

#### Review

# Interactions between electromagnetic radiation and biological systems

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#### **SUMMARY**

Even though the bioeffects of electromagnetic radiation (EMR) have been extensively investigated during the past several decades, our understandings of the bioeffects of EMR and the mechanisms of the interactions between the biological systems and the EMRs are still far from satisfactory. In this article, we introduce and summarize the consensus, controversy, limitations, and unsolved issues. The published works have investigated the EMR effects on different biological systems including humans, animals, cells, and biochemical reactions. Alternative methodologies also include dielectric spectroscopy, detection of bioelectromagnetic emissions, and theoretical predictions. In many studies, the thermal effects of the EMR are not properly controlled or considered. The frequency of the EMR investigated is limited to the commonly used bands, particularly the frequencies of the power line and the wireless communications; far fewer studies were performed for other EMR frequencies. In addition, the bioeffects of the complex EM environment were rarely discussed. In summary, our understanding of the bioeffects of the EMR is quite restrictive and further investigations are needed to answer the unsolved questions.

#### INTRODUCTION

Biological systems have developed clever strategies to sense and to make use of the matters and energy in the environment. Among different forms of energy is electromagnetic radiation (EMR), which is pervasive in the earth's atmosphere since before the inception of life. The bioresponses of the visible frequency bands are obvious. In contrast, the bio-responses to the nonradiative EMR just next to the visible range have been poorly understood. But it is intuitively irrational if the biological systems have selected only an extremely narrow band of frequency as the sensitive range. Thus, there might be different forms of bio-responses to the EMR including radio frequency to be discovered, which remains to be an interesting research topic. One of the difficulties of discovering a new bioeffect of the EMR is the lack of hint: people cannot knowingly sense the existence of EMR surrounding them. Another problem is that the possible bioeffects of the EMR are difficult to be isolated from a complex bioeffect caused by other factors accompanied with the EMR, such as heat. Despite such difficulties, many studies have been carried out to examine the bio-responses to EMR using different approaches, as summarized in Scheme 1.

#### STUDIES OF IMPACTS OF EMR ON HUMANS

#### Overview of the epidemiological investigations and experiments on humans

The level of nonradiative EMR in the environment of our daily life has been drastically increased since the 1950s with the rapid development of the techniques of wireless communication. The highest power flux density is over 10<sup>18</sup> times higher than the natural level, <sup>1–3</sup> and people of certain occupations are exposed to EMR of power density even higher, especially the radio frequency EMR (RF-EMR) in the range between 300 kHz and 300 GHz. Epidemiological studies of humans, especially those with occupational exposure to high levels of EMR, can provide important evidence of the risks of the exposure to EMR and indicate potential reporter systems that could be affected by the EMR. The corresponding reporting systems mainly include physiological and pathological effects, diseases from epidemiological retrospective studies, clinical symptoms, and diseases after daily or occupational exposure to EMR. Guidelines are written accordingly for the prevention, diagnosis, and treatment of EMR-related health problems and illnesses. <sup>4,5</sup>

The epidemiological investigations of the impact of EMR on humans should be carefully designed to integrate the variables in the complicated electromagnetic environment. Among them, questionnaire studies and case reports are superior in providing information of self-report symptoms induced by EMR exposure; while double-blind cohort studies are typically used for analysis of pathogenesis and impact factors.<sup>6,7</sup>

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1. Studies of impacts of	1.1 Overview of the epidemiological investigations and experiments on humans	Physiological and pathological effects, diseases from epidemiological retrospective studies, clinical symptoms, and diseases after EMR daily or occupational exposure							
EMR on humans	1.2 Epidemiological investigations	Short-term effects, cumulative effects, and thermal effects of EMR exposure							
	1.3 Electrosensitivity and magnetosensitivity	Worth of further confirmation							
		Static electric field	Static magnetic field	Low frequency EMR	RF-EMR				
	2.1 Overview of the animal experiments	Bioeffects of EMR in model animals							
2. Animal experiments	2.2 Studies about the EMR impacts on animals	Electrosensitive for hunting	Navegation and magnetosensitivity	Promote the regeneration of planarians, reduces the fertility of C. elegans, inhibit the growth of tumors in mice	Reduced capacity of total antioxidant, suppressed the inflammatory responses, reduced spermatogenesis, altered functions of central nervous system, increased occurrence of tumor				
	2.3 Challenges of the animal experiments	The complexity	of the animal experin	nent					
	3.1 Overview of the experiments on cellular systems	The advantage o	f the cells and tissues	3					
3. In-vitro cell systems	3.2 Studies about the effects of EMR on the multicellular system		The differentiation of cells	Calcium signaling and cell growth	Reduced cell proliferation and increase the level of ROS				
	3.3 Studies about the effect of EMR on the unicellular system	Cell migration	The formation of biofilms	Decreased cell viabilities	Antibiotic resistance				
	3.4 Challenges of the experiments in cell systems	The disadvantage of the cells and tissue							
	4.10verview of the in-vitro biochemical experiments	The advantage of carefully designed in-vitro biochemical experiments							
4. In-vitro biochemical	4.2 Challenges of the biochemical experiments	Systematic error and random errors							
experiments	4.3 Studies about the effect of EMR on the biochemical reactions	Cryptochrome and catalytic activity of crucial enzymes							
5. Dielectric	5.1 Overview of the dielectric spectroscopy	Dielectric spectroscopy indicate possible interactions between the substance and the EM wave							
spectroscopy	5.2 Challenges of the dielectric spectroscopy	The disruption fi	om the signals of the	e water and ions					
6. Detection of the EMR	6.1 Overview of the detection of the EMR emission	These observation	ons are worth of furth	er confirmation					
emitted by biological systems	6.2 Challenges of the detection of the EMR emission		high sensitivity and l s communication term		el of the background EMR due to the				
	7.1 Overview of the theoretical approach	Theoretical prediction based on physical theories and models to explain the mechanism underlying the bioeffects of the EMR							
7. Theoretical predictions	7.2 Ion cyclotron resonance model	The ions acceleration	ated by the magnetic	field leading to alterations of	f variables as exemplified by ion				
predictions	7.3 Radical pair model	A reaction system containing radical pairs of singlet state and triplet state exposed to an external magnetic field will shift the energy level of the triplet states, and further result in an altered balance of singlet-triplet interconvertion.							
8. Additional	8.1 EMR heating	thermal effects			es directly triggered by the EMR and the				
issues	8.2 Modulation of the EMR	*	•	•	ation pattern of the EMR. Bioeffects of in those of the single-frequency carrier				
	8.3 Complexity of the EMR environment	Complexity of the EMR environment							

Scheme 1. Investigations of the bioeffects of the EMR

### **Review**



EMR Frequency	Dose of EMR	Modulation pattern	Exposure duration	Bioeffect of EMR	Reference
Quasi-static magnetic field	35 μΤ	Rotation	7 min	Altered electroencephalography (EEG)	Wang et al. <sup>32</sup>
Static/50 Hz electric field	Tens of kV/m	-	-	Cutaneous sensations	Kato Blondin Odagiri-Shimizu Chapman Jankowiak et al. <sup>27–31</sup>
GSM: 900 MHz TETRA: 385 MHz	GSM SAR: 2 W/kg TETRA SAR: 6 W/kg	GSM: 2, 8, 14, 217, 1736 Hz pulse TETRA: 17.6 Hz pulse	30 min at weekly intervals	Altered EEG in sleep	Huber Schmid Danker-Hopfe <sup>8–10</sup>
900 MHz	Peak SAR: 0.49, 0.70, 0.93 W/kg	GSM	26 min	Unchanged heart rate variability	Wallace et al. <sup>11</sup>
800-2200 MHz	-	UMTS/HSDPA/ HSUPA	1-4 h/day active cell phone usage	Decreased semen quality	Rago Al-Bayyari et al. 19,235
Analog phones: 450–900 MHz; GSM phones: 850–1900 MHz 3rd generation phones: ~2 GHz	0.12–1.6 W/kg body weight	1 <sup>st</sup> /2 <sup>ND</sup> /3 <sup>rd</sup> generation cell phone communications	0-4 h/day		Fejes Agarwal Chalabi <sup>16–18</sup>
Cell phones: 850–1800 MHz; Wi-Fi: 2.45 GHz	3.19 W/kg	3 <sup>rd</sup> /4 <sup>th</sup> generation cell phone, Wi-Fi	30-120 min/day		Yildirim, Ding et al. <sup>20,21</sup>
3.6–10 GHz	-	-	Mean duration: 8 years	Worse gonadic function	Lancranjan <sup>14</sup>

Consequently, the epidemiological investigations of EMR are mostly focused on the impact of RF-EMR that are widely used in wireless communication, including those used by broadcasts, mobile phones, and wireless fidelity (Wi-Fi). Representative investigations of EMR impacts on humans are listed in Table 1.

#### **Epidemiological investigations**

Short-term exposure to 900 MHz EMR causes alternations in the sleep EEG of the volunteers, 8-10 but did not significantly change the heart rate variability. These findings indicated that the influence of the EMR is most likely to be mild but cumulative and the influence of long-term exposures might be more easily observed. For example, a study of young workmen with exposure to microwaves of 3.6-10 GHz (the mean duration is 8 years) showed a higher occurrence of worse gonadic function, including libido decrease, sexual dynamic disturbances in the framework of the asthenic syndrome, and various alterations of spermatogenesis. Exposure to EMR of mobile phones (800 MHz-2.2 GHz) with the specific absorption rate (SAR) of no more than 2 W/kg is associated with reduced sperm motility, viability, and concentration. Series also the effect of the EMR on sperm motility can be mediated by mitochondrial activity. However, the mechanisms that underlies the reported bioeffects of the EMR on the human are much less discovered.

In these studies, it is very important to figure out the appropriate dose of the EMR applied to the biological system. It is well understood that the energy of the EMR can be partly absorbed by materials and transformed into heat. The SAR is the power absorbed by a subject when exposed to EMR and is used to indicate the heating effect of the EMR.<sup>23</sup> To evaluate the dose of EMR applied in the experiments, one could estimate the distribution of the electromagnetic fields, currents, SAR, and heat generation inside the human body induced by external EMR before performing experiments in two ways. The first is to simulate the EMR distribution using a finite element analyzer based on Maxwell's electromagnetic equations. The second is to prepare an EM-radiated dummy, i.e., a human-shaped container filled with phantom mimicking the dielectric properties of the body, and perform measurements on the dummy using an electromagnetic probe. A group of researchers reported that a temperature rise of  $0.1^{\circ}$ C is induced in the tissue by a 60-min exposure to mobile phone communication according to simulation.<sup>24</sup> Calculations also suggested that the strength of electric field induced in the human body varies in different body parts, forming hotspots that are highly risked to overheating.<sup>25</sup> Another study shows that a passenger exposed to the EMR of the pantograph of a high-speed train receives a peak electric field of 300 V/m at the soles of the shoes and a peak current density of 35  $\mu$ A/m<sup>2</sup> at the ankle.<sup>26</sup>





#### **Electrosensitivity and magnetosensitivity**

downstream bioeffects are interesting topics for further studies.

Yet, it is unclear whether human can sense EMR, and it is still unrevealed which specific organism or molecule that might play as the receptor of the electromagnetic signals is still unrevealed. People exposed to strong direct current (DC) or 50-Hz alternating current (AC) electric fields of tens of kV/m reported cutaneous sensations such as tingling or itching, and the threshold for this sensation is correlated to both the frequency of the electric field and the humidity of the air. <sup>27–31</sup> However, it is still unknown whether humans could perceive or respond to electric fields weaker than the reported strengths or EM signals of other frequencies. Thus, further investigations are needed to answer these questions.

Another study in 2019 reported that the variations of the magnetic field altered the alpha event–related desynchronization of the human brain, indicating that the brain is potentially magnetosensitive. <sup>32</sup> This observation is worth further confirmation, and its molecular basis and

#### **ANIMAL EXPERIMENTS**

#### Overview of the animal experiments

An intuitionistic experimental approach to investigate the bioeffect of EMR is to expose animals to an EMR environment. The animals are excellent subjects to facilitate the discovery of new bio-responses induced by EMR, even though it might be complicated to reveal the related molecular basis. The pattern of the EMR is usually chosen according to the waveforms widely used in daily life, such as those of the mobile phones, Wi-Fi, and Bluetooth. To facilitate the observation of the bioeffects, researchers usually apply long-term EMR exposures to the animals and push the power of the EMR to the upper limits of the communication protocols. Some of the studies about the EMR impacts on animals use common model animals including *Caenorhabditis elegance (C. elegans)*, <sup>33–40</sup> planarians, <sup>41–46</sup> *Drosophila*, <sup>47–51</sup> and rodents. <sup>52–70</sup> Other studies exploit animals that are assumed to be sensitive to EMR or those with navigating abilities. For example, there are marine species <sup>71</sup> (i.e., sharks, <sup>72</sup> skates, <sup>73,74</sup> and eels <sup>75,76</sup>), insects (i.e., bees <sup>77,78</sup> and the Australian bogong moth <sup>79</sup>), and navigating birds (i.e., European robins <sup>80–86</sup> and pigeons <sup>87–90</sup>). Representative investigations of EMR impacts on animals are listed in Table 2.

#### Studies about EMR impacts on animals

#### Static electric field

Many species are electrosensitive. For example, bumblebees are able to sense the electric field of flowers of about 100 V/m using mechanosensory hairs, <sup>77,91</sup> and possibly communicate with each other through the variation of the electric fields. <sup>92</sup> *C. elegans* were found able to navigate in a DC electric field toward the negative pole, and were thus assumed to have the potential to detect electrical currents or electromagnetic fields. <sup>35</sup> Their navigating abilities were suggested to be related to the expression of a group of genes encoding the amphid sensory neurons and the AWC<sup>ON</sup> neurons, including eat-4, ceh-36, and nsy-5/inx-19. <sup>34,38</sup> Also, a variety of marine species can make use of electromagnetic fields for distant sensing. For example, *Electrophorus electricus* can stun prey by generating high-voltage discharge (~860 V) and communicate with each other through low-voltage discharge (~10 V). <sup>76</sup> Many marine species can detect distant preys and predators through the ampullae of Lorenzini by sensing the variation of the faint electric field. <sup>71</sup> The keys to the distant electric sensing ability are ion channels, such as the voltage-gated potassium channels of sharks <sup>72</sup> and the calcium-activated potassium channel in skates. <sup>74</sup> Homologs of these channels might be potential targets for studies on EM sensing. However, our knowledge of electrosensitivity is still limited. The lower limit of the electrosensitivity is still unknown, while the impact of alternating EM signals on the electrosensitivity is poorly understood.

#### Static magnetic field

The navigating instinct of animals is assumed to be related to magnetosensitivity. Iron-rich clusters that are considered as potential sensors of the magnetic fields were found in some species, as reported in *C. elegans* and pigeons.  $^{89,93}$  In contrast, the magnetoreceptors of other navigating animals are still controversial.  $^{47-51}$  European robins were the first reported animals to show the light-dependent orientation of flight,  $^{80,81}$  presumably due to the magnetoreception through photoreceptors (cryptochrome) on the retina.  $^{82}$  Later, *Drosophila* were proposed to be light-dependent magnetosensitive based on the following two types of behavioral experiments. One is the binary choice experiments, in which the flies showed naive and trained responses to a magnetic field.  $^{47}$  The other is the negative geotaxis experiment, in which the climbing abilities of the flies were disrupted by the presence of a 500- $\mu$ T magnetic field.  $^{49}$  However, contradicting results are reported by another group using a larger sample size (10,960 flies in total).  $^{50}$  Weak static magnetic field were found to alter stem cell-mediated growth in planarians.  $^{46}$  And the regeneration ability of the planarian was significantly inhibited by 72-h stimulation of static magnetic field of 200  $\mu$ T, which was related to alterations in the levels of reactive oxygen species (ROS) and heat shock protein 70 (Hsp70).  $^{43}$ 

#### Low frequency EMR

Planarians exposed to a magnetic field combining DC ( $42\pm0.1~\mu T$ ) and AC ( $3.7~Hz,100\pm0.5~n T$ ) for 4 h were promoted in fission and regeneration. find a comparative study, a burst-firing magnetic field ( $5~\mu T$ ) reduced the activity of planarian by about 50%. Extremely low frequency electromagnetic fields (ELF-EMR) slowed down the cephalic regeneration in planarians. However, ELF-EMR exposure of planarians during the initial 3-day post-surgery caused a significant increase in regeneration and an elevation in the level of hsp70 and phospho-ERK expression.

C. elegans displayed sensitivity to ELF-EMR, which exerted distinct effects on their metabolism processes and body lengths across different exposure generations. 37,39,40 Exposure of C. elegans to pulsed electric field (intensity: tens of kV/m; pulse width: 10 ns; burst

EMR Frequency	Dose of EMR	Modulation pattern	Exposure duration	Animals	Bioeffect of EMR	Reference
Static electric field	~100 V/m	-	-	Bumblebees	Preference in binary choice	Clarke <sup>77</sup>
Static magnetic field	1-50 μΤ			Drosophila	Preference in binary choice	Gegear, and Gegear et al. <sup>47,48</sup>
	500 μΤ				Disruption of climbing	Fedele et al. <sup>49</sup>
	0, 90, 220, 300, 500 μΤ				No magnetosensing behavior	Bassetto et al. <sup>50</sup>
	44-189 μΤ			Pigeons	Preference in binary choice	Mora et al. <sup>88</sup>
	45 μT (Geomagnetic level), 200 μT		0-72 h	Planarians	Decreased blastema sizes	Van Huizen et al. <sup>46</sup>
Static/60 Hz/ Static +60 Hz magnetic field	DC: 51.1, 78.4 μT AC: peak 1.0–80.0 μT	-	12 days		Regeneration anomalies with tumor-like protuberances	Jenrow et al. <sup>41</sup>
AC magnetic field: FM: 0.4–167 Hz GM: 0.065–500 Hz	FM: 0.1–2.5 μT GM: 0.5–5 μT	FM: frequency-modulated pulses GM: wideband pulses	6.5 h/day FM for 1–5 days, 6.5 h/day GM for 1–5 days		Dissolution of planarian	Murugan et al. <sup>44</sup>
50 Hz magnetic field	400 μΤ	Sinusoidal	24 h/day for 60 days	Rats	Improved the cognitive and pathological symptoms of AD	Liu, and Zuo <sup>58,66</sup>
	2.4 mT		2 h		Altered brain lipid profile	Martínez-Sámano et al. <sup>67</sup>
	1.6 mT		2-48 h	Honeybees	Altered structure of chemical compounds	Koziorowska et al. <sup>78</sup>
Static magnetic field + 0.65/1.315/2.63 MHz	DC: 46, 92 μT, EMR: 5, 15, 48, 150 nT		-	European robins	Disorientation of flight	Ritz et al. <sup>82</sup>
50 kHz - 5 MHz	Peak intensity 0.1–50 nT	Wideband noise				Engels et al. <sup>83</sup>
00 kHz	2 V/cm	Sinusoidal	6 days	Mice	Inhibited growth of tumors	Kirson et al. <sup>54</sup>
P00 MHz	90 mW/kg		12 h/day for 7 days		DNA damage in sperm	Aitken et al. <sup>53</sup>
	0.9 W/kg	GSM	2 h/day for 35 days	Rats	Altered sperm cells	Kesari et al. <sup>55</sup>
	$1\pm0.4~\mathrm{mW/cm^2}$ SAR 2 W/kg	Sinusoidal	1 h/day for 21 days during the gestation period		Neuronal damage in hippocampus	Erdem Koç et al. <sup>61</sup>
	$1\pm0.4~\mathrm{mW/cm^2}$ SAR 2 W/kg	Sinusoidal	1 h/day between GD 1 to the end of gestation		Increased total kidney volume; decreased the numbers of glomeruli	Ulubay et al. <sup>57</sup>
P15 MHz	Continuous wave: 3 W Pulse: 1–10 W	Sinusoidal, 8-215 Hz pulse modulation	2 h		Increased permeability of the blood-brain barrier	Persson et al. <sup>52</sup>

(Continued on next page)



Table 2. Continued						
EMR Frequency	Dose of EMR	Modulation pattern	Exposure duration	Animals	Bioeffect of EMR	Reference
900 MHz	4.5–13.4 V/m; SAR: 0.01 W/kg	Sinusoidal	1 h/day for 25 days		Altered cerebellar morphology & reduced number of neurons	Aslan et al. <sup>62</sup>
	SAR: 1.5, 3.0, 6.0 W/kg	GSM, CDMA; cycle of 10-min on and 10-min off	18 h/day from prenatal life to 106 weeks after birth		Increased incidences of Schwannomas and Schwann cells hyperplasia, and malignant glial tumors	Wyde et al. <sup>65</sup>
1.8 GHz	0, 5, 25, 50 V/m SAR: 0.1, 0.03, 0.001 W/kg	GSM	19 h/day from prenatal life to natural death			Falcioni et al. <sup>64</sup>
900 MHz	0.25, 0.5 W/kg	GSM	45 min/day 5 days/week from postnatal day 35 to natural death		No significant difference	Ouadah et al. <sup>69</sup>
1.9 GHz	3.2 V/m	DECT	24 h/day for 8 weeks	Lizards	Suppressed inflammatory responses	Mina et al. <sup>101</sup>
2.4 GHz	8 W	Sinusoidal, 100 Hz pulse modulation	1-9 days	Mice	Increased time of wakefulness	Liu et al. <sup>70</sup>
2.45 GHz	-	Wi-Fi	24 h/day for 10 weeks	Rats	Altered oxidative defense system	Kamali et al. <sup>68</sup>
			2 h/day along gestation till parturition		Behavioral and biochemical impairments	Othman et al. <sup>63</sup>
1.8 GHz, 1.9 GHz, 2.4 GHz	GSM: 5.53 V/m – 50 nT; DECT: 3.75 V/m; Wi-Fi: 2.1 V/m	GSM, DECT, Wi-Fi	0.5, 1, 3, 6, 24 h	C. elegance	No statistically significant differences	Fasseas et al. <sup>36</sup>





frequency:  $0.1-100\,\mathrm{kHz}$ ) reduced the fertility without inducing heating effects. Also, FTIR spectra of the chemical compounds, extracted from the honeybees indicated structural alterations of the compounds, were induced by the exposure to an ELF-EMR of 50 Hz,  $1.6\,\mathrm{mT}$ .

The exposure of Alzheimer's disease rat to ELF-EMR of 50 Hz, 400  $\mu$ T for 60 continuous days improved the cognitive and pathological symptoms of the rats through the RKIP-mediated NF- $\kappa$ B signaling pathway. <sup>58,66</sup> Alteration of brain lipid profile was observed in the rats exposed to 50 Hz, 2.4-mT ELF-EMR. <sup>67</sup> And the exposure to 200-kHz EMR of 2 V/cm inhibited the growth of tumors in mice. <sup>54</sup>

#### RF-EMR

Like the epidemiological studies of humans, the investigations of the RF-EMR impact on animals are mainly focused on the frequencies of the wireless communications. It has been reported that the exposures of animals to RF-EMR are correlated with behavioral or functional changes, clinical symptoms, and diseases. 36,52,53,55-57,59-65,68-70,82-86,95-111

Most widely adopted bio-responses to the RF-EMR exposures are related to the heating effect of high-power EMR<sup>95,107</sup> or accumulative effects caused by the long-term exposure to EMR.<sup>64,65</sup> The alterations induced by the high-power or long-term RF-EMR exposures are summarized as follows.

Physiological processes. Continuous exposure of rats to EMR of 2.45 GHz for 10 consecutive weeks significantly reduced the capacity of total antioxidant and the activities of antioxidant enzymes.<sup>68</sup> Similar phenomena were also observed in rats exposed to RF-EMR of 900 MHz or 1.8 GHz.<sup>98,100,105</sup> Additionally, continuous exposure of lizards to RF-EMR of 1.9 GHz DECT for 8 consecutive weeks suppressed the inflammatory responses.<sup>101</sup>

Spermatogenesis and development of embryos. High-power or long-term microwave exposures caused alternations in the spermatogenesis and worse metrics of semen (such as reduced population, reduced motility, increased proportion of abnormal morphology, etc.). 53,55,95,99,109 While the exposure of embryos of zebrafish to 100 MHz EMR from 24 to 72 h post fertilization altered the development of the embryos. 104

*Blood-brain barrier.* The blood-brain barrier was altered by the exposure to RF-EMR. 52,56,59,108 And pulse modulated RF-EMR of 900 MHz or 1.8 GHz induced increasement of the permeability of blood-brain barrier in rats. 52,56,59

Nervous system. RF-EMR also affects the neurons, the cerebral morphology, the neurogenesis in the early development, and the functions of central nervous system (i.e., emotion, memory, and recognition). 60,62,63,96,102,103,110,111 The sleep pattern of the mice was altered by the consecutive exposure to a pulse-modulated RF-EMR of 2.4 GHz for nine days. 70 Prenatal exposure of rats to 2.45-GHz RF-EMR altered post-natal development, and leaded to anxiety, motor deficit, and exploratory behavior impairments. 63 And the prenatal exposure to 900 MHz RF-EMR induced alterations in the hippocampus in rats. 57,61

*Tumorigenesis.* Lifelong exposure to Code Division Multiple Access (CDMA) or Global System for Mobile Communications (GSM) signals of 900 MHz or 1.8 GHz resulted in increased occurrence of tumor in rats. <sup>64,65</sup> However, another study reported that rats with C6 brain tumors showed no significant difference in the survival (31 days post-graft median), tumor volume, mitotic index, vascularization, infiltration, necrosis or cell division) in the groups exposed or unexposed to 900-MHz GSM RF-EMR <sup>69</sup> Therefore, the duration of the exposure to RF EMR seems to be an essential factor of the alterations in tumorigenesis.

Low-dose RF-EMR are mild stimulations, and the corresponding bio-effects are not evident or remain controversial. <sup>82,83,85,86,106</sup> *C. elegans* exposed to 1.8 GHz GSM, 1.9 GHz DECT, or 2.4 GHz Wi-Fi signals for up to 24 h showed no significant alteration on the lifespan, fertility, growth, memory, levels of ROS, apoptosis, or gene expression. <sup>36</sup> The light-dependent flight orientation abilities of the navigating birds were affected by the single-frequency EMR of several MHz or by the wideband EMR with the spectrum extending from tens of kHz to several MHz. <sup>83,97</sup> However, some of the experimental evidence of the disturbance of magnetoreception in European robins using EMR is inconsistent with the prediction of the radical-pair model. <sup>84,85</sup>

#### Challenges of the animal experiments

One of the greatest challenges for animal experiments investigating the bioeffects of EMR is to determine the proper EMR pattern (e.g., the frequency, amplitude, and modulation). Once the pattern of EMR is determined, the experiment is highly consuming of labor, material, and time, yet the corresponding bio-responses can hardly be extrapolated to other patterns of EMR. Consequently, the attempt to cover all the EMR patterns using animal experiments is unrealistic. It is obligatory to exploit certain strategies to narrow down the patterns of EMR for selection and focus on those most possibly trigger bio-responses. The bio-responses of the animal to the EMR exposure are also affected by the gender of the animals, as reported in the literature, <sup>56,59,65</sup> probably due to the remarkable difference of the hormone levels between males and females. Another limitation of the animal experiment is that it is hard to cover the enormous diversity of the biological world. The few categories of animals are studied, but the observations can hardly be extrapolated to other species. Thus, there is a universe of species that are unexplored for the bio-impacts of the EMR.





#### **IN-VITRO EXPERIMENTS ON CELLULAR SYSTEMS**

#### Overview of the experiments on cellular systems

Animals are complex integrations of different organs and tissues. In contrast, cells are subjects of lower-level structure for the investigation of bio-responses to external stimuli. Since the *in vitro* cultivation of cells is conducted in the incubators with accurate control of temperature, component of the culture medium and the gas environment, it offers more interfaces for parametric studies. The cells can be exposed to an EMR stimulation for a period, and their responses can be examined using a variety of biomarkers, providing clues for the possible mechanism of the bio-responses.<sup>112–119</sup>

The experiments using cell systems are less costly than those using animals. The cell systems are also easily accessed, replicated, and operated, and compatible with gene editing. Moreover, *in vitro* cultivated cells are more sensitive to the environmental conditions than the whole body, due to the lack of feedback regulations from nervous and endocrine systems.<sup>120</sup>

Unicellular organism is an interesting category of cell-based systems, including prokaryotes such as bacteria and eukaryotes such as yeast. They live in the wild nature and maintain the basic living activities at the single-cell level. Like for other cell systems, it is convenient to set different exposure periods, frequency modulations or input powers to the unicellular organisms. The unicellular organism generally shows growth rates much higher than that of the multicellular organism. The rapid growth rate of bacteria or yeast makes them ideal models for observing the cumulative effects of external stimuli on growth of an organism and for the screening assays for potential drug targets or other stimuli (e.g., EMR patterns). High growth rate of the unicellular organism also leads to its excellent adaptability and high rate of evolution. Table 3.

#### Studies about the effects of EMR on the multicellular system

Currently, most studies focus on the EMR impacts on the physiological functions of cells, including but not limited to the morphology, viability, motility, DNA damage, membrane potential, the oxidative stress status, nitric oxide signaling, gene expression and functions, etc. 54,111,112,123–135136-168

#### Static magnetic field

Magnetic field promotes the differentiation of various cells, including mice's neural progenitor cells (mNPCs), murine embryonic stem cells (mESCs), human-induced pluripotent stem cells (hiPSCs), and oligodendrocytes precursor cells (OPCs). <sup>158,166</sup> In the presence of the magnetic nanoparticles, magnetic field also stimulates neurite initiation or axon elongation and direct the orientation of the PC12 cells. <sup>147</sup> Magnetic fields also affect the cell viability and morphology. <sup>169</sup> An 8-T static magnetic field altered the direction of growth of the Schwann cells. <sup>134</sup>

#### Low frequency EMR

The ELF-EMR was proposed to match with the frequency of the ion cyclotron resonance (ICR)<sup>124</sup> and predicted to be able to cause variations of the membrane potential of cells. <sup>145</sup> Cells exposed to EMR of the ICR frequency were altered in calcium influx, calcium signaling, ROS level, growth, differentiation, and apoptosis. <sup>125,127–129,131,136,140,146,152</sup> For example, HaCaT exposed to an ELF-EMR of 7 Hz, 100  $\mu$ T for 1 h (twice daily) was promoted in differentiation. <sup>137</sup> Pulsed magnetic fields of 0.6 mT with 5-ms bursts fired at 15 Hz induced significant increase of the nitrite concentration and DNA content of osteoblasts. <sup>133</sup> The calcium uptake of the rat thymocytes was altered by the exposure to ELF-EMR of 60 Hz. <sup>125,127</sup> Besides, the exposure of human sperm to 50 Hz ELF-EMR for 5–30 min lead to reduced motility of the spermatozoa. <sup>162</sup> However, other studies claimed that no significant variation in the cells after the exposure to the EMR of the ICR frequency. <sup>130,157</sup>

The growth rates of a variety of tumor cell lines are inhibited by a stimulation of continuous-mode EMR around 100–300 kHz. This stimulation specifically affects tumor cell division by either arresting cell proliferation, disrupting cells undergoing division, or increasing tumor cells membrane permeability, resulting in a slowdown of tumor growth *in vitro* and *in vivo*. 54,112,155 Similar findings have been reported in other studies involving different types of tumors. 143,150,160,163

#### **RF-EMR**

The studies of EMR impacts on the cells are also focused on the RF-EMR, due to its wide application in the daily life. For example, human colon cancer cells HT-29 and SW480 exposed to RF-EMR of 13.56 MHz were reduced in cell proliferation and clonogenicity compared to the cells heated with water bath. <sup>164</sup> A 27.12-MHz RF-EMR pulse modulated at 2 Hz caused higher levels of nitric oxide signaling in neuronal cells after lipopolysaccharide (LPS) challenge. <sup>141</sup> Apart from that, a 10-MHz RF-EMR pulse modulated with 10 kHz pulses inhibited thrombin-induced endothelin-1 mRNA expression through a nitric oxide-related pathway. <sup>135</sup> Moreover, alternating electric fields between 100 Hz and 100 MHz can induce dielectrophoretic force on a variety of cells in cell suspensions, thus can be used as tools to manipulate suspended cells in microfluidics. <sup>123,126,132</sup>

High-power RF-EMR increased the level of ROS, resulting in downstream damaging effects to proteins, lipids, carbohydrates, and nucleotides. 111,139,144,148,149,153,159 For instance, exposure of human semen samples to RF-EMR of 1.8 GHz mobile phone signals or 2.45-

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OPEN ACCESS	<b>Cell<sup>P</sup>ress</b>

		Modulation				
EMR Frequency	Dose of EMR	pattern	Exposure duration	Cell type	Bioeffect of EMR	Reference
Static magnetic field	20-35 mT	-	9, 48 h	Bacteria (E. coli)	Altered rates of growth & formation of biofilms	Letuta, Berdinskiy and Letuta, Tikhonova <sup>178,179</sup>
	200 mT		18 h	Bacteria (Pseudomonas aeruginosa)	Increased swarming motility	Raouia et al. <sup>176</sup>
	444 mT		24 h		Suppressed biofilms; enhanced ciprofloxacin activity	Bandara et al. <sup>175</sup>
7 Hz	100 μΤ	Sinusoidal	1 h × 2 times/ day x 3 days	Human epithelial cells	Altered morphology	Lisi et al. <sup>137</sup>
15 Hz	0.6 mT	5-ms bursts	15 days	Osteoblasts	Increased levels of nitrite concentration & DNA content	Diniz et al. <sup>133</sup>
13.75 Hz	2.5 μΤ	Sinusoidal	5 days	Mouse skeletal muscle cell	Altered growth rate & phase	De Carlo et al. <sup>140</sup>
20, 40, 50 Hz	1-4 mT		1, 2, 6 h	Bacteria (E. coli; Staphylococcus aureus)	Inhibition of colony forming units; alternation of the crucial physicochemical processes	Bayır and Oncul et al. <sup>180,181</sup>
50 Hz	1 mT		24 h	Human neuroblastoma	Increased ROS level	Reale et al. <sup>146</sup>
60 Hz	13, 22 mT		1 h	Rat thymocytes	Altered calcium flux	Walleczek and Liburdy et al. <sup>125,127</sup>
10, 50, 100 Hz	5, 10 mT	Square waves	2, 4, 24 h	Human glioblastoma	Altered growth rate	Akbarnejad et al. <sup>152</sup>
100-300 kHz	1–2.5 V/cm	Sinusoidal	24-72 h	Human & rodent tumor cell lines	Decreased growth rate	Kirson et al. <sup>112</sup>
Static magnetic field +7 MHz	45μT + 10 μT <sub>RMS</sub>	Sinusoidal	2, 3 days	Rat pulmonary arterial smooth muscle cells	Altered O <sub>2</sub> ··· & H <sub>2</sub> O <sub>2</sub> production	Usselman et al. <sup>144</sup>
10 MHz	1.25, 1.92 V/m SAR: 0.98, 2.31 mW/kg	10 kHz pulse modulated	8, 24 h	Bovine aortic endothelial cells	Altered mRNA expression	Morimoto et al. <sup>135</sup>
13.56 MHz	SAR: 40 W/kg	Sinusoidal	1 h	Human colon cancer cells	Reduced cell proliferation and clonogenicity	Wust et al. <sup>164</sup>

(Continued on next page)



Table 3. Continued						
EMR Frequency	Dose of EMR	Modulation pattern	Exposure duration	Cell type	Bioeffect of EMR	Reference
27.12 MHz	$2.5\mu\text{T}$ , $41\pm10\text{V/m}$	2 Hz pulse modulated	Neuronal cells: 5 days; Human fibroblasts 15 min	Neuronal cells & human fibroblasts	Increased nitric oxide level	Pilla <sup>141</sup>
900 MHz	1 W/kg	GSM modulated	24, 48, 72,120 h	SN56 cholinergic cell line & rat primary cortical neurons	Reduced number of neurites	Del Vecchio et al. <sup>138</sup>
900 MHz	2 W	GSM modulated	2 h	Human peripheral blood Mononuclear Cells	Increased ROS production	Kazemi et al. <sup>149</sup>
900 MHz	10 W, 134–145 V/m	Sinusoidal	0, 30, 60, 90 min	Human peripheral blood cells	Unchanged miRNA expression level of the blood cells	Lamkowski et al. <sup>165</sup>
1.8 GHz	1, 2, 4 W/kg	-	1, 2, 3 days	Embryonic neural stem cells	Inhibited neurite outgrowth	Chen et al. 142
1.8 GHz	0.4–27.5 W/kg	Sinusoidal	16 h	Human spermatozoa	DNA damage	De Iuliis et al. <sup>139</sup>
1.95 GHz	3 W/kg	Sinusoidal	24 h	Mouse Leydig cells	Inhibited testosterone secretion	Lin et al. <sup>154</sup>
2.45 GHz	2-10 W/kg	-	4, 24 h	HL-60 cells	No effects on neutrophil chemotaxis & phagocytosis	Koyama et al. <sup>151</sup>
2.45 GHz	1.0-2.5 W/kg	Wi-Fi	45, 90 min	Human semen	Increased ROS level	Ding et al. <sup>156</sup>
2.45 GHz	1 W	50 Hz pulse modulated, 1/3 duty cycle	6, 48 h	OLN-93, BV-2, HT-22, rat primary astrocyte	Increased expression of C/EBP $\beta$ at 6 h	Huang et al. <sup>119</sup>



#### Review



GHz Wi-Fi signals significantly increased the levels of ROS, glutathione peroxidase, and superoxide dismutase in the samples. <sup>139,156</sup> Besides, exposure of SH-SY5Y cells to 935 MHz, 4 W/kg RF-EMR for 24 h caused an impairment of mitochondrial function. <sup>161</sup> In addition, the 24-h exposure of mouse Leydig cells to 1.95-GHz RF-EMR of 3 W/kg inhibited the testosterone secretion. <sup>154</sup> The RF-EMR of 900 MHz and 1.8 GHz also affected the neurite outgrowth of neuronal cells. <sup>138,142</sup>

However, some other investigations of cell systems have revealed little or no effect of RF-EMR exposure. For example, a 2.45-GHz RF-EMR at the SAR of up to 10 W/kg for up to 24 h induced very little or no effect on either chemotaxis or phagocytosis in differentiated human HL-60 cells. <sup>151</sup> While a group of researchers reported no significant change in the level of miRNA expression of the human blood cells exposed to 900-MHz EMR for up to 90 min. <sup>165</sup>

#### Studies about the effects of EMR on unicellular systems

Studies on the impact of EMR on unicellular systems mainly focused on the growth or viability, mobility, genotoxicity, and global gene expression change of the unicellular systems, and the antibiotic resistance and biofilm formation ability of the bacteria.

#### Static electric fields

Static electric field affects cell migration, and is key to the healing of wounds.  $^{170}$  Phosphatidylinositol-3-OH kinase- $\gamma$  and PTEN were involved in the migration of cells in electric fields,  $^{114}$  yet the specific receptor of the electric field is still unknown.  $^{171}$ 

#### Static magnetic fields

There are magnetoreceptive microorganisms containing magnetosomes, an object that is sensitive to the magnetic fields. <sup>172–174</sup> Static magnetic field also affects the formation of biofilms of bacteria. <sup>175–177</sup> For example, a 444-mT magnetic field suppressed the biofilms and enhanced ciprofloxacin activity of *Pseudomonas aeruginosa* when mixed with magnetic nanoparticles. <sup>175</sup> *E. coli* exposed to a static magnetic field of 20–35 mT showed higher rates of growth and faster formation of the biofilm in the culture medium containing magnetic isotope <sup>25</sup>Mg than in the medium containing <sup>24,26</sup>Mg. <sup>178,179</sup> Additionally, a 200-mT magnetic field significantly increased the swarming of *P. aeruginosa* strain. <sup>176</sup> However, the mechanisms of these variations are still poorly understood.

#### Low frequency EMR

Exposure of Gram-positive and Gram-negative bacteria to ELF-EMR of 20–50 Hz, 1-4 mT leaded to decreased cell viabilities and shifted membrane potentials. 180-182

#### RF-EMR

An 835-MHz EMR did not affect the reverse mutation frequency or DNA degradation in the *E. coli* in a genotoxicity study. <sup>183</sup> Meanwhile, a 2.4-GHz RF-EMR of Wi-Fi altered antibiotic resistance of *E. coli* and *Listeria monocytogenes*, <sup>184,185</sup> increased biofilm formation of *E. coli*, *Staphylococcus aureus*, and *Staphylococcus epidermis*, <sup>185</sup> and altered gene expression of *E. coli* (especially in the metabolism-related pathways). <sup>186</sup> Similar results were also reported in the study conducted by Crabtree et al. <sup>187</sup>

#### Challenges of the experiments in cell systems

Compared to the animals, the cell system is more sensitive to the environmental conditions. Thus, the cell systems require higher quality control, and parallel experiments are obligatory to reduce the influence of hazardous factors. The limitation of the cell system is that it shows only the cell-level responses, lacking in the systematic information. Likewise, cells are complex integrity containing intricate network composed of numerous pathways of signal transduction. So, they are not preferable subjects for reductionist experiments with nice and clean single-variable controls. It is very difficult to obtain direct evidence from the cell experiments about the receptor that directly interacts with EMR. Up to now, the reported cell responses to the EMR stimulation are most likely to be the down-stream changes. The key molecules interacting with the EMR are still unknown.

#### **IN-VITRO BIOCHEMICAL EXPERIMENTS**

#### Overview of the in vitro biochemical experiments

In vitro biochemical experiments aim to reveal the molecular basis of the biochemical reactions in the living organisms, and to provide evidence how biomolecules, as exemplified by proteins and nucleic acids, interact with each other. The *in vitro* biochemical system is a practical system for the reductionist approach because the reaction system can be simple in chemical composition and can be precisely defined. Carefully designed *in vitro* biochemical experiments with well-controlled variables can help to identify the key functional sites of the biomolecules.

Biochemical experiments are applicable to medical and pharmaceutical studies, as exemplified by those for the interactions between receptors and ligands or antibodies. The *in vitro* biochemical experiments for bio-impacts of EMR mostly focus on the gene transcription and translation, the structure and function of proteins, the reactive oxidative species, the DNA damage, and other *in vivo* reactions. This approach is an important complementation to the experiments of animals and cells because it provides direct evidence to the molecular basis of the possible bio-responses to the EMR. Representative investigations of EMR impacts on biochemical reaction systems are listed in Table 4.



		Modulation				
EMR Frequency	Dose of EMR	pattern	Exposure duration	Target molecules	Bioeffect of EMR	Reference
10-50 Hz	15–18.5 mT	Sinusoidal	2, 4, 6, 8 h	Laccase	Increase activity and shift in optimum pH	Wasak et al. <sup>191</sup>
50, 100 Hz	50 Hz: 2.7 mT; 100 Hz: 5.5 mT.	Sinusoidal	5 min	Horseradish peroxidase (HRP)	50 Hz decreases the maximum rate and catalytic efficiency of HRP	Caliga et al. <sup>194</sup>
50-400 Hz	1 mT	Sinusoidal	1, 2, 3, 4 h	Horseradish peroxidase (POD)	Distinctly affect the catalytic activity of soluble or insoluble POD	Portaccio et al. <sup>136</sup>
75 Hz	2.5 mT	Square wave	20 min	Alkaline phosphatase, acetylcholinesterase, phosphoglycerate kinase	Decreased activities of these membrane- associated enzymes	Morelli et al. <sup>193</sup>
500, 900 MHz	0.01, 0.1, 1 μW	Sinusoidal	5 min	L-Lactate Dehydrogenase (LDH)	Increase the bioactivity of LDH	Pirogova et al. <sup>192</sup>
0.1, 1, 1.9 GHz	Up to 5 kV/m 0.3 kV/m	Sinusoidal GSM	Real-time	The thermosensor protein GrpE	No effect of EMR on conformation of GrpE	Beyer et al. <sup>195</sup>

#### Challenges of the biochemical experiments

It is not easy to identify a biochemical reaction that is sensitive to the EMR from a complex network of regulations and feedback pathways of the biological system. Once a reaction system is radiated by the EMR, its temperature of must be carefully controlled to rule out the thermal effect of the EMR. Moreover, the experiments should be carefully designed to avoid systematic error and to prevent false positives or false negatives caused by random errors or by major flaws of the experimental design.

#### Studies about the effect of EMR on the biochemical reactions

Cryptochrome is presumably a molecular magnetoreceptor that mediates the light-dependent orientation of navigating birds. <sup>188</sup> In vitro biochemical experiments showed that cryptochrome can be photo-reduced efficiently and forms long-lived spin-correlated radical pairs via a tetrad of tryptophan residues. <sup>189</sup> Another putative magnetoreceptor is a protein corresponding to electromagnetic perceptive gene (EPG) screened from the total mRNA of glass catfish (*Kryptopterus bicirrhis*). It will lead to increased intracellular calcium concentrations when activated by EMR. <sup>190</sup>

The *in vitro* biochemical experiments for impacts of EMR focus on the catalytic activity of crucial enzymes. Exposure of laccase to a rotating magnetic field leaded to increased catalytic activity and a shift in the optimal pH.<sup>191</sup> Extremely low-power microwave stimulations of 500 MHz and 900 MHz enhanced the bioactivity of the L-lactate dehydrogenase enzyme without inducing temperature rise.<sup>192</sup> However, exposures of purified horseradish peroxidase or certain membrane-associated enzymes to ELF-EMR resulted in significant decrease in their activities.<sup>193,194</sup> And ELF-EMR of 130–150 Hz, 1 mT affects the catalytic activities of the soluble and insoluble horseradish peroxidase.<sup>136</sup> The real-time conformation of the isolated protein GrpE exposed to EMR of 0.1–1.9 GHz was monitored under strictly controlled conditions, and appeared to be insensitive to the EMR.<sup>195</sup>

#### **DIELECTRIC SPECTROSCOPY**

#### Overview of the dielectric spectroscopy

Complex permittivity is a macro-scale physical describing the property of a substance regarding its capability to store (real part) and absorb (imaginary part) the EM energy. The dielectric spectroscopy is to characterize the complex permittivity of a substance and can provide information of possible interactions between the substance and the EMR. In contrast to the experiments with long-term exposure to EMR, the dielectric spectroscopy focuses on the intermediate response of the substance to EM signal with sweeping frequencies. Consequently, signals indicating stronger interactions of a biological subject with EMR can be extracted from the complex permittivity, and the frequency ranges corresponding to these signals are most promising in triggering bioeffects of the subject.

According to the frequencies of the EMR most promising to induce bioeffects provided by the complex permittivity of a target substance, one can easily design experiments to further investigate the factors that influences the interaction between the EMR and biological subjects. The selection of proper EMR frequency and reporter system is clear. Thus, the targets less likely to be affected by the EMR can be excluded,





and those showing strong EMR interactions will be studied in precedence. The complex permittivity of material can provide direct evidence of interactions between materials and the EMR from the perspective of energy and is thus indispensable in identification of the bio-receptor of the EMR.

#### Challenges of the dielectric spectroscopy

The complex permittivity of a biological subject generally includes the signals of ionic components and water. These signals are less interesting but disrupting for the observation of other signals. One method for discriminating different signals is model-fitting method. To perform this method, one could fit the experimental data with dielectric models, such as Debye model on Cole-Cole model, obtaining the best-match parameters of different signals. Thus, the signals of the ions and the water can be discriminated and ignored. This model-fitting method is quite effective, but the analysis requires certain amount of calculation and is not quite straight-forward for beginners.

Another way to minimize the disruption from the signals of the water and ions is to introduce an ionic aquatic solution as a reference. The complex permittivity of the biological subject could be normalized by that of the reference solution, highlighting the signals of interest. The data processed using this method shows highlighted signals of different cells and liposomes, indicating the ability of the closed structures formed by lipid-bilayer membranes to interact with the EMR. <sup>198</sup>

Even though the background interaction signals of the ions and water can be separated from the complex permittivity, the signal-to-background ratio is still critical for the detection of the effective signals of the biological components. Thus, the concentration of the biological subject should be high enough. For example, the concentration of the lipid component in the liposome emulsions of the literature <sup>198</sup> is no less than 0.5% (weight to volume); while the volume proportion of the cells is up to 28% in the cell suspensions. Composite solution such as tissue homogenate can also be subjects of dielectric spectroscopy, but the signals of each composition are most likely to be difficult to separate with each other due to the complexity of the sample and the low concentration of each composition. Thus, in this specific approach, samples with simple chemical compositions and high concentrations are preferable.

#### **DETECTION OF THE EMR EMITTED BY BIOLOGICAL SYSTEMS**

#### Overview of the detection of the EMR emission

The nonradiative EMR signals are not intuitively sensed by human like infrasonic or ultrasonic signals. In 1966, ultrasound emitted by plants were detected using sensitive ultrasonic detectors. <sup>199</sup> EMR signals emitted by biological subjects, by contrast, are still waiting to be discovered. Sufficient sensitivity of the EMR detector is obligatory in discovering biological sources of the EMR. The detection of EMR emission will directly identify the subject that plays as a transmitter of EMR and prove the existence of the bio-EM interactions. The specific subject that emits the electromagnetic signal should include certain functional module that transforms other forms of energy into EM wave.

An emission of "biophoton" in the range of infrared and visible band was recorded using an ultra-sensitive camera and was assumed to be emitted by sliced bio-tissues. <sup>200,201</sup> An emission of 3.6-MHz EMR was also recorded from *in vitro* cultivated cells in BioEM 2022. <sup>202</sup> These observations are worth of further confirmation and the sources of the signals are interesting for further investigation.

#### Challenges of the detection of the EMR emission

There are challenges in the detection of the EMR emitted by biological systems. The first challenge is to realize both high sensitivity and large bandwidth in the detector. A large gain-bandwidth product is required, to enable detection of the faintest EMR emitted by the living matters. And there is still a need of a trade-off between the gain and the bandwidth. In practice, multiple highly sensitive detectors with complementary operating frequency bands can be employed synchronously. Some EM signals decay sharply along the distance of transmission, so near-field detection is preferred. Thus, the antenna of the detector should be arranged with proper location and orientation relative to the target, so that optimal performance of the EM detection can be achieved.

The high level of the background EMR from the crowded wireless communication terminals in the environment is also challenging for the detection of EMR emitted from biological systems. The detection must be performed inside an effective EM shielding providing a low background EM noise that facilitates the detection of faint EMR signals. In addition, false positive signals of stochastic EM noises emitted by distant transmitters must be carefully excluded. To discriminate between the signal emitted by the biological target and the signal from distant transmitters, the EMR signals both inside and outside the EM shielding should be monitored synchronously. The EMR signal is emitted by the biological target only when the signal recorded inside the shielding is much larger than the one recorded outside. Moreover, the signal-to-noise ratio should be further improved from the aspect of circuit design. For example, a band-pass filter can be employed to remove the wideband noise out of the range of the sensitive frequency of each detector.

#### THEORETICAL PREDICTIONS

#### Overview of the theoretical approach

Theoretical prediction of the bioeffect of EMR based on physical theories and models is an indispensable complement to the experimental approaches. It proposes hypotheses explaining the mechanism of the bioeffects of the EMR, provides guidance for the choice of frequency and amplitude of the EMR in the experiments, and suggests the potential receptors of the EMR and the related reporter systems for measurement. Thus, the experiments can be designed accordingly.





However, the theories that have been proposed for the interactions between biological systems and EMR are very limited, namely the ICR model and the radical pair model. They are limited in the applicable range of frequency, leaving most of the spectrum vacant. More theoretical investigations are needed for better understanding of the mechanisms of the interaction between the EMR and the biological systems.

#### Ion cyclotron resonance model

The ICR model was proposed in the 1980s. It assumes that the magnetic field and the ions in cells could interact with each other through Lorentz force, and that the motions of the ions are affected by the magnetic field oscillating at the cyclotron resonance frequency of the ions, resulting in alterations of ion flux and concentration. <sup>124,203,204</sup> The cyclotron resonance frequencies of the abundant ions of cells are in the order of tens of Hz, in the range of ELF-EMR. <sup>203</sup> Therefore, investigations have focused on the impact of ELF-EMR on cells in the aspect of alterations of calcium flux, ion concentrations, membrane potential, neuro activities, etc. <sup>125,127–131,140,145,152,157,205,206</sup> A summary of the ICR model explaining the EMR effect on the calcium influx and the downstream signaling pathways is shown in Scheme 2A. However, the reported bio-responses of the ELF-EMR are mostly faint, and some of the observations are inconsistent with each other. <sup>125,127,130,157</sup> So far, the key evidence is still missing about whether the EMR of cyclotron resonance frequency could trigger alterations in the biological systems.

#### Radical pair model

The radical pair model is another well-known model to explain the bioeffects of the magnetic field or RF-EMR <sup>207–210</sup> It was based on the Zeeman effect of magnetic fields on spin states, i.e., the energy levels of the degenerated spin states of radical pairs are differentiated by the variation of the magnetic field.<sup>207,211</sup> In a reaction system containing singlet-state and triplet-state radical pairs, an external magnetic field shifts the energy level of the triplet states, and further alters the balance of singlet-triplet inter-conversion, and changes the concentrations of singlet-state radicals, triplet-state radicals, and the products of the downstream reactions. <sup>97,208,209,211–213</sup> The radical pair model is applicable to biochemical reactions as exemplified by those involving the photoreceptor cryptochrome <sup>208,212,214</sup> and ROS. <sup>98,144,215–218</sup>

The light-dependent orientation of navigating birds suggested that certain photoreceptors in the retina are potential magnetosensitive molecules for their navigational ability. A widely recognized such photoreceptor in the retina is rhodopsin, a complex of a retinal and an opsin protein. The retinal absorbs a green-blue light photon, undergoes a conformational change from *cis*-retinal to *trans*-retinal, and subsequently triggers a conformational change in opsin. Thus, the rhodopsin is transformed into an active-state meta-rhodopsin that subsequently activates downstream G-protein-coupled receptor (GPCR) signaling pathways.<sup>219</sup>

A frequently mentioned magnetosensitive photoreceptor, a flavin adenine dinucleotide (FAD) bounded with cryptochrome (Cry), is shown in Scheme 2D. It assumes that the FAD is excited by a blue photon (FAD $\rightarrow$ FAD\*) and subsequently protonated (FAD\* $\rightarrow$ (FADH\*)\*). Then three electron transfers occur sequentially: the first one is from the tryptophan residue (W<sub>A</sub>) of the Cry to (FADH\*)\*, the second from tryptophan residue W<sub>B</sub> to W<sub>A</sub>, and the third from tryptophan residue W<sub>C</sub> to W<sub>B</sub>, generating magnetosensitive singlet and triplet radical pairs ( $^{5}$ [FADH• W<sub>A/B/C</sub>• $^{+}$ ] and  $^{7}$ [FADH• W<sub>A/B/C</sub>• $^{+}$ ]). The activity of the different spin states of the radical pairs vary from each other. The singlets  $^{5}$ [FADH• W<sub>A/B/C</sub>• $^{+}$ ] quickly (in  $\sim$ 1  $\mu$ s) transform into either the radical pairs [FADH• $^{+}$  W<sub>A,B,&C</sub>•] (RP2) or the ground states (FAD + W<sub>A,B,&C</sub>). In contrast, the triplets  $^{7}$ [FADH• W<sub>A/B/C</sub>• $^{+}$ ] only transform into RP2. Radical pairs RP2 last for an average lifetime of  $\sim$ 1 ms, and then transform back to the ground states.

However, whether the FAD-binding Cry is the molecular magnetic compass is still in dispute.  $^{221}$  A recent report has shown that the FAD-binding domain of Cry seems to be nonessential in the response of neuroactivity to magnetic fields.  $^{51}$  Superoxide  $O_2 \cdot ^-$  was proposed to be a possible alternative to the react with the FAD radical, as shown in Scheme 2E.  $^{144}$  Even though the stand-alone  $O_2 \cdot ^-$  is devoid of hyperfine couplings, the radical pair [FADH $\cdot$   $O_2 \cdot ^-$ ] is supposed to be more sensitive to geomagnetic fields than the radical pairs [FADH $\cdot$  W<sub>A/B/C</sub> $\cdot ^+$ ].  $^{222}$  Another model assumed the magnetic receptor to be the protein complex (MagR)/Cry because the protein crystals exhibited strong intrinsic magnetic polarity and rotated in synchrony with the external magnetic field.  $^{223}$ 

The radical pair model states that an external static magnetic field causes the hyperfine splitting of the triplet states, and that the magnetic sensitivity of the corresponding biochemical reactions can be affected by the EMR of Larmor frequency, i.e., those with energy of the photons exactly equal to the differences between the energy levels of the singlet and that of the triplet states.

There is experimental evidence in support of the radical pair model. The flight orientation of the navigating birds was interrupted by Larmor-frequency EMR.<sup>82</sup> And the biochemical reactions involving the triplet  $(O_2 \cdot \bar{\ })$  and singlet  $(H_2 O_2)$  states of the ROS in cells is affected by a 7-MHz EMR in the presence of a static magnetic field of 45  $\mu$ T.<sup>144</sup>

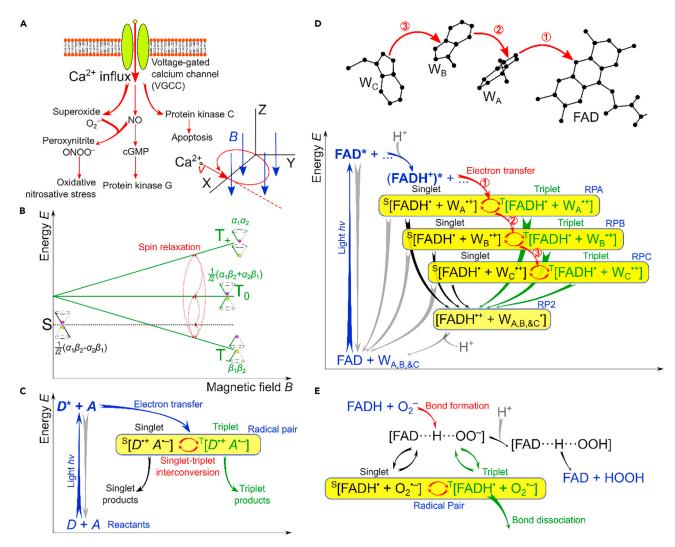
#### **ADDITIONAL ISSUES**

#### **EMR** heating

When EMR are applied to the biological subjects, a proportion of the energy of the EMR will be absorbed by the subject and eventually converted to heat.<sup>224</sup> If the heat induced by the EMR is not dispersed promptly, it will accumulate within the subject and causes an increase of temperature. This will further affect heat-sensitive biochemical reactions in the subject and the down-stream responses.<sup>115</sup> Therefore, researchers must pay special attention to such thermal effects, and carefully discriminate the bio-responses directly triggered by the EMR and those caused by heating.

A convenient way to evaluate the EMR heating is to monitor the temperature of the subject during EMR stimulation. But this method is not suitable for thermostatic animals, because they will automatically adjust the body temperature. The absorption of EMR can be evaluated





Scheme 2. Current theories for explaining the bioeffects of EMR

(A) Ion cyclotron resonance model applied to EMR effects on calcium influx and downstream signaling pathways (adapted from  $^{204,236}$ ); (B and C) Radical pair theory. (B) Energy diagram of electronic spin states (S, T<sub>0</sub>, T<sub>+</sub>, and T<sub>-</sub>) of a radical pair in a magnetic field B. The vector representation corresponding to each spin state were shown by the cartoon next to the curve. The triplet spin states (T<sub>0</sub>, T<sub>+</sub>, and T<sub>-</sub>) are energy degenerate at B = 0, but T<sub>+</sub> and T<sub>-</sub> are split to higher and lower energy from T<sub>0</sub> at B > 0. Meanwhile, the energy level of the spin states S and T<sub>0</sub> are unaffected by the magnetic field B (adapted from  $^{211}$ ). (C) Reaction scheme for a radical pair reaction with magnetic field-dependent reaction products. The radical pair is generated by an electron transfer from a donor molecule D, which is excited by light, to an acceptor molecule A. The external magnetic field affects the interconversion between the singlet and triplet states of the radical pair (adapted from  $^{207,208}$ ).

(D) Radical pair reaction of Cry. A flavin adenine dinucleotide (FAD) bounded with cryptochrome (Cry) is excited by a photon (FAD  $\rightarrow$  FAD\*) and then protonated (FAD\*  $\rightarrow$  (FADH\*)\*). Three electron transfers occur sequentially: the first one is from the tryptophan residue (W<sub>A</sub>) of the Cry to (FADH\*)\*, the second from tryptophan residue W<sub>B</sub> to W<sub>A</sub>, and the third from tryptophan residue W<sub>C</sub> to W<sub>B</sub>, generating magnetosensitive singlet and triplet radical pairs ( $^{5}$ [FADH\* W<sub>A/B/C</sub>\*]). The different spin states of the radical pairs act differently in the reaction cascade (adapted from  $^{212,220,237}$ ).

(E) Magnetosensitive radical pair reactions involving radical pairs of enzyme-bound neutral flavin FADH and superoxide (singlet state  $^{S}[FADH \cdot O_{2} \cdot ^{-}]$  and triplet state  $^{T}[FADH \cdot O_{2} \cdot ^{-}]$ ) (adapted from  $^{144}$ ).

through calculations of the SAR according to the dielectric parameters of the subject and the strength of the EMR obtained either by measurement or by simulation. By contrast, in the detection of bioelectromagnetic emissions, no external EM energy is introduced, so there is no need to consider thermal effects.

#### Modulation of the EMR

The bio-responses induced by the EMR are affected not only by the frequency and amplitude, but also the modulation pattern of the EMR.<sup>225</sup>
Amplitude-modulated EMR affects the biosystems differently from the single-frequency carrier EMR.<sup>226,227</sup> Many studies also focus on pulse





modulated EMR (P-EMR), because it allows applying large field strengths without inducing significant EMR heating, <sup>228</sup> and that the waveforms of the wireless communication signals of GSM or CDMA protocols contain plenty of pulses. <sup>229,230</sup> The P-EMR affects self-assembly of tubulin, <sup>231</sup> enhances cell proliferation and differentiation, <sup>133,152</sup> affects the expression and activity transcription factor, <sup>119</sup> reduces hypoxia and inflammation damage, <sup>232</sup> and induces ultrastructural damage in cells. <sup>148</sup> The P-EMR also alters the sleep pattern<sup>70</sup> and the permeability of the blood-brain-barrier <sup>108</sup> of rodents, and causes pathological changes in their sinoatrial node tissues. <sup>233</sup> P-EMR was also assumed to be related to certain neurodevelopmental and neurobehavioral changes in children. <sup>234</sup> The interesting bioeffects of P-EMR indicate that the biosystems are possibly sensitive to the envelope of the EMR through certain nonlinear mechanisms.

#### Complexity of the EMR environment

In the experiments, a well-controlled stable and uniform EMR environment is usually preferred, but it is very different from the one in our daily life. The real EMR environment is quite complicated, containing various and stochastic EMR signals of all frequencies and patterns from all the directions. The possible nonlinearity of the bio-responses to the EMR makes it difficult to extrapolate the observations under well-controlled EMR stimulation to the complex EMR conditions. A representative nonlinear bio-electromagnetic response is observed in neurons. The neurons are insensitive to 2 kHz electric stimulations, but are activated by an electric signal containing two frequency components around 2 kHz.

#### **CONCLUDING REMARKS**

The investigations focusing on the bioeffects of nonradiative EMR are performed by exposing various biological systems to EMR and detecting the bio-responses in the systems. The biological systems of these studies include humans, animals, *in vitro* cell systems, and biochemical reaction systems. Alternative approaches include dielectric spectroscopy, detection of bioelectromagnetic emissions, and theoretical predictions. Most studies of the EMR impacts on the biological systems are confined to the EMR frequencies commonly used in the daily life, such as the power-frequency of 50–60 Hz, mobile phone communication bands of 800–935 MHz, 1.8 GHz, and 1.9 GHz, and Wi-Fi communication bands of 2.4–2.45 GHz. In contrast, bioeffects of the EMR of other frequencies were studied much less. Thus, the frequency specificity of the reported bioeffects of the EMR is still unclear. Moreover, the real-time monitoring the bio-response to the EMR is still hard to realize, so the time-course responses of the bioeffects of the EMR stimulation is unsolved.

Many bioeffects of high-power EMR are side effects of the EMR heating. In some of the investigations, the influence of the EMR heating was not properly excluded in the control experiments. In contrast, the bio-responses observed under exposure to low-dose EMR are mild and inconsistent, and the corresponding response mechanisms are mostly unclear. Recent investigations have reported interesting findings indicating that the neural system might be able to respond to electromagnetic waves through mechanisms awaiting to be revealed. 32,70,119,138,142,158,227,232 These responses to the EMR are even possibly related to molecular switches highly organized as supramolecular architectures that allows infinite reverie, such as arrays resembling array antennas, bifurcation structure resembling trees, etc.

Last but not the least, the EMR in the real environment is complicated: it is usually stochastic, and contains many different frequency components, varying in amplitude and direction of the fields, and changing with time and location. Given the possibility that the bio-responses to the EMR is nonlinear, the bioeffects of the total EMR of the environment can be different from the summary of those of each single component. It is highly desirable, but still very difficult to define an EMR condition in the experiments that is representative to the complex real EMR environment.

#### **ACKNOWLEDGMENTS**

We thank Songfeng Chen and Xiaofei Wang from Tsinghua University, Dr. Yahong Wang and Dr. Yujing Huang from Westlake University, and Dr. Hu Deng from Beijing Huilongguan Hospital for their helpful advice to this article. This work was supported by funds from the National Natural Science Foundation of China (31930059 and 81920108015 to Y.S.), the Key R&D Program of Zhejiang Province (2020C04001 to Y.S.), and the National Key R&D Program of China (2020YFA0509300 to Y.S.).

#### **AUTHOR CONTRIBUTIONS**

L.L., B.H., and Y.L. contributed equally to this work. L.L., B.H., Y.L., Y.Z., X.T., and Y.S. wrote this paper.

#### **DECLARATION OF INTERESTS**

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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