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# БИОСЕНСОР НА ОСНОВЕ ТЕРАГЕРЦ-ГРАФЕНОВОЙ МЕТАПОВЕРХНОСТИ С ДВУХРЕЗОНАНСНЫМ ОТКЛИКОМ КАК ИНСТРУМЕНТ ДЛЯ ВЫЯВЛЕНИЯ РАКА С ИСПОЛЬЗОВАНИЕМ СПЕЦИФИЧЕСКОЙ ДЛЯ КЛЕТОК ЧАСТОТЫ

***Аннотация****: раннее выявление является наиболее важной стратегией контроля и лечения рака, которая может значительно увеличить коэффициент выживаемости за счет выявления заболевания на ранних стадиях и быстрого лечения и предотвращения прогрессирования болезни. Исходя из существования клеточных частот в виде реакции каждой клетки на свою частоту и разницы между уровнями частот нормальных и опухолевых клеток как отличительного признака для выявления рака, мы предлагаем использовать метаповерхности на основе графена. Благодаря выдающимся физическим свойствам графена, его биосенсорные датчики, реализованные с помощью терагерцовой метаповерхности, широко обсуждаются и изучаются. Новый дизайн графеновой метаповерхности представляет собой индивидуальное графеновое кольцо и Н-образную графеновую структуру. Графеновая метаповерхность демонстрирует двухрезонансный отклик, резонансная частота которого сильно зависит от ее геометрических параметров. Результаты моделирования ясно показывают, что теоретическая чувствительность, коэффициент полезного действия и значение предложенной графеновой метаповерхности для клеток молочной железы достигают 1,21 ТГц/RIU, 2,75 RIU-1 и 2,43, соответственно. Эти результаты могут открыть новые пути для перспективного применения в диагностике раковых заболеваний.*

***Ключевые слова****: терагерц-графеновая метаповерхность, нанобиосенсоры, выявление рака, клеточная частотность.*

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# TERAHERTZ-GRAPHENE-METASURFACE BASED BIOSENSOR WITH DUAL-RESONANCE RESPONSE AS A TOOL FOR CANCER DETECTION USING CELL SPECIFIC FREQUENCY

***Abstract:*** *early detection is the most important strategy for controlling and management of cancer, which can significantly increase the survival rate by detecting disease in the early stages and rapid treating and preventing the progression of the disease. Based on existence of specific cell frequencies in the form of the response of each cell to its own specific frequency and the difference between normal and tumor cell frequency levels as a hallmark for cancer detection, we suggest using Graphene-based metasurfaces. Owing to the outstanding physical properties of graphene, its biosensing applications implemented by the terahertz metasurface are widely concerned and studied.a novel design of the graphene metasurface, proposed by ( Tan et al., 12) consists of an individual graphene ring and an Hshaped graphene structure. The graphene metasurface exhibits a dual-resonance response, whose resonance frequency strongly varies with its geometrical parameters. The simulated results clearly show that the theoretical sensitivity, figure of merit, and quantity of the proposed graphene metasurface for breast cells reach 1.21 THz/RIU, 2.75 RIU-1, and 2.43, respectively. These findings may open up new avenues for promising applications in the diagnosis of cancers.*

***Keywords***: *Terahertz-Graphene-Metasurface, Nanobiosensers, Cancer detection, Cell-specific frequency.*

## 1. Introduction

### 1.1. Diagnostic and Therapeutic Uses of Electromagnetic Fields

High-energy ionizing radiation used commonly in medicine for both the diagnosis and treatment of disease. The use of low-intensity RF EMF in medicine is far much less common (*Figure 1*). While uncertainties regarding efficacy remain, there is evidence that some forms of RF EMF exposure may be useful for the diagnosis and treatment of disease [1].

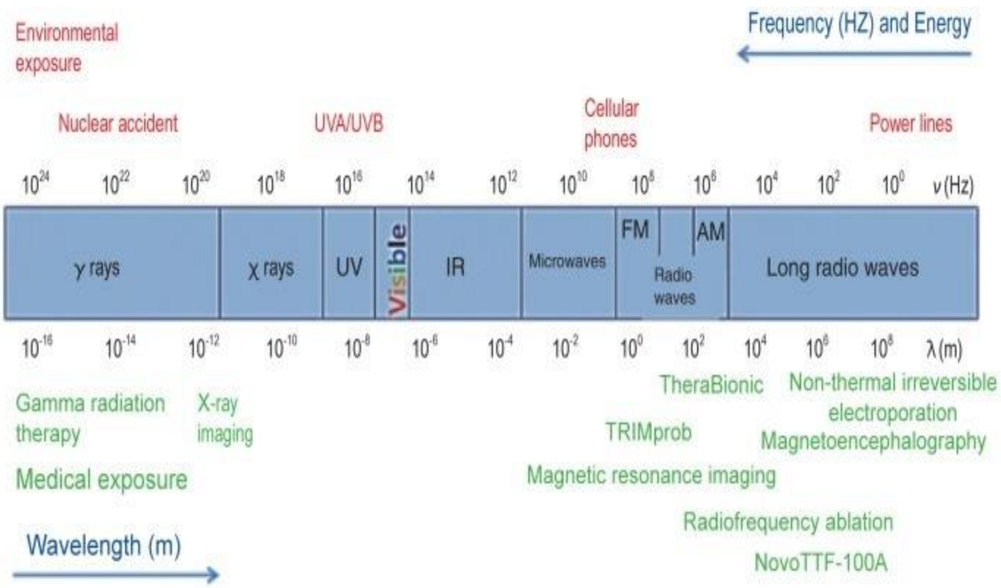


Fig. 1. The electromagnetic spectrum and common exposures:
The electromagnetic spectrum is depicted in blue. Environmental exposures with known or possible negative consequences are shown in red. Exposures received as part of medical diagnosis or treatment are shown in green

As shown in (Table 1) EMF has also been used as a therapeutic modality.

**Table 1.**

**Summary of clinical studies evaluating the efficacy of electromagnetic ı diagnostic or therapeutic modalities**

| Application | Study | Modality | Results |
|---|---|---|---|
| Diagnostics | Pearlman *et al.*[13] | Magnetoencephalography | Non-invasive modality for differentiating amc designed to be used in combination with CT a |
| | Vannelli *et al.*[14] | TRIMprob | Exploited tissue resonance differences betwe tissue, used in the diagnosis of prostate and r |
| | Barbault *et al.*[20] | TheraBionic | Identified a tumor-specific frequency signatu cancer |
| Therapeutics | Aaron *et al.*[16] | Electric fields and EMF to facilitate fracture healing | Suggested that EMF has efficacy similar to a ; nonunion fractures and spinal fusions |
| | Pasche *et al.*[28] | LEET to treat physiologic insomnia | Demonstrated decreased sleep latency and ir patients treated with LEET in a double-blind ( |
| | Stupp *et* | NovoTTF-100A | Delivery of electric fields rather than chemot |

Fig. 1. Table 1. Summary of clinical studies evaluating the efficacy of electromagnetic fields (EMF) as diagnostic or therapeutic modalities

Pulsed EMF have shown efficacy on osteoarthritis [2]. Alternating electric fields have been used to induce fracture healing, with suggested efficacy similar to that of bone graft [3]. The proposed action of pulsed EMF is via the induction of directed migration and differentiation of bone marrow-derived mesenchymal stem cells [4]. In the present time, RF EMF is used as a therapeutic option in cases of tibial stress fractures and spinal cord injury.

1.1.2. Radio-frequency ablation

Radiofrequency ablation (RFA) is a therapeutic option mainly used to treat malignancies including breast cancer, colorectal cancer, and hepatocellular carcinoma (HCC), and in particular surgically unresectable metastases [5]. RFA is administered with medical devices operating between 460 and 550 kHz and delivering therapeutic energy to soft tissues [7]. This modality destroys tumor tissue by means of heat-induced necrosis raising their temperature to about 100°C for approximately 15 min [6].

1.1.3. Anti tumor EMF with no hyperthermia

Laboratory and clinical evidence suggests that particular frequencies the RF EMF spectrum may have antitumor effects without causing hyperthermia in patients with breast cancer, HCC, ovarian cancer, thyroid cancer, or glioblastoma multiforme[8; 9]. The NovoTTF-100A technology applies alternating electric fields by means of electrodes placed on the skin overlying tumor-harboring body parts. This was the first EMF device of its kind to be approved by the Food and Drug Administration (FDA) based on the results of a phase III trial for treating recurrent glioblastoma showing efficacy akin to the standard-of-care chemotherapy regimen but with fewer adverse effects [10].

1.1.4. RF EMF combined with chemotherapy

One last consideration with RF EMF-based therapies is possible synergy with frequently used chemotherapies. RF EMF in combination with bevacizumab and cyclophosphamide demonstrated no increase in adverse effects clinically, and similar findings were reported in vitro when EMF was used together with paclitaxel or cisplatin [8; 10]. These findings suggest that patients may not experience additional adverse effects from undergoing both chemotherapy and RF EMF therapy; moreover, simultaneous treatment with both modalities might have a synergistic effect.

1.2. Mechanism of Action

large body of research reports a wide range of biological effects post exposure to RF EMF. The findings from these studies can be broadly categorized into: cellular function and metabolism; dysregulation and risk for malignancy; intercellular and systemic effects; cell morphology and differentiation; enzyme effects; pharmacologic effects as shown in (*Figure 3*). Overall, studies have focused on possible negative impacts of EMF exposure, ranging from DNA damage to a possible role as a cancer promoter. Previously, little emphasis has been placed on the possible positive impacts of controlled exposure to EMF; however, this paradigm has begun to shift [1].

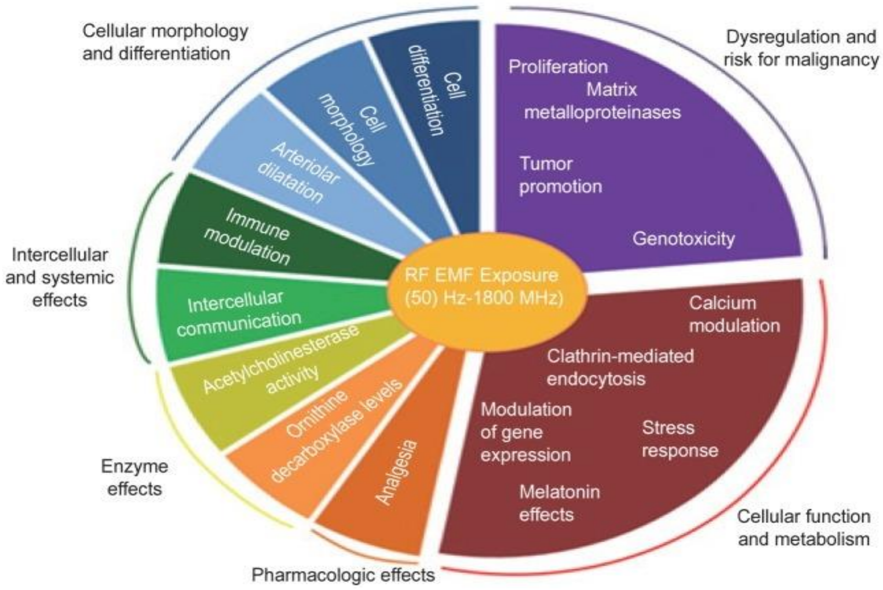


Fig. 3. Reported biological effects of RF EMF exposure

Figure 4 below shows possible treatment responses to RF EMF.

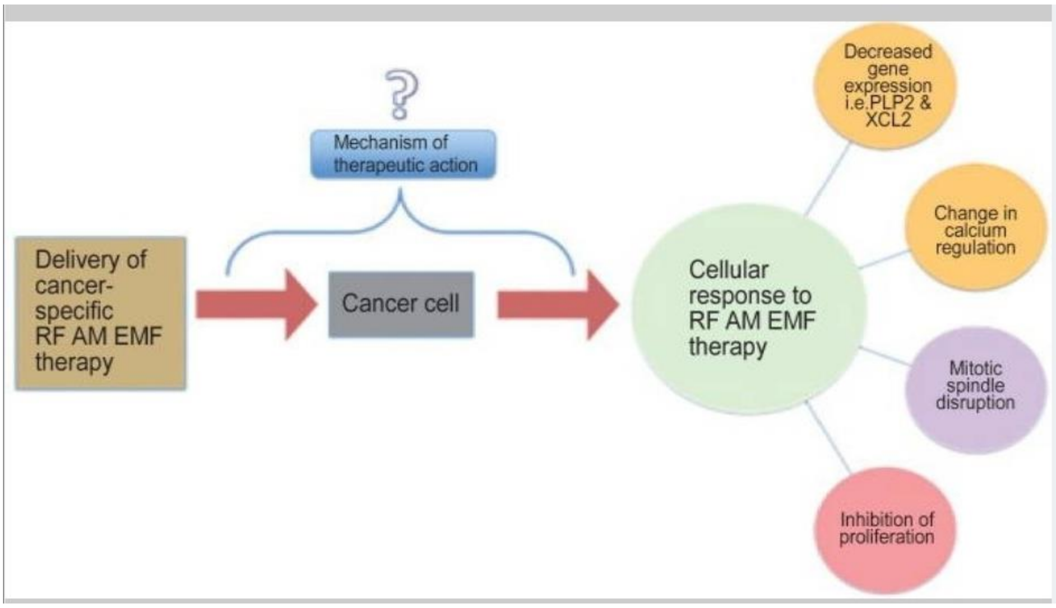


Fig. 4. Theoretical flowchart representing the published biological responses to amplitude-modulated RF EMF therapy that may in part explain the antitumor effect

1.3.1. The cell-specific frequency evaluation as a new hallmark in cancer detection

Studies in cancer treatment using the amplitude-modulated electromagnetic fields reveal that each type of cell has a specific response to the emitted frequencies. Observations show that frequencies of 1873.477 Hz, 2221.323 Hz, 6350.323 Hz, and 10456.383 Hz are especifically allocated to patients with breast cancer, hepatocellular carcinoma, prostate cancer and pancreatic cancer, respectively [10; 11]. Frequency specificity for the hepatocellular tumor is 85% and 75% for breast cancer, which indicates a good level of frequency response specificity [11]. Frequency application in addition to the therapeutic aspect can also be used in diagnostic applications.

1.3.2. Cell specific frequencies

The results obtained in cancer treatment using the amplitude modulated electromagnetic fields indicate that each type of cell has a specific response to the emitted frequencies. Also, the results reveal that the recorded frequencies of prostate and breast cancers are lower compared to the normal cells associated with these tissues. There are more evidences for the existence of specific cell frequencies in the form of the response of each cell to its own specific frequency and the difference between normal and tumor cell frequency levels [20]. Based on these evidences, it can be introduced as a hallmark with the ability to the distinction between normal and tumor cells for cancer detection.

2.1. Terahertz-Graphene-Metasurface-Based Nano-antenna

Owing to the outstanding physical properties of graphene, its biosensing applications implemented by the terahertz metasurface are widely concerned and studied. (Tan et al.) presented a novel design of the graphene metasurface, that consists of a single graphene ring and an H shaped graphene structure. The graphene metasurface exhibits a dual-resonance response, whose resonance frequency considerably varies with the geometrical parameters of the proposed metasurface,the carrier density of graphene, and the analyte composition. The transparency window, including width and position, can be artificially controlled by adjusting the geometrical parameters or the Fermi energy [12].

In this article the sensing parameters of the graphene metasurface for cancerous and normal cells are investigated, focusing on two factors, namely cell quantity and position on the metasurface.

2.1.1. Schematic structure

The schematic proposed structure of the graphene metasurface is illustrated in *Figure 5*. The unitcell comprises a toroidal ring and an H-shaped pattern of graphene monolayer positionedon the surface of a 500-µm-thick SiO2 substrate with the refractive index n = 1.956 [13]. The graphene-based unit cells are arranged in a periodic array in the x-y plane, as depicted in *Figure 5a*. P represents the periodicity of the array patterns. The spacing distance of the concentric inner and outer graphene rings and the corresponding ring width of the inner and outer rings are designated as g1, w0 and w1, respectively. The gap size of the H-shaped pattern is indicated as g0. In addition, the width of the graphene strip positioned at the center of the inner graphene ring is the same as that of the two graphene rings. The geometrical parameters of the unit cell are described specifically in Figure 4b. As a rule-of thumb graphene films are synthesized by using chemical vapor deposition techniques and can be patterned lithographically to fabricate the designated graphene geometries at controlled locations [14]. One study showed that the laser-induced graphene method can be used in the fabrication of graphene metasurfaces and metamaterials [15].

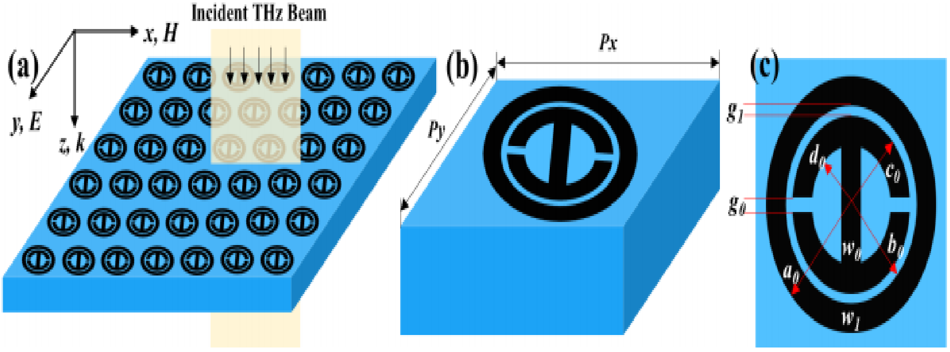


Fig. 5. Schematic diagram of the proposed graphene-based metasurface on SiO2 substrate. (a) Periodicstructure where the incident THz waves with y-polarization is along the z-axis. (b) A unit cell and (c) its top view with geometrical parameters. a0 = 18 μm, b0 = 12 μm, c0 = 11 μm, d0 = 7 μm, g0 = 1 μm, g1 = 1 μm, w0 = 4 μm, and w1 = 6 μm. The periodicity is set to 50 μm in both x and y directions

As proposed by ( Tan et al.) the thickness of monolayer graphene is set as 0.35 nm [16]. The incident plane wave with y-polarization propagates vertically in a direction paralleling to the z-axis to the graphene metasurface. The transmission spectrum as a function of the incident wavelengths and the electric field distributions at resonance peaks are calculated in the fullwave electromagnetic simulator, COMSOL Multiphysics [12]. In order to obtain the response characteristic of the graphene metasurface in the THz domain, wan effective surface conductivity approach was used to characterize the graphene monolayer.

Theoretically, the surface conductivity of the graphene can be forseen within the Kuboapproximation,

being composed of the intra-band and inter-band contribution of the electron transitions. According to the Kubo formula, the corresponding surface conductivity and electron transition contributions are as follows [16 ].

$$\sigma(\omega, \Gamma, \mu_c, T) = \sigma_{intra}(\omega, \Gamma, \mu_c, T) + \sigma_{inter}(\omega, \Gamma, \mu_c, T) \quad (1)$$

where $\sigma_{intra}$ and $\sigma_{inter}$ are expressed as:

$$\sigma_{intra}(\omega, \Gamma, \mu_c, T) = \frac{ie^2 k_B T}{\pi\hbar^2(2\pi v\lambda^{-1} + i\tau^{-1})}[\frac{\mu_c}{k_B T} + 2ln(exp(-\frac{\mu_c}{k_B T}) + 1)] \quad (2)$$

$$\sigma_{inter}(\omega, \Gamma, \mu_c, T) = \frac{ie^2}{4\pi\hbar} ln[\frac{2|\mu_c| - (2\pi v\lambda^{-1} + i\tau^{-1})\hbar}{2|\mu_c| + (2\pi v\lambda^{-1} + i\tau^{-1})\hbar}] \quad (3)$$

In which v = 299,792,458 m/s is the velocity of light in vacuum, λ is the incident wavelength,kB = 1.3806488 × 10–23, J/K is the Boltzmann’s constant, T = 300 K, h¯ = h/2π is the reduced Plank constant, e = 1.602176565×10–19, and C is the electron charge.

In the THz and mid-infrared regime, the surface conductivity of graphene is dominated by the intra-band transition due to kBT |μc|. Therefore, the interband transition is neglected, and the surface conductivity of graphene can be simplified as [16].

$$\sigma = \frac{ie^2\mu_c}{\pi\hbar^2(2\pi v\lambda^{-1} + i\tau^{-1})}$$

3. Discussion

The metasurface presents a behavior of dual-resonance response, which may be favorable for improving the sensing capacity of human cancers. The dual-resonance feature is controlled by adjusting the spacing size, but is unchanged by the gap size of the Hshaped microstructure and the carrier density of graphene [12]. The size and position of the transparency window are highly sensitive to the geometrical parameters of the proposed metasurface and the carrier density of graphene. Thus, the transparency window can be adjusted over a broad frequency range. The sensing parameters are dependent on the cell count, cell type and the position of cells on the graphene metasurface. Such a graphene metasurface achieves an acceptable S, FOM, and Q, and the corresponding values are 1.21 THz/RIU, 2.75 RIU-1, and 2.43, respectively. This may offer new possibilities for exploiting graphene or other 2D materials as sensing materials for cancer diagnosis [12].

*Figure 6* Shows the schematic diagram of the breast cancer cell and their sensing process in a. And it also shows the possible sites of MCF10A and MCF7 on the graphen metasurface. (c,d) The transmission spectra of single MCF7 and MCF10A on different sites in panel (b).

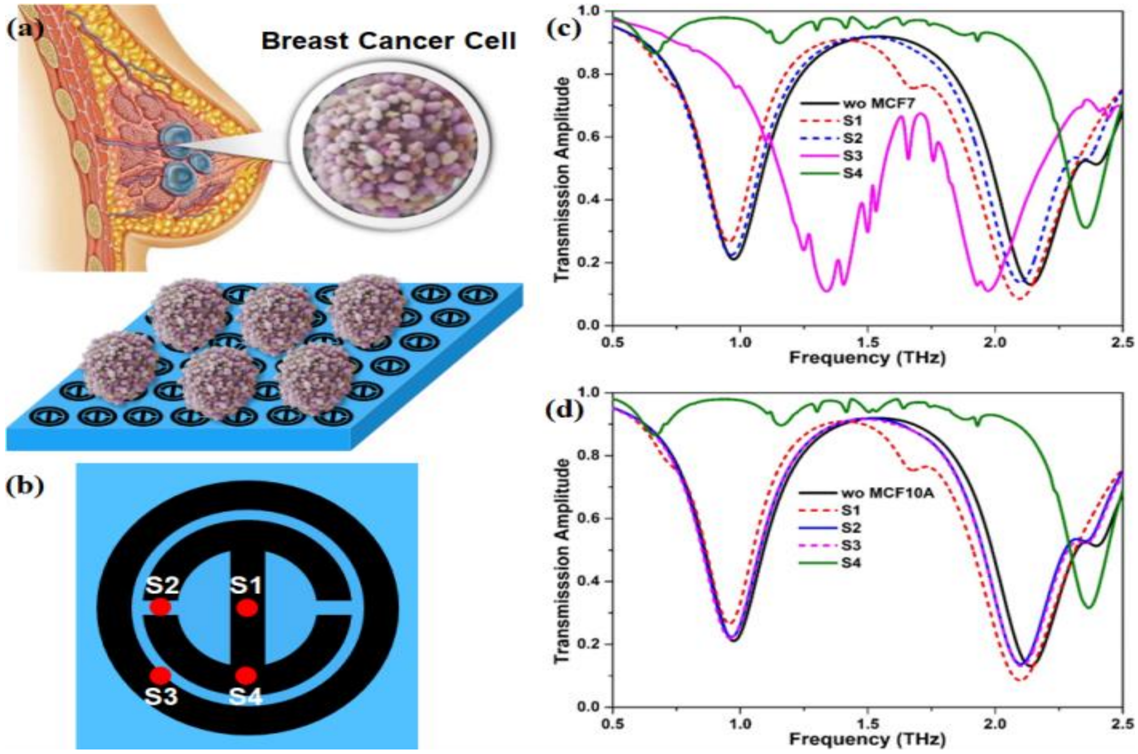


Fig. 6. Schematic Diagram of Antenna Detection of breast cancer

Hearing the Voice of Cancer

Jafari & Hassazadah suggested designing and developing a non-invasive, affordable, biocompatible and miniaturized tools, such as nano-antennas and implantable biosensors that able to detect and record cell-specific frequencies as shown in *Figure* (*7*), will revolutionize this field. Designing transducers to convert the cell-specific frequency to a sound or other measurable signal will accomplish the job Cell-specific frequency measurement, which is derived from cell activity, can be introduced as a biomarker for early detection of cancer [20].

The development of studies aimed at expanding research and designing instruments for detection of the frequency with the goal of establishing a comparative library of cell-specific frequency for all cell types, especially non-communicable diseases as cancer [20].

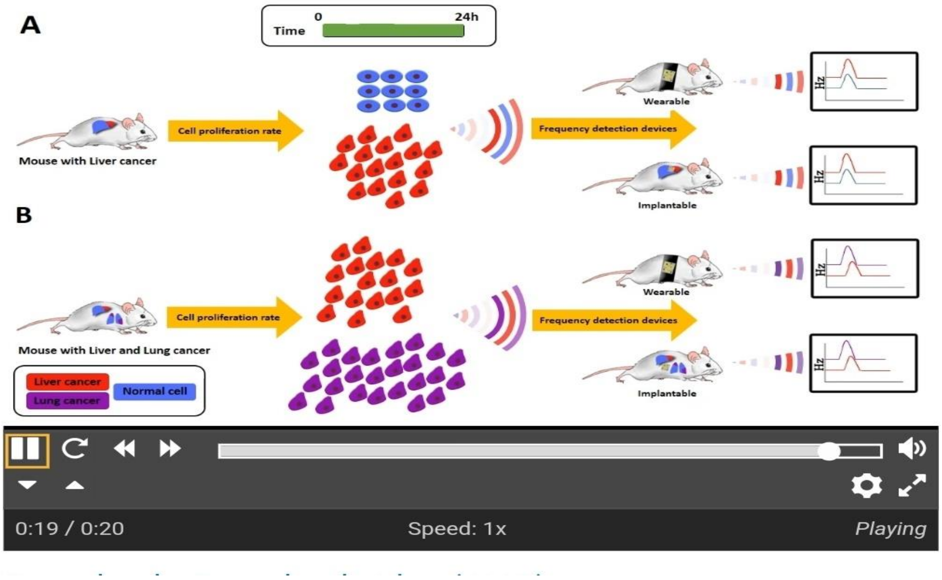


Fig. 7. Principles of cell- specific frequency detection strategies and Methods

4. Conclusion

Nowadays, nanotechnology, especially nano-antennas [21] and implantable biosensors [22; 23], are interestingly encouraged by world health societies to be widely used for health monitoring and point of care (POC) applications as high accuracy, cost-effective, biocompatible and non-invasive methods.

The ultimate goal is to plan the idea of developing modern tools and hallmark for early detection of cancer as one of the most important global strategies for administrating the disease by introducing new parameters with a high-accuracy and in proportion and direct relationship with the activity and functioning of the body, without any affecting exogenous interference [20].

This review was built upon the hypothesis that, frequency is an exogenous element, and the response of target cells to their own specific frequency is considered as an indicator in therapeutic or detection applications as described by Jafari & Hassazadah [20]. Frequency is considered as a marker and intrinsic index of the cell, whose amount is directly related to cellular activity such as the rate of cell proliferation. This can be introduced as a hallmark with the ability to the distinction between normal and tumor cells for cancer detection. We can also obtain information about disease progression by measuring the level of frequency. Such a platform will provide an opportunity to identify the stage of disease or track the frequencies of the metastatic organ [2]. Accurate information about the disease state, and stage of or organ of origin of the metastasis, helps the therapist choose the appropriate treatment protocol, and in addition to reducing the length of treatment and the side effects of the medication, leads to lower treatment costs and increase the probability of patient survival [20].

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