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

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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.

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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 ($0-3\times10^{11}$ Hz) discussed in the present study cannot directly cause ionization, except for very strong field intensities ($\geq 10^6$ 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).

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

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):

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

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 Ca²⁺ ions), $q_e=1.6\times10^{-19}$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:

$$r = \frac{E_o z q_e}{\beta\omega}\,cos\,\omega t + \frac{E_o z q_e}{\beta\omega} \qquad (3)$$

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:

$$A = \frac{E_o z q_e}{\beta\omega} \qquad (4)$$

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:

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

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:

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

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): $dF=8.16\times10^{-13}$ 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: $dr=4\times10^{-12}$ 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 nm³ (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

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

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. Ca²⁺) 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:

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

where $k = \frac{z q_e}{2\pi\beta} = \frac{u_o}{2\pi E_m} \cong 4\times10^{-9}$ 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:

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

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

$$F_B = B u z q_e \qquad (13)$$

exerted on an ion with charge $z q_e$, 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:

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

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

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

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

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

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

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:

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

(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, $B z q_e (dr/dt)$, 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 $E \sim 10$ kV/m and $B \sim 0.1$-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), $E \sim 10$ V/m and $B \sim 1$ 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, $E \sim 1$ V/m and $B \sim 0.1$ mG
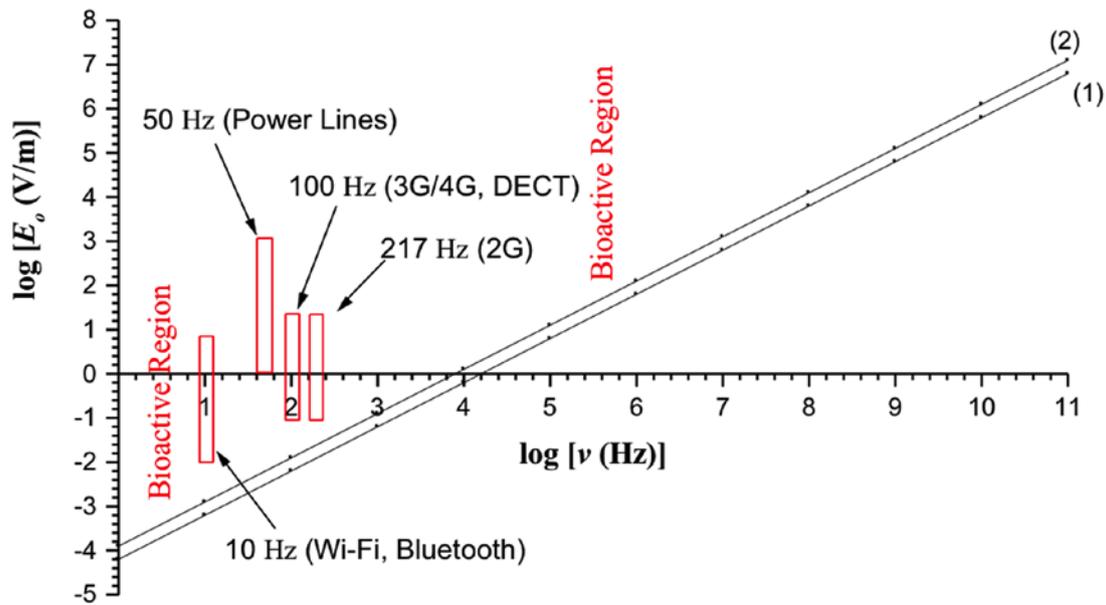
Figure 1. E-field bioactivity diagram showing the bioactive combinations of electric field intensity and frequency capable of inducing biological/health effects according to the ion forced-oscillation mechanism for dysfunction of voltage-gated ion channels in cells. The ELF electric fields of power lines, 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 (•), 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 ($O_2^{•-}$) and nitric oxide ($NO^•$) (109). These may result in hydroxyl radical ($OH^•$) 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 $NO^•$, it can be diffused everywhere in the cell (181). Superoxide anion radical ($O_2^{•-}$) is catalyzed by superoxide dismutase enzymes in the cytosol or the mitochondria and is converted to hydrogen peroxide (H_2O_2) (109,182):

$$2O_2^{•-} + 2H^+ \rightarrow H_2O_2 + O_2 \tag{20}$$

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 $OH^•$, 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 $NO^•/ONOO^-$ 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 $O_2^{\cdot-}$ production by the electron transport chain in the mitochondria and/or activation of nitric oxide synthase (NOS), to generate more $NO^{\cdot}$. $NO^{\cdot}$ 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 $NO^{\cdot}$ 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 $OH^{\cdot}$ 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 $O_2^{\cdot-}$ (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. $OH^{\cdot}$ is considered the most potent oxidant of DNA. The main mechanism for $OH^{\cdot}$ 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 $OH^{\cdot}$ 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).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^- \tag{21}$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO^\bullet + H^+ \qquad (22)$$
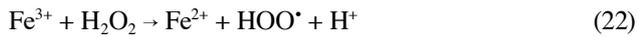
The net effect is the conversion of two hydrogen peroxide molecules to produce two different oxygen-radical species, with water ($H^+ + OH^-$) as a byproduct.

$$2H_2O_2 \rightarrow OH^\bullet + HOO^\bullet + H_2O \qquad (23)$$

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 $RO^\bullet$):

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

$$RH + OH^\bullet \rightarrow R^\bullet + H_2O \qquad (25)$$

$$or\ RH + OH^\bullet \rightarrow RO^\bullet + H_2 \qquad (26)$$

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 ($\sim 10^{-3}$ 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 over-production 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.

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.

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