Bio-acoustic signalling; exploring the potential of sound as a mediator of low-dose radiation and stress responses in the environment.

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Abstract

Objectives: This commentary reviews and evaluates the role of sound signals as part of the infosome of cells and organisms. Emission and receipt of sound has recently been identified as a potentially important universal signalling mechanism invoked when organisms are stressed. Recent evidence from plants, animals and microbes suggests that it could be a stimulus for specific or general molecular cellular stress responses in different contexts, and for triggering population level responses. This paper reviews the current status of the field with particular reference to the potential role of sound signalling as an immediate/early bystander effector (RIBE) during radiation-induced stress.

Conclusions: While the chemical effectors involved in intercellular and inter-organismal signalling have been the subject of intense study in the field of Chemical Ecology, less appears to be known about physical signals in general and sound signals in particular. From this review we conclude that these signals are ubiquitous in each kingdom and behave very like physical bystander signals leading to regulation of metabolic pathways and gene expression patterns involved in adaptation, synchronisation of population responses, and repair or defence against damage. We propose the hypothesis that acoustic energy released on interaction of biota with electromagnetic radiation may represent a signal released by irradiated cells leading to, or complementing, or interacting with, other responses, such as endosome release, responsible for signal relay within the unirradiated individuals in the targeted population.

Keywords: bio-acoustics; electromagnetic acoustic induction; bio-phonon; phonon, mechanotransduction; cell-to-cell signalling; cellular stress response; ionising radiation; radioecology; RIBE.

Introduction

A variety of mechanisms have evolved throughout the animal, microbe and plant kingdoms by which communication can be mediated. At the level of whole organisms the development of special sensing mechanisms, smell, taste, touch, sight and hearing are all involved in inter-organismal communication as well as in sensing the outside world, and have evolved to mediate the interaction of organisms from bacteria to humans with each other and their environment, including individuals of their own and different species (Stevens 2013).

Of particular interest is the evolution of signaling between individuals in response to threat or distress which may be due to predators or physiological stress. Such communication largely involves the interpretation of the environment and relay to other individuals. It can be intra- or interspecific (Goodale et al. 2010) but is generally advantageous to a species, its kin, or local guilds. For example, chemical cues from urine affect behavior both within and between species, (Apfelbach et al. 2015), and volatile compounds such as jasmonic acid (Farmer and Ryan 1990, Heil and Karban 2010, Karban et al. 2010) are widely used by plants to communicate threats both between and within species. Such communication may involve multiple mediators, singly or in ensemble. For example, a recent study elegantly describes the visual and olfactory modes of communication between fruit flies as in the acute response of fruit flies to the presence of predatory wasps (Kacsoh et al. 2018). Other types of cues are widely used and for example sound is extensively used in animal species and, as in the case of the fruit fly example above may be species discriminatory and information rich. The examples of acoustic communication between cetaceans, bats and higher mammals are well known, but the generation of and response to sonic vibratory signals of plants and prokaryotes is only recently becoming understood, with some remarkable findings such as the ability of plants to respond metabolically and with changes in gene expression to specific sound stimuli (Ghosh et al. 2019, Md. Emran Khan et al. 2014), frequency-specific growth-

enhancement in, for example, *Phaseolus spp*. (Collins and Foreman 2001) and defensive action initiated by plants whose leaves are being chewed by caterpillars (Appel and Cocroft 2014)

At the level of cells and tissues, Intercellular communication relies on the release, detection and transduction of physical or molecular signals which can range from electromagnetic (EM) radiation of various wavelengths (Le, McNeill, et al. 2015, Le et al. 2018), small molecules such as hydroxyl radicals (Schieber and Chandel 2014), peptide growth factors and extracellular vesicles (Margolis and Sadovsky 2019) to complex extracellular matrix interactions (Hastings et al. 2019). While such cues are essential for morphogenesis and tissue homeostasis, we are particularly interested here in the cues regulating cell proliferation and death in response to extrinsic and intrinsic damage. Cell death or senescence are classically induced in response to radiation damage (Sia et al. 2020) . This may be through p53-associated apoptosis or other mechanisms which are p53 independent, or related to necrosis, such as necroptosis, seen in some systems (Kuwahara et al. 2018). Evidence has recently been accumulating from non-radiation studies that suggests there are significant community effects following apoptosis induction (Eroglu and Derry 2016). Apoptotic cells release what are often described as “find me“ and “eat me” signals for macrophage clearance, but it is becoming apparent that neighboring cells can be induced to undergo apoptosis in a non-autonomous fashion (Pérez-Garijo and Steller 2015). In some cases this due to effects mediated by macrophages (Lemke 2019) but in other cases by direct effects of factors released by dying cells such as TNF-related compounds (Pérez-Garijo et al. 2013) or the mechanical effects of crowding (Eisenhoffer et al. 2012). This form of assisted suicide can have profound non-cell-autonomous effects on surrounding tissues by affecting the cell division, cell fate and tissue remodelling, involving mechanical forces exerted on the

cytoskeleton as well as cell replacement and proliferation (Gudipaty et al. 2018). It has also become clear recently that elements of metastatic behaviour can be transmitted from cell to cell via extracellular vesicles (Zomer et al. 2015).

Developments in our understanding of the effects of low-dose radiation on cells and whole organisms in recent years have raised some puzzling questions concerning the evident transmission of cellular phenotypes from one cell or organism to other non-irradiated organisms or cells, the radiation induced bystander effect (RIBE) (Mothersill and Seymour 2013). To date various mediators have been suggested, amongst them exosomes (Al-Mayah et al. 2012, Du et al. 2020, Jella et al. 2014, Le, Fernandez-Palomo, et al. 2017) and UV photons (Le, McNeill, Seymour, Rainbow and Mothersill 2015, Mothersill et al. 2019). However, these mechanisms still fail to explain all the reported phenomena (Mothersill et al. 2006, Mothersill and Seymour 2009, Mothersill et al. 2012). While our accumulated knowledge of communication between animals, plants and cells at multiple levels implicates the likely interaction of multiple systems, we still have no idea what other forms of communication might be responsible for the transfer of the “irradiated phenotype”.

The observation that the “irradiated state” can be passed from one whole organism to another raises the question of how such a transfer might occur between individuals in the same or different species in a contaminated environment and how such transfer of information might affect the response of the ecosystem to contamination as well as how the genetics of the response mechanism might be subject to selective pressures over time, as we see happening with the response to anthropogenic sound in many species (Harding et al. 2019).

In this commentary we present an integrated view of sound as a means of stress communication and to highlight areas of biology where the contribution of acoustic mechanisms is still unknown or understanding in its infancy. We explore the possibility that passively-generated acoustic signals may act as direct or indirect mediators of transfer of the "irradiated state" at multiple levels of organisation, to stimulate discussion of what is emerging as a novel and potentially important mode of communication between cells and organisms.

Sound and electromagnetic waves as communication mechanisms

Sound waves are a longitudinal mechanical harmonic oscillation of vibrational energy or pressure waves inside a molecular lattice medium (Rayleigh 1877). The density of this medium fluctuates by compressions and rarefactions (migrates into low and high pressure regions) in such a way that a mechanical sensor, such as the ear, can detect them. They exert a physical pressure at the wavefront, which along with amplitude and frequency constitute the characteristics of acoustic waves.

The properties of electromagnetic waves differ fundamentally from acoustic mechanical waves due to the fact that they do not require a medium through which to travel. They are transverse oscillations of electric fields and magnetic fields, traveling with the speed of light in vacuum and electromagnetic waves and sound waves differ fundamentally in their spatial shape and mode of propagation. Sound and EM waves represent complementary mechanisms for information transfer between entities that are acoustically and electromagnetically active (e.g. (Preisig 2007).

While this description of acoustic phenomena may be familiar, the related vibrational concept of the phonon, which is relevant here to the generation of acoustic force from the ionising radiation induced interaction with matter. A phonon is a discrete unit or quantum of vibrational mechanical energy, therefore having both wave and particle duality, which arises from oscillation of a collection of atoms or molecules. It may be considered as a Nambu-Goldstone Boson with broken symmetry consequent on translation across a long range structure (Leutwyler 1997) but may be considered naively as a "particle of heat".

Atoms behave as if they are connected by tiny springs which establish the shape of molecules and components of tissue structure. The atoms of the lattice vibrate with their own thermal energy and in response to applied forces/energy. The generation of a packet of mechanical waves can be defined today as ''bio-phonon'' in the context of biological systems, and which can travel and carry heat and sound through biomaterials with a discrete energy and momentum. The more dense the biological medium the faster bio-phonons travel through it; the more dense a medium the faster sound waves travel through it. A recent report suggests that phonons may traverse a vacuum at the nanoscale through quantum fluctuation, but the implications for the role of acoustic signals discussed here are unclear (Fong et al. 2019). We return to the interaction between electromagnetic and acoustic waves below.

Communication through acoustic signals requires an actuator process and a receiver, an environment permissive to the propagation of an acoustic signal, and some kind of discrimination/ filtration and transcription among signals by receiver. Such signals can travel long distances in a relatively short period of time (Bradbury and Vehrencamp 1998), are independent of time of day and availability of light, are rapidly transmitted at the cellular

level, as they do not rely on the speed of diffusion of small molecules like paracrine growth factor and are not precluded by lack of lines of sight. Both energy and information can be transmitted due to the capacity of acoustic signals to undergo modulation of frequency, amplitude and intensity. They can modulate direction depending on temporal and spatial coherence of mode of generation and propagation, through transmittance, reflection and refraction dependent upon the dielectric and sound wave absorption coefficient and attenuation coefficient properties of each molecule constituents of the environmental milieu.

The limitation of acoustic communication is directly influenced by the composition of environment. The environment is a heterogeneous medium composed of different matter with specific acoustic properties (Lorén et al. 2009). Sound waves represent a physical energy field successfully transferred from one point to another via diverse communication mechanisms exploited by a biological entity as part of adaptation to a specific complex environment. Such environments, composed of heterogeneous and irregularly distributed media, make inter-organism or intercellular biological communicative system very complex (Gillooly and Ophir 2010).

Interactions with environmental media

Sound waves are intrinsically short wavelength and have a frequency-dependent attenuation with increased scattering of higher frequencies (D'Astous and Foster 1986). This is medium-dependent and high frequencies of sound are absorbed/ attenuated rapidly in dry air compared to those of lower frequencies (Bond et al. 1992, Sakai et al. 1990, Sharan Verma 1950). However, in humid air, water droplets massively reduce attenuation/absorbance at low frequency but increase attenuation and thermal loss at high frequency as the speed of sound propagation ~340m/sec at sea level in air and five times more in far more dense medium such

as water (1480 m/s) and can reach several km/s in metals (Del Grosso and Mader 1972, Ludwig 1950, Shyu and Gaspari 1969). Electromagnetic waves by comparison travel a million times faster than sound waves (~$3x10^8$ m/sec). In contrast to sound waves that travel faster in a denser environment, light waves travel slower in a denser environment (Bludman and Ruderman 1968). These characteristics determine their differential utility in different environments and for different purposes.

Sound and electromagnetic waves are different forms of energy and can be interchanged/transduced from one to another in order to effect an efficient way of communication through different media. This exchange of forms of energy can be defined today as biological electromagnetic acoustic transducers (bio-EMATs) for biological systems. Both, separately or combined, are potentially important as modes of information transmission, and reward investigation in order to understand the mechanism of biological communication and environmental stress (Gagliano, Renton, et al. 2012). While electromagnetic waves such as light photons are successful carriers of information for long distance communication in air, in this review we mainly focus on sound waves to reflect their efficient transmission in water or electrolyte solutions such as sea water or tissue fluid (which are poor transmitters of EM waves) and the fact that biological systems are mainly composed of water and dense biomaterial (Woodard and White 1986).

Acoustic signals interact with the environment in which they are generated and, depending on its complexity and the physical relationship between signal, source and receipt offer a rich mode of communication at all ranges of scale from single cell to single cell, to the macroscopic level of whole organisms. There is considerable literature on the acoustics of metazoan vocalisation and other forms of biophonic communication in the environment. While aquatic environments offer an ideal medium for low frequency biophony the

relationship between distance, frequency and energy is much more complex in a terrestrial macroenvironment and for high frequency acoustics signals. What has not so far been considered is the acoustic equivalent of paracrine communication, acting over short distances between cells in close physical proximity, such as those in tissues, where signal attenuation will be minimal and it is possible to consider phonon mediated transmission through contiguous cellular structures, such as the membrane or gap junctions.

Electromagnetic induction of acoustic signals (EMA)

There is an intrinsic relationship between electromagnetic forces (mediated by photons) and acoustic vibration (mediated by phonons), experimentally established in the 19th century (Bell 1881). Photons are responsible for all the interactions between atoms that produce the compression or shear forces that generate sound waves. It is not therefore surprising to see this interaction reflected in the ability of ionising radiation induce an acoustic signal passing through water (Sulak et al. 1979), and in 1983 with the demonstration that synchrotron X-ray photons could generate an acoustic response from tissues (Kim and Sachse 1983) later giving rise to the strategy for probing the deep structure of materials, such as tissues, with X-ray-induced acoustic emissions (Bowen et al. 1991).

The mechanism by which ionising and non-ionising electromagnetic radiation induces an acoustic wave from matter originates through the interaction of photons and electrons (see figure 1). On exposure to ionised photons, inner-shell electrons of the biological molecules are excited, generating photoelectrons, Auger electrons, or electromagnetic radiation (e.g. photoluminescence) – which decay producing cascades of secondary electrons as these decay processes transfer kinetic energy to surrounding atoms to reach thermal equilibrium. These processes generate thermal energy into the biological structure as fluorescence reabsorption, Auger electron absorption, and photoelectron absorption. (Garcia et al. 1988, Nie et al. 2008)

[INSERT FIGURE 1 HERE]

Ionising photons themselves may also interact with outer shell orbital electrons and undergo Compton scattering, ejecting the orbital electron with kinetic energy net of the incident and scattered photons. Compton processes play a key role in ionised energy deposition into the material structures (Tong et al. 1995).

The resulting electron-phonon interactions in the surrounding atoms created by these processes lead to a localised increase of temperature in the irradiated matter and resulting a transient thermoelastic expansion of the biological structure generating pressure waves which constitute X-ray induced acoustic signals (Garcia, Pastor and Bennemann 1988). These are directionless and propagated in three dimensions and form, for example, the basis of X-ray acoustic imaging investigated for the recent past decades. (Bowen, Chen, Liew, Lutz and Nasoni 1991, Hickling et al. 2014). Exploitation of this process is under development for particularly dosimetry and radiation monitoring during radiotherapy (Hickling et al. 2016, Liangzhong et al. 2013). While resolution of whole tissue imaging by this method is poor, work is now being undertaken to examine the possibility for use in , X-ray acoustic computed tomography (XACT) for medical diagnosis (Liangzhong, Bin, Colin, Guillem, Yu and Lei 2013, Samant et al. 2020, Xiang et al. 2014, Xiang et al. 2013) allowing low-dose, real-time, three dimensional imaging requiring only single site access by an electro-acoustic probe.

The signal amplitude of EMA is directly proportional to electromagnetic absorber density and the deposited dose of energy. This thermal elastic wave expansion process is widely exploited in the optical frequency range to induce photoacoustic (PA) signals generated from the visible absorbers (e.g. myoglobin, hemoglobin, melanin, cytochrome, and DNA/RNA) or near-infrared absorber (e.g. glucose, lipid (Cao et al. 2018, Chi et al. 2013, Christison and

MacKenzie 1993, Da-Kang et al. , Danielli et al. 2015, Longo et al. 2017). The EMA signal requires only a short pulse of light excitation for efficient signal generation. Furthermore, an EMA wave propagates in 3 dimensions regardless of the angle or the geometry of the electromagnetic excitation beam. From these principles we can adduce that the interaction of electromagnetic radiation of any kind (e.g. RF radiation, thermal radiation, or optical radiation), and that of energy high enough to be ionising, will induce an acoustic signal on interaction with matter, of a greater or lesser energy and wavelength depending on the linear energy transferred, the molecular nature of the target and the medium through which the acoustic wave is propagated, together with temperature and the acoustic impedance. All organisms are therefore expected to elicit a bio-acoustic signal of some type on irradiation as a consequence of their physicochemical makeup.

Effects of ionising radiation on non-biotic sound emission

Before discussing the sound generation and response of biota to ionising radiation it is worth noting that sources of ionising radiation otherwise contained, such as in nuclear power plants or in radiaoactive waste repositories are expected to emit an acoustic signal. Radioactive heat sources produce a unique spatial and temporal thermoelastic stresses in which an acoustic wave expands and will affect surrounding elastic media (such as soil, sand, rocks and minerals) generating acoustic pressure waves (APW) which may interact with the surrounding biota. Such radiation induced sonic emissions are in widespread use for non-invasive structural testing (Tang et al. 2018) and may be a way of remotely monitoring radioactivity and subsequent heat generation within containment structures.

Acoustic emissions may have pleiotropic effects on affected cells through several mechanisms, one of which is the generation of reactive oxygen species which accompanies

thermoelastic expansion. The generation of ROS in this way is well characterised and here is evidence for free radicals produced in aqueous and nonaqueous solutions induced by ultrasound (Carmichael et al. 1986, Christman et al. 1987, Riesz et al. 1985). Recent experiments link the generation of intracellular ROS by low intensity ultrasound to cell killing in a number of cell lines (eg. (Xia et al. 2020))

Acoustic signals in the production of and response to stress in the environment

Acoustic signals in the environment may be divided into two main categories. Firstly, biogenic signals can be generated as active signals or passively through activities such as movement and feeding, *biophony,* including those present in the ambient environment such as those resulting from human activity, *anthropophony*. Secondly from the natural abiotic environment, *geophony*. These comprise the components of the acoustic ecology of an environment (Pijanowski et al. 2011). Active or passive biophony may either inadvertently elicit a stress response or be calculated to do so as a form of information transfer.

Metazoan animals

The phenomena of active vocalisations or mechanically generated signals, such as tail slapping or foot thumping is out of scope for this commentary. However we do note the detrimental and stressing effect of anthropogenic sound on non-human ecosystems. We do not know yet how such acoustic contamination affects multiscale systems below those mediated through a cognitive response.

Anthropophonic contamination effects have become increasingly prominent in the 20th and 21st centuries and result in numerous consequences, some of which are not well appreciated.

For example, the overfishing of trout primarily known to cause population reduction, environmental pollution (caused by fishing boats), and has overall effects on the food chain. However, elevated fishing activities have also led to rising, unwarranted levels, of underwater noise. In the presence of boat noise, tuna schools were observed to be less coordinated, resulting in fish straying off by either going to the surface or the bottom of the ocean floor to avoid the disruption (Slabbekoorn et al. 2010b) . The effects on whale populations are also well known since anthropogenic noise interferes with the highly complex "songs" of whales which can travel trans-oceanic distances (Erbe et al. 2019). Studies performed on captive fish, which were subject to anthropogenic noise, had increased levels of heart rate, cortisol secretion and muscle metabolism. Other effects include potential lower egg viability and reduced larval growth rates (Slabbekoorn, Bouton, van Opzeeland, Coers, ten Cate and Popper 2010b). Over the years, since the trout overfishing events, authorities have enforced stricter laws for fishermen and fishing companies to abide by, in order to protect all fish species. One of which includes, placing a ban on fishing during mating seasons. The increased underwater noise levels in mating areas can skew the information that lies within a males' mating call. When combined with potential harmful effects on reproduction, the presence of fishing boats during mating seasons can greatly affect the ability of these fish to procreate. Similar consequences have also been observed in other species (i.e. birds and frogs) that are subject to alternate forms of anthropogenic noise (Fay and Popper 2000, Kaiser and Hammers 2009, Slabbekoorn et al. 2010a, Sun and Narins 2005).

Effects at a cellular level

Molecular electromechanical coupling is the basis of sound perception in a wide range of metazoan species. The coupling between mechanical stimulus generated by acoustic waves and cellular response provides a paradigm for the receipt of a passively or actively generated

acoustic signal and its effects on cellular metabolism. For example when outer hair cells (OHC) of guinea pigs when subject to ultrasonic waves, Fridberger (1998), found that overstimulation of the outer hair cells led to increased concentrations of calcium influx (Fridberger, Flock, Ulfendahl, & Flock, 1998; Fridberger & Ulfendahl, 1996). Sustained levels of calcium ions can be detrimental to the targeted cell and the surrounding cells, as this can lead to apoptosis (Duchen 2000, Sen 1992). It is interesting to note that calcium influx is the first observable event in cells receiving a radiation-induced bystander signal (Lyng et al. 2000) and has been observed to mediate cell death in response to a variety of stressors including low doses of ionizing radiation (Stevenson et al. 1987). The proposed mechanism of conversion from mechanical to chemical energy is that the rising calcium levels activate proteinases that rearrange the actin cytoskeleton. Subsequent to this, rounding of the cell or cytoplasmic blebs occur (Fridberger et al. 1998, Olwell et al. 2005). Similar to gas bubbles from cavitation, cytoplasmic blebs are bulges of the plasma membrane which arise from changes in the cytoplasmic pressure due to contractions produced by actin, ultimately leading to apoptosis (Fridberger et al., 1998).

Another consequence of higher calcium levels, leading to apoptosis, is the activation of endonucleases which cleave DNA, producing multiple fragments (Szydlowska and Tymianski 2010)(Fridberger et al., 1998). Overstimulation can lead to degeneration of the outer hair cells, due to loss of tip links connecting neighboring stereocilia (White et al. 2020)(Fridberger et al., 1998). With outer hair cells relying on calcium for electromechanical transduction, the associated ion channels serve as its primary source. However, with acoustical damages, calcium cannot enter through these ion channels and instead enters through its basal membrane (Hudspeth 1989)(Fridberger et al., 1998). With a 50-fold increase in endolymph calcium concentrations, this huge influx as result of overstimulation, can

severely reduce functioning of outer hair cells and lead to overall hearing loss (Fridberger et al., 1998; Fridberger & Ulfendahl, 1996). Much of the calcium post-treatment were found to coalesce in areas of dense mitochondria concentrations, again paralleling the response to bystander signaling (Hei et al. 2008), in the nuclei of cellular debris and in the cytoplasm of the hair cells. Mitochondria also play a major role in the death of outer hair cells subject to overstimulation, via activation of mitochondria-mediated cell death pathways (Vicente-Torres & Schacht, 2006). It begins with the activation of calcineurin, a calcium-dependent phosphatase, leading to the activation of Bcl-2-associated death promoter (BAD) and its translocation to the mitochondria (Vicente-Torres & Schacht, 2006). As is known, *Bcl-2* and *Bax*, are apoptotic-regulatory genes that when activated (through dephosphorylation), increase the permeability of the mitochondrial membrane releasing cytochrome C and endonuclease G, both of which are proapoptotic compounds (Vicente-Torres & Schacht, 2006). It was observed that overstimulation causes mitochondria to localize; however, certain studies also suggest that this may occur near the nucleus (Vicente-Torres & Schacht, 2006). These compounds would then be able to easily bind to the DNA inducing cell death. Similar studies performed by Ashush et al. (2000), on human myeloid leukemia cells (HL-60, K562, U397 and M1/2) were testing for the pathways involved with apoptotic induction when subject to therapeutic ultrasound of 750 kHz (Ashush et al., 2000). The results were similar to those cells subjected to γ-irradiation (Mothersill et al. 2001, Mothersill et al. 1999), suggesting a potential role for ultrasound waves in facilitating two of the most common types of low-dose radiobiological responses: the bystander effect and the radioadaptive response (Bonner 2003).

As well as pathological calcium influx the generation of reactive oxygen species by acoustic energy has also been implicated in cell death (Feng et al. 2010). It has been recently

established that at least in the OHC of the vertebrate ear acoustic trauma gives rise to redox imbalance, alteration of distribution of NADPH within the cell, lipid peroxidation and changes in membrane structure accompanied by ROS generation (Maulucci et al. 2014) with the implication that the resulting mitochondrial stress might engage apoptotic signaling in exposed cells (Raimundo et al. 2012). Such cellular generated ROS are in addition to the ROS known to be generated in aqueous media by acoustic energy itself (Christman, Carmichael, Mossoba and Riesz 1987, Riesz, Berdahl and Christman 1985).

Bio-acoustic signaling in vascular plants and microbes

While the reception and transmission of sound signals are usually associated with specialised sound sensing organs in metazoan animals, various studies have shown the existence of acoustic emissions and responses in plants, invertebrates and bacteria

Vascular plants

There is considerable evidence for bio-acoustic emissions from vascular plants, and increasing indications that plants are responsive to external acoustic stimuli (Gagliano, Mancuso, et al. 2012, Khait et al. 2019). In general these are associated with stress responses and there are several mechanisms postulated for their generation. Much less well developed are models for the sensing of acoustic signals, and evidence for these and potential signal transduction mechanisms is discussed below. It is important to stress that such mechanisms are not “voluntary” emissions by the plant but a consequence of the physicochemical and anatomical properties of their constitution.

Drought stress and predation constitute two of the major physiological stressors of vascular plants. Under drought stress some plants produce measurable bio-acoustic emissions (De Roo

et al. 2016). The mechanisms for generating these signals are not fully understood but may involve the effects of decreasing hydrostatic pressure in xylem, leading to the production of ultrasonic sound emissions variously measured as >20kHz (Tyree and Dixon 1983) and from 10 to300 kHz (Laschimke et al. 2006). With rapidly decreasing pressure in the xylem, collapse of bubbles caused by cavitation has been suggested as one mechanism for the generation of sound, but an alternative hypothesis derived to explain the "violent acoustic activity" detected in *Ulmus sp*. in response to drought stress, is release of energy from the xylem-adherent bubble system that normally contributes to water flow (Gagliano 2013, Gagliano, Mancuso and Robert 2012, Gagliano, Renton, Duvdevani, Timmins and Mancuso 2012, Laschimke, Burger and Vallen 2006, Zweifel and Zeugin 2008). Respiration and metabolic growth activity of the cambium is another method suggested to be involved (Zweifel and Zeugin 2008). The cambium is the portion between the xylem and phloem where cells are rapidly dividing and is responsible for secondary growth of stems and roots (Schöner et al. 2016, Zweifel and Zeugin 2008). At night-time when the plant is subject to drought stress, the cambium has increased turgor pressure due to increased respiration. This increased pressure causes greater levels of carbon dioxide to enter the xylem, resulting in more gas bubbles and subsequent acoustic emissions. In the absence of drought stress and consequent xylem cavitation, young corn roots are able to produce clicking sounds under water - the reason for retaining or developing this mechanism is unknown (Schöner, Simon and Schöner 2016) . It is apparent that a variety of plant species have developed mechanisms for sound production.

Acoustic responsiveness.

Our understanding of the mechanisms for sensing and transducing acoustic signals is in its infancy and currently there are no mechanisms elucidated (ten Cate 2012). However there is

increasing evidence for a physiological response to external signals (Collins and Foreman 2001, Khait, Obolski, Yovel and Hadany 2019, Veits et al. 2019), and some molecular correlates which implies that there must be a mechanism at work.

There is evidence that acoustic signaling may modify growth and maturation of plants and fruits. Jung et al produced a review of this field in 2018 (Jung et al. 2018), showing that in a wide range of plants, physical triggers could modulate physiological traits such as ripening and could influence downstream signaling pathways. They concluded that sound wave treatment could be a new way to improve fitness and protect against unfavourable conditions. The "organ" responding to sound has not been identified in plants but may be a systemic response to vibrational waves through liquids in the plant as discussed above. A table in Jung et al (2018) lists the results of studies on thirteen different plants and fruits, where effects range from yield changes and delayed ripening in tomatoes (Hassanien et al. 2014, Hou et al. 2009, Kim et al. 2018) to effects on photosynthesis (Hassanien, Hou, Li and Li 2014, Kwon et al. 2012). Kim et al. (Kim, Jeong and Ryu 2018) later linked the tomato delayed ripening effects to regulation of both coding and non-coding RNAs and transcription factor genes. An earlier study performed by Kim et al. (Kim et al. 2015), found that tomatoes that were exposed to 1 kHz sound waves for 6 hours displayed delayed onset of ripening due to reduced ethylene levels (hormone responsible for early development and senescence in fruits), and reduced expression of the associated genes. These genes include the ethylene biosynthesis-related genes (*LeACS2, LeACS4 and Le ACO1*) and the ethylene-inducible genes (*E4* and *E8*). Reduced expression was not only observed in genes responsible for ethylene production but also in those regulating the on-set of ripening: *RIN, LeHB-1, CNR, NOR* and *TAGL1*. The potential adaptive effects and ecological relevance of phytoacoustics is an emerging field which could be harnessed to manipulate agriculturally relevant features

such as synchronized or staggered ripening of fruits (Khait, Obolski, Yovel and Hadany 2019).

Additional molecular evidence is emerging that plants have stress or signal-activated genes that enable them to process sound. Jeong and co-workers (Jeong et al. 2008), found that transgenic rice plants up-regulated the expression of the *ald* gene, when subject to frequencies of 125 and 250 Hz. Similarly, when an *ald* promoter was administered with a GUS reporter, GUS expressions also increased at 250 Hz. This suggests that the *ald* gene is associated with (transgenic rice plants in this case) processing of specific acoustic frequencies for gene regulation instead of light, to which it is also responsive. Other mechanisms include phytohormone production and germination and growth, through which plants are able to respond to sound waves (Schöner, Simon and Schöner 2016). Remarkably, recent studies link an adaptive response in *Arabidopsis* to acoustic signals (Bhandawat et al. 2020, Ghosh, Choi, Kwon, Bashir, Bae and Bae 2019), the former suggesting some form of learning response, thus linking together signal perception, transduction, changes in gene expression and a physiological response with an advantageous adaptation to stress.

The details of a plant acoustic perception apparatus are as yet unknown but it has been suggested they may similar to the way outer hair cells function in mammals, by altering membrane potentials of subcellular structures. Altering cell membrane and cell wall potentials have been shown to produce acoustic waves from kHz to THz range (Gagliano, Renton, Duvdevani, Timmins and Mancuso 2012), myosin is also believed to be involved as it can produce mechanical vibrations within cells by sliding against actin filaments (Gagliano 2013). These vibrations can then propagate through cytoplasm and create a vibrational cascade with surrounding cells causing cytoplasmic streaming. A process known as coherent

excitation, where multiple cells work collectively could also produce sound signals in frequencies between 150-200 kHz (Gagliano 2013). We discuss hypotheses for potential mechanisms below. At the range of frequencies most often described it is likely that any plant to plant signal transmission will occur at a very short distance given air movement and acoustic attenuation but in a natural context it is not possible to rule out transmission underground or at the interface of substrate and air via soil water and mass where signals might be expected to travel much further.

Microbes

Bacteria have highly developed acoustic communication. Matsuhashi et al. (Matsuhashi et al. 1998), found that certain bacterial cells, such as *Bacillus subtilis* and *B. carboniphilus*, process sound waves as a form of growth-regulation when the two populations are in close proximity (Matsuhashi et al., 1998). *B. carboniphilus* under high-temperature and potassium-chloride stress becomes extremely sensitive to growth-promoting acoustic signals (Matsuhashi et al., 1998) leading to a regulation of growth rate which is highly controlled by environmental factors. The acoustic signals from Bacillus subtilis were able to cross petri dishes, even when there was a 2mm iron barrier, leading to the production of more spores and greater overall growth (Matsuhashi et al., 1998). *B. subtilis* were found to emit sound waves of frequencies between 8 and 43 kHz, while *B. carboniphilus* were seen to form colonies when subjected to frequencies between 6 and 38 kHz. The overlapping frequency ranges suggests communicative purposes for the acoustic emissions. Similarly, increase in colony counts was also observed in E. coli, when subject to frequencies of 1, 5, and 15 kHz (Lee Ying et al., 2009).

As previously mentioned adverse effects of cell membrane thinning, localized heat production and free radical formation, along with bacterial inactivation and deagglomeration of bacterial clusters, all arise from acoustical cavitation (Joyce et al., 2003). Shear forces from ultrasound waves produce a pressure gradient, subsequently, creating low-pressure gas bubbles (Joyce et al., 2003). When the surrounding pressure becomes too high, these gas bubbles burst, sending a shockwave damaging the bacterial membrane and cell wall (Joyce et al., 2003). Consequently, giving rise to either a positive (increased resistance) or negative (cell death) signaling cascade, as a result of calcium ion leakage

Although ultrasound frequencies are known for such adverse effects as cell membrane thinning, localized heating and free radical production (Joyce et al., 2003; Lee Ying et al., 2009), they are also responsible for growth-regulatory signaling as observed with *Staphylococcus epidermis* and *Pseudomonas aeruginosa* (Pitt & Ross, 2003). The mechanisms involved in bacterial acoustic signaling are not clear but are believed to involve vibration of bacterial membranes, while perception of sound is thought to be mediated through activating ion channels (Matsuhashi et al., 1998). The production and transduction of these acoustic signals, in bacteria, could provide insight into its role at the cellular level.

Puzzles and knowledge gaps in the field of acoustic biology

Before discussing the puzzles in the field of radiation-induced bystander effects and the potential of acoustic biology to inform radiation biology, we should draw attention to knowledge gaps and questions in the field of acoustic biology itself; these include:

1. “Listening” as a biological event

While much is known about acoustic receptors in organisms, little is currently known about the cellular processes involved in acoustic signal reception outside specialised sensory organs. There is however some limited evidence of the activation of specific mechanotransduction receptors which we discuss below. Any specificity is likely to lie in such macromolecular signalling mechanisms as opposed to chemical signalling through generation of ROS, although in principle both might occur separately or together (discussed below).

2. How might the cell or tissue distinguish an acoustic "alarm" from an "adapt" signal?

The answer to this is unknown at present. It is likely that the cell does not distinguish an alarm from an adapt response. Alarm is probably the default response but if the environment is favourable, the cell or its progeny (or the population of organisms) may adapt. Those outcomes will probably depend more on what else is happening in the cell/population, signal cross-talk, and the responsive state of the cells stimulated.

3. How might an acoustic signal be sensed by non-sensory cells?

We understand the nature and physics of acoustic waves and therefore there are existing paradigms on which to base hypotheses. The physical displacement of molecules as part of an acoustic wave produces a pressure and that pressure in principle will act to reversibly deform any elastic structure with which they interact. It is now very well established that low-intensity ultrasound causes cytoskeletal structural and gene expression changes in cells (Louw et al. 2013, Miller et al. 2017, Samandari et al. 2017). Potential mechanisms for this involve changes in the structure and composition of the cell membrane and cytoskeleton (reviewed in (Kruglikov and Scherer 2019)), (Mizrahi et al. 2012, Ye et al. 2016a), redistribution or modification of expression of caveolin (Ye

et al. 2016b), and stimulating exosome release (Li et al. 2019, Yuana et al. 2017, Zeng et al. 2019). The opening of specific mechanosensory channels and activation of receptors has been reported (Liao et al. 2020, Prieto et al. 2018), changes in membrane structure (Shoham and Kimmel) and possibly in some circumstances sonoporation (Li et al. 2018). There is an existing well-developed model for the opening of Ca^{2+} channels by acoustic stimulus in the Piezo 1 channel (Liao et al. 2019), although whether this might be feasible *in vivo* depends on measurement of the acoustic pressure or energy exerted at the surface of an individual cell, its geometry, acoustic modulus and possibly its substrate. Such measurements have not yet been made, but it is hoped that given the known ability of mechanosensory receptors to be opened by ultrasound, such a mechanism is attractive and worthy of investigation. Mechanosensory receptors are an unusual family of proteins, both functionally and structurally and currently and there are currently thought to be only 18 mechanosensitive ion channels in humans. However similar molecules are present in plants, bacteria and archaea, so are very widespread. It is unclear if a potential acoustic signal receptor may be one of the already characterised genes or a novel function for another functionally associated gene.

The profound effects that these signal sensing mechanisms have on cell death, cell division (Zhou et al. 2004) and differentiation (Miller, Chama, Louw, Subramanian and Viljoen 2017) suggest that acoustic signals might contribute an important component to the bystander response. The involvement of exosome release, changes in miR expression (Costa et al. 2019) and calcium influx in well characterised sound responses (Lee et al. 2020, Takahashi et al. 2019, Zhang et al. 2012) is very reminiscent of observations in the RIBE (see below), and is persuasive of a hypothesis in which local acoustic emissions may be the trigger for the RIBE, followed sequentially by other more familiar

processes of intercellular communication. To what extent this might be operative at a macroscopic level in the environment is currently unknown.

4. How could we identify and monitor the receptor mechanisms?

Identification of a receptor protein or structure would be greatly assisted by identification of a response spectrum to radiation-induced acoustic emission, and in principle analysis of cellular response using knockout cells or model organisms. Human genetic studies on radiation sensitivity or possibly therapeutic response might also yield evidence for involvement of mechanoreceptor involvement.

5. Could we block, inhibit or boost this reception machinery?

This is possible in principle once a mechanism has been determined. One interesting avenue might be to use sonic enhancing agents such as Sonovue a stabilised microbubble preparation used as a contrast agent in clinical US studies. Similarly membrane composition manipulation may provide some circumstantial evidence. Known mechanoreceptors do have specific inhibitors such as gadolinium (Bae et al. 2011) and ruthenium red (Syeda et al. 2015) and activators such as Yoda, but these do not affect all classes of mechanoreceptors.

Puzzles in the RIBE at whole organism and cellular level; a communication problem.

While many of the mechanisms involved in RIBE have been worked out – particularly the response to signals (Hei et al. 2011, Le, Fernandez-Palomo, McNeill, Seymour, Rainbow and Mothersill 2017), some key puzzles remain.

- What is the “first cause”; what happens to the energy from the ionising radiation that is deposited in the target?
- How does the energy (dose) measured in joules per kilogram get converted to chemical energy?
- How are the contents of exosomes, that are the putative vehicles carrying information, modified by the irradiated target, and what stimulates their release?
- What is the relationship between RIBE and genomic instability (non-clonal transgenerational instability)?
- Is inter-organism RIBE the same as inter-cellular RIBE or is it a different process?
- Is acoustic signalling a potentially fundamental “first cause” or just one of many possible signals?

Most of these questions remain unanswered at this time but it is worth discussing why we consider them to be *puzzles* and why we believe that the induction of acoustic signals is a neglected potential mechanism by which the RIBE might be initiated or propagated.

1. A perusal of any of the many textbooks of radiobiology would suggest this question was answered years ago; energy deposition caused generation of free radicles and direct or indirect damage to cellular components. DNA damage is most critical and damage to DNA is proportional to the dose of energy deposited. Most damage gets repaired after low-dose exposures (generally accepted to be <100mGy, 0.05mGy/day) but mis-repair can happen leading to the dose-related generation of mutations (e.g. (Elkind et al. 1967, Hall and Giaccia 2012). The puzzles start with the discontinuity between low dose effects and high dose effects – non-linearity is seen and both “good” and “bad” effects can occur (although these terms are highly dependent on context). Genomic instability, hormesis and adaptive responses are examples of effects that are not accommodated by classical target theories of energy deposition

(Mothersill and Seymour 2019). The missing element in this first puzzle may be a failure to consider the importance of excitation after low dose exposure. It is well known that both ionisation and excitation occur during irradiation but because of the paradigm linking energetic free radicals to biological damage, excitation is dismissed as unimportant. Puzzle 2 assumes it is actually VERY important at low doses

2. The evidence for the importance of excitation mainly comes from experiments of Le et al (Le, Fernandez-Palomo, McNeill, Seymour, Rainbow and Mothersill 2017, Le, McNeill, Seymour, Rainbow and Mothersill 2015, Le, McNeill, Seymour, Rusin, Diamond, Rainbow, Murphy and Mothersill 2018, Le, Mothersill, et al. 2015, Le, Mothersill, et al. 2017) and (Cohen et al. 2020). These document the generation of photons, assumed to result from excitation decay, during ionising radiation exposure to beta and gamma radiations. These photons were collected in the UVA range (around 340nm) but unpublished spectral analysis shows emissions right across the EM spectrum. Photon emission has been directly and quantitatively linked to RIBE and exosomes harvested from photon exposed bystander cells can substitute for photons and induce secondary RIBE (Le et al 2017b). The puzzle here is all the data were collected using a filter collecting UVA photons but can other photon energies or acoustic energies initiate biological effects?
3. The third puzzle concerns how energy is transduced in a way that modifies the cargo of exosomes to transmit altered instructions to the bystander cells (or organisms)? It is known that calcium channels are critical in this process but the biophysical processes are far from clear. If the excitation decay products open channels, perhaps acting like a nerve impulse, how do the cells discriminate between the process induced by radiation and natural processes involving calcium channels induced by normal metabolic processes? Exosomes generated by photon exposed cells induce the RIBE

phenotype but exosomes harvested from control or sham exposed cells do not (Le, Fernandez-Palomo, McNeill, Seymour, Rainbow and Mothersill 2017).

4. Another puzzle that is critically important when trying to ascertain the role of RIBE in radiation risk assessment involves the relationship between RIBE and radiation-induced genomic instability (RIGI). In the last 40 years RIGI was actually documented before RIBE although evidence of both under other names can be found in the old literature (Mothersill and Seymour 2019). The key issue here is what drives RIGI? The manifestation of RIGI is effectively permanent and once induced cannot be "reset". However, it is not due to a mutation that can be identified but rather it is a state resulting in a higher tolerance for mutations of all types. Non-clonal mutations arise sporadically and unpredictably in the system in perpetuity (Mothersill et al. 2000). Some try to explain the state as resulting from a genetic mutation leading to a "mutator phenotype" (Loeb 2016) but mutator phenotypes lead to accumulation of mutation over time while RIGI leads to sporadic non-clonal mutations occurring at a higher than normal rate in cells which have up to that point been perfectly normal. The suggestion is that the RIBE signal-generating phenotype is an epigenetic maintainer of the RIGI phenotype. Why this phenotype would persist is unknown and how it would not be selected out in cultures or in organisms is a puzzle taxing the minds of radiobiologists concerned about evolution of radiation-induced traits in populations.

5. When inter-organism transfer of the RIBE phenotype was first seen in the radiation field in mice (Surinov et al. 2004) and in fish (Mothersill, Bucking, Smith, Agnihotri, Oneill, Kilemade and Seymour 2006) it was a cause of amazement but quickly dismissed as not the same as cellular RIBE. Subsequent demonstration of inter animal, yeast and plant transfer (reviewed in (Mothersill et al. 2018)) established the

phenomenon as real but it is still not clear if the mechanisms are similar or if whole organism transfer is a sub-category of the type of acoustic, light or chemical communication well documented in the ecology field. The paper that gives us the strongest evidence for a role for EM signalling other than light is one where irradiated fish were placed in an aquarium inside another larger tank in with unirradiated fish were swimming (Mothersill, Smith, Fazzari, McNeill, Prestwich and Seymour 2012). The unirradiated fish picked up the bystander signals and showed evidence of having acquired the irradiated phenotype. We then repeated the experiment but covered the inner tank with aluminium foil to prevent light signals from reaching the unirradiated fish. The same result was seen. Calculations performed to study the attenuation of the signal could not exclude sound as a possible signal but others such as photo-voltaic reactions are also possible. This work has not been followed up.

6. Acoustic signalling is well documented in the animal and plant world so question 5 above really pertains to whether acoustic or light signals are fundamental first causes of RIBE which can manifest at multiple levels of organisation from sub-cellular to organismal. Ultimately even in a whole organism, the signal has to be generated in a cell. Systems which allow the signals from multiple cells to be coordinated so as to be strong enough include quorum sensing in bacteria emitting light signals (Pena et al. 2019) and chemical sensing in slime molds where aggregation is triggered by a range of species-specific ions or peptides (Loomis 2014).

These puzzles have no immediate answers and raise many new questions which will undoubtedly keep us busy exploring the rise of bioacoustics as evidence in the years to come.

A cellular acoustic response in the bystander effect?

We do not consider that the received acoustic signal is in itself a damaging agent but a secondary relay from the cell hit by radiation and damaged. We hypothesise that the initial radiation interaction produces acoustic pressure in the surrounding medium or cellular milieu and the surrounding cells respond to that pressure. We believe it unlikely that the acoustic signal itself induces damage but rather we propose that there is some form of signal detection and transduction. either in the way of direct molecular interaction – discussed below, or through the mediation of induced reactive oxygen species (ROS). Neither might be expected to necessarily damage DNA directly, although the latter might.

There is evidence that ultrasound can generate DNA damaging effects, both as naked DNA or DNA within cells. (Furusawa et al. 2012, Milowska and Gabryelak 2007, Saliev et al. 2018). However the acoustic energy released from a single irradiated cell is likely to be much less than that directly applied across volumes or fields of cells in these published studies. It is difficult to establish a prediction of local acoustic pressure generated by irradiation in a field of cells. We can however demonstrate that a relationship may be established between absorbed dose and generation of acoustic pressure but we can predict that radiation energy and quality, and the material absorbance spectrum will affect the range of wavelengths emitted [Supplemental file 1].

If each randomly irradiated cell generates an acoustic signal it is very difficult to estimate the energy deposition into a neighbouring cell in the surrounding field or volume without direct measurement. This will be affected by the geometry of both activated and responding cells, the relative distribution of activated cells and the attenuation effect of both cytoplasm (between cell border and nucleus) and any intervening cells. The acoustic attenuation effect of cells is of the order of in 10^3 x in comparison to water (Pasternak et al. 2015) and so a

significant modulator of signal strength. It is consequently unlikely that the effect of ultrasound signal from an irradiated cell is likely to damage DNA in the nucleus of a neighbouring cell.

We consider that generation of reactive oxygen species by the acoustic wave or a direct effect on a macromolecular structure are more likely methods of signal detection and transduction. As to whether acoustic pressures at this scale might be enough to elicit an active signal; 3mPa externally applied ultrasound has been shown to elicit a biological response with Ca^{2+} influx in HUVEC cells (Hwang et al. 2014) but with no effect on cell viability, although no direct titrations are available in the literature and the authors of the study did not use stimuli lower than 3mPa. Whether elicited acoustic signals from medium to low doses of radiation fall in to this range is yet to be directly ascertained.

Conclusions

We have reviewed the evidence for the emission of acoustic signals from irradiated biota of many different species, and conclude that all biological material has the potential to emit sound on interaction with ionising radiation. There is not so far any evidence of sustained acoustic emission outside the time period of dose delivery, which would require either extremely inefficient relaxation processes or the triggering of an unknown energy-dependent cellular mechanism for producing sound. However, in situations of chronic exposure, such as external irradiation or internal contamination such as are found in contaminated ecosystems we would expect there to be sustained sound production if doses are sufficiently high. This is complicated by issues of intense local irradiation for example in internal contamination and raises problems already discussed about the meaning of environmental dosimetry (Beaugelin-Seiller et al. 2020). Transmission distances of such sound in air are likely to be short, given

the acoustic modulus of air, its movement, and the presence of physical barriers to transmission such as interspersed objects in the environment. The physical characteristics of sound however suggest that transmission through the underlying matrix or at the interface of matrix and air, especially in wet environments, could be more efficient. Persuasive evidence exists that biota of all types, at the level of cells and organisms can respond to sound, and that in some cases to biophony. This strongly suggests that the ability to perceive and respond to the sounds emitted by biota under stress may be a widespread phenomenon.

Experiments on the RIBE raise many issues about the mechanism and response to the irradiation of neighbouring cells and organisms. The properties of the information-carrying entities predicted by these experiments are often contradictory and are at odds with well-established paradigms. We were struck however by the parallels with the experiments of Gagliano and Renton (Gagliano and Renton 2013) , who showed that *Ocimum basilicum* can stimulate the germination of chilli seeds, even when all obvious routes of signal transmission were blocked, implying that neither chemical nor light signals were involved.

It was the intention of this commentary to stimulate discussion on the neglected role of radiation-induced acoustic emission in the response of cells and organisms to radiation and we hope that in turn this will stimulate experimentation to establish its role.

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Figure legend

Figure 1. Mechanisms by which electromagnetic radiation induce the emission of sound signals and phonons. a.) Diagram of Photoelectron absorption, Auger electron absorption and Photon re-absorption. and b.) Schematic of a biological tissue receiving EM photon excitation, the photo-luminescence from a biological absorber/emitter, the local temperature rise and the sound wave generation associated from thermo-elastic deformation.

a.

Photoelectron Absorption

Auger electron Absorption

Photon re-absorption

Photo-electron emission

Auger electron emission

Unoccupied electronic state

M

L

K

Photon excitation

Photo-electron absorption

Non-radiative relaxation

Heat & Phonon emission

Photon excitation

Photon excitation

Non-radiative Auger recombination

Auger electron absorption

Non-radiative relaxation

Heat & Phonon emission

Photon excitation

Internal conversion

Vibrational relaxation

Radiative relaxation

photon re-absorption

Photon emission

Non-radiative relaxation

Heat & Phonon emission

b.

Photon excitation

Absorber & emitter

Photon excitation

Tissue

Photon emission

Photon emission

Local temperature rise

Heat source & Thermoelastic deformation

Local pressure rise and propagation

Sound wave