Evaluation of the Potential Biological Effects of the 60-GHz Millimeter Waves Upon Human Cells

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Abstract—We investigate potential biological effects of low-power millimeter-wave radiation on human cell viability and intracellular protein homeostasis. A specific exposure system allowing to perform far-field exposures with power densities close to those expected from the future wireless communications in the 60-GHz band has been developed and characterized. Specific absorption rate (SAR) values were determined for the biosamples under test using the FDTD method. It was shown that millimeter-wave radiation at 60.42 GHz and with a maximum incident power density of 1 mW/cm^2 does not alter cell viability, gene expression, and protein conformation.

Index Terms—Bioelectromagnetics, biological effects, millimeter waves, numerical dosimetry, wireless communications.

I. INTRODUCTION

IN THE LAST decade, progress in computational and experimental millimeter-wave electronics has allowed to identify the millimeter-wave frequency band as highly promising for a number of high-resolution and high-speed wireless systems [1]–[6]. If we restrict our attention to the interactions with biological tissues, current and near-future applications of millimeter waves can be divided into two subgroups depending on the radiated power: 1) high-power systems inducing a significant heating of the human body surface, like nonlethal weapons (e.g., active denial systems at 94–95 GHz) and therapeutic applications at 42.25, 53.57, and 61.22 GHz [7]; 2) low-power communications, imaging, and radar systems in V- and W-bands that do not induce any substantial temperature increase (typically less than 0.5°C) of human tissues, but may possibly produce biological and health effects due to prolonged exposure of the users.

In particular, the unlicensed 57–64 GHz subband is of strong interest today for high data rate (> 1 Gb/s) short-range point-to-point and point-to-multipoint communications (e.g., wireless USB2.0, wireless video, streaming data, telecom backhauls) [8]–[12]. From the bioelectromagnetic point of view, the

human body has never been exposed in natural conditions to radiations in the 60-GHz band since these frequencies, which correspond to the peak of molecular oxygen absorption, are strongly attenuated in the atmosphere [13]. Furthermore, a large number of spectral lines of molecular groups containing carbon or oxygen molecules are located around 60 GHz. Moreover, these frequencies have also been used in several countries for biomedical purposes [14], thereby suggesting that molecular interactions between the millimeter waves and the human body are possible.

A few theories were proposed to explain potential biological effects of millimeter waves [15]. A number of experimental efforts have been also undertaken and have shown that millimeter-wave radiations may interfere with several cellular processes under certain exposure conditions. For instance, it was demonstrated that these radiations can induce changes in gene expression [16]. Additionally, millimeter waves were found to reduce tumor metastasis [17] and protect cells from toxicity of anticancer medicines [18]. It was also reported that cellular metabolism and cell proliferation can be affected by exposure to low-power millimeter waves [19]. Furthermore, it was recently demonstrated that these radiations can modify the structural state of phospholipids within biomembranes [20], [21]. However, there remains a crucial lack in identification of exact cellular targets of millimeter waves, and today there is no well-established scientific interpretation for the observed effects. Within this context, from the general public safety viewpoint, it is important to investigate the possible biological effects of low-power communication systems in the 60-GHz band before their wide, near-future deployment within domestic and professional environments.

Various environmental factors can cause significant changes in the organization and conformation of biological macromolecules. DNA and proteins are the cellular components most affected by variations of physical and chemical conditions. DNA damages are induced by high-energy treatments (e.g., ionizing radiations), whereas proteins are particularly fragile and affected by relatively weak disruptive treatments, such as heat. Millimeter waves are nonionizing radiations and, as expected, it was shown that they are not genotoxic [22]. Nevertheless, physical principles do not exclude that these radiations might alter the protein conformations or cause a proteotoxic stress. Denaturation of proteins due to environmental insults may have many biological consequences. It may lead to various cellular dysregulations, such as defects in enzymatic activities, signal transduction, cellular organization, or cell growth. Finally, prolonged stress conditions may also affect the cellular
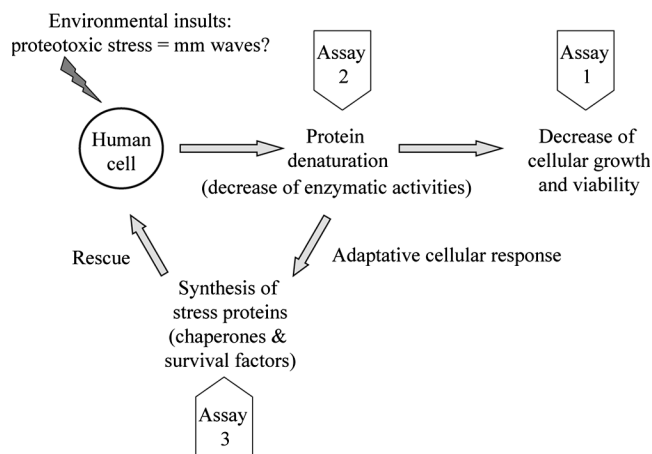
Fig. 1. Methodology implemented to investigate potential in vitro biological effects of millimeter waves. Assay 1: Cell growth measurement. Assay 2: Luciferase assay on purified proteins. This reflects the possibility of direct protein denaturation after exposure to millimeter waves. Assay 3: Quantitative reverse transcription polymerase chain reaction (RT-PCR). This technique enables one to measure gene expression of stress-inducible factors in order to verify if millimeter waves could trigger cellular adaptive response.

Fig. 2. Experimental setup and exposure system. *Signal generation subunit (QuinStar Technology Inc., CA)*: 1—60.42 GHz Gunn oscillator. 2— -3 dB power divider (58–62 GHz). 3—V-band power amplifiers (25-dB gain). 4—Power combiner (58–62 GHz). 5—Isolator (20-dB isolation). *Frequency control subunit*: 6— -20-dB directional coupler HP V752D. 7—Isolator HP V365A (30-dB isolation). 8—Mixer M15HWD. 9—Spectrum analyzer R3182. *Exposure chamber*: 10—17-dB-gain pyramidal horn antenna. 11—Absorbing materials. 12—Incubator MEMMERT UE400. 13—6-well or 96-well tissue culture plate. 14—Thermocouple.

viability and trigger apoptosis, a form of programmed cell death that can lead to severe diseases when deregulated. Consistently, cells have developed sophisticated molecular systems to sense and respond rapidly to changes in their environment [23]. In the presence of stress conditions, cells express specific chaperones and stress factors to cope with the accumulation of misfolded proteins. These factors also have protective functions that allow cells to survive.

Consequently, a relevant and accurate way for the investigation of biological effects of millimeter waves at the cellular level consists of studying and quantifying the most sensitive cellular responses to stress as indicators (biomarkers) of cellular homeostasis. As cellular stress is a multistep process, we developed and applied several assay systems to assess potential stress induction after exposure. Our methodology is summarized in Fig. 1. Several complementary aspects of the cell physiology have been considered in this work, starting with relatively general characterization of cellular viability (assay 1) and then investigating potential subcellular modifications at the level of protein conformation (assay 2) and gene expression (assay 3).

As human skin is the primary target for the millimeter waves, we used the immortalized keratinocytes HaCaT cells derived from human epidermis [24]. Additionally, to validate and compare the results obtained using keratinocyte cells, the human astrocytoma glial cell line U-251 MG was used as a relevant and well-characterized biological model to investigate cellular stress.

This paper is organized as follows. We describe in Section II the structure and characteristics of our exposure system and provide numerical dosimetry data for the exposed biosamples. Some details about the biological protocols are also provided at the end of this section. The experimental results of the biological tests after exposure of human cells at 60.42 GHz are described in Section III. Finally, discussions and conclusions are given in Section IV.
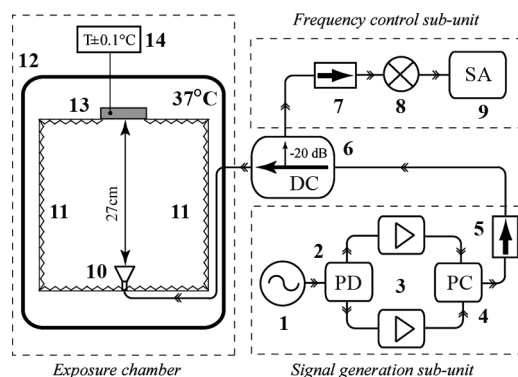
II. EXPERIMENTAL SYSTEMS AND NUMERICAL DOSIMETRY

In our experiments, the biological samples were placed in standard 6-well or 96-well tissue culture dishes and were exposed or sham-exposed to low-power millimeter waves. In this section, the exposure system and experimental setup are described. Then, numerical dosimetry data on the specific absorption rate (SAR) within the exposed biological samples are provided. Finally, some specific characteristics of the considered cells and bioassays used to quantify potential bioeffects are given.

A. Experimental Setup

A narrowband exposure system for in vitro studies has been specifically developed for human cells exposure under far-field conditions. Fig. 2 schematically represents the three main subunits of this system, namely the signal generation subunit, the frequency control subunit, and the exposure chamber.

A low-power CW signal is generated by a Gunn oscillator at the center frequency $f_c = 60.42$ GHz. This frequency value coincides with the maximal oxygen-induced absorption peak in V-band. A mechanical tuning system enables one to shift the resonant frequency by ± 150 MHz around f_c. This signal is amplified and transmitted toward a 17-dB-gain pyramidal horn antenna with aperture dimensions 22.2 mm $\times$ 16.7 mm through a set of WR-15 rectangular waveguides and a directional coupler. In this work, the output power P equals 180 mW; this corresponds to a maximum incident power density (IPD) of 1 mW/cm^2 at the center of the tissue culture plate. This value coincides with the general public exposure limit established by international guidelines and recommendations [25].

The radiated power was carefully checked before and after each exposure. The use of a Gunn oscillator guarantees a very satisfactory frequency stability of the output signal as highlighted in Fig. 3, ($\Delta f_c = \pm 0.006$ GHz). This also ensures its location within the peak region of oxygen absorption.
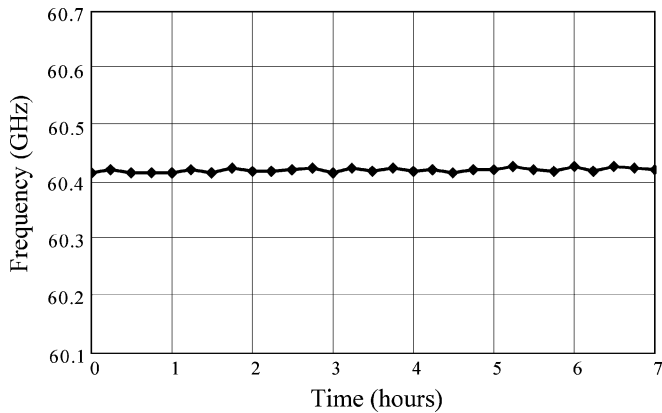
Fig. 3. Frequency stability of the output signal versus exposure duration. The center frequency is equal to 60.42 GHz.

The tissue culture plates $(8.5 \text{ cm} \times 12.7 \text{ cm})$ with cells were exposed or sham-exposed under far-field conditions in two different moments in the incubator at 37°C and then compared later. Sham-exposures were performed under the same experimental conditions as exposures, but with the generator switched off.

B. Numerical Dosimetry

The exposure levels of biological samples at millimeter waves are typically characterized by two parameters, namely the IPD and the SAR values. IPD data have been previously reported for 6-well and 24-well tissue culture plates illuminated by a pyramidal horn antenna [26]. Here, we mainly focus on determination of the average SAR for the two exposure scenarios corresponding to the three assays defined in Fig. 1: 1) exposure of cell monolayers located in 6-well or 96-well culture plates (assays 1 and 3); 2) exposure of purified protein solutions in a 96-well tissue culture plate (assay 2).

1) Average SAR in Cell Monolayers: The analysis of gene expression modifications after exposure at 60.42 GHz (Section III-C) was performed using standard 6-well culture plates made of polystyrene. In the experiments, each plate was illuminated under far-field conditions by a pyramidal horn antenna 27 cm apart, as illustrated in Fig. 2. The cell monolayer is located at the bottom of each well and is covered by a culture medium whose height is equal to 1 cm. In the modeling, the thickness of the monolayer was assumed to be 30 μm. Previously, it was shown that the SAR within the cell layers in the tissue culture plates is not critical to the thickness variations of the monolayer ranging from 10 to 30 μm [27]. The wells and culture plates are schematically represented in Fig. 4.

The dielectric properties of the cell monolayer and culture medium were determined applying Maxwell's mixture equation to the free-water permittivity data. The corresponding data are available in [27] from 30 to 100 GHz. They are given at 60.42 GHz in Table I.

The distribution of the electromagnetic field within each of the six wells was computed using the FDTD method (XFDTD software from REMCOM Inc.) that proved to be very well adapted for biomedical electromagnetic dosimetry [28]–[30].
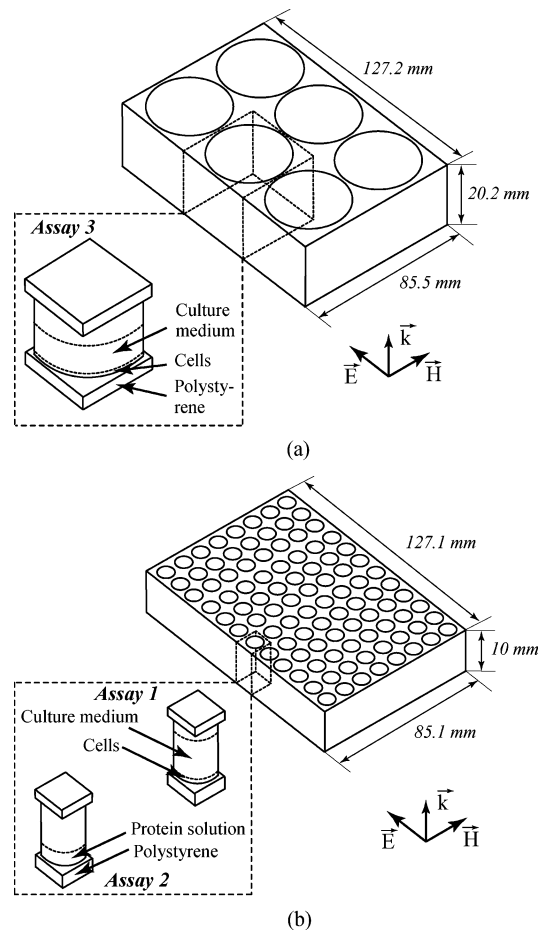

(a)

(b)

Fig. 4. Dimensions of 6-well and 96-well tissue culture plates, and schematic representation of individual wells. (a) 6-well tissue culture plate. (b) 96-well tissue culture plate.

TABLE I
PROPERTIES OF THE MATERIALS USED IN THE MODELING AT 60.42 GHz

Material	Relative permittivity	Electric conductivity (S/m)
Air	1	0
Polystyrene	2.3-0.003j	0.01
Culture medium	15.2-22.4j	77.1
Cells	10.9-14.5j	50.4
Protein solution	14.7-21.7j	47.1

All simulations were performed using adaptive rectangular mesh with a cell size d ranging from $l/10$ (3 μm) up to $\lambda/20$ (250 μm in free space), where λ and l are the wavelength in the considered substructure and the smallest dimension of this substructure, respectively. We assumed the incident field to be a normally incident, linearly-polarized plane wave. Each computation was performed for single-well applying boundary conditions as defined in Fig. 5.

The average SAR over the cell monolayer volume was determined from the electric field values, electric conductivity, and average mass density of the cells $\rho = 1.11$ g/cm^3 (Fig. 5). This modeling strategy has already been validated experimentally using infrared thermometry for 24-well plates [27]. As the
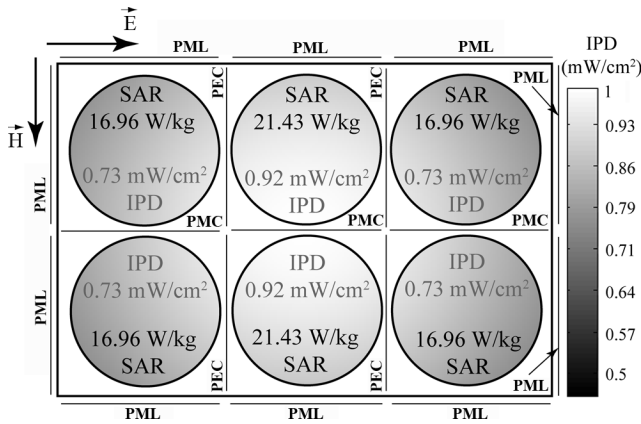
Fig. 5. IPD distribution (grayscale), average IPD, and average SAR in each well of the 6-well tissue culture plate. PML, PEC, and PMC denote the perfectly matched layer, the perfect electric conductor, and the perfect magnetic conductor boundary conditions, respectively.

four corner wells and two central wells are symmetrical from the electromagnetic point of view, their average SAR is the same.

The SAR was also computed for monolayers located in 96-well tissue culture plates. Such plates have been employed to study cell viability (Section III-A). Here, taking into account the large number of wells, periodic boundary conditions were applied at four lateral sides of a well. For a peak IPD of 1 mW/cm^2, the average SAR ranges from 26.2 (center well) down to 13.7 W/kg (corner wells).

2) Average SAR in Purified Protein Solutions: The direct effect on possible protein conformation changes after exposure to the millimeter waves was studied using a purified protein solution located in a 96-well tissue culture plate (Section III-B). Each well was filled with $50 \mu\text{L}$ of protein solution forming a cylinder whose height and diameter equal 1.8 and 6 mm, respectively. The volume of the solution was carefully chosen to get enough material for the biological tests and, at the same time, to ensure a maximum variation of the average SAR at different heights of the solution smaller than ± 5 dB with respect to the averaged SAR over the total volume of the solution.

The relative permittivity and electric conductivity of our solution were determined as explained in Section II-B1; they are given in Table I. It is important to note that due to the diffraction, multiple reflections, and mutual coupling between neighboring wells, the protein solution was also partly exposed from the lateral sides and from the top that increases the averaged over the solution volume SAR. It is also worthwhile to mention that due to the Brownian motion and convection, the protein solution is constantly mixed, which ensures more homogeneous exposure conditions.

The electromagnetic problem was solved using the FDTD method by applying periodic boundary conditions on opposite lateral sides of a single well. Depending on the well location in the culture plate, the averaged SAR over the solution volume was found to be in the range 4.3 ± 1.3 W/kg. The resulting averaged SAR values are much smaller than for cell monolayers (Fig. 5) since the penetration depth of millimeter waves is smaller than the protein solution height [27].

C. Cell Culture and Bioassays

1) Cell Culture: Immortalized HaCaT cells [24], derived from human epidermis, were kindly provided by Dr. M-D. Galibert-Anne (University of Rennes 1, Rennes, France), and they were grown in Dubelcco's modified Eagle medium (Gibco/Life Technologies), supplemented with 10% of Fœtal Calf Serum, 100 units/mL penicillin, 100 μg/mL streptomycin, and 0.25μg/ml amphotericin (Gibco/Life Technologies).

We also used human astrocytoma cell line U-251 MG [31], as they are highly sensitive and respond with great efficiency to environmental perturbations. Cell culture of U-251 MG was performed as described previously [32], using the same culture medium as for the HaCaT cells.

Both cell lines were maintained at $37°$C under 5% CO_2 in the air. The cell cycle durations for HaCaT and U-251 MG cells are 20 and 24 h, respectively. Cells were spread in order to have around 60%–70% of confluence at the end of the exposure experiments.

2) Bioassays: As summarized in Fig. 1, three series of biological assays were carried out after exposure to millimeter waves: 1) study of cell growth and viability; 2) analysis of direct protein denaturation; 3) determination of possible modifications of gene expression. In each case, multiple exposures were performed to ensure appropriate statistics. The corresponding experimental results are given in Section III.

Cell growth and viability (assay 1 in Fig. 1) were measured using the "cell growth determination kit" from Sigma-Aldrich. Cell viability was determined by measurements of cellular metabolic activity, which is proportional to the number of viable cells in the culture dish. This method is based on the cleavage of the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (also known as MTT) by the mitochondrial dehydrogenases of viable cells. Cells spread in a 96-well plate were sham-exposed or exposed to 60.42 GHz radiation for 24 h. The cells were incubated with the MTT reagent for the last 3 h of the culture. Cleavage by metabolically active cells leads to the formation of purple formazan crystals. The latter were solubilized and measured by a spectrophotometric method, according to the manufacturer's recommendations.

The direct protein denaturation was studied using in vitro luciferase (Luc) assay (assay 2 in Fig. 1). The cDNA encoding the luciferase enzyme from firefly (*Photinus pyralis*) was inserted into the pGEX-3X plasmid (GE Heathcare Bio-Sciences, Uppsala, Sweden), which corresponds to a Glutathione S-Transferase (GST) expression vector. The presence and the orientation of the insert within the recombinant plasmid were verified by restriction enzyme analysis. *E. coli* BL21 bacteria cells were transformed with the resulting pGEX-Luc expression vector and selected colonies were tested for protein production. Recombinant GST-Luc fusion protein was expressed and purified as described in GE Healthcare Life Sciences protocols [33]. Briefly, whole cell lysates were obtained from transformed bacteria grown at $32°$C and induced with 0.5 mM IPTG for 5 h. Soluble proteins were separated from insoluble materials by centrifugation. Then, the GST-Luc fusion protein was purified by affinity chromatography using glutathione-agarose beads. The purified GST-Luc ($50 \text{ ng}/\mu\text{L}$,
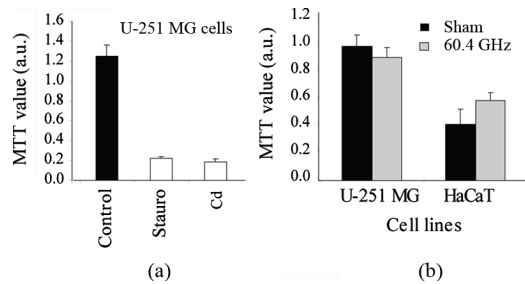
Fig. 6. Cell viability test results. (a) Positive control in presence of cell death inductors. (b) Cell viability for cells exposed or sham-exposed to millimeter waves. Data is shown for 12 samples as mean value and standard deviation.
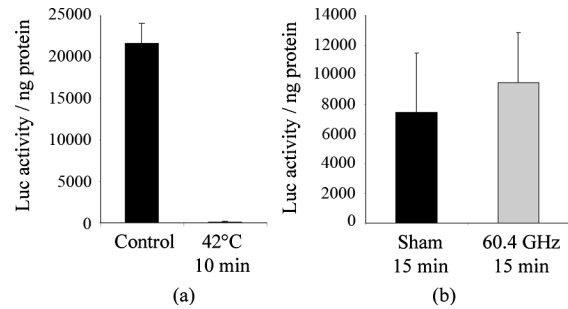

Fig. 7. Protein luciferase activity after exposure or sham-exposure to 60.42-GHz radiation. (a) To demonstrate how sensitive the luciferase enzyme to denaturing conditions is, a heat shock treatment ($42\,^\circ$C, 10 min) was performed and compared to control ($4\,^\circ$C, 10 min). (b) Activity of exposed at 60.42 GHz and sham-exposed samples ($37\,^\circ$C, 15 min). Data provided for four samples.

580 nM) was incubated in $50\ \mu$L of phosphate buffered saline (PBS) in a 96-well plate. The purified GST-Luc was exposed or sham-exposed to millimeter waves for 15 min at $37\,^\circ$C. Its enzymatic activity was then determined in a luminometer using a luciferase assay system kit (Promega). As a positive control, thermal denaturation of luciferase (10 min at $42\,^\circ$C) was performed under the same conditions.

Finally, to assess potential modifications of gene expression (assay 3 in Fig. 1), we used reverse transcription polymerase chain reaction (RT-PCR) analysis. Total RNA from U-251 MG or HaCaT cells, exposed or sham-exposed for 24 h, were prepared and reverse-transcribed as previously described [32]. The mRNA expression levels of stress-induced survival factors (HSP70, BiP) were measured by real-time PCR and normalized as explained in [34].

Statistical significance of the performed essays was evaluated by using Student's t test within the Minitab 15.1.1 software. $P > 0.05$ was considered as a criterion of nonsignificance.

III. RESULTS

In this section, we present the experimental results on the potential modifications induced at cellular (viability of cells) and subcellular (protein conformation and gene expression) levels after cell exposure to low-power millimeter-waves.

A. Viability of Cells

To address the potential cytotoxicity of millimeter-wave radiation, the MTT assay was performed after 24 h of exposure to 60.42 GHz (Fig. 6).

As a positive control demonstrating the decrease of cell viability as a reaction to stress, the MTT test was performed for U-251 MG cells in the presence of cell death inductors, namely 10 μM staurosporine (Stauro: a potential anticancer drug that provokes apoptosis) or 8 μM cadmium (Cd: a highly toxic heavy metal). Under these conditions, the cell viability was decreased by a factor larger than 6 [Fig. 6(a)].

Then, the cell viability was compared for the exposed ($P = 180$ mW, $\text{IPD}_{\max} = 1$ mW/cm^2, $\text{SAR}_{\text{av}} = 13.7 - 26.2$ W/kg) or sham-exposed cells ($P = 0$ mW). Our results are given in Fig. 6(b). They clearly show that, in contrast to the positive controls, millimeter-wave radiation does not decrease cell viability or cellular proliferation for the cell lines used in our study.

B. Effects on Protein Conformation

Purified protein luciferase dissolved in saline solution was exposed to 60.42 GHz or sham-exposed. The choice of the biological system under test was determined by its extremely high sensitivity to various physical and chemical conditions.

As a positive control, an in vitro denaturation experiment was performed, demonstrating that a short incubation at $42\,^\circ$C is sufficient to entirely denature the luciferase [Fig. 7(a)].

The protein solution was exposed or sham-exposed for 15 min at $37\,^\circ$C ($P = 180$ mW, $\text{IPD}_{\max} = 1$ mW/cm^2, $\text{SAR}_{\text{av}} = 3 - 5.6$ W/kg). This experiment was restricted to very short-term exposure time as purified luciferase is extremely fragile and its prolonged incubation may rapidly abolish its enzymatic activity. Our experimental results [Fig. 7(b)] show that millimeter waves do not significantly change luciferase activity under the considered exposure conditions. Taking into account relatively nonhomogeneous distribution of the SAR in the protein solution, further complementary investigations in this direction might be useful.

C. Effects on Gene Expression

Finally, we studied whether prolonged exposure to millimeter-wave radiation has a proteotoxic effect strong enough to trigger cellular adaptive response and overexpression of stress factors. To address this issue, we selected two stress-biomarker genes, namely the heat shock protein 70 (HSP70) and the immunoglobulin heavy-chain binding protein (BiP). These two genes are highly inducible by cellular stresses and can be used as perfect indicators of cellular aggression [35], [36]. To monitor the cellular stress level, cells were exposed to 60.42 GHz ($P = 180$ mW, $\text{IPD}_{\max} = 1$ mW/cm^2, $\text{SAR}_{\text{av}} = 21.43$ W/kg for central well, $\text{SAR}_{\text{av}} = 16.96$ W/kg for corner well) or sham-exposed for 24 h. Then, total RNA was purified for quantitative real-time PCR analysis. This technique is considered nowadays as the most sensitive and accurate one for gene expression measurement.

For the positive control, cells were incubated for 3 h 30 min at $42\,^\circ$C. The expression of HSP70 and BiP increased 2.2- and 9.2-fold, respectively, after heat shock treatment [Fig. 8(a)].

Our experimental results have shown that the mRNA levels of HSP70 and BiP do not increase after exposure of the cells to
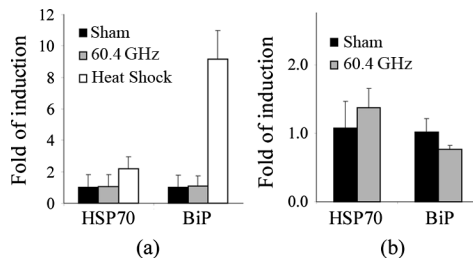
Fig. 8. Gene expression of stress-related proteins after exposure to 60.42 GHz or sham-exposure. (a) Human astrocytoma glial cell line U-251 MG. (b) Human epidermis cells HaCaT. Each test was performed at least in triplicate.

millimeter waves for two human cell lines, namely the glial cells U-251 MG [Fig. 8(a)] and the keratinocytes HaCaT [Fig. 8(b)].

IV. DISCUSSIONS AND CONCLUSION

In this study, we investigated potential biological effects of millimeter waves at 60.42 GHz upon human cells (skin cells and glial cells). A specific exposure system for in vitro studies was developed and characterized. The output power level was selected to achieve superficial power densities on biological samples close to those typically expected from the future wireless communication systems in the 60-GHz band.

First, the average SAR values within cell monolayers or protein solutions used in our bioelectromagnetic experiments were computed with the FDTD method. The numerical results demonstrated that, for the maximum IPD of $1 \, \text{mW/cm}^2$ (exposure limit for general population), the average SAR values range between 17 and 21.4 W/kg and between 13.7 and 26.2 W/kg for 6-well and 96-well tissue culture plates, respectively. The average SAR (4.3 ± 1.3 W/kg) for purified protein solutions in 96-well plates is 4.7 times lower than for cell monolayers due to the shallow penetration of millimeter waves in the solution.

Then, various biological assays were defined and implemented to assess the effects of low-power millimeter wave at the cellular, subcellular, and molecular levels. Our experimental results demonstrated that, for the IPD lower than $1 \, \text{mW/cm}^2$, exposure to millimeter waves does not modify cell growth and viability. Furthermore, the experiments did not show any statistically significant effect on protein conformation and adaptive gene expression. These data confirm recent studies showing that, if care is taken to avoid thermal effects, exposures to low-power millimeter-wave have no proteotoxic effects and do not induce protein chaperones expression [26], [34], [37].

In conclusion, our results indicate that exposure to low-power radiations around 60 GHz does not cause any significant effect. However, they do not exclude a possibility of existence of local subcellular effects or effects potentially induced by prolonged exposures. Moreover, we cannot neglect possible synergistic effects and eliminate the possibility that other exposure parameters, like frequency, exposure time, or field polarization may have effects on biosystems. Therefore, additional gene markers and radiation parameters should be further analyzed for an extensive investigation of the potential biological effects of millimeter waves.

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