = \lambda \cdot \nu \tag{3}$$

The wave intensity $\vec{J}$ ("Poynting vector"), is:

$$\vec{J} = \vec{c}\varepsilon_0 E^2 = c^2 \varepsilon_0 \vec{E} \times \vec{B} \tag{4}$$

And the average value of its amplitude:

$$J_{ave} = \frac{1}{2} c \varepsilon_0 E_0^2 \tag{5}$$

Thus, the wave intensity depends upon the square of the electric field intensity.

Superposition of Electromagnetic Waves/Fields

Superposition of Unpolarized EMR/EMFs. Consider two incoherent, unpolarized electromagnetic rays with electric components E_1, E_2, reaching a certain point P in space at a certain moment t in time. Let us assume for simplicity that the two waves are plane harmonic. The two vectors $\vec{E}_1$, $\vec{E}_2$ due to the different polarizations oscillate on different planes. Since the two waves are not polarized, their polarizations vary randomly with time. The total angle ϕ between the two vectors each moment is determined by the different polarizations, plus the different phases, and varies randomly in time.

The resultant electric field $\vec{E}$ (electric component of the resultant electromagnetic wave) each moment at point P, is given by the equation:

$$E = \sqrt{E_1^2 + E_2^2 + 2E_1 E_2 \cos \phi} \tag{6}$$

E varies with time due to the temporal variations of E_1, E_2, $\cos\phi$. But the average value of $\cos\phi$ is zero:

$$\frac{1}{2\pi} \int_0^{2\pi} \cos\phi \, d\phi = 0,$$

and the averages of E^2, E_1^2, and E_2^2 are $E_0^2/2$, $E_{01}^2/2$ and $E_{02}^2/2$ respectively (E_0, E_{01}, E_{02} the amplitudes of E, E_1, E_2).

The average resultant electric field is then:

$$E_{ave} = \sqrt{\frac{1}{2}(E_{01}^2 + E_{02}^2)} \quad \text{or} \quad E_0^2 = E_{01}^2 + E_{02}^2 (=\text{constant})$$

and (according to Eq. 5):

$$J_{ave} = J_{1,ave} + J_{2,ave} (=\text{constant}) \tag{7}$$

Even when the two component waves have the same frequency and phase, due to the randomly changing polarizations, the result is still the same.

Thus, the total time average wave intensity due to the superposition of two (or more) rays of random polarizations (natural EMR/EMFs) is the sum of the two individual average intensities, and it is constant at every point and - macroscopically - there is no local variation in the resultant intensity, i.e. no interference effects.

Wave Intensity versus Field Intensity of Unpolarized EMR. Although the sum average wave intensity due to superposition of natural unpolarized waves is the sum of individual average intensities each one depending on the square amplitude of individual electric field (Eq. 7), the sum electric field from an infinite number of individual waves (as e.g. with natural light), is zero:

$$\lim_{n\to\infty} \sum_{i=1}^{n} \vec{E}_i = \vec{E}_1 + \vec{E}_2 + \vec{E}_3 + \ldots + \vec{E}_n = 0 \tag{8}$$

Let us explain this in more detail: Consider many photons of natural unpolarized light superposed on each other at a particular point in space. Let us assume for simplicity that these photons have equal amplitudes and are of the same frequency but have different polarizations meaning that their electric vectors have all possible orientations forming angles between each two of them from 0° to 360°. Since all possible orientations have equal probabilities, the superposition of a large number of such equal vectors applied on the same point in space will be the sum of vectors applied on the centre of a sphere with their ends equally distributed around the surface of the sphere. The sum of an infinite number of such

vectors (all applied on the same point – centre of the sphere – and with their ends evenly distributed at all points of the sphere surface) tends to become zero.

In other words, at any given location, any moment, the sum electric field of a large number of incident photons of random polarization tends to be null, since the individual vectors are in all possible directions diminishing each other when superimposed (destructive interference of electric vectors). Similarly for the sum magnetic field:

$$\lim_{n\to\infty} \sum_{i=1}^{n} \vec{B}_i = 0$$

Thus, the result of superposition of a large number of incident natural waves is increased wave intensity, but negligible electric and magnetic fields approaching zero with infinite number of individual waves/photons. Since the electric forces on charged particles depend directly on electric and magnetic field intensities ($\vec{E}$, $\vec{B}$), but not on the wave intensity $\vec{J}$, unpolarized EMFs/EMR cannot induce any net forced-oscillations on any charged particles (e.g. biological molecules). They may only induce heat, i.e. random oscillations in all possible directions due to momentary non-zero field intensities, but this does not result to any net electric or magnetic field, or to any net forced-oscillation of charged molecules.

Superposition of Coherent Polarized Waves/Fields of the same polarization. When two or more waves/fields of the same polarization and frequency are in addition coherent, in other words, when their phase difference at the location of superposition is:

$$\varphi = 2n\pi, \text{ (with } n = 1, 2, 3, \ldots), \tag{9}$$

the result is constructive interference, meaning that the resultant wave has an amplitude (intensity) equal to the sum of amplitudes of the single waves that interfere at the particular location.

When two waves of same polarization have opposite phases at another location, in other words, when their phase difference is:

$$\varphi = (2n + 1)\pi, \tag{10}$$

then the result of their superposition is destructive interference, i.e. a wave of the same polarization but with diminished intensity.

The electrical components of two such waves (plane harmonic waves of the same polarization and frequency) reaching a certain location after having run different distances r_1, and r_2 from their two coherent sources, are given by the equations:

$$E_1 = E_{01} \sin(k_w r_1 - \omega t) \tag{11}$$

$$E_2 = E_{02} \sin(k_w r_2 - \omega t) \tag{12}$$

Again, the amplitude E_0 of the resultant electric field $\vec{E}$ (electric component of the resultant electromagnetic wave), is:

$$E_0 = \sqrt{E_{01}^2 + E_{02}^2 + 2E_{01}E_{02} \cos\varphi} \tag{13}$$

where $\varphi = \frac{2\pi}{\lambda}(r_1 - r_2)$ depending in this case only upon the difference in the distances run by the two waves, and not upon polarization.

At any location where: $\varphi = 2n\pi$, Eq. 13 gives:

$$E_0 = \sqrt{E_{01}^2 + E_{02}^2 + 2E_{01}E_{02}} \ (=|E_{01} + E_{02}|) \tag{14}$$

At these locations we have constructive interference.

At any location where: $\varphi = (2n+1)\pi$, Eq. 13 gives:

$$E_0 = \sqrt{E_{01}^2 + E_{02}^2 - 2E_{01}E_{02}} \ (=|E_{01} - E_{02}|) \tag{15}$$

At these locations we have destructive interference.

The intensity of the resultant wave at any location is:

$$\vec{J} = \vec{J}_1 + \vec{J}_2 \tag{16}$$

The amplitude of the resultant wave intensity will be, correspondingly:

$$J_0 = c\varepsilon_0(E_{01} + E_{02})^2 \tag{17}$$

(at the locations of constructive interference), and

$$J_0 = c\varepsilon_0(E_{01} - E_{02})^2 \tag{18}$$

(at the locations of destructive interference).

Thus, at the locations of constructive interference, the electric field vectors of the two waves/fields are parallel and in the same direction, and both the resultant field and the resultant wave intensity are maximum (Eqs. 14 and 17).

For two identical sources ($E_{01} = E_{02}$): $E_0 = 2E_{01}$ and $J_0 = 4c\varepsilon_0 E_{01}^2 = 4J_{01}$

For N identical sources:

$$E_0 = NE_{01} \tag{19}$$

and:

$$J_0 = N^2 J_{01} \tag{20}$$

This is why series of parallel RF/microwave antennas are often used to produce high-intensity beams in certain directions[18].

At the locations of destructive interference the electric field vectors of the two waves are anti-parallel, and thus, both the resultant field and the resultant wave intensity are minimum (Eqs. 15 and 18). For identical sources ($E_{01} = E_{02}$): $E = 0$, $J = 0$.

Thus, for N number of polarized coherent electromagnetic sources of the same polarization, frequency, and different intensities, with electric components E_1, E_2, …, E_N, it comes that at the locations of constructive interference, the resultant electric field is the sum electric field from all the individual sources (e.g. antennas):

$$E = E_1 + E_2 + E_3 + \ldots + E_N \tag{21}$$

The bigger the number of coherent superimposed waves/fields (from the same or different sources), the higher and narrower the peaks[18]. That situation can create very sharp peaks of wave and field intensities at certain locations, not easily detectable by field meters, where any living organism may be exposed to peak electric and magnetic field intensities. Such locations of increased field/radiation intensity, also called "hot spots", were recently detected within urban areas, due to wave/field superposition from mobile telephony base towers[21]. Any location along the midperpendicular to the distance d between two antennas is a location of constructive interference in the case of two identical antennas.

Thus, the difference between superposition of unpolarized and polarized electromagnetic waves/fields, is that while in the first case we have increased average wave intensity but zeroed net fields at any location, in the second case we have increased both wave intensity and fields at certain locations where constructive interference occurs. This difference is of crucial importance for understanding the differences in biological activity between natural and man-made EMFs/non-ionizing EMR.

Induction of Forced-Oscillations in living tissue by Polarized EMFs

All critical biomolecules are either electrically charged or polar[11]. While natural unpolarised EMF/EMR at any intensity cannot induce any specific/coherent oscillation on these molecules, polarized man-made EMFs/EMR will induce a coherent forced-oscillation on every charged/polar molecule within biological tissue. This is fundamental to our understanding of the biological phenomena. This oscillation will be most evident on the free (mobile) ions which carry a net electric charge and exist in large concentrations in all types of cells or extracellular tissue determining practically all cellular/biological functions[11]. Although all molecules oscillate randomly with much higher velocities due to thermal motion, this has no biological effect other than increase in tissue temperature. But a coherent polarized oscillation of even millions of times smaller energy than average thermal molecular energy[26] can initiate biological effects.

A forced-oscillation of mobile ions, induced by an external polarized EMF, can result in irregular gating of electrosensitive ion channels on the cell membranes. That was described in detail in Panagopoulos *et al.*[19,20]. According to this theory - the plausibility of which in actual biological conditions was verified by numerical test[27] - the forced-oscillation of ions in the vicinity of the voltage-sensors of voltage-gated ion channels can exert forces on these sensors equal to or greater than the forces known to physiologically gate these channels. Irregular gating of these channels can potentially disrupt any cell's electrochemical balance and function[11], leading to a variety of biological/health effects including the most detrimental ones, such as DNA damage, cell death, or cancer[28].

Most cation channels (Ca^{+2}, K^+, Na^+, etc) on the membranes of all animal cells, are voltage-gated[11]. They interconvert between open and closed state, when the electrostatic force on the electric charges of their voltage sensors due to transmembrane voltage changes, transcends some critical value. The voltage sensors of these channels are four symmetrically arranged, transmembrane, positively charged helical domains, each one designated S4. Changes in the transmembrane potential on the order of 30 mV are normally required to gate electrosensitive channels[29,30]. Several ions may interact simultaneously each

moment with an S4 domain from a distance on the order of 1 nm, since - except for the single ion that may be passing through the channel pore when the channel is opened - a few more ions are bound close to the pore of the channel at specific ion-binding sites (e.g. three in potassium channels)[31]. Details on the structure and function of cation electrosensitive channels can be found in[11,29,31].

Consider e.g. four potassium ions at distances on the order of 1 nm from the channel-sensors (S4), and an externally applied oscillating EMF/EMR. The electric (and the magnetic) force on each ion due to any unpolarized field is zero (Eq. 8). In contrast, the force due to a polarized field with an electrical component E, is $F = Ezq_e$. For a sinusoidal alternating field $E = E_0 \sin \omega t$, the movement equation of a free ion of mass m_i, is[19,20]:

$$m_i \frac{d^2 r}{dt^2} + \lambda \frac{dr}{dt} + m_i \omega_0^2 r = E_0 z q_e \sin \omega t \tag{22}$$

where r is the ion displacement due to the forced-oscillation, z is the ion's valence ($z = 1$ for potassium ions), $q_e = 1.6 \times 10^{-19}$ C the elementary charge, λ the damping coefficient for the ion displacement (calculated to have a value within a channel $\lambda \cong 6.4 \times 10^{-12}$ Kg/s), $\omega_0 = 2\pi\nu_0$ (ν_0 the ion's oscillation self-frequency taken equal to the ion's recorded spontaneous intracellular oscillation frequency on the order of 0.1 Hz), $\omega = 2\pi\nu$ (ν the frequency of the field/radiation), and E_0 the amplitude of the field[19,20].

The general solution of Eq. 22, is[19,20]:

$$r = \frac{E_0 z q_e}{\lambda \omega} \cos \omega t + \frac{E_0 z q_e}{\lambda \omega} \tag{23}$$

The term $\frac{E_0 z q_e}{\lambda \omega}$ in the solution, represents a constant displacement, but has no effect on the oscillating term $\frac{E_0 z q_e}{\lambda \omega} \cos \omega t$. This constant displacement doubles the amplitude $\frac{E_0 z q_e}{\lambda \omega}$ of the forced-oscillation at the moment when the field is applied or interrupted, or during its first and last periods, and the ion's displacement will be twice the amplitude of the forced-oscillation. For pulsed fields (such as most fields of modern digital telecommunications) this will be taking place constantly with every repeated pulse. Thus, pulsed fields are - theoretically - twice more drastic than continuous/non-interrupted fields of the same other parameters, in agreement with several experimental data[1,32].

The amplitude of the forced-oscillation (ignoring the constant term in Eq. 23), is:

$$A = \frac{E_0 z q_e}{\lambda \omega} \tag{24}$$

The force acting on the effective charge q of an S4 domain, via an oscillating single-valence free cation, is: $F = \frac{1}{4\pi\varepsilon\varepsilon_0} \cdot \frac{q \cdot q_e}{r^2}$, ($r$ is the distance of the free ion from the effective charge of S4). Each oscillating cation displaced by dr, induces a force on each S4 sensor:

$$dF = -\frac{q \cdot q_e}{2\pi\varepsilon\varepsilon_0 r^3} dr \tag{25}$$

While in the case of a non-polarized applied field $\sum d\vec{r} = 0$, and $\sum d\vec{F} = 0$, in the case of a polarized applied field, the sum force on the channel sensor from all four cations, is:

$$4dF = -2\frac{q \cdot q_e}{\pi\varepsilon\varepsilon_0 r^3} dr$$

This is an even more crucial difference between polarized and unpolarized EMFs in regard to biological activity than the ability of interference.

The effective charge of each S4 domain is found to be: $q = 1.7\, q_e$[30]. The minimum force on this charge required normally to gate the channel - equal to the force generated by a change of 30 mV in the membrane potential[30] - is calculated[19] to be:

$$dF = 8.16 \times 10^{-13} \text{N}.$$

The displacement of one single-valence cation within the channel, necessary to exert this minimum force is calculated from Eq. 25 to be:

$$dr = 4 \times 10^{-12} \text{m}$$

For 4 cations oscillating in phase and on parallel planes due to an external polarized field/radiation, the minimum displacement is decreased to: $dr = 10^{-12}$ m.

Therefore, any external polarized oscillating EMF able to force free ions to oscillate with amplitude $\frac{E_0 z q_e}{\lambda \omega} \geq 10^{-12}$m, is able to irregularly gate cation channels on cell membranes. For $z = 1$ (potassium ions), and substituting the values for q_e, λ on the last condition, we get:

$$E_0 \geq 0.25\nu \times 10^{-3} \tag{26}$$

(ν in Hz, E_0 in V/m)

For double-valence cations ($z=2$) (e.g. Ca^{+2}) the condition becomes,

$$E_0 \geq \nu \times 10^{-4} \tag{27}$$

(ν in Hz, E_0 in V/m)

[An in depth description of the briefly presented mechanism can be found in[19,20].]

For electric power fields ($\nu=50$ Hz), Condition 27 becomes,

$$E_0 \geq 0.005\text{V/m} \tag{28}$$

Thus, power frequency EMFs with intensities exceeding 5 mV/m are potentially able to disrupt cell function. For N number of EMF-sources of the same polarization (e.g. N number of parallel power lines) the last value is divided by N (according to Eq. 19) at the locations of constructive interference, and thus even more decreased. Such minimum power frequency field intensity values are abundant in urban daily environments, and even more close to high-voltage power transmission lines[7].

For pulsed fields the second part of Condition 27 is divided by 2, and becomes:

$$E_0 \geq 0.5\nu \times 10^{-4} \tag{29}$$

(ν in Hz, E_0 in V/m).

For digital mobile telephony fields/radiation emitting ELF pulses with a pulse repetition frequency $\nu=217$ Hz (among other ELF frequencies they transmit)[33], Condition 29 becomes:

$$E_0 \geq 0.01\text{V/m} \tag{30}$$

For the pulse repetition frequency of $\nu=8.34$ Hz (also included in mobile telephony signals)[33,34], Condition 29 becomes:

$$E_0 \geq 0.0004\text{V/m} \tag{31}$$

As is evident from the described mechanism, the field does not gate the channel by forces exerted directly on the channel sensors. It would take a field on the order of the transmembrane field (10^6–10^7 V/m) for that. It is the mediation of the oscillating free ions in close proximity to the S4 channel sensors that allows such weak fields to be able to exert the necessary forces to gate the channel.

Thus, ELF electric fields emitted by mobile phones and base stations stronger than 0.0004 V/m are also potentially able to disrupt the function of any living cell. This ELF intensity value is emitted by regular cell phones at distances up to a few meters and base stations at distances up to a few hundred meters[6,34,35]. For N number of mobile telephony antennas vertically oriented, the last value is divided by N (according to Eq. 19) at locations of constructive interference.

We do not distinguish between externally applied EMFs and internally induced ones within living tissue, especially in the case of ELF for the following reasons: 1. Living tissue is not metal to shield from electric fields and certainly is not ferromagnetic metal (Fe, Co, Ni) to shield from magnetic fields. Moreover, it is known that especially ELF fields cannot be easily shielded even by Faraday cages and in order to significantly minimize them it is recommended to totally enclose them in closed metal boxes[6]. Thus, ELF electric fields penetrate living tissue with certain degree of attenuation, and magnetic fields penetrate with zero attenuation. 2. Even in case that the ELF fields are significantly attenuated in the inner tissues of a living body, the eyes, the brain, the skin cells, or the myriads of nerve fiber terminals that end up on the outer epidermis, are directly exposed to the field intensities measured externally on the surface of the living tissue.

It has been shown that tissue preparations (such as bovine fibroblasts or chicken tendons) respond to externally applied pulsed or sinusoidal ELF electric fields (by changes in DNA or protein synthesis rates, proliferation rates, alignment with respect to the field direction, etc), at very low thresholds ~10^{-3} V/m[1,36–38]. These thresholds are very close to those predicted by the present study.

Except for direct electric field exposure by an external field, there can be an electric field within tissues induced by an externally applied oscillating magnetic one, which as explained penetrates living tissue with zero attenuation. Tuor *et al.*[34] measured ELF magnetic fields from cell phones on the order of 1 G ($=10^{-4}$ T) at 217 Hz. This can induce electric fields on the order of ~0.1 V/m within the human body, as can be shown by application of Maxwell's law of electromagnetic induction:

$$\oint_l \vec{E}_{ind} \cdot d\vec{l} = -\frac{d}{dt}\int_S \vec{B} \cdot \vec{u}_N dS \tag{32}$$

($\vec{B}$, $\vec{E}_{ind}$, the magnetic and the induced electric field intensities respectively, $d\vec{l}$ an incremental length along a closed path l of induced electric field circulation enclosing a surface S. $\vec{u}_N$ is the unit vector vertical to the surface S).

Assuming $\vec{E}_{ind}$ parallel to and independent of l, $\vec{B}$ vertical to and independent of S, and l a circular path of radius α including the surface S, Eq. 32 becomes:

$$E_{ind} \oint_l dl = -\frac{dB}{dt} \int_S dS$$

which gives:

$$E_{ind} = 0.5\alpha \frac{dB}{dt} \tag{33}$$

(E_{ind} in V/m, B in T, α in m).

By replacing in the last equation $\alpha = 0.20$ m (a reasonably large radius for a circumference within an adult human body), and $\frac{dB}{dt} = 1\mathrm{T/s}$, [according to Tuor *et al.*[34]], we get $E_{ind} \sim 0.1$ V/m. This is the induced electric field intensity within a human body by the 217 Hz pulses of mobile telephony, and it is about ten times larger than the minimum estimated value able to initiate biological effects at this frequency according to Condition 30.

Discussion

In the present study we showed that polarized EMFs/EMR, such as every type of man-made EMF, have the ability to create interference effects and amplify their field intensities at specific locations where constructive interference occurs, and that this phenomenon cannot occur with natural EMFs/EMR which are not polarized.

Any location at equal distances from identical sources (antennas), in other words any location along the midperpendicular to the distance d between the two sources, is a location of constructive interference and increased field and wave intensities. As the number of sources (e.g. antennas) increases, the amplification of the resultant field intensities (E, B) at certain locations increases too (Eq. 19), and for a large number of sources field intensities may become very sharp. This explains theoretically the detected "hot spots" from mobile telephony base stations in urban environments[21]. The result of field superposition at those locations are standing waves (i.e. they do not change with time) when the two or more sources of the same polarization are in addition coherent (i.e. same frequency, same phase difference). Within biological tissue, at those locations of constructive interference we can have increased biological activity due to the polarized EMFs.

The most usual case is, when the multiple incident fields/waves are of the same polarization but not coherent (i.e. different frequency and/or varying phase difference), as e.g. the waves from all different radio, television, and mobile telephony antennas vertically oriented. Then, the resultant fields/waves are not standing but timely varying, creating momentary constructive interference at unpredictably different locations each moment. This fact may represent an extraordinary ability of man-made/polarized EMFs to trigger biological effects.

Using the forced-oscillation mechanism[19,20] we showed that the resultant force exerted on the S4 sensors of electrosensitive ion channels on cell membranes by several ions forced to oscillate on parallel planes and in phase by an applied polarized EMF (and even more by constructively superimposed fields from several polarized EMF-sources), is able to irregularly gate these channels. The result can then be the disruption of the cell's electrochemical balance, leading to a variety of biological/health effects[28]. This is in contrast to the null force exerted by any number of ions oscillating on non-parallel random planes and with different phases from each other due to any number of non-polarized applied EMFs, and in contrast to the null force exerted by the random thermal movement of the same ions[20,26].

In experiments testing the role of different polarization types on the biological activity of RF EMR, exposure of E. coli to 51.76 GHz radiation resulted in inhibition of DNA repair when linear or right-handed circularly polarized radiation was used, while left-handed circularly polarized radiation caused no effects. Exposure to 41.32 GHz similar EMR was reported to reverse the effect: In this case, only linear or left-handed circularly polarized radiation inhibited the DNA repair[39]. In both frequencies, the right-handed or the left-handed circularly polarized radiation induced a greater effect than the linearly polarized radiation. When the structure of the DNA was altered by ethidium bromide intercalation, a change in intensity of the effect of polarization was reported[40]. Chromatin condensation (a sign of cell death) was induced by elliptically polarized 36.65 GHz microwave radiation. The effect increased with intensity. Right-handed polarization induced a stronger effect than left-handed[41]. These experiments show that not only linear but circular and elliptical polarizations are important parameters for the biological action of EMR, and that molecular structure of biomolecules may be important for the interaction between polarized EMF and the biological tissue. In all these studies there was no comparison with unpolarised field of identical other parameters, but only comparison between different types of

polarization. Again, it is important to note that circularly and elliptically polarized 50–60 Hz EMFs are formed around 3-phase power transmission lines.

Experiments with non-polarized and polarized EMFs/EMR of identical other characteristics (intensity, frequency, waveform, etc) on certain biological models should be performed to test the validity of the present theoretical study. This should be the subject of a future experimental study.

The present theoretical analysis shows that polarized man-made EMFs/EMR can trigger biological effects while much stronger and of higher energy (frequency) unpolarized EMFs/Non-Ionizing EMR (e.g. heat, or natural light) cannot.

This is the reason why polarized microwave radiation of maximum power 1 W emitted by a mobile phone can damage DNA and cause adverse health effects[2,3,5,6,35], while non-polarized infrared, visible, and ultraviolet radiation from a 100 W light bulb, or ~400 W infrared and visible EMR from a human body[14,16], cannot. Similarly with solar EMR the intensity of which incident on a human body (~8–24 mW/cm^2) is hundreds of times higher than radiation intensity incident from e.g. a cell phone on a user's head/body during a usual phone-conversation with the handset in touch with the head (less than 0.2 mW/cm^2), or incident intensities from other RF, ELF sources of human technology[6,7,12,13]. The total daily duration of human exposure to the sunlight is also much longer normally than the total daily duration of cell phone exposure during conversations[5,6,12,13]. Moreover the frequency (energy) of sunlight is also significantly larger than any man-made RF or ELF frequencies. Yet, there are no adverse biological effects due to normal/non-excessive exposure to sunlight. On the contrary, it is beneficial and vital/necessary for human/animal health, in contrast to cell phone radiation. Similarly, there are no adverse biological effects due to exposure (mainly in the infrared and visible regions) from one human body to another (with an incident intensity ~20 mW/cm^2)[16]. Although all animals on Earth have adapted throughout evolution to exposures to EMFs from the sun and the earth, these fields are non-polarized (even though natural light may become partially polarized in a small average degree due to atmospheric scattering or reflections). Moreover, terrestrial electric and magnetic fields are mainly static, emitting very weak non-polarized ELF radiation due to slight variations in their intensities. However, larger variations on the order of 20% of their normal intensities due to solar activity with a periodicity of about 11 years result in increase of human/animal health incidents[15]. Therefore, living organisms on Earth are adapted to natural (non-polarized or even partially polarized) EMFs since the beginning of life, but not to variations in their normal intensities on the order of 20%, and thus we would not expect them to adapt to man-made (totally polarized) EMFs/EMR. The present study explained how this difference in polarization results in corresponding differences in biological activity between natural and man-made EMFs.

Increased biological activity does not necessarily result in observable biological/health effects, since there are adaptive mechanisms operating at cellular-tissue-organism levels in response to ever occurring changes. However, these mechanisms may not always be totally effective, especially when the organism is under additional stress or increased metabolic needs (e.g. sickness, childhood/development, old age, etc.). Then exposure to polarized (man-made) EMFs may considerably increase the probability for the initiation of adverse health effects. The effect of polarized EMF-exposure may even be beneficial in certain cases of applied static or pulsed electric or magnetic fields of specified orientation and intensities that enhance the action of endogenous physiological fields within living cells/organisms e.g. during development, wound healing, bone fracture healing etc.[38,42].

The role of polarization in the ability of EMFs/non-ionizing EMR to induce biological effects, as described in the present study, is - up to today - largely underestimated in the EMF-bioeffects literature. Thus, we believe that the present study contributes significantly towards a better understanding of the mechanisms underlying EMF-bioeffects.

References

1. Goodman, E. M., Greenebaum, B. & Marron, M. T. Effects of Electro- magnetic Fields on Molecules and Cells. *International Review of Cytology* **158,** 279–338 (1995).
2. Phillips, J. L., Singh, N. P. & Lai, H. Electromagnetic fields and DNA damage. *Pathophysiology* **16,** 79–88 (2009).
3. Blackman, C. Cell phone radiation: Evidence from ELF and RF studies supporting more inclusive risk identification and assessment. *Pathophysiology* **16,** 205–16 (2009).
4. Johansson, O. Disturbance of the immune system by electromagnetic fields-A potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment. *Pathophysiology* **16,** 157–77 (2009).
5. Khurana, V. G., Teo, C., Kundi, M., Hardell, L. & Carlberg, M. Cell phones and brain tumors: a review including the long-term epidemiologic data. *Surgical Neurology* **72,** 205–14 (2009).
6. Panagopoulos, D. J. "Analyzing the Health Impacts of Modern Telecommunications Microwaves", In Berhardt, L. V. (Ed), *Advances in Medicine and Biology* Vol. 17, Nova Science Publishers, Inc., New York, USA (2011).
7. Panagopoulos, D. J., Karabarbounis, A. & Lioliousis, C. ELF Alternating Magnetic Field Decreases Reproduction by DNA Damage Induction. *Cell Biochemistry and Biophysics* **67,** 703–716 (2013).
8. IARC. Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields, Vol. 80 (2002).
9. IARC. Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields, Vol. 102 (2013).
10. Hodgkin, A. L. & Huxley, A. F. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117,** 500–544 (1952).
11. Alberts, B. *et al. Molecular Biology of the Cell*, Garland Publishing, Inc., N.Y., USA (1994).
12. Roller, W. L. & Goldman, R. F. Prediction of solar heat load on man. *Journal of Applied Physiology* **25,** 717–721 (1968).
13. Parsons, K. C. *Human thermal environments*, Taylor and Francis, London (1993).
14. Presman, A. S. *Electromagnetic Fields and Life*, Plenum Press, New York (1977).
15. Dubrov, A. P. *The Geomagnetic Field and Life - Geomagnetobiology*, Plenum Press, New York (1978).

16. Gulyaev, Yu. V., Markov, A. G., Koreneva, L. G. & Zakharov, P. V. Dynamical infrared thermography in humans, *Engineering in Medicine and Biology Magazine, IEEE* **14,** 766–771 (1995).
17. Beiser, A. *Concepts of Modern Physics*, McGraw-Hill, Inc (1987).
18. Alonso, M. & Finn, E. J. *Fundamental University Physics,* Vol. 2*: Fields and Waves*, Addison-Wesley, USA (1967).
19. Panagopoulos, D. J., Messini, N., Karabarbounis, A., Filippetis, A. L. & Margaritis, L. H. A Mechanism for Action of Oscillating Electric Fields on Cells, *Biochemical and Biophysical Research Communications* **272,** 634–640 (2000).
20. Panagopoulos, D. J., Karabarbounis, A. & Margaritis, L. H. Mechanism for Action of Electromagnetic Fields on Cells, *Biochemical and Biophysical Research Communications* **298,** 95–102 (2002).
21. Sangeetha, M., Purushothaman, B. M. & Suresh Babu, S. "Estimating cell phone signal intensity and identifying Radiation Hotspot Area for Tirunel Veli Taluk using RS and GIS", *International Journal of Research in Engineering and Technology* **3,** 412–418 (2014).
22. Arago, D. F. J. & Fresnel, A. J. "On the action of rays of polarized light upon each other", *Ann. Chim. Phys.* **2,** 288–304 (1819).
23. Pohl, R. (1960) "Discovery of Interference by Thomas Young", *Am. J. Phys.* **28,** 530.
24. Chen, H. S. & Rao, C. R. N. Polarization of light on reflection by some natural surfaces. *Brit. J. Appl. Phys.* **1,** 1191–1200 (1968).
25. Cronin, T. W., Warrant, E. J. & Greiner, B. Celestial polarization patterns during twilight. *Applied Optics* **22,** 5582–5589 (2006).
26. Panagopoulos, D. J., Johansson, O. & Carlo, G. L. Evaluation of Specific Absorption Rate as a Dosimetric Quantity for Electromagnetic Fields Bioeffects. *PLoS ONE* **8,** e62663, doi: 10.1371/journal.pone.0062663 (2013).
27. Halgamuge, M. N. & Abeyrathne, C. D. A Study of Charged Particle's Behavior in a Biological Cell Exposed to AC-DC Electromagnetic Fields, *Environmental Engineering Science* **28,** 1–10 (2011).
28. Pall, M. L. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med* **17,** 958–65 (2013).
29. Noda, M. *et al.* Existence of distinct sodium channel messenger RNAs in rat brain. *Nature* **320,** 188–192 (1986).
30. Liman, E. R., Hess, P., Weaver, F. & Koren, G. Voltage-sensing residues in the S4 region of a mammalian K^+ channel. *Nature* **353,** 752–756 (1991).
31. Miller, C. "An overview of the potassium channel family". *Genome Biology* **1,** 1–5 (2000).
32. Penafiel, L. M., Litovitz, T., Krause, D., Desta, A. & Mullins, J. M. Role of Modulation on the effects of microwaves on ornithine decarboxylase activity in L929 cells. *Bioelectromagnetics* **18,** 132–141 (1997).
33. Tisal, J. *GSM Cellular Radio Telephony*, J. Wiley & Sons, West Sussex, England (1998).
34. Tuor, M., Ebert, S., Schuderer, J. & Kuster, N. Assessment of ELF Exposure from GSM Handsets and Development of an Optimized RF/ELF Exposure Setup for Studies of Human Volunteers, BAG Reg. No. 2.23.02.-18/02.001778, IT'IS Foundation (2005).
35. Panagopoulos, D. J., Chavdoula, E. D. & Margaritis, L. H. Bioeffects of Mobile Telephony Radiation in relation to its Intensity or Distance from the Antenna. *International Journal of Radiation Biology* **86,** 345–357 (2010).
36. McLeod, K. J., Lee, R. C. & Ehrlich, H. P. Frequency dependence of electric field modulation of fibroblast protein synthesis. *Science* **236,** 1465–9 (1987).
37. Cleary, S. F., Liu, L. M., Graham, R. & Diegelmann, R. F. Modulation of tendon fibroplasia by exogenous electric currents. *Bioelectromagnetics* **9,** 183–94 (1988).
38. Lee, R. C., Canaday, D. J. & Doong, H. A review of the biophysical basis for the clinical application of electric fields in soft-tissue repair. *Journal of Burn Care and Rehabilitation* **14,** 319–335 (1993).
39. Belyaev, I. Y., Alipov, Y. D. & Shcheglov, V. S. Chromosome DNA as a target of resonant interaction between Escherichia coli cells and low-intensity millimeter waves. *Electro- and Magnetobiology* **11,** 97–108 (1992).
40. Ushakov, V. L., Shcheglov, V. S., Belyaev, I. Y. & Harms-Ringdahl, M. Combined effects of circularly polarized microwaves and ethidium bromide on E. coli cells. *Electromagnetic Biology and Medicine* **18,** 233–242 (1999).
41. Shckrobatov, Y. G. *et al.* Effects of differently polarized microwave radiation on the microscopic structure of the nuclei in human fibroblasts. *J Zhejiang Univ-Sci B* (*Biomed & Biotechnol*) **11,** 801–805 (2010).
42. Panagopoulos, D. J. "Electromagnetic Interaction between Environmental Fields and Living Systems determines Health and Well-Being", *In Electromagnetic Fields: Principles, Engineering Applications and Biophysical Effects*, Nova Science Publishers, New York, USA (2013).

Acknowledgements

The study was supported by the Karolinska Institute, Stockholm, Sweden, the Irish Doctors Environmental Association, and the Alliance for Irish Radiation Protection. Dr Panagopoulos wishes to thank Drs G. Pantelias and A. Stubos at the National Center for Scientific Research "Demokritos", Athens, Greece. Prof. Johansson wishes to thank Einar Rasmussen, Norway, and Brian Stein, UK, for their general support.

Author Contributions

Analyzed the data: D.J.P., O.J. and G.L.C. Wrote and reviewed the paper: D.J.P., O.J. and G.L.C. Conceived and designed the study: D.J.P. Wrote equations and Performed calculations: D.J.P.

Additional Information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Panagopoulos, D. J. *et al.* Polarization: A Key Difference between Man-made and Natural Electromagnetic Fields, in regard to Biological Activity. *Sci. Rep.* **5**, 14914; doi: 10.1038/srep14914 (2015).

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/

scientific reports

Check for updates

OPEN

Biophysical mechanism of animal magnetoreception, orientation and navigation

Dimitris J. Panagopoulos[1,2]✉, Andreas Karabarbounis[3] & George P. Chrousos[1,4]

We describe a biophysical mechanism for animal magnetoreception, orientation and navigation in the geomagnetic field (GMF), based on the ion forced oscillation (IFO) mechanism in animal cell membrane voltage-gated ion channels (VGICs) (IFO-VGIC mechanism). We review previously suggested hypotheses. We describe the structure and function of VGICs and argue that they are the most sensitive electromagnetic sensors in all animals. We consider the magnetic force exerted by the GMF on a mobile ion within a VGIC of an animal with periodic velocity variation. We apply this force in the IFO equation resulting in solution connecting the GMF intensity with the velocity variation rate. We show that animals with periodic velocity variations, receive oscillating forces on their mobile ions within VGICs, which are forced to oscillate exerting forces on the voltage sensors of the channels, similar or greater to the forces from membrane voltage changes that normally induce gating. Thus, the GMF in combination with the varying animal velocity can gate VGICs and alter cell homeostasis in a degree depending, for a given velocity and velocity variation rate, on GMF intensity (unique in each latitude) and the angle between velocity and GMF axis, which determine animal position and orientation.

Keywords Geomagnetic field, Animal magnetoreception, Orientation, Navigation, Electromagnetic fields, Voltage-gated ion channels, Ion forced-oscillation mechanism

Abbreviations

ELF	Extremely Low Frequency
EMF	Electromagnetic field
ESR	Electron Spin Resonance
GEF	Geoelectric field
GMF	Geomagnetic field
IFO	Ion forced oscillation
RF	Radio Frequency
ULF	Ultra Low Frequency
VGIC	Voltage-gated ion channel
VLF	Very Low Frequency

Geomagnetic field and navigation—animal migration

It is widely accepted that animals have a sense of orientation on Earth which allows them to migrate toward specific directions, travel long distances and find specific locations, with most migratory animals (including birds) migrating at night[1–4]. The biophysical explanation of this phenomenon has been a great challenge in science and, especially after the early 1970s, one of the hottest topics in bioelectromagnetics/electromagnetic biology with hundreds of scientific publications trying to explore and resolve this mystery[1,2,5,6]. It was reasonable to assume that such an ability is related to the sensing of the geomagnetic field (GMF), which is mainly static with specific orientation and a magnetic axis forming an angle of a few degrees with the Earth's geographic north–south axis and reversed polarity, i.e. the geomagnetic north pole is close to the geographic south pole and vice-versa. The intensity of the GMF is maximal at the poles and minimal at the equator having an average value at intermediate latitudes of ~ 0.5 G or ~ 50 μT[5–7]. Magnetic compasses, which are thin magnets rotating around

[1]Choremeion Research Laboratory, 1st Department of Paediatrics, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece. [2]Electromagnetic Field-Biophysics Research Laboratory, Athens, Greece. [3]Department of Physics, Section of Nuclear and Particle Physics, National and Kapodistrian University of Athens, Athens, Greece. [4]Medical School, University Research Institute of Maternal and Child Health and Precision Medicine, and UNESCO Chair On Adolescent Health Care, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, Athens, Greece. ✉email: dpanagop@biol.uoa.gr

a vertical axis in their center, orient parallel to the GMF lines indicating the geomagnetic south which is very close to the geographic north pole. This is how people have been navigating for centuries by use of magnetic compasses since they were discovered in the ancient times.

During the past fifty years, several hypotheses for mechanisms of animal magnetoreception have been proposed, related mainly to a) biogenic magnetite found in living organisms, b) light-sensitive chemical magnetoreception, and c) electromagnetic induction. There are certain weaknesses in those hypotheses which we believe is one reason why the phenomenon of animal magnetoreception and navigation has remained unexplained to this day[1,3,4,8–11]. According to[1], "determining how animals orient themselves using Earth's magnetic field can be even more difficult than finding a needle in a haystack. It is like finding a needle in a stack of needles."

Suggested hypotheses for a mechanism of animal magnetoreception

The first hypothesis is based on the existence of magnetite nanoparticles (Fe_3O_4) in living organisms[12,13]. Such particles were first found in denticle caps of chitons and in magnetotactic bacteria[14–18]. Later it was reported that they were also detected in certain other species including humans, birds and bees[1,9,11,13]. It was suggested that chains of magnetite crystals called magnetosomes found in the aforementioned organisms, reoriented by the GMF could act as compass needles subserving their magneto-sensing ability. It was claimed that magnetosome chains anchored to nerve cell membranes near mechanically-gated ion channels were present in fish[10,19,20], and was hypothesized that these chains aligned under the action of the GMF they could possibly cause gating (opening/closing) of such ion channels[1,3,4,9–13,21–24]. Yet, despite the many publications on magnetite-based magnetoreception, no numerical calculations of the force/torque exerted by the GMF on magnetosomes were presented or shown to produce the pressure required to open/close mechanically-gated ion channels. Neither was shown how exactly this pressure is exerted on such ion channels by reorientation of magnetosomes supposedly anchored in the plasma membrane. Thus, suggestions on magnetite-based magnetoreception remain largely hypothetical, and in our view, complicated and unlikely. Ernst and Lohmann[25] observed orientation changes (lasting at least 10 h after exposure) in Caribbean spiny lobster (*Panulirus argus*) in response to magnetic pulses that could theoretically cause magnetite rotation. But the effect could also be due to the fact that electromagnetic pulses affect cells in various ways and initiate a plethora of biological effects[26–29]. Thus, the observed effect may be compatible with, but does not actually confirm the magnetite hypothesis. In a series of experiments Malkemper et al.[30] found no evidence of magnetite-based magnetoreceptor in the pigeon ear and suggested that any possible inner ear magnetoreceptor would likely be activated by electromagnetic induction. This is in line with Treiber et al.[31], and Edelman et al.[32] who found that structures previously suggested as strong candidates for magnetite-based magnetoreceptors in pigeons were macrophages or non-magnetite iron accumulations. Moreover, Edelman et al.[32] correctly pointed out that in order for magnetic particles to be magnetoreception sensors they should be found inside cells at exactly the same location and be associated with nerve tissue in many individuals (in fact in all) of a certain species, which is definitely not the case with the animals in which magnetosomes have been found. Thus, even though Kirschvink et al.[10] claimed that magnetite biomineralization is common in all living organisms including all animals and is the key for magnetoreception, this is apparently not the case, apart perhaps from the magnetotactic bacteria, in which magnetosome chains of similar length to the bacteria were clearly detected, and may indeed orient like magnetic needles in the GMF, dragging and orienting in this way the entire organism.

The second hypothesis suggests that a light stimulus on a cryptochrome protein, a photoreceptive molecule in the retina of bird eyes, induces the formation of pairs of free radicals (atoms/molecules each one having an unpaired electron) which, in the presence of a magnetic field, align their spin momentums parallel or antiparallel to the field, and, in this case, the GMF may change a radical pair from a singlet (parallel spins) to a triplet (antiparallel spins) state and vice-versa. Then the corresponding signal related to changes in the singlet/triplet yield is transferred to some hypothetical specialized sensory cell type that recognizes the GMF intensity and direction[4,10,11,33–38]. This possibility has been specifically examined for birds and is considered the most prevailing hypothesis, supposedly supported by chemical, physical, and biological facts[4,39,40]. But it has never been explained how exactly the singlet/triplet yield in a sensory cell could provide the animal with the sense of the GMF intensity and direction. Moreover, all free radicals are extremely bioactive because of their unpaired electron and have an extremely short lifetime (usually ~10^{-11}-10^{-7}s)[41–44]. How do they provide sufficient time for a complicated biological event to take place? Certain authors refer to "long-lived" radical pairs[4] but they do not report their molecular identity or how much longer are their lifetimes than those of ordinary free radicals. Most importantly, how can light which is non-ionizing, apart from vacuum ultraviolet which gets absorbed in the upper atmosphere, induce the formation of radical pairs which is ionization? The only known physical effect that induces the formation of radical pairs with non-ionizing radiation is the Electron Spin Resonance (ESR) effect, in which the formation of free radical pairs with opposite electronic spins is induced by Radio Frequency (RF)/microwave (300 kHz-300 GHz) radiation (usually 9–36 GHz) in the presence of a very strong and spatially inhomogeneous magnetic field with corresponding intensities ranging between 100 μT and 1.3 T (already significantly stronger than the GMF which actually is locally homogenous). The equation connecting the frequency (ν) with the magnetic field intensity (B) in the ESR effect in the case of free electrons, is:

$$h\nu = g_s \frac{q_e \hbar}{2m_e} B$$

(g_s is the spectroscopic splitting factor, $\frac{q_e \hbar}{2m_e} = 9.27 \times 10^{-24}$ J/T the Bohr's magnetone with q_e, m_e the electronic charge and mass respectively and $\hbar = h/2\pi$, h the Planck's constant)[45]. If a radical pair is to be formed by visible light, this would require about four orders of magnitude even stronger magnetic field (than 100 μT—1.3 T),

which is at least 20,000 times stronger than the GMF. The above facts make extremely unlikely the formation of radical pairs by light in the presence of the GMF, if not impossible. Furthermore, if light is necessary for animals to be able to orient and navigate, why most migratory animals (including birds) migrate at night? The argument provided by Mouritsen[4]that light-dependent magnetoreception could (hypothetically) be activated by just a few photons and such a quantity of light is always present, is not convincing. Even if birds migrating during the night receive a few photons in darkest nights, what about migrating fish at the bottom of oceans or animals moving underground with literally no photons present? And why should an important sense be based on a trigger that is limitedly available or not available at all? In our view, this hypothesis is also completely conjectural and unrealistically complicated. It is unlikely that nature would work via complicated and thus, energy-consuming mechanisms, when it could work in simpler and more economic terms (Occam's razor or law of parsimony)[46]. We searched for the facts supporting the hypothesis that magnetoreception requires light[4,33,34]. We did find evidence that bird orientation is affected by light[37], which is reasonable, as birds definitely use visual landmarks as complementary cues for their navigation, but we found no evidence that bird or other animal orientation requires light and that it cannot occur without it. Therefore, it is mystifying to us that dozens of publications insist on a hypothesis that combines magnetoreception with light sensitivity. An experimental study that showed birds losing their orientation in the presence of "electromagnetic noise"[47]and was reported[3]to support the radical-pair hypothesis states that "the effects might be explained if hyperfine interactions in light-induced radical pairs or large clusters of iron-containing particles are involved". Thus[47], provided neither proof nor support of the radical-pair or the magnetite hypotheses, but simply speculated that perhaps the recorded effect could be explained by one of these two hypotheses. Another study found that an Extremely Low Frequency (ELF) magnetic field (300 μT, 50 Hz) shortened the 24-h circadian period in fruit flies and that this effect did not occur in mutated flies that could not produce cryptochrome[48]. This result was also interpreted as supporting the role of cryptochrome in magnetically sensitive behaviour (and, thus, the radical pair magnetoreception hypothesis) which is again not the case, as the circadian period in all forms of life on Earth is controlled by the 24-h light periodicity, the sensing of which involves cryptochrome/photoreceptive proteins. If the authors studied magnetic field effects not related to circadian rhythms and light they would find no dependence on cryptochrome, as is the case with the vast majority of the recorded ELF magnetic field effects on living organisms[6,7,26–29,49,50].

The third hypothesis is based on the Faraday-Henry law of electromagnetic induction[51] which states that when the magnetic flow through a surface S enclosed by a closed conductive line l changes with time, a voltage (and consequently an electric field) is induced along the closed line. The law implies that any accelerating animal movement in a static and locally homogenous magnetic field such as the GMF will induce an electric field in its body. In this way, the magnetic field would be converted into an electric signal detectable by putative voltage-sensing cells/organs named electroreceptors, such as the ampullae of Lorenzini in elasmobranches (e.g. sharks, rays, etc.)[1,52–55], or the inner ear, or the olfactory epithelium tissue of birds[23,56]. This scenario has not been investigated in invertebrate species, because no "identified" electroreceptors have been attributed to these animals[57]. Electromagnetic induction has been studied in elasmobranches[58,59]and was recently proposed to underlie the navigation of pigeons[30,60], as suggested earlier[56]. It is considered that for animals to be able to sense the GMF via electromagnetic induction, large internal ring-shaped structures filled with conductive liquid would be needed which are more likely to exist in aquatic animals, and, thus, for terrestrial animals another mechanism should be sought[4]. But in all living organisms, including terrestrial mammals, including humans, there are endogenous weak electric currents consisting of ion flows through cells, cell membranes, and whole tissues/organs, controlling practically all cellular/tissue functions. These endogenous physiological currents flow through the extracellular and intracellular aqueous solutions and through ion channels in the plasma membranes[61–63]. Therefore, while electromagnetic induction is an apparent physical effect, we do not see why specific tissue structures are needed for electromagnetic induction to take place in any animal.

The possibility of electromagnetic induction in the GMF as a mechanism for animal orientation/navigation has not been considered so far in accordance with the voltage-gated ion channels (VGICs) and the ion forced-oscillation (IFO)-VGIC mechanism, which is an accepted biophysical mechanism for electromagnetic field (EMF)-bioeffects[44,64–67]. By contrast, it was considered in relation to some hypothetical unknown organ or cell type ("electroreceptor") presumably located in the eyes[34]or in the olfactory epithelium[23]. But the eyes or any sensory tissues are connected to neurons that transport the electromagnetic signals to the brain, and nerve cells have higher percentages of VGICs in their plasma membranes than other types of cells[49,68,69].

Apart from the various hypotheses for a mechanism to explain animal magnetoreception, orientation and navigation with the weaknesses discussed above, the experimental work in the field is extensive, sophisticated, and important by itself[1–4,9–11,15–25,30–32,34–40].

Animal sensors for magnetoreception

The existence of specific organs to detect EMFs seems to be a common assumption among many researchers who study animal electro/magnetoreception[4]. Threshold electric field values that can be detected by various animals/organisms have been reported in papers to be as low as 10^{-5}-10^{-4} V/m and even lower for certain species such as the elasmobranches (~10^{-6} V/m)[1,70].

But why should there be specific organs (receptors) to detect EMFs when all animals and plants/trees are equipped with the most sensitive EMF-sensors, in large numbers in all membranes of each of their trillions of cells, which are no other that the VGICs, the most abundant class of transmembrane proteins forming ion channels in the cell membranes in all cells of all animals[68,69]? It seems that this fact has escaped researchers' attention even though certain studies had long ago indicated the importance of VGICs as potential EMF sensors[71–73]. Also, it seems that our published theoretical model has escaped attention, even though it has demonstrated, by equations and accurate numerical calculations based on molecular data on the structure and function of VGICs, that polarized and coherent applied oscillating EMFs, especially in the lower frequency bands, namely Ultra

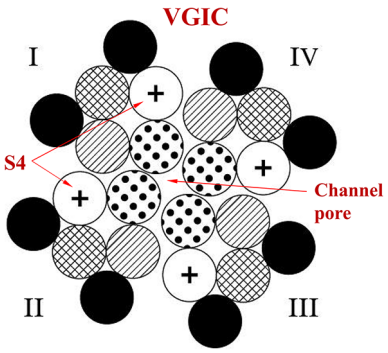


Fig. 1. Schematic cross-section of a VGIC with the four units (I-IV) in symmetrical positions around the channel pore. Each unit consists of six parallel α-helices/subunits (S1-S6). The voltage-sensors of the VGIC are the four S4 positively charged helices (+) one in each unit. The S4 are the closest to the pore-forming S5-S6 helices having less than 1 nm distance from the pore (modified from[74]).

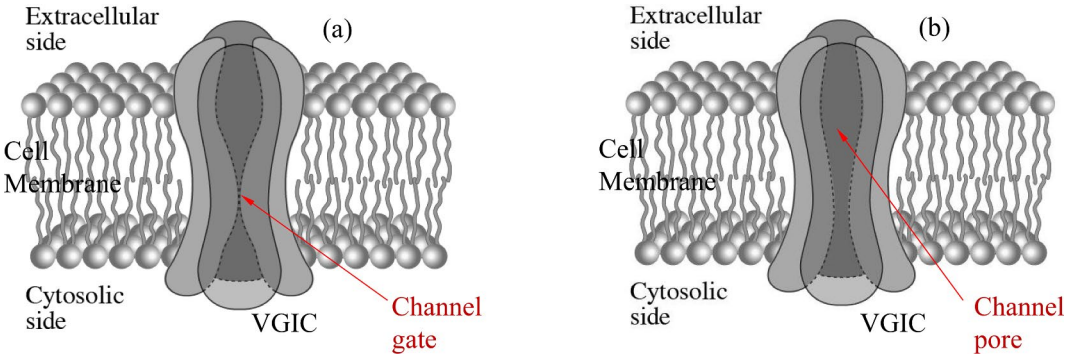


Fig. 2. Schematic representation of a VGIC (**a**) closed; (**b**) opened.

Low Frequency (ULF: 0–3 Hz), ELF (3–3000 Hz), and Very Low Frequency (VLF: 3–30 kHz), can induce gating (opening/closing) in VGICs at very low threshold intensities (down to ~10^{-5} V/m)[44,64–66]. Instead, complicated scenarios involving specific hypothetical organs supposedly serving as "electroreceptors" or "magnetoreceptors" have been considered and developed. While several studies have considered the involvement of ion channels in the final steps of eliciting a cellular effect in combination with the various suggested hypothetical mechanisms[3,10], only a few recent studies have suggested a critical role of the VGICs, mostly in combination with electromagnetic induction-based magnetoreception[58–60], and even those few studies, did not consider our detailed theoretical model.

The suggestion we have introduced that VGICs serve as the sensitive EMF detectors in animals[44,64–66]does not contradict the existence of specific structures in certain animals such as the ampullae of Lorenzini in elasmobranches[1,52,53]which may act as signal amplifiers in those animals, collecting and amplifying signals from many VGICs and many cells. The existence of amplifying mechanisms in certain species may explain their enhanced electromagnetic sensitivity compared to other animals and to the VGIC sensitivity that we have theoretically calculated[1,44,66].

VGICs: The most sensitive electro/magnetoreceptors. Structure and function. Purpose of the study

It is known that VGICs convert from open to closed states and vice-versa by membrane voltage changes $dV \geq 30$ mV which exert forces on their voltage-sensors (more specifically VGICs respond to changes between ~30 and ~100 mV). The voltage sensors of the VGICs are four symmetrically arranged, transmembrane, positively charged α-helices (subunits), each one named S4. They occupy the 4th position in a group of 6 parallel α-helices (S1-S6) (Fig. 1). They are the closest helices to the pore apart from the S5-S6 helices which form the pore walls. The channel consists of four identical such groups (units I-IV) in symmetrical positions around the pore of the channel (Fig. 1, 2a, b). More specifically, the sensors are positive Lys and Arg amino-acids in the S4 helices. The effective (net) charge on each S4 sensor has been calculated to be $q = 1.7q_e$, where q_e is the elementary charge. The positive charges of the S4 sensors are paired with negative charges from adjacent helices so that the net charge in the pore of the channel is zero. The ions pass dehydrated and in single file through the channel pore. The narrowest part of the pore is called the pore gate. At least four dehydrated mobile ions are very close any moment to the S4 sensors at a distance of the order of 1 nm, as – except for the ion(s) that may be passing through the pore gate any moment or is just outside the pore gate ready to pass – at least three more are bound

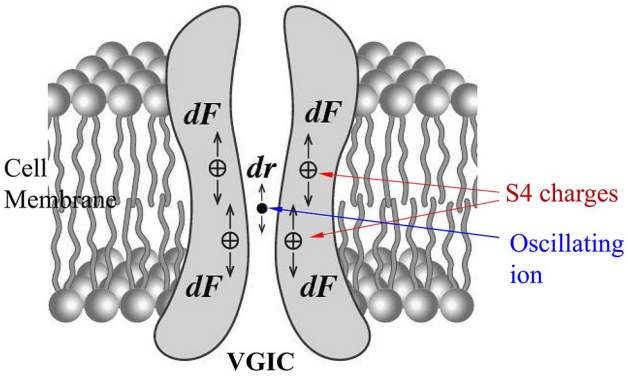


Fig. 3. Schematic representation of the forces ***dF*** exerted on the S4 positive charges in a VGIC due to displacement ***dr*** of an oscillating ion in the channel pore.

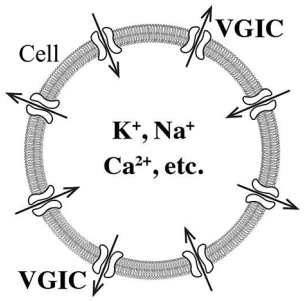


Fig. 4. A cell with inward and outward ion flows through VGICs in its plasma membrane and consequent alterations in intracellular concentrations of critical ions (K^+, Na^+, Ca^{2+}, etc.).

at specific ion-binding sites very close to the gate[67,69,74–78]. While VGICs are normally gated by ~30–100 mV voltage changes in the very strong transmembrane field, in other words respond to field changes between 3×10^6 and 10^7 V/m, they may also respond to very weak polarized, coherent, and varying EMFs down to ~10^{-5} V/m via the forced-oscillation such EMFs induce on mobile ions in close proximity (<1 nm) to the sensors. This happens because the force exerted on the S4 sensors by oscillating ions in close proximity, depending upon the inverse third power of the distance between charges (see Eq. 2 below), is much greater than a direct force from an externally applied EMF[44]. The aforementioned (at least) four ions close to the pore gate, once forced to oscillate in phase, exert constructive forces on the S4 sensors able to gate the channel, and this is a critical point for understanding the described IFO-VGIC mechanism (Fig. 3). The ion transit time through an open VGIC (e.g. a VGIC sodium channel) is calculated to be ~0.4×10^{-7}s[64,65,67], and the time needed for the channel to open/close is ~2.5×10^{-5}s[69]. This gives enough time to any polarized EMF oscillating with a frequency up to ~100 kHz to interact with the channel sensors during just one semi period and cause gating (opening/closing) with subsequent alterations in intracellular ionic concentrations and cell redox state and homeostasis (Fig. 4).

We have shown in the IFO-VGIC mechanism by precise numerical calculations that VGICs respond to changes of polarized and coherent electric fields down to ~10^{-5}-10^{-4}V/m[44,65–67], which is in impressive agreement with the reported threshold intensities for man-made EMFs to be sensed by various animals and cell/tissue cultures[1,70,79,80], and very close to the increased sensitivity of elasmobranches. VGICs exist in great numbers in all cell membranes of all living cells. Moreover, as mentioned already, their numbers/percentages are significantly greater in neurons (nerve cells) as the Na^+ and K^+ VGICs are necessary for the transmission of the nerve impulses, and especially in brain neurons[49,68,69].

The purpose of this theoretical study is to test whether the IFO-VGIC mechanism can explain the sensing of the GMF by moving animals, and specifically, whether it can explain the sensing of their direction and position in relation to the GMF, which are both necessary for orientation and navigation.

Biophysical mechanism of animal orientation and navigation

Applying the IFO-VGIC theory to the problem

Consider an animal, e.g. a bird, moving in any direction parallel to the Earth's surface with a drift velocity u_{an} ~ 20 m/s (Fig. 5). Every charged particle in its body, and specifically a mobile ion of charge zq_e (z the ion valence, and q_e the elementary charge) within a VGIC and close to the S4 sensors (at a reasonable distance of ~1 nm) in a plasma membrane in any cell of this animal, is subjected to a magnetic force by the GMF of magnitude,

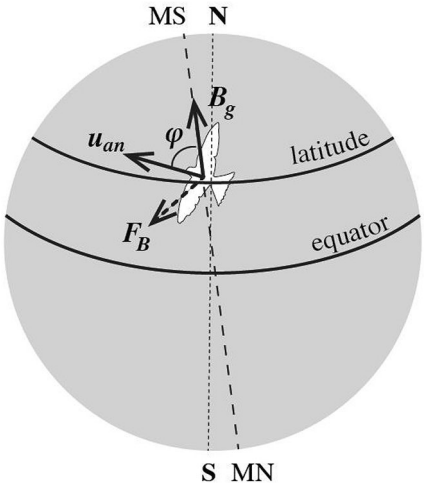


Fig. 5. Magnetic force $\boldsymbol{F_B}$ on electrically charged particles (mobile ions) in the cells of a migrating bird on Earth flying with velocity $\boldsymbol{u_{an}}$ in a direction forming angle $\boldsymbol{\varphi}$ with the geomagnetic field intensity $\boldsymbol{B_g}$ which is unique at every latitude. For any given velocity magnitude and velocity variation rate, the magnetic force depends upon $\boldsymbol{\varphi}$ and $\boldsymbol{B_g}$ (direction of motion and latitude), providing the migrating animal with the sense of its direction and position on Earth. (N: geographic north pole. S: geographic south pole. MN: magnetic north pole. MS: magnetic south pole).

$$F_B = zq_e u_{an} \times B_g, \text{ or } F_B = zq_e u_{an} B_g \sin\varphi \tag{1}$$

(φ is the angle between the animal velocity u_{an} and the GMF intensity B_g).

This magnetic force is vertical to the animal velocity and would result in a curved motion of the ion within the channel protein. The radius of this curve ($r = m_i u_{an}/zq_e B_g$) depending upon ion mass (m_i), charge (zq_e), velocity (u_{an}), and B_g is calculated to be of the order of 0.1 m. This is too large compared to the available space for an ion within a channel protein (a few Å), and thus we can reasonably accept that the ion's displacement dr within the channel due to the magnetic force is practically linear.

Such magnetic forces will be exerted on any mobile ion in the animal's body and specifically within any VGIC, causing a displacement dr from its "initial" position which in turn exerts an additional Coulomb force dF on the S4 voltage-sensors of the VGIC which may result in the opening/closing (gating) of the channel[64,65,73] (Fig. 3). This additional Coulomb force on each S4 sensor due to the ion displacement dr is described by the equation:

$$dF = -\frac{q \cdot zq_e}{2\pi\varepsilon\varepsilon_o r^3} dr \tag{2}$$

with $q = 1.7\ q_e$ the effective (net) charge of the S4 sensor, zq_e the mobile ion charge, $\varepsilon_o = 8.854 \cdot 10^{-12}$ N^{-1} m^{-2}C^2 the vacuum permittivity, $\varepsilon \sim 4$ the relative permittivity of the ion channel, and $r = 1$ nm the "initial" distance between the two charges[75,81].

The minimum required force on the S4 charge, perpendicular to the membrane, generated by a change of 30 mV in the transmembrane voltage required to gate the channel normally, is calculated to be[44,64–66]:

$$dF = 8.16 \times 10^{-13}\ \text{N} \tag{3}$$

This force, according to Eq. 2, corresponds to a minimum required displacement of one z-valence ion within the channel along the direction of the channel axis[44,64–67]:

$$dr = 4 \times 10^{-12}/z\ (\text{in m}) \tag{4}$$

According to the IFO-VGIC mechanism and the standard oscillation mechanics, the equation that describes the motion of this mobile ion in an animal moving with velocity u_{an} forming an angle φ with the GMF intensity B_g, with the forces exerted on it, is written as:

$$m_i \frac{d^2 r}{dt^2} + \beta \frac{dr}{dt} + m_i \omega_o^2 r = zq_e B_g u_{an} \sin\varphi \tag{5}$$

where m_i is the ion mass (e.g. $m_i \sim 3.8 \times 10^{-26}$ kg for sodium ions), r the ion position during its displacement due to the applied magnetic field, z the ion valence, $q_e = 1.6 \times 10^{-19}$ C the elementary charge, β the damping coefficient (found to be within channels, $\beta = \frac{E_m z q_e}{u_o} \cong 6.4z \times 10^{-12}$ kg/s, with $E_m \sim 10^7$ V/m the transmembrane electric field, and $u_o = 0.25$ m/s the maximum ion velocity through an open channel), and $\omega_o = 2\pi\nu_o$ (ν_o the ion's oscillation self-frequency)[44,64,65,67].

The right part of Eq. 5 is the magnetic force on the ion. The first term of the left part ($m_i \frac{d^2r}{dt^2}$) is the resultant force, the second term ($\beta \frac{dr}{dt}$) is a damping force, and the third term ($m_i\omega_o{}^2 r$) a restoring force exerted by the medium[44,64–66]. These are the standard forces in a forced-oscillation equation, with their parameters depending on the specific system.[Note: The damping force is always opposite to the velocity of the particle. The restoring force is always directed toward the equilibrium position and it is a function only of the position of the particle. Any particle within a material medium displaced from a considered position will receive a restoring force toward its initial position.]

In order for an applied polarized and coherent electric or magnetic field to be able to gate (open/close) a VGIC it has to be oscillating/varying in time. Invariable static fields such as the very strong cell membrane field or the geomagnetic and the geoelectric field (GEF) do not normally cause VGIC gating and subsequent initiation of biological/health effects. Those fields only induce biological/health effects during 20–30% changes in their intensities taking place physiologically during membrane depolarizations, or during magnetic storms respectively[6,7,82]. In the case of an oscillating/varying magnetic force, Eq. 5 describes a forced-oscillation of the ion (IFO). In the simplest case of a harmonically oscillating magnetic force $F_B = F_{Bo} sin\omega t$ with amplitude F_{Bo} and circular frequency $\omega = 2\pi\nu$ (ν the frequency) due to a harmonically varying animal velocity,

$$u_{an} = u_{ano} \sin \omega t \tag{6}$$

in a direction forming an angle φ with the GMF B_g, the solution of Eq. 5 describing the forced-oscillation of the mobile ion is[44,64,65,67]:

$$r = \frac{B_g u_{ano} z q_e \sin \varphi}{\beta\omega} \cos\, \omega t + \frac{B_g u_{ave} z q_e \sin \varphi}{\beta\omega} \tag{7}$$

Since the animal velocity varies but is always in one direction, $sin\omega t > 0$, or $0 < \omega t < \pi$. This does not affect Eq. 7. In this case u_{ano} is the average velocity (~ 20 m/s) which varies with animal movement, e.g. in birds with winging.

The first term of the solution (Eq. 7) is an harmonically oscillating term with an amplitude

$$A = \frac{B_g u_{ano} z q_e \sin \varphi}{\beta\omega} \tag{8}$$

and the second is a constant term equal to this amplitude A. The constant term displaces the whole oscillation at a distance equal to A. Thus, the moment when the variable force is applied (i.e. when the animal acceleration, e.g. winging, starts) there is a sudden-instant push of the whole oscillation at a distance equal to A due to this constant term (Fig. 6). For pulsing fields with on/off pulses this instant push takes place repeatedly at the onset of every next pulse, making the pulsing fields considerably more bioactive than corresponding continuous-wave fields. The maximum displacement of the ion in one direction during the forced-oscillation is always $2A$ (Fig. 6).

When the temporal variation in the velocity is not harmonic but periodic in general, the result is still the same, with the time dependence of the varying term not harmonic but simply periodic.

Therefore, in order for an applied oscillating EMF to be able to induce biological effects via opening/closing of VGICs it must be able to displace a z-valence mobile ion at a distance equal or greater to the distance given by Eq. 4, in other words it must induce an IFO that satisfies the condition

$$2A \geq 4 \times 10^{-12}/z \text{ (in m)} \tag{9}$$

Hence, the potential of an EMF to induce VGIC gating is proportional to the IFO amplitude, and thus, proportional to its intensity and inversely proportional to its frequency (Eq. 8).[Note: In previous publications we wrote $A \geq 4 \times 10^{-12}$ m for a single-valence ion and considered a double amplitude ($2A$) only for pulsed fields. Actually, the max displacement is always $2A$ whether the field is continuous-wave or pulsed.]

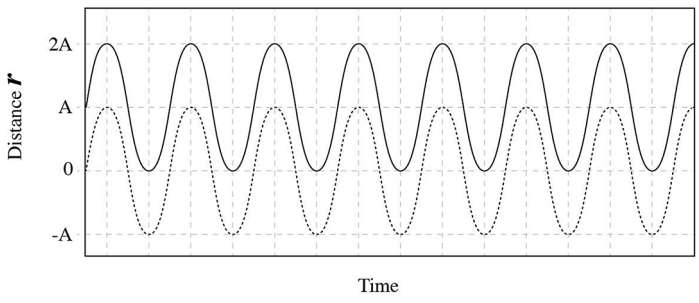


Fig. 6. Representation of the ion oscillation (displacement ***r*** from initial position with respect to time) due to a harmonically varying applied electric or magnetic force (solid line) (as described by Eq. 7 in the case of the GMF). The same oscillation without the constant term in Eq. 7 is represented by the dashed line. In both cases the maximum ion displacement in one direction during the oscillation is $2A$ (A the oscillation amplitude). The moment the force is applied there is an instant displacement of the whole oscillation at a distance equal to A.

Let us accept that u_{an} varies by ± 50% from the average velocity u_{ano} due to the bird's winging (which is a reasonable variation for a moving animal), with the bird winging a few times within 1 s (accelerating), and then continuing without winging (decelerating) for another 9 s which is a usual case for a flying bird/moving animal, and that this mode of winging is repeated during its flight (Fig. 7). In such a realistic case the basic frequency of velocity variation is 0.1 Hz.

What is necessary for an animal/human to navigate is a coordinate system with a reference axis (which in this case is the GMF axis) and a zero point on it. Then, in cyclic coordinates in two dimensions, the location and orientation at each point of the journey is determined by a) the distance from the zero point, and b) the angle between animal velocity and the reference axis. We may reasonably accept that the zero point is the starting point, usually the home or birthplace of the animal.

In the following, instead of the resultant GMF intensity B_g, we shall consider separately the effects of its horizontal ($B_{g//}$) and vertical ($B_{g\perp}$) components which have unique values at every specific location along the GMF axis (i.e. at every different latitude).

Sensing the direction of motion (angle between velocity and $B_{g//}$)

The intensity of the horizontal component of the GMF $B_{g//}$ at a specific location required to gate a VGIC oriented parallel to the magnetic force via one z-valence ion moving with a periodically varying animal velocity of average value u_{ano} = 20 m/s in a direction forming an angle φ with $B_{g//}$ must satisfy Condition 9:

$$2\frac{B_{g//}u_{ano}zq_e\sin\varphi}{\beta\omega} \geq 4\times10^{-12}/z \quad (\omega \text{ in rad/s}, u_{an} \text{ in m/s}, B_{g//} \text{ in T}) \tag{10}$$

Replacing u_{ano} by 0.5 u_{ano} to incorporate the velocity variation, and substituting the values of the various parameters, we get:

$$B_{g//}\sin\varphi \geq 0.5\times10^{-4}\nu/z \quad (\nu \text{ in Hz}, B_{g//} \text{ in T}), \tag{11}$$

or

$$B_{g//}\sin\varphi \geq 50\nu/z \quad (\nu \text{ in Hz}, B_{g//} \text{ in } \mu\text{T}) \tag{12}$$

For four double-valence ions acting simultaneously on the S4 sensors, the right part is divided by 8 and the condition becomes:

$$B_{g//}\sin\varphi \geq 6.25\nu \quad (\nu \text{ in Hz}, B_{g//} \text{ in } \mu\text{T}) \tag{13}$$

Substituting ν by 0.1 Hz, we finally get, approximately:

$$B_{g//}\sin\varphi \geq 0.6\,\mu\text{T} \tag{14}$$

which is the final condition for the magnitude of the horizontal component $B_{g//}$ of the GMF at a specific location to be sensed by an animal moving horizontally with an average velocity u_{an} ~ 20 m/s forming an angle φ with $B_{g//}$. For $\sin\varphi = 1$, this final condition is well satisfied (by ~ 25–58 times), since $B_{g//}$ ~ 15–35 μT at North African and European latitudes[83].

In this case the animal velocity is vertical to $B_{g//}$. Thus, when the animal moves vertically to $B_{g//}$, i.e. approximately in the east–west direction, its motion in the GMF causes a maximum effect on VGIC gating, which

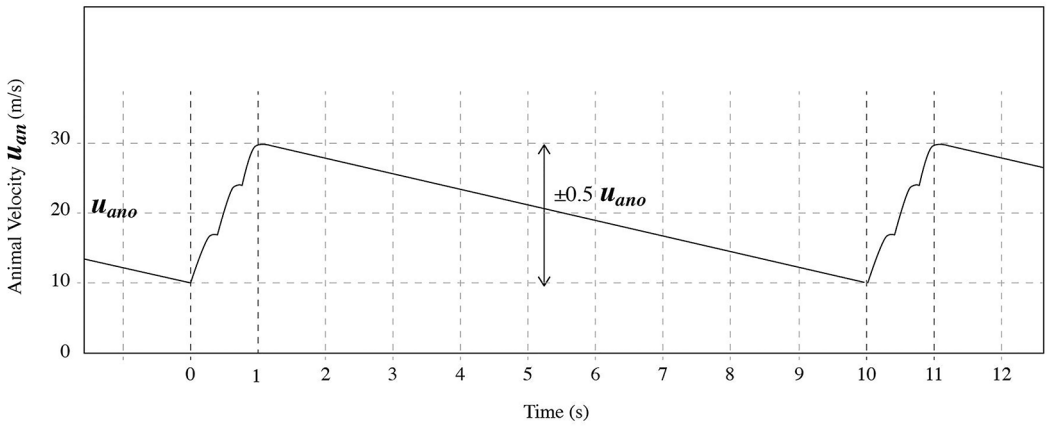


Fig. 7. Periodic variation in the velocity u_{an} of a migrating bird with respect to time: Increase in the velocity from 0 to 1 s by three flutters, slowing down for the next 9 s with no fluttering, acceleration by another three flutters between 10th and 11th s, and so on.

may be sensed by the animal as a type of mild cellular stress. The effect on VGIC gating and the corresponding cellular stress will diminish as the angle between the animal velocity and the $B_{g//}$ decreases from $\pm\pi/2$ to zero depending on $sin\varphi$, and thus, the sensing will be different for every different direction of the animal motion, and the effect will be zero when the animal moves along $B_{g//}$. Because Cond 14 for $sin\varphi = 1$ or $\varphi = \pm\pi/2$ is satisfied by ~ 25–58 times, it comes that for $0 < \varphi < \pi/2$ it is still satisfied enough to provide the animal with a direction sensitivity of ~1.5–3.6 degrees which is reasonable and adequate for migration.

Thus, it seems that a migrating animal senses zero stress and has a most relaxed journey when it moves along the north–south direction of the GMF (along $B_{g//}$). The migrating animal receives a mild stress when it moves in any other direction, with this mild stress increasing as φ changes from 0 to $\pm\pi/2$ and becoming maximum with $\varphi = \pm\pi/2$ when the animal moves vertically to $B_{g//}$. This automatically provides the animal with the sense of direction in its motion. Whether the direction is left or right with regard to $B_{g//}$ we may assume it is known to a migrating animal, as all animals and humans have the sense of right and left at any moment.

Therefore, we have shown that animal acceleration parallel to the earth surface with any angle other than 0 (or 180) degrees from the horizontal component of the GMF induces a magnetic force on mobile ions in VGICs in their brains/bodies capable of altering VGIC state, and, consequently, cell homeostasis. This magnetic force depends upon the horizontal component of the GMF ($B_{g//}$) which has a unique value at every different latitude, the animal velocity (u_{an}), the angle between these two vectors, and the magnitude and rate of velocity variation. For any given values of $B_{g//}$, velocity, and velocity variation, it depends only upon $sin\varphi$ as shown by Cond. 14, providing the animal with the sense of direction (i.e. orientation).

Sensing the latitude (position along $B_{g//}$)

Sensing the declination of its velocity from the GMF north–south axis alone is not enough for a migrating animal to navigate. For this, the additional sensing of its position along the north–south axis (latitude) is required. Here comes the role of the vertical component of the GMF $B_{g\perp}$: Let us consider a drifting animal (e.g. bird, mammal, fish, insect, etc.) accelerating in any direction parallel to the Earth surface and thus vertically to the vertical component of the GMF $B_{g\perp}$. In this case $sin\varphi = 1$, and the requirement for a static magnetic field and an animal average velocity $u_{ano} = 20$ m/s varying periodically by ± 50% in order to be able to cause VGIC gating (opening/closing) is (as Cond 13):

$$B_{g\perp} \geq 6.25\nu \quad (\nu \text{ in Hz}, B_{g\perp} \text{ in } \mu\text{T}) \tag{15}$$

and again, for the accepted basic rate of 0.1 Hz in the ± 50% variation of the average velocity, the condition becomes approximately

$$B_{g\perp} \geq 0.6\,\mu\text{T} \tag{16}$$

The final Condition is well satisfied (by ~ 50–83 times), since $B_{g\perp}$ ~ 30–50 μT (for North Africa – Europe, or USA – Canada latitudes)[83], and thus, the animal can sense the vertical component of the GMF during its motion. This effect is independent of the direction of animal motion and only depends upon the magnitude of the GMF vertical component $B_{g\perp}$, which is (alike $B_{g//}$) unique for every different location along the north–south direction (latitude). Thus, the animal can sense the latitude of each location along its motion. As the animal moves from the meridian toward the poles, the magnitude of the vertical component of the GMF $B_{g\perp}$ increases and vice-versa, and this provides a unique sense of its position along the GMF north–south axis.

We note that, according to our calculations, the effect of sensing the latitude is about twice stronger than the maximum effect of sensing the direction of motion (Cond. 16 is satisfied by 50–83 times, while Cond. 14 is satisfied by 25–58 times when $sin\varphi = 1$).

Electromagnetic induction and its complementary role in sensing the latitude

As we showed, the GMF can directly induce a biological response related to the declination of animal velocity from the GMF north–south axis and the latitude of the location. A similar effect in sensing the latitude can be elicited indirectly by the magnetically induced electric field E_{ind} in the accelerating animal body according to the Faraday-Henry law of electromagnetic induction (Maxwell's third equation of EMF):

$$\oint_l \vec{E}_{ind} \cdot d\vec{l} = -\frac{d}{dt}\int_S \vec{B} \cdot \vec{u}_N dS \tag{17}$$

($\vec{B}$, $\vec{E}_{ind}$, the magnetic and the induced electric field intensities respectively, $d\vec{l}$ an incremental length along a closed conductive path l of induced electric field circulation in the animal body enclosing a surface S, and $\vec{u}_N$ the unit vector vertical to S).

The left part of Eq. 17 represents the circulation of the induced electric field along the closed line l, and the right part is the temporal change of the magnetic flow $\int_S \vec{B} \cdot \vec{u}_N dS$ through the enclosed surface S.

Let us consider S parallel to the Earth surface. In this case the horizontal component of the GMF $B_{g//}$ has no effect as the second part of Eq. 17 is zero. Since $B_{g\perp}$ is vertical to and independent of S and can be considered invariable in time at the specific location, and assuming E_{ind} parallel to and independent of l, Eq. 17 becomes:

$$E_{ind} \oint_{l} dl = -B_{g\perp} \frac{dS}{dt} \tag{18}$$

Assuming for simplicity that l is by average a circular path of radius r including the surface S, and active S swept by the magnetic flow (considering S as an ellipse the one half axis of which r' is in the direction of motion with its length varying in time proportionally to the animal's acceleration a, thus $dr'/dt = a\kappa$, and $S = \pi r r'$, with r the other half axis) depending on animal acceleration*, we get

$$E_{ind} 2\pi r = B_{g\perp} \pi r \, a\kappa \tag{19}$$

or

$$E_{ind} = (B_{g\perp}/2) \;\; a\kappa \tag{20}$$

(E_{ind} in V/m, $B_{g\perp}$ in T, r in m, a in m/s^2, and κ a proportionality coefficient).*[Note: For $a>0$, $r'>r$; for $a<0$, $r'<r$; and for $a=0$, $r'=r$. Since acceleration/deceleration interchange during motion, we may accept that average r' equals r.]

Interestingly, we see that the induced electric field in the animal body is independent of r, the radius of the circular path, and thus independent of the animal's size, depending only upon $B_{g\perp}$ and a.

By replacing in Eq. 20, $a = 20$ m/s^2 the magnitude of bird acceleration during its flight that we have accepted ($2 \times 0.5 \times 20$ m/s^2), and $\kappa = 1$ s for simplicity, we get:

E_{ind} (in μV/m) $= 10 B_{g\perp}$ (in μT), and for $B_{g\perp} \sim 30$–50 μT, we get $E_{ind} \sim 300$–500 μV/m, or

$$E_{ind} \sim (30 - 50) \times 10^{-5} \, \mathrm{V/m} \tag{21}$$

This is the induced electric field intensity along a closed conductive path in the body/brain of a flying bird/moving animal.

According to the IFO-VGIC mechanism, in order to be able to cause VGIC gating, the induced electric field E_{ind} with circular frequency $\omega = 2\pi\nu$ (ν the frequency) and in the case of four z-valence ions oscillating in parallel and in phase, must satisfy the condition[44,64–67]:

$$\frac{E_{ind} z q_e}{\beta \omega} \geq 10^{-12}/z \tag{22}$$

where $q_e = 1.6 \times 10^{-19}$ C the elementary charge, and β the damping coefficient (being within an ion channel $\beta \cong 6.4\, z \times 10^{-12}$ kg/s). For double-valence ions we get:

$$E_{ind} \geq 1.2\nu \times 10^{-4} \quad (\nu \text{ in Hz}, E_{ind} \text{ in V/m}) \tag{23}$$

Substituting $\nu = 0.1$ Hz, the variation rate in animal velocity, the condition finally becomes:

$$E_{ind} \geq 1.2 \times 10^{-5} \, \mathrm{V/m} \tag{24}$$

The final condition provides the minimum induced electric field required to elicit a biological effect via VGIC gating and, as we can see, the calculated E_{ind} (Eq. 21) is greater by ~ 25–42 times.

Therefore, it comes that the effect of the magnetically induced electric field E_{ind} due to electromagnetic induction is about 50% smaller than the direct effect of the vertical component of the GMF $B_{g\perp}$ (which satisfies the corresponding Cond. 16 by ~ 50–83 times), and thus, E_{ind} contributes complementarily to the sensing of the latitude by the moving animal.

Altogether, it comes that the sensing of latitude by a migrating animal, via both the direct effect of $B_{g\perp}$ and the indirect effect of E_{ind}, is about 3 times stronger than the maximum sensing of its direction of motion via $B_{g//}$.

The case of stationary or slow-moving animals that quickly move their heads/bodies

The above numerical results refer to fast moving animals that accelerate towards the direction of their journeys (such as birds, fishes, wild mammals, hunting dogs, etc.). Yet, the described mechanism can also work for animals that move slowly or they are even confined/tethered but quickly move their heads/bodies perpendicularly to their body axis, i.e. left–right or up-down with respect to their body axis. In such a case we can assume similar movement rates as in Fig. 7, i.e. an animal that moves its body perpendicularly to its body axis three times left–right per second and then remains still for the next few seconds and all this is repeated every 10 s. We may assume a reasonable average left–right (or up-down) velocity of its head/body of approximately 1 m/s and a corresponding acceleration of approximately 12 m/s^2. We have 20 times smaller velocity than in the previous calculations (for Cond. 14, 16, and Eq. 21) but we now have 100% variation in the velocity (it varies from $-u_{ano}$ to u_{ano}) , and applying Cond. 10 we get approximately ten times weaker effect. Specifically we get $B_{g//} sin\varphi \geq 500\nu/z$ (ν in Hz, $B_{g//}$ in μT) instead of Cond 12, which for four double-valence ions, it becomes $B_{g//} sin\varphi \geq 62.5\nu$, and for $\nu = 0.1$ Hz, we finally get approximately $B_{g//} sin\varphi \geq 6$ μT which is satisfied by ~ 2.5–5.8 times for $sin\varphi = 1$ (which is now the case when the animal body axis is parallel to the GMF north–south axis). This shows that even a confined or tethered animal with zero velocity forward can still sense its orientation with respect to the GMF north–south axis by quickly moving its head/body perpendicularly to its body axis. Similarly, we can

get a corresponding condition to Cond 16 (with approximately ten times weaker effect) for the sensing of the latitude (vertical GMF component) $B_{g\perp} \geq 6$ μT, (satisfied by ~ 5–8.3 times), but only when the animal moves its head/body left–right ($sin\varphi = 1$) and not up-down, as in the latter case $sin\varphi = 0$ and there is no effect. Finally we can get a corresponding equation to Eq. 20 for the induced electric field in its head/body, in this case due to the horizontal GMF component $E_{ind} = (B_{g//}/2)\, a\kappa$ with ~ 1.7 times weaker effect due to the smaller acceleration (20/12). This gives $E_{ind} \sim (18–29) \times 10^{-5}$ V/m (instead of Eq. 21) which satisfies Cond 24 by ~ 15–24 times. In this case the induced electric field complements the sensing of the horizontal GMF component (orientation).

Thus, even stationary (confined/tethered) animals that quickly move their heads/bodies can sense their position and orientation in a lesser but still significant degree than the fast-travelling animals. In fact, all animals in some degree move their heads/bodies perpendicularly to their body axis during their journeys, increasing in this way their sensitivity of navigation.

Figure 8 shows a graphical summary of the mechanism described above for animal magnetoreception, orientation, and navigation.

Discussion

Review articles have underscored the inability of previously suggested biophysical mechanisms to explain animal magnetoreception, orientation and navigation on Earth[1,3,4,10], and more specifically, the "lack of biophysical mechanism through which the weak GMF might lead to the controlled depolarization of a sensory nerve membrane"[10]. In the present study we have described such a biophysical mechanism, even though we did not consider membrane depolarization specifically, but VGIC gating, which is a closely connected event, as VGICs are normally gated by membrane voltage-changes (including depolarizations) and vice-versa[68,69,77]. Specifically, we have described a biophysical mechanism of controlled VGIC-gating in the animal cells, due to magnetic (or magnetically induced) forces depending on animal position and direction of motion, and consequent alterations of intracellular concentrations of critical ions (K^+, Na^+, Ca^{2+}, etc.). These controlled alterations in cell homeostasis provide the animal with the sense of orientation and position on Earth and, thus, with the ability of navigation.

We have shown that the angle between animal velocity and GMF axis (direction of motion) as well as the position along the GMF axis (latitude) can be sensed by moving and periodically accelerating animals on Earth. The sensing is accomplished via the change elicited by the horizontal and vertical components of the GMF intensity and the induced electric field in the electrochemical balance of the plasma membranes in the animal cells, which in turn determines redox state and homeostasis in all cells, including neural. Hunting dogs have been observed to run a fast curse of 20–30 m before taking the direction to return home[50,84]. By doing this, they seem to activate their biological compass and their sense of orientation and position as the present study describes. Since nerve cells, especially in the brain, have higher percentages of VGICs than other types of cells/tissues, they are reasonably expected to be more affected in their electrochemical balance/homeostasis by EMFs including the GMF.

As repeatedly reported in the EMF-bioeffects literature, living organisms are not particularly affected by static electric or magnetic fields but mostly by oscillating/varying (and polarized) ones. This is of particular importance for understanding the IFO-VGIC mechanism, and the essence of the biological effects of EMFs, as the VGICs are not gated by the normal voltage/electric field across the cell membrane, but only by membrane

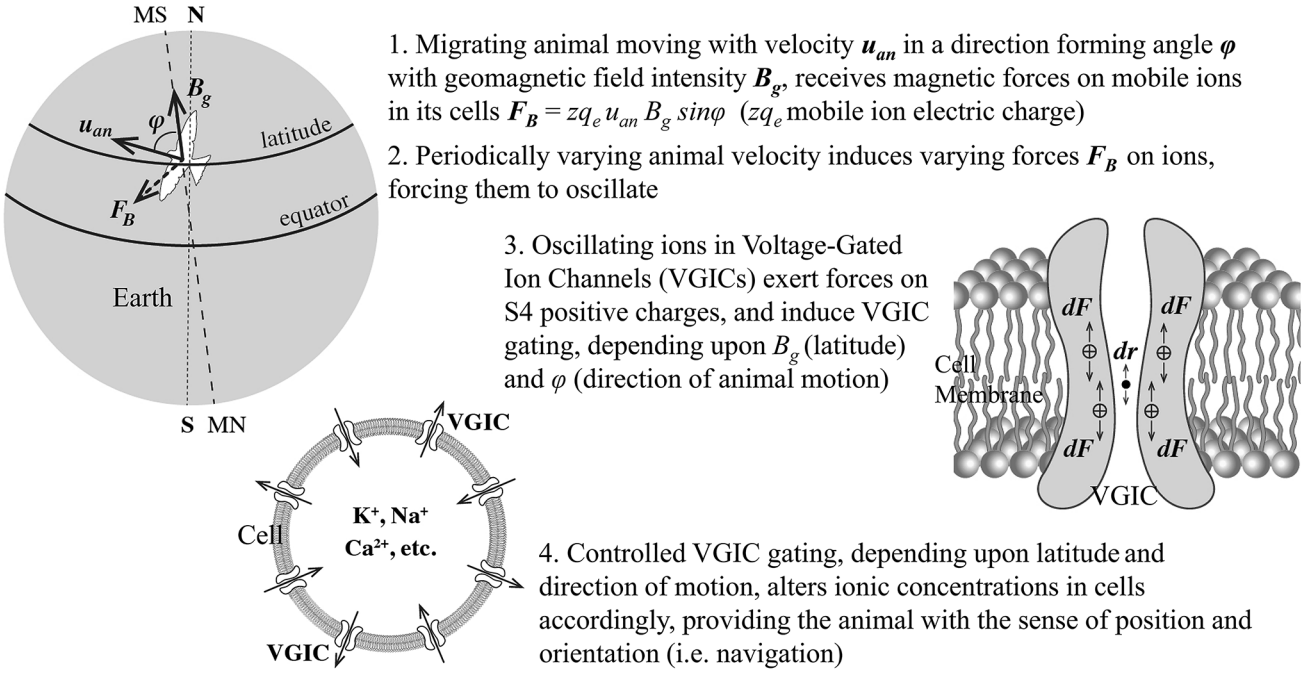


Fig. 8. Graphical Summary of the mechanism of animal magnetoreception, orientation, and navigation.

voltage changes of the order of 30% in this voltage/field that cause membrane depolarization. In other words, VGICs do not respond simply to the presence of an invariable (static) electric field. The same holds for the static magnetic fields. This is the reason why the GMF and the GEF are not particularly bioactive under normal conditions but they become bioactive when ~20% changes in their normal intensities occur during magnetic storms[6]. Biological effects from static electric or magnetic fields have been reported in the literature and they may be due to either very strong intensities that can directly interfere with the endogenous electric currents in cells and tissues, or to the onset/removal of the static field exposure, or to various other fields in the form of noise that most of the times coexist with the static fields and are due to the electric/electronic circuits that are used to generate the static fields. This should be investigated by those groups who have reported biological effects of static electric or magnetic fields.

As most people have observed, birds wing only sporadically during flight. They usually wing a few times and then fly a long distance for several seconds without winging. Similarly, fishes and other aquatic animals move their bodies/tails left–right or up-down a few times and then drift for several seconds while their bodies are still. As the present study shows, this is obviously done not only for energy saving reasons, but also for activating their sensing of orientation and position. We showed that according to the IFO-VGIC mechanism, the lower the winging (or body movement) rate (frequency of velocity variation) the stronger the induced effect and the corresponding sensing of their orientation and position. This comes from the IFO-VGIC theory[44,64–67] which shows that the bioactivity of an applied EMF, represented by the amplitude of the ion forced oscillation, is inversely proportional to its frequency (Eq. 8). The physical explanation of this result is that, due to inertia, the higher the frequency of the applied force, the smaller the amplitude of the forced oscillation, as the ion cannot follow the fast changes of the force, except if its oscillation amplitude becomes smaller.

The effect in a moving animal's brain/body due to periodic acceleration within the GMF, as estimated in the present study, varies according to the animal's velocity, and acceleration, with velocity variation rates in the ULF (0–3 Hz) range. The dependence on velocity, velocity variation, and frequency (variation rate) is shown in Eqs. 1, 5, 20, and Conditions 10, 13, 15. The forces exerted on the VGIC S4 voltage sensors are slow-varying at ULF rates, arising from the variations in the animal velocity. The slow-varying forces are in a specific direction related to the direction of motion, and thus are polarized which is a condition for the application of the IFO-VGIC mechanism[66,67]. These polarized slow-varying electromagnetic forces arising whenever the animal accelerates (e.g. when a bird flutters) or decelerates, are applied on the VGIC S4 sensors in the plasma membranes of various cells at different angles with respect to the channel axes depending on the orientation of each VGIC. Those channels that their axes are oriented parallel to the forces (vertically to the GMF intensity) will receive forces on their voltage-sensors most effective in altering their channel state from opened to closed and vice-versa.

Our present study shows that animals/living organisms do not need specific organs/cells for sensing polarized EMFs (including the GMF), as they are all equipped with VGICs in great numbers in all their cell membranes, especially in neurons/brain cells, which according to the IFO-VGIC mechanism can sense ELF/ULF electric fields down to ~10^{-5} V/m[44,64–67]. This explains all known EMF-bioeffects including magnetoreception. Yet, this does not contradict the role of specific organs in certain electrosensitive animals that move slower than e.g. birds such as the ampullae of Lorenzini in elesmobranches which may further amplify VGIC signals.

We demonstrated by accurate calculations that migrating animals can sense; a) their direction of motion with respect to the GMF north–south axis through the effect exerted on them by the horizontal component of the GMF ($B_{g//}$), and b) their latitude through the direct effect exerted on them by the vertical component of the GMF ($B_{g\perp}$), and complementarily through the indirect effect of the corresponding induced electric field. These effects on animals take place through the variations in the force exerted on their VGIC sensors due to corresponding variations in their velocity.

Because the GMF varies by less than 1 μT over distances of several km along the GMF north–south direction, and we have shown (Cond. 14) than the weakest magnetic field a moving animal can detect is ~0.6 μT, migrating animals may not sense differences within less than ~10 km along the axis, and therefore they use additional senses such as vision, smell, etc., and environmental signals, such as differences in humidity, temperature, altitude/atmospheric pressure, etc. to find exact locations[2,4,6]. Perhaps this difficulty in sensing the latitude by a migrating animal due to the small differences in GMF intensity per km is the reason why the sensitivity in the latitude (resulting from the combined effect of $B_{g\perp}$ and E_{ind}) is found to be about 3 times higher than the max sensitivity in the direction of motion.

It should be noted that in the solution (Eq. 7) of the differential equation (Eq. 5) for the ion forced-oscillation due to the oscillating force exerted by the externally applied EMF (in this case the GMF), the constant term does not actually increase the ion maximum displacement which is always twice the amplitude of the forced oscillation (Cond. 9) but it doubles the ion displacement only during the first semi-period, and displaces the whole oscillation at a distance equal to its amplitude. With a pulsing field emitting on/off pulses, the displacement of the whole oscillation is repeated in a unique direction with the onset of every successive pulse. Most importantly, the pulse repetition frequency is always significantly smaller than the carrier frequency within the pulses, making the pulsed EMF exposure significantly more bioactive, as bioactivity is inversely proportional to the frequency according to the IFO-VGIC theory (Eq. 8, 10). These are the reasons why pulsing EMFs are found in many studies to be more bioactive than uninterrupted (continuous-wave) EMFs of the same intensity and carrier frequency. For a review of comparison studies between pulsing and corresponding continuous-wave manmade EMFs with respect to their bioactivity, see[85].

Even though for standing animals/humans on Earth, it has been shown that a ULF/ELF electric field may be more bioactive than a magnetic field of the same frequency and waveform in inducing VGIC gating[26,44,64,65,67], the magnetic field becomes increasingly bioactive for moving animals, especially fast moving ones such as birds, or humans in fast moving vehicles, as the magnetic force on the ions close to VGIC sensors is proportional to the animal/human velocity (Eq. 1). This increases the bioactivity of magnetic fields in the case of moving animals/

humans than in the case of stationary ones. Indeed, for a still stationary animal, the maximum ion velocity is that through an open ion channel (0.25 m/s)[64,67], while in the case of a moving animal with $u = 20$ m/s the velocity of the ions and the corresponding GMF force on them is 80 times greater. In cases of stationary or very slowly moving animals the effect of the magnetic field (including the GMF) can again become significant when the animal quickly moves its head/body left–right or up-down with respect to its body axis.

Certainly, anthropogenic ELF/ULF magnetic fields of similar magnitude to the GMF, e.g. from electric power transmission lines, wireless communication base antennas/towers, etc., can interfere locally with the GMF distorting its intensity and/or direction, and thus disrupting the ability of animals to orient and navigate[25,47,55,86].

We showed that the IFO-VGIC mechanism can explain the orientation and navigation ability of the moving and accelerating animals on Earth. This may contribute significantly to resolving the problem of animal magnetoreception, which has been a mystery for centuries and has remained as such until today, despite the systematic research on this during the past 50–60 years (see[1–4,10]).

We showed that the IFO-VGIC mechanism plausibly explains animal magnetoreception, orientation and navigation according to established physical laws, molecular/biological data, and accurate mathematical operations. Additional confirmation on the validity of this mechanism is: a) Already in Panagopoulos et al. (2002)[65] (Fig. 3) it was shown that the intensities and frequencies used in many experiments that had shown ELF EMF bioeffects in cells and animals were within the bioactive values predicted by this theory. Since then, it has been shown that this theory explains most (if not all) recorded bioeffects including oxidative stress and genetic damage induced by anthropogenic ELF EMFs[44,67]. b) The same mechanism has explained the sensing of upcoming thunderstorms by sensitive individuals[87], and the sensing of upcoming earthquakes by animals[88]through the action of the partially polarized natural ULF/ELF EMFs associated with these phenomena. c) It is experimentally confirmed that ELF EMFs can gate VGICs in cell membranes of various cell types and alter intracellular ionic concentrations at very low field intensities[49,89–92]. d) It is experimentally confirmed that ELF EMFs induce biological effects in isolated tissues at very low threshold intensities ($\sim 10^{-3}$V/m)[79,80] as those predicted by this theory. e) It is experimentally confirmed that ELF EMFs are sensed by animals at very low threshold intensities ($\sim 10^{-5}$-10^{-4}V/m) coinciding with those predicted by this theory[1,70]. Such evidence does not exist for the previously published hypotheses.

For further and more specific experimental confirmation of the IFO-VGIC mechanism in animal orientation and navigation, an experimental setup could possibly consist of a) a proper biological system (e.g. cell cultures or isolated cells/neurons); b) similar conditions of motion as those described in our numerical calculations (e.g. as in Fig. 7 and/or for a stationary animal that quickly moves its head/body perpendicularly to its body axis); c) assessment of intracellular concentrations of critical ions (e.g. Ca^{2+}, Na^{+}, K^{+} etc.) and/or measurement of VGIC ion currents before and after motion, without and with use of channel blockers; d) testing of different motion orientations with respect to the north–south GMF axis.

In contrast to the previously suggested hypotheses to explain animal magnetoreception which restricted in qualitative descriptions on how these mechanisms might work at cellular level, our proposed mechanism results in accurate numerical predictions and a complete description of the VGIC-gating effect induced in the cells of a moving and periodically accelerating animal on Earth, depending on the specific values of GMF intensity, animal velocity, acceleration, and acceleration rate, which in turn determine animal orientation and navigation. While previously suggested hypotheses were unrealistically complicated, none of them had specifically shown how exactly migrating animals determine their direction and position and they only restricted in searching how the GMF could elicit a cellular/biological effect in general, without finding that either.

Kirschvink et al.[10] stated that over the past years "a plethora of biophysical transduction hypotheses have been winnowed down to two or three that have experimental support: some form of electrical induction, specialized receptor cells involving biogenic magnetite …and that of weak-field magnetic effects on photochemically generated radical pairs in the eye". But they did not consider our proposed mechanism which was already published[64,65], as well as other previous publications focusing on the VGICs for the explanation of the effects of magnetic fields on living cells/organisms[71–73]. Moreover, they and others did not consider the vast and undeniable experimental evidence that environmentally existing anthropogenic polarized EMFs affect VGICs and consequently alter the cell redox status and homeostasis initiating a plethora of biological/health effects (see reviews in[44,49,90,93]).

The scientific literature contains already thousands of studies during the past 60 years presenting a panorama of biological/health effects of various types of man-made EMFs on a wide variety of animals (including humans) and cell/tissue types, and in addition, a plausible biophysical mechanism explaining all those recorded effects is published for more than 20 years (having already been referenced in more than a thousand other publications altogether). Yet, the research focusing on the explanation of animal magnetoreception did not seem to be affected by the above scientific progress, and insisted on specific hypothetical mechanisms namely the magnetite and the radical pair hypotheses, even though it was admitted that there was no progress with resolving the problem in this way[3,4,10,11,36,38].

Here, we have presented a plausible biophysical mechanism for animal magnetoreception, orientation and navigation, based on molecular data for the structure and function of VGICs in all animals, and combined with accurate mathematical calculations predicting that the GMF is indeed able to affect cell homeostasis and thus be sensed by migrating animals.

Data availability

All data generated or analyzed during this study are included in this published article and its references.

Received: 19 July 2024; Accepted: 25 October 2024
Published online: 03 December 2024

References

1. Johnsen, S. & Lohmann, K. J. Magnetoreception in animals. *Phys. Today* **61**(3), 29–35 (2008).
2. Komolkin, A. V. et al. Theoretically possible spatial accuracy of geomagnetic maps used by migrating animals. *J. R. Soc. Interface* **14**, 20161002 (2017).
3. Nordmann, G. C., Hochstoeger, T. & Keays, D. A. Magnetoreception - A sense without a receptor. *PLoS Biol* **15**(10), e2003234. https://doi.org/10.1371/journal.pbio.2003234 (2017).
4. Mouritsen, H. Long-distance navigation and magnetoreception in migratory animals. *Nature* **558**, 50–59 (2018).
5. Presman, A. S. *Electromagnetic Fields and Life* (Plenum Press, 1977).
6. Dubrov, A. P. *The Geomagnetic Field and Life* (Plenum Press, 1978).
7. Panagopoulos D. J. Electromagnetic Interaction between Environmental Fields and Living Systems determines Health and Well-Being, *In* "Electromagnetic Fields: Principles, Engineering Applications and Biophysical Effects", Nova Science Publishers, New York. (2013).
8. Creasey WA and Goldberg RB, (2001), A new twist on an old mechanism for EMF bioeffects?, *EMF Health Report*, 9 (2), 1–11. [Available in: https://www.emfsa.co.za/wp-content/uploads/2021/06/Creasey-WA-Goldberg-RB-2001-A-new-twist-on-an-old-mechanism-for-EMF-bioeffects.pdf]
9. Johnsen, S. & Lohmann, K. J. The physics and neurobiology of magnetoreception. *Nat Rev Neurosci* **6**, 703–712. https://doi.org/10.1038/nrn1745 (2005).
10. Kirschvink JL, Winklhofer M, Walker MM, (2010). Biophysics of magnetic orientation: strengthening the interface between theory and experimental design. *J R Soc Interface*. (Suppl 2):S179–91.
11. Shaw J, Boyd A, House M, et al, (2015). Magnetic particle-mediated magnetoreception. *J. R. Soc. Interface*, 20150499. https://doi.org/10.1098/rsif.2015.0499
12. Kirschvink, J. L. Magnetite biomineralization and geomagnetic sensitivity in higher animals: an update and recommendations for future study. *Bioelectromagnetics.* **10**(3), 239–259 (1989).
13. Kirschvink, J. L., Kobayashi-Kirschvink, A. & Woodford, B. J. Magnetite biomineralization in the human brain. *Proc Natl Acad Sci U S A* **89**, 7683–7687 (1992).
14. Lowenstam, H. A. Magnetite in denticle capping in recent chitons (Polyplacophora). *Geol. Soc. Am. Bull.* **73**(4), 435–438 (1962).
15. Bellini, S. *Su di un particolare comportamento di batteri d'acqua dolce (On a unique behavior of freshwater bacteria)* (University of Pavia, Italy, 1963).
16. Bellini, S. *Ulteriori studi sui "batteri magnetosensibili" (Further studies on magnetosensitive bacteria)* (University of Pavia, Italy, 1963).
17. Blakemore, R. P. Magnetotactic bacteria. *Science* **190**, 377–379 (1975).
18. Blakemore, R. P. Magnetotactic bacteria. *Annu. Rev. Microbiol.* **36**, 217–238 (1982).
19. Walker, M. M. et al. Structure and function of the vertebrate magnetic sense. *Nature* **390**, 371–376 (1997).
20. Diebel, C. E., Proksch, R., Green, C. R., Neilson, P. & Walker, M. M. Magnetite defines a vertebrate magnetoreceptor. *Nature* **406**, 299–302 (2000).
21. Cadiou, H. & McNaughton, P. A. Avian magnetite-based magnetoreception: a physiologist's perspective. *JFR Soc. Interface* **7**(suppl 2), 193–205. https://doi.org/10.1098/rsif.2009.0423.focus (2010).
22. Winklhofer, M. & Kirschvink, J. L. A quantitative assessment of torque-transducer models for magnetoreception. *J. R. Soc. Interface* **7**, 273–289. https://doi.org/10.1098/rsif.2009.0435.focus (2010).
23. Eder, S. H. K. et al. Magnetic characterization of isolated candidate vertebrate magnetoreceptor cells. *Proc. Natl. Acad. Sci.* **109**(30), 12022–12027 (2012).
24. Kavokin, K. V. Compass in the ear: can animals sense magnetic fields with hair cells?. *Eur. Phys. J. Spec. Top.* **232**, 261–268. https://doi.org/10.1140/epjs/s11734-022-00654-y (2023).
25. Ernst, D. A. & Lohmann, K. Effect of magnetic pulses on Caribbean spiny lobsters: implications for magnetoreception. *J. Exp. Biol.* **219**(Pt 12), 1827–1832. https://doi.org/10.1242/jeb.136036 (2016).
26. Goodman, E. M., Greenebaum, B. & Marron, M. T. Effects of Electro- magnetic Fields on Molecules and Cells, *International Rev. Cytol.* **158**, 279–338 (1995).
27. Huber, R. et al. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. *J Sleep Res.* **11**(4), 289–295 (2002).
28. Santini, M. T., Ferrante, A., Rainaldi, G., Indovina, P. & Indovina, P. L. Extremely low frequency (ELF) magnetic fields and apoptosis: a review. *Int J Radiat Biol.* **81**(1), 1–11 (2005).
29. Panagopoulos, D. J. (ed.) *Electromagnetic Fields of Wireless Communications: Biological and Health Effects* 1st edition. (CRC Press, 2023).
30. Malkemper, E. P. et al. No evidence for a magnetite-based magnetoreceptor in the lagena of pigeons. *Current Biology* **29**(1), R14–R15 (2019).
31. Treiber, C. D. et al. Clusters of iron-rich cells in the upper beak of pigeons are macrophages not magnetosensitive neurons. *Nature* **484**, 367–370 (2012).
32. Edelman, N. B. et al. No evidence for intracellular magnetite in putative vertebrate magnetoreceptors identifed by magnetic screening. *Proc. Natl Acad. Sci. USA* **112**, 262–267 (2015).
33. Schulten, K., Swenberg, C. E. & Weller, A. A biomagnetic sensory mechanism based on magnetic field modulated coherent electron spin motion. *Z. Für Phys. Chem.* **111**(1), 1–5 (1978).
34. Ritz, T., Adem, S. & Schulten, K. A model for photoreceptor-based magnetoreception in birds. *Biophys. J.* **78**(2), 707–718 (2000).
35. Ritz, T., Thalau, P., Phillips, J. B., Wiltschko, R. & Wiltschko, W. Resonance effects indicate a radicalpair mechanism for avian magnetic compass. *Nature* **429**, 177–180 (2004).
36. Ritz, T., Ahmad, M., Mouritsen, H., Wiltschko, R. & Wiltschko, W. Photoreceptor-based magnetoreception: optimal design of receptor molecules, cells, and neuronal processing. *J. R. Soc. Interface* **7**, S135–S146 (2010).
37. Wiltschko, W. & Wiltschko, R. Light-dependent magnetoreception in birds: the behaviour of European robins, Erithacus rubecula, under monochromatic light of various wavelengths and intensities. *J Exp Biol* **204**, 3295–3302 (2001).
38. Hore, P. J. & Mouritsen, H. The Radical-Pair Mechanism of Magnetoreception. *Annu Rev Biophys* **45**, 299–344 (2016).
39. Worster, S., Mouritsen, H. & Hore, P. J. A light-dependent magnetoreception mechanism insensitive to light intensity and polarization. *J. R. Soc. Interface* **14**, 20170405. https://doi.org/10.1098/rsif.2017.0405 (2017).
40. Wiltschko, R. & Wiltschko, W. Magnetoreception in birds. *J. R. Soc. Interface* **16**, 20190295. https://doi.org/10.1098/rsif.2019.0295 (2019).
41. Casarett, A. P. *Radiation Biology* (Prentice-Hall Inc, 1968).
42. Coggle, J. E. *Biological Effects of Radiation* (Taylor & Francis, 1983).
43. Hall, E. J. & Giaccia, A. J. *Radiobiology for the Radiologist* 6th edn. (Lippincott Williams & Wilkins, 2006).
44. Panagopoulos, D. J., Karabarbounis, A., Yakymenko, I. & Chrousos, G. P. Human-made electromagnetic fields: Ion forced-oscillation and voltage-gated ion channel dysfunction, oxidative stress and DNA damage. *International Journal of Oncology* **59**, 92 (2021).
45. Swartz, H. M. et al. (eds) *Biological Applications of ESR* (John Wiley and sons, 1972).
46. Sober, E. The Principle of Parsimony. *Brit. J. Phil. Sci.* **32**, 145–156 (1981).

47. Engels, S. et al. Anthropogenic electromagnetic noise disrupts magnetic compass orientation in a migratory bird. *Nature* **509**, 353–356 (2014).
48. Fedele, G. et al. Genetic analysis of circadian responses to low frequency electromagnetic fields in Drosophila melanogaster. *PLoS Genet* **10**, e1004804. https://doi.org/10.1371/journal.pgen.1004804 (2014).
49. Bertagna, F., Lewis, R., Silva, S. R. P., McFadden, J. & Jeevaratnam, K. Effects of electromagnetic fields on neuronal ion channels: a systematic review. *Ann N Y Acad Sci.* **1499**(1), 82–103 (2021).
50. Balmori A, (2022). Effects of Man-made and Especially Wireless Communication Electromagnetic Fields on Wildlife. *In*: DJ Panagopoulos (Editor), "Electromagnetic Fields of Wireless Communications: Biological and Health Effects", CRC Press, Taylor and Francis, Boca Raton.
51. Alonso M and Finn EJ, (1967): *Fundamental University Physics, Vol. 2: Fields and Waves*, Addison-Wesley, USA.
52. Kalmijn, A. J. The electric sense of sharks and rays. *J. Exp. Biol.* **55**, 371–383 (1971).
53. Kalmijn AJ, (1973). Electro-orientation in sharks and rays: Theory and experimental evidence. *Office of Naval Research, National Technical Information Service, US Department of Commerce*.
54. Kalmijn, A. J. Electric and magnetic field detection in elasmobranch fishes. *Science* **218**, 916–918 (1982).
55. Meyer, C. G., Holland, K. N. & Papastamatiou, Y. P. Sharks can detect changes in the geomagnetic field. *J R Soc Interface* **2**, 129–130 (2005).
56. Jungerman, R. L. & Rosenblum, B. Magnetic induction for the sensing of magnetic fields by animals–an analysis. *J. Theor. Biol.* **87**, 25–32 (1980).
57. Albert L, Deschamps F, Jolivet A, Olivier F, Chauvaud L, et al., (2020): A current synthesis on the effects of electric and magnetic fields emitted by submarine power cables on invertebrates. *Marine Environmental Research*, 159, pp.104958.ff10.1016/j.marenvres.2020.104958ff. ffhal-02559660.
58. Bellono NW, Leitch DB, (2017). Julius D. Molecular basis of ancestral vertebrate electroreception. *Nature.* 543(7645):391–96.
59. Bellono, N. W., Leitch, D. B. & Julius, D. Molecular tuning of electroreception in sharks and skates. *Nature* **558**, 122–126 (2018).
60. Nimpf, S. et al. A Putative Mechanism for Magnetoreception by Electromagnetic Induction in the Pigeon Inner Ear. *Current Biology* **29**, 4052–4059 (2019).
61. Nuccitelli R, (2011), Measuring Endogenous Electric Fields. *In*: C.E. Pullar (Ed), The Physiology of Bioelectricity in Development, Tissue Regeneration and Cancer, CRC Press, Taylor and Francis, Boca Raton.
62. Levin M. Endogenous Bioelectric Signals as Morphogenetic Controls of Development, Regeneration, and Neoplasm. *In*: C.E. Pullar (Ed), The Physiology of Bioelectricity in Development, Tissue Regeneration and Cancer, CRC Press, Taylor and Francis, Boca Raton. (2011).
63. Titushkin I, Sun S, Rao V, and Cho M. Stem Cell Physiological Responses to Noninvasive Electrical Stimulation. *In*: C.E. Pullar (Ed), The Physiology of Bioelectricity in Development, Tissue Regeneration and Cancer, CRC Press, Taylor and Francis, Boca Raton (2011).
64. Panagopoulos, D. J., Messini, N., Karabarbounis, A., Filippetis, A. L. & Margaritis, L. H. A Mechanism for Action of Oscillating Electric Fields on Cells. *Biochemical and Biophysical Research Communications* **272**(3), 634–640 (2000).
65. Panagopoulos, D. J., Karabarbounis, A. & Margaritis, L. H. Mechanism for Action of Electromagnetic Fields on Cells. *Biochemical and Biophysical Research Communications* **298**(1), 95–102 (2002).
66. Panagopoulos DJ, Johansson O, Carlo GL, (2015): Polarization: A Key Difference between Man-Made and Natural Electromagnetic Fields, in regard to Biological Activity, *Scientific Reports* 5, 14914; https://doi.org/10.1038/srep14914.
67. Panagopoulos DJ, (2022): Mechanism of Ion Forced-Oscillation and Voltage-Gated Ion Channel Dysfunction by Polarized and Coherent Electromagnetic Fields. *In*: DJ Panagopoulos (Editor), "Electromagnetic Fields of Wireless Communications: Biological and Health Effects", CRC Press, Boca Raton.
68. Alberts, B. et al. *Molecular Biology of the Cell* (Garland Publishing Inc, 1994).
69. Stryer L. (1995), Biochemistry, 4th ed., W.H. Freeman and Co, New York.
70. England, S. J. & Robert, D. The ecology of electricity and electroreception. *Biological Reviews* **97**, 383–413 (2022).
71. Cain, C. A. Biological effects of oscillating electric fields: role of voltage-sensitive ion channels. *Bioelectromagnetics* **2**(1), 23–32 (1981).
72. McLeod, B. R., Liboff, A. R. & Smith, S. D. Electromagnetic gating in ion channels. *J Theor Biol.* **158**(1), 15–31 (1992).
73. Balcavage, W. X. et al. A mechanism for action of extremely low frequency electromagnetic fields on biological systems. *Biochem. Biophys. Res. Commun.* **222**, 374–378 (1996).
74. Noda, M. et al. Existence of distinct sodium channel messenger RNAs in rat brain. *Nature* **320**, 188–192 (1986).
75. Liman, E. R., Hess, P., Weaver, F. & Koren, G. Voltage sensing residues in the S4 region of a mammalian K^+ channel. *Nature* **353**, 752–756 (1991).
76. Miller C, (2000). An overview of the potassium channel family. *Genome Biol* 1(4).
77. Sandipan C, and Baron C. (2015): Basic mechanisms of voltage sensing, *In:* Zheng J, and Trudeau MC (Eds), Handbook of Ion Channels, CRC Press, Boca Raton.
78. Zhang, X. C., Yang, H., Liu, Z. & Sun, F. Thermodynamics of voltage-gated ion channels. *Biophys Rep* **4**(6), 300–319 (2018).
79. McLeod, K. J., Lee, R. C. & Ehrlich, H. P. Frequency dependence of electric field modulation of fibroblast protein synthesis. *Science* **236**(4807), 1465–1469 (1987).
80. Cleary, S. F., Liu, L. M., Graham, R. & Diegelmann, R. F. Modulation of tendon fibroplasia by exogenous electric currents. *Bioelectromagnetics* **9**, 183–194 (1988).
81. Honig, B. H., Hubbell, W. L. & Flewelling, R. F. Electrostatic Interactions in Membranes and Proteins. *Ann. Rev. Biophys. Biophys. Chem* **15**, 163–193 (1986).
82. Panagopoulos, D. J. Comparing DNA Damage Induced by Mobile Telephony and Other Types of Man-Made Electromagnetic Fields. *Mutation Research Reviews* **781**, 53–62 (2019).
83. NOAA (US National Oceanic and Atmospheric Administration) (2023): Magnetic Field Estimated Values (https://www.ngdc.noaa.gov/geomag/calculators/magcalc.shtml# igrfwmm)
84. Benediktová, K. et al. Magnetic alignment enhances homing efficiency of hunting dogs. *Elife* **9**, e55080 (2020).
85. Panagopoulos DJ, Karabarbounis A, Lioliousis C. Defining Wireless Communication (WC) Electromagnetic Fields (EMFs): A. Polarization is a principal property of all man-made EMFs; B. Modulation, pulsation, and variability are inherent parameters of WC EMFs; C. Most man-made EMF exposures are non-thermal; D. Measuring incident EMFs is more relevant than Specific Absorption Rate (SAR); E. All man-made EMFs emit continuous waves, not photons; F. Differences from natural EMFs. Interaction with matter. *In*: DJ Panagopoulos (Editor), "Electromagnetic Fields of Wireless Communications: Biological and Health Effects", CRC Press, Boca Raton (2022).
86. Hutchison, Z. L., Gill, A. B., Sigray, P., He, H. & King, J. W. Anthropogenic electromagnetic fields (EMF) influence the behaviour of bottom-dwelling marine species. *Sci Rep.* **10**(1), 4219 (2020).
87. Panagopoulos, D. J. & Balmori, A. On the biophysical mechanism of sensing atmospheric discharges by living organisms. *Science of the Total Environment* **599–600**(2017), 2026–2034 (2017).
88. Panagopoulos, D. J., Balmori, A. & Chrousos, G. P. (2020): On the biophysical mechanism of sensing upcoming earthquakes by animals. *Sci Total Environ.* **717**, 136989 (2020).
89. Piacentini, R., Ripoli, C., Mezzogori, D., Azzena, G. B. & Grassi, C. Extremely low-frequency electromagnetic fields promote in vitro neurogenesis via upregulation of Ca_v1-channel activity. *J. Cell. Physiol.* **215**, 129–139 (2008).

90. Pall, M. L. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med* **17**, 958–965 (2013).
91. Cecchetto C, Maschietto M, Boccaccio P, Vassanelli S, (2020): Electromagnetic field affects the voltage-dependent potassium channel Kv1.3. *Electromagn Biol Med*. 39(4):316–322.
92. Zheng, Y., Xia, P., Dong, L., Tian, L. & Xiong, C. Effects of modulation on sodium and potassium channel currents by extremely low frequency electromagnetic fields stimulation on hippocampal CA1 pyramidal cells. *Electromagn Biol Med*. **17**, 1–12 (2021).
93. Panagopoulos DJ, Yakymenko I, and Chrousos GP. Electromagnetic field-induced dysfunction of voltage-gated ion channels, oxidative stress, DNA damage, and related pathologies. *In*: DJ Panagopoulos (Editor), "Electromagnetic Fields of Wireless Communications: Biological and Health Effects", CRC Press, Boca Raton (2022).

Acknowledgements
The study was supported by the Special Account for Research Grants of the National and Kapodistrian University of Athens. We thank graphic designer Angela Dounas for precious help with the figures.

Author contributions
D.J.P. designed the study, wrote equations, preformed calculations, and wrote the main manuscript. A.K. checked all equations and calculations, reviewed and evaluated all data. G.P.C. reviewed and evaluated all data.

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to D.J.P.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2024