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**ARE PULSED MILLIMETRE WAVES FOR BIOLOGICAL/THERAPEUTIC USE  
SUITABLE TO AVOID THERMAL EFFECTS AND MAGNIFY SPECIFIC  
ELECTROMAGNETIC EFFECTS?**

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## ABSTRACT

This paper presents a reflection (not a review) about the basic mechanisms involved in biological and therapeutic effects of millimetre waves (MMW). From articles, reviews and meta-analysis, a special interest was given to low power exposure to MMW (approximately 10 mW/cm<sup>2</sup> or less). Excluding thermal effects, several exclusive electromagnetic interactions were presented, with mainly membrane and volt gated calcium channel as targets (VGcc), involving calcium influxes and water contribution. It appeared that thermal effects were not necessary and could be avoided. This led to consider and discuss the use of pulsed MMW signals (not continuous waves) that could limit or avoid thermal effects, allow lower power requirement, best spectral bandwidth targeting, and specific properties related to currents onset/cut-off.

## INTRODUCTION

The designation “millimetres waves” (MMW) coarsely covers electromagnetic radiation at frequencies ranging from 30 to 100 GHz. Until the 2010s, millimetres waves applications were mainly intended for the military domain (radar detection, non-lethal crowd control systems, etc.). Other civilian applications, such as car driving assistance, had been developed since the 1970s. Recently, the advent of 5G has brought into play these frequency bands (up to 27GHz currently) and higher frequencies (6G, up to THz) will be employed in the near future to improve the number and the speed of communication systems. Besides, medical applications had been identified and developed in the former Soviet Union in the 80s, mainly as painkiller, healing, or anti-inflammatory<sup>1</sup>. However, their use was mostly empirical and no clear scientific explanation of the mechanism of action was identified. For these reasons, concomitantly with the development of improved pharmaceutical solutions, MMW therapy stopped being used as a treatment of first intent, or even as an alternative to chemical medication. After the collapse of the Eastern Bloc, several research teams kept studying MMW therapy for different applications, such as wound healing<sup>2</sup>, diabetes<sup>3</sup>, cancer<sup>4</sup> and the treatment of chronic pains<sup>5</sup>, as presented in the reviews of Pakhomov<sup>4,6</sup> (1998, 2000). Cutaneous thermal skin receptors have been early identified as MMW transducers involving the peripheral stimulation, the nerve conduction to CNS and the central endorphin secretion as a response leading to hypoalgesia effect. The effects of MMWs can be easily explained for power surface densities over several tenths of  $\text{mW}/\text{cm}^2$ , directly related with the well-known mechanism of dipolar relaxation, which induces water heating<sup>7</sup>. This mechanism is even the basis of international protection standards against non-ionizing radiation in these frequency ranges<sup>8,9</sup>, supported by Maxwell’s equations and energy balancing. Conversely, such mechanisms are not consistent with the biological effects of MMW observed for low power density exposures, i.e. less than  $10\text{mW}/\text{cm}^2$ ; here thermic effects are almost negligible, and other -non thermal- effects have to be identified<sup>10</sup>. Mainly, since the end of 20th century, research has been continuously performed to understand the physiological MMW mechanism of action on biological systems as well as the elementary/physics supports. Given that mechanisms are still incompletely known, the reflection (not an extensive review) presented in this paper –would present some

more or less plausible mechanisms, and finally suggest possible evolution of MMW pulsed emitting systems for biomedical applications, targeting thermal effect avoidance and increased effectiveness.

#### **GENERAL CONSIDERATIONS ON THERMAL RECEPTORS.**

Thermal Receptors are sensitive neurons which axonal endings are located in skin depth. Normally, their membrane potential (MP) results from a dynamic equilibrium involving passive mechanisms (for example diffusion, or homogenization of components between membrane layers - phosphatidylserine-, ....) and active mechanisms (ion pumps, flippases<sup>11</sup> for PS) allowing to preserve the functional asymmetry of the membranes. The thermal stimulus acts by variation of membrane potential (depolarization). This depolarization can generate action potentials when it reaches a critical threshold. MP generation starts at 30°C and their frequency increase with temperature up to 45°C. Higher temperatures activate nociceptive receptors<sup>12</sup>.

#### **NON THERMAL BIOLOGICAL EFFECTS OF MMW**

The effects induced by low level millimetre radiation on biological systems gave rise to numerous studies and to several reviews, from historical Motzkin work<sup>13</sup> to Pakhomov<sup>6</sup>. From a mechanistic point of view, Ramundo-Orlando<sup>10</sup> in 2010 underlined the roles of membrane as a target for MMW, even if no *“permanent structural change of lipid bilayer could arise under low level (less than 10 mW/cm<sup>2</sup>) millimetre waves irradiation<sup>13”</sup>*. She suggested the role of membrane proteins and related intracellular Ca<sup>2+</sup> /and related Ca<sup>2+</sup> dependant molecular processes. She also evoked the role of bound water and phospholipid organization and evoked, from Fröhlich<sup>14</sup> theory, the possibility of physiological collective oscillations in biological systems as a possible target of MMW by the induction of coherent electric vibrations. Whereas these conclusions remain valid, later works made them more precise as shown below.

##### **1. MMW action on Ca<sup>2+</sup>, membrane voltage gated calcium channels (VGCC) and consequences.**

Previous work has evoked two different pathways for the membrane interaction of MMWs, directly or via collective membrane interactions. The cell membrane was already a "major target" for low-power MMW, as MMW-induced membrane associations appear produced by both Ca<sup>2+</sup> influx and collective electromagnetic interactions.

Le Pogam et Al.<sup>15</sup> have carried out integrative metabolomics and lipidomics (UPLC-Q-Exactive) studies on human HaCaT keratinocytes in culture exposed for 24 hours at 60 GHz 20mW/cm<sup>2</sup>. The authors

highlighted a limited number of altered features in lipidomic sequences and in intracellular metabolomic analyses. On the other hand, significant dysregulations appear in the extracellular metabolomic profiles, not related to the slight changes that could be reported throughout the transcriptomic studies. They deduced that MMWs could modify the permeability of cell membranes.

**11. Direct stimulation of VG<sub>CC</sub>** by penetrating magnetic components of MMW (Pall 2013<sup>16</sup>, Pall 2016<sup>17</sup>, Pall 2020<sup>18</sup>).

It is generally admitted that the "thermal background noise" generates ion fluxes and local currents capable of stimulating voltage-sensitive receptors, and especially voltage-gated calcium channels (VG<sub>CC</sub>). The result is a twist of the 4 intramembrane chains of this VG<sub>CC</sub>, opening the channel like an optical diaphragm. The result is a net influx of calcium, leading by itself to trigger physiological activities in a non-thermal way, e.g. release of neurotransmitters<sup>19</sup>.

Beside the well-recognised low MMW penetration through skin (about a fraction of millimetres at 60GHz), Pall built a theory by considering separately the electric (E) and the magnetic (H) components of MMW in CW mode. *He stated that whereas E is easily damped and absorbed in the first mm of skin (dielectric constant of water of 79), H is not, and thus can induce forces on ions present in the biological medium. The resulting motion would result in local currents and a new local electric field.*

Following his point of view, whereas the expected field could appear weak, local amplification, related to both Coulomb and Ohm physical laws and to the presence of 20 charges in VG<sub>CC</sub> (5 net charges for each of the 4 alpha intramembrane S4 segments), would provide a factor of 7.2 million (20 (charges in voltage sensor) X 120 (from the dielectric constant) X 3000 (amplification at the plasma membrane) = 7.2 million<sup>10</sup>) the amplification of local EMF forces<sup>9,20</sup>. The result could then be (as described by Heck and Coll) *"a sliding-helix mechanism for electromechanical coupling in which outward movement of gating charges in the S4 transmembrane segments catalysed by sequential formation of ion pairs pulls the S4-S5 linker, bends the S6 segment, and opens the pore<sup>21</sup>".* It is worth to note that such a "transduction" mechanism should operate without involving any change in transmembrane potential<sup>22</sup>. Immediate consequence is calcium influx, local changes in the intracellular calcium concentration leading to Ca<sup>2+</sup> dependent signalling cascades and the release of chemical neurotransmitters. This at least unconventional theory generated numerous reactions, and is presently violently undermined by various authors<sup>23,24</sup> both on the basis of electromagnetism (violation of Maxwell's equations, coupling and damping of E, H, etc., existence of spatial temporal coherences/inconsistencies, etc.), direct numeric calculations<sup>22</sup> and from ethical considerations

(compared to previous work (in which he himself would have participated and then neglected<sup>23</sup>); critics finally asked to withdraw Pall's article<sup>25</sup> published in 2021.

## **12. Indirect stimulation: the membrane as first target.**

As suggested above, Ramundo-Orlando already evoked cell membrane as “major target” for low-level MMW<sup>4</sup>, in association with water and pore contributions. Based on numerous studies performed up today, the membrane structure and the dynamics of MMW-induced modifications appear both provoked by Ca<sup>2+</sup> influx and overall electromagnetic interactions.

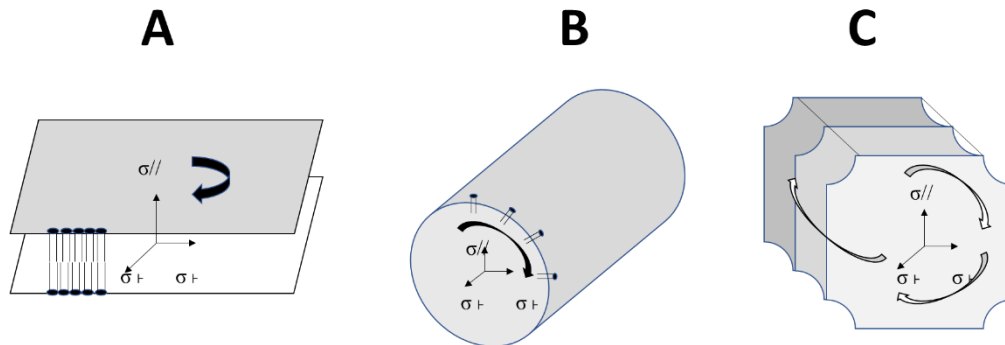
### 12.1. Membrane structure and dynamics

*Passive diffusion* : phospholipid model membranes offer an easy way to observe overall effects of MMW on structure, functions and dynamics. Cojocar<sup>26</sup> (2005) showed an increased proton transport through black films of phospholipid membranes (phosphatidyl cholines, DPPC) loaded with ionophores after 42.25GHz at 4mW/cm<sup>2</sup> exposure; this result was interpreted as passive diffusion related to surface hydration of the layer. Later, Ramundo-Orlando<sup>27</sup> (2009) used cationic liposomes of DPPC (dipalmitoyl phosphatidyl choline), stabilized by cholesterol and positively charged by stearylamine. She observed that the diffusion of paranitrophenol acetate (PNA, i.e. the substrate of carbonic anhydrase incorporated inside the liposome) was significantly enhanced when exposed to 53.37GHz, CW, MMW at 10mW/cm<sup>2</sup>. The improved permeability for small molecules (PNA) was related by the author to a change of polar head packing due to modified membrane curvature, itself related to water bound in the glycerol region of DPPC.

*Induced diffusion* : Cell membranes exhibit asymmetric distribution of phospholipids; especially, phosphatidylserine (PS) is mainly located at the inner layer. Following Ca<sup>2+</sup> influx, (physiologic or following MMW- stimulation, see section 1.1) Ca-associated system tends to externalize. It is important to recall the particular properties of PS. Typical phospholipids (phosphatidylcholine) self-organize in membranes as bilayers in liquid crystalline phase over phase transition temperature. In such systems <sup>31</sup>P-NMR studies<sup>28,29</sup> proved that polar head reorientation mainly occurs within the membrane plane (so called  $\sigma_{\parallel}$ , 2 contributions orthogonally placed in the membrane plan) while reorientation from tangent to normal are less frequent ( $\sigma_{\parallel}$  to  $\sigma_{\perp}$ , see figure 1a ). Due to the small size and charge of its polar head, PS tends, especially in the presence of Ca<sup>2+</sup>, to build unusual phases, i.e. hexagonal H<sup>II</sup>-inverted or even cubic phases. In the former case, reorientation within the “roller” becomes easy (between one  $\sigma_{\parallel}$  to  $\sigma_{\perp}$  while the exchange of  $\sigma_{\parallel}$  with the other, longitudinal  $\sigma_{\parallel}$

becomes much more difficult; see figure 1b). In cubic phases (figure 1c) isotropic reorientations easily occur giving a single resonance at the “isotropic” position.

**Figure 1 : artist drawing of different membrane structures , lamellar (A); hexagonal HII (B); cubic (C); inspired from from classical results as presented by De Kruijff et Al<sup>30</sup>, and e.g. by Garrab et Al<sup>31</sup>.**



The consequences of such biophysical mechanisms in biological membranes are clearly evoked in Jouhet et Coll<sup>32</sup> review. Given that she questioned if these structures occur in vivo, she pointed out that “most natural membranes are composed of two main glycerolipids: a bilayer forming lipid and a HII forming lipid”, and that “the structures formed may be of high importance for some enzyme activities”, such as enzymes like the calcium pump in the sarcoplasmic reticulum<sup>33</sup>. A supplementary link was proposed from previous studies<sup>34</sup>, and more recently in the NMR work of Antila<sup>35</sup> : PS commonly interacts with proteins via nonspecific electrostatic interactions as well as via specific binding. Moreover, in the presence of calcium ions, PS lipids can induce membrane fusion and phase separation<sup>36</sup>. Hence, PS headgroup is more rigid than that of phosphatidylcholines, owing possibly to electrostatic interactions or formation of a hydrogen bond network between the headgroups. This is especially the case for divalent cations -such as Ca<sup>2+</sup> - that can form “strong dehydrated molecular complexes with PS lipids<sup>19</sup>”, even leading to phase separation. Application in biological systems of such structures have been evidenced by Jouhet<sup>19</sup> and before observed by Yeagle<sup>37</sup> in the calcium pump of the sarcoplasmic reticulum. Local isotropic fusions (cubic) or axially fast transmembrane reorienting (hexagonal) structures, result in fluidity increase, in favour of membrane potential equalization (depolarisation), in facilitated mobility in S4 helix bending of VGcc, and finally in action potential trigger.

## 122. Collective electromagnetic interactions

A. De Ninno<sup>38</sup> proposed the concept of electromagnetic homeostasis, as “ the capability of the human body to maintain the balance of highly complex electromagnetic interactions within, in spite



of the external electromagnetic noisy environment". This would lead to a dynamic -metastable- electromagnetic homeostasis directly supporting cell and molecular physiological properties. Therefore, external electromagnetic interactions could affect normal functions and health, in a deleterious or favourable manner.

Geesinck et Al. in their extensive meta-analysis<sup>39</sup> (724 publications, 2021) proposed a *descriptive* model, and built a "all frequencies theory" for the non-thermal electromagnetic fields effects on biological systems. The physics basis he invoked was the so called "Bose-Einstein condensates", calculated by Einstein<sup>40</sup>. It initially stated that at extremely low temperatures (several  $\mu\text{K}$  or less) when de Broglie waves length was longer than the available space, bosons preferentially occupied the lowest energy state. This property was confirmed for inorganic systems (the experience of Young slits showed interferences necessarily related with coherent systems) and also directly observed later in macroscopic constructions<sup>41</sup>. Fröhlich postulated and calculated later that this concept could be applied to biology leading to the extremely simplify notion that part of the electromagnetic waves could be used, not in thermic production, but rather in order/structuration properties. From him, current metabolic processes would provide the existence of these coherent -collective- states, directly involving ionic and molecular motions. This would imply resonances in MMW (orientational modes) and THz-IR frequencies (vibrational modes). Such a constantly dynamic "equilibrium", - which means that no definitive steady state is present, could be related to the high sensitivity of living cells to external non-thermal millimetres waves (MMW) and to the higher frequencies resonances. Numerous studies were published under this scope, that Geesink's meta-analysis gathered<sup>14</sup>, covering all frequencies from quasi static fields up to visible and ultra-violets bands. This descriptive equation formalized some coherent/incoherent oscillation modes of energy (frequencies) distributions in a 3D semi-harmonic oscillator manner, by using sets of integer values, some of them not clearly defined, evoking Fourier series, with frequency-related energy multicomponent. This led him to class frequency domains in coarsely coherent, incoherent and intermediates: *"The coherent and decoherent (chaos-like) frequencies can be aligned at a frequency scale and are arranged according to an alternating ordering, while transition frequencies are located just in between the coherent and decoherent frequencies"* (Geesink and Meijer<sup>42</sup>), with strong variations depending on modulation or superimpositions, for instance. Our aim is not to criticize this extensive work. They pointed out three basic concepts:

- Dynamic equilibrium of biological systems, including charge motions/currents
- Potential structuration by MMW, even at low power exposure levels (i.e. less than  $10\text{mW}/\text{cm}^2$ )

- Role of water, water structure, hydrogen bonding, hydration of biomolecules, cluster free/water equilibrium ...

As mentioned above, as THz/IR frequencies would interact in vibrational modes, MMW (up to 300GHz) can only act in rotational modes. Water contribution is discussed in the next section.

However, many criticisms, similar as those pointed in Pall model (see section 11), make this theory at least subject to caution; for instance, terms like “coherent” clearly evoke phase, time and space coherence directly associated with MASER or LASER, which is certainly not the case. Pseudo periodic separations in frequency domains, presented as very well correlated with benefits or deleterious effects. Even if one supposes that it is the fact, a correlation doesn't mean cause-and-effect relationship...Furthermore, as several parameters in Geesinck's equation are not defined, one cannot draw any definitive conclusion from these propositions.

### **13 Role of water**

MMW mechanisms of interaction with (or through) water imply several different concepts, such as cluster formations/dissociations, free/bond water, coherent/incoherent domains, that differ whereas closely overlapped.

For instance, Ramundo-Orlando<sup>4</sup> attributed to MMW transfer through water, changes in the size and concentration, hydrogen-bonded water clusters formation and increase in water dissociation, resulting in electrical conductivity changes<sup>43</sup>. The result would be reactive oxygen species formations and, in turns to *“modulate Ca-dependent metabolic mechanisms...It has been suggested that the effect of 64.5 GHz, in correspondence with oscillating resonance frequency of water hexagonal structure, was direct on water solution. Consequently, by changing the structure of bound water, the thermic stability of different nucleotide pairs can change<sup>44</sup>”*.

Mae wan Ho<sup>45</sup> prepared and observed by electronic microscopy the formation of water clusters at room temperature and pressure. They noticed that electromagnetic fields could induce the formation of *“large, stable coherent domains (CDs) of about 100 nm in diameter at ordinary temperature and pressure, and these CDs may be responsible for all the special properties of water”*. According to Frölich<sup>46</sup> and Davidov-derived<sup>47</sup> theories, they considered that these CD could trap EMF since *“the photon acquires an imaginary mass, so the frequency of the CD EMF becomes much smaller than the frequency of the free field with the same wavelength”*. The two states of water, i.e. CD and non CD should be in equilibrium. CD structures were presented under different forms in this paper, of about 100nm diameter.

De Ninno<sup>35</sup>, under an energetic point of view, also considered water in equilibrium between two states. Hence, he assumed that, in the *ground state* all electrons are tightly bound, whereas in the *excited state* configuration *“electrons are only 0.54 eV below the ionization threshold ( $E_{exc} = 12.6 eV$ )”*;

thus, they can be considered as “quasi-free” or very loosely bound”. The result is a *coherent state*, a superposition of the ground state (83%) and the excited state (17%). Besides, it is worth to consider the existence of water surface layers on biomolecules and membranes, called “*vicinal water*”. Water/surface interaction leads to changes in dielectric constants (10 to be compared at 80 of bulk water), and partial structuration -lower entropy- regards to the bulk. Such changes exceed of 0.1–0.2 nm thickness expected from single electrostatic interactions. As mentioned above, Geesink (2021)<sup>26</sup> supports both Mae wan ho<sup>24</sup> and De Ninno<sup>25</sup> approaches, considering coherent and incoherent well defined structures (and frequencies domains) and also intermediate states between them realizing the less defined link between them. Water associated with ions, charged groups of proteins and DNA modifies their dielectric properties. Thus, MMW in sub thermal intensity could result in resonances able to induce electron tunnelling and finally ionic rearrangements in the protein DNA complexes<sup>48</sup>. This would operate in the various wave parameters, e.g., frequency domains as suggested in the Geesink *descriptive* model. He concluded that the primary electromagnetic fields target in DNA water solutions are the water molecules. Davidov theory (1977) proposed a model for energy transfer and conformational states in biomolecules, especially DNA, where the solitons play a role in the energy transfer and conformational states of biomolecules. Solitons can be defined as “*self-reinforcing solitary wave that travels at constant speed without changing shape*”. Geesink also mentioned that “*His theory showed how a soliton could travel along the hydrogen bonded spines of the alfa helix or protein molecular chains*”.

## **DISCUSSION /CONCLUSION**

In the aim of biological/medical applications of low power millimetres waves, thermal receptors have been clearly identified as the first target. As cited below, the several different mechanisms evoked here do not involve heating effects (at least those of significant contribution). Whereas not completely known, main target are clearly identified: VGcc, membrane, collective interactions, water structure, via electromagnetic, biophysical but not thermic mechanisms. Hence, some papers rather underline that the thermal effects would be deleterious, by activating different metabolic pathways of the normal thermal perception. For instance, Pall (2013. 2015) identified two different mechanistic pathways following MMW induced VGcc stimulation. This operates through NO synthesis, G-kinase and nuclear factor erythroid 2 related factor" (Nrf2) activity via raise of cyclic GMP levels, leading to therapeutic effects. Excessive VGcc stimulation, and consequently intracellular Ca<sup>2+</sup> increase, results in the setting up of “*peroxynitrite / free radical /oxidative stress pathway each contribute to pathophysiological responses*”.

Exposure to CW MMW implies energy transfer. At low level (typically around or less than  $10\text{mW}/\text{cm}^2$ ), this effect is overcome by local and general homeostasis processes<sup>10</sup>. At the skin level, an important parameter is the<sup>49</sup> thermal diffusivity. The ratio between thermal conductivity and thermal capacity is that a significant thermal diffusivity means that heat transfer is easier than storage. The efficiency of the thermal diffusivity is assessed via the time required for the target tissue temperature to decrease by 50%. This characteristic time is called thermal relaxation time (TRT). This point is of first importance and leads to consider the use of pulsed MMW. For instance, for a pulse of short duration compared to the TRT of the epidermis (3 to 10 ms), the exposed cells will have time enough to cool down between successive pulses (Ross et al. 1999<sup>50</sup>): this is achieved if the product R,

$$R = \text{pulse duration (ms)} * \text{pulse repetition relative frequency (\%)},$$

is short respect to the reference time (i.e. the duty cycle, DC). For example, this would be easily achieved for an equivalent power density of  $10\text{mW}/\text{cm}^2$ , by a 5ms pulse repeated 50 times/sec, (25% DC), which in terms corresponds to  $2.5\text{mJ}/\text{cm}^2$ , a very small energy release.

Beside this strict thermal aspect, Panagopoulos<sup>51</sup> already proposed in 2002 a biophysical model of interactions of oscillating electromagnetic fields within cells, including “*forced vibrations*” of free ions, and the possibility to exert mechanical forces-pressure on the plasma membrane, “*able to upset the membranes electrochemical balance, ... by opening or closing mechanically gated channel proteins*”. In the mathematical formulation he identified a particular term, that should be independent from vibrational contribution. This term should play a role at the onset of the MMW field and when the field is interrupted (on/off effect). He concluded that pulsed EMF could be most biologically active than continuous ones (at least by a factor of 2).

Another advantage of pulsed systems can be deduced from Fourier transform properties. CW exposure leads to selective excitation frequency. Conversely, an infinitely short pulse (Dirac) could theoretically cover all the frequency bands. In fact, pulses have a given duration and, for instance a square pulse would ensure the stimulation of a given “frequency spectral width”. The band consists of a sinus cardinal signal (*sinc*) centred on the carrying frequency with side bands on both upper and lower frequencies bands; this property is extensively used in military domain (ultra-wide band frequency jamming) or in research, e.g. in NMR spectroscopy. Bo<sup>52</sup> (2021), in particular, compared on neuroblastoma cells the effects of sinusoidal wave irradiation in the frequency range of 100GHz – 3 THz with gaussian pulses covering the same frequency range. The frequency response (after Fourier transform) is also a gaussian while side bands are more homogenous than sinc signals. He observed the variation of membrane potential, transmembrane calcium fluxes through VGCCs and intracellular calcium concentration. He found that THz pulses exhibited much more efficacy than CW in all the

parameters observed. Besides, he underlined that “*in the case of the relatively large amplitudes, THz Gaussian pulse irradiation reduces the concurrent temperature rise compared with THz sinusoidal wave irradiation. That would contribute to less side effect from the THz-induced temperature rise*”. Pulse form has thus to be selected to priorities onset/cut-off (square pulse) and the continuous spectral width (gaussian) to cover, with better homogeneity, the selected bandwidth (revolved gaussian).

It is noteworthy that these signals are exclusively positive. Hence, all electromagnetic gradients, ions derived currents and mechanical displacements should be vectorial, which means net -not averaged- effects and less energy involvement, as Bo said. From another perspective, Wang and Coll. recently proposed<sup>53</sup> to overcome gaussian pluses heterogeneity by using revolved gaussian pulses, finally obtaining reduced energy consumption, and at the same time a lowering of the maximum temperature.

Finally, one can expect from the use of positively pulsed MMW rather than CW modes: *i/* to better control the frequency band to use, *ii/* to preclude any thermal effect, *iii/* to magnify electromagnetic and mechanical stimulation such as forced resonances, both on membrane itself and at VGcc level.

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