Passive microwave radiometry in biomedical studies

ELSEVIER

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Passive microwave radiometry (MWR) measures natural emissions in the range 1–10 GHz from proteins, cells, organs and the whole human body. The intensity of intrinsic emission is determined by biochemical and biophysical processes. The nature of this process is still not very well known. Infrared thermography (IRT) can detect emission several microns deep (skin temperature), whereas MWR allows detection of thermal abnormalities down to several centimeters (internal or deep temperature). MWR is noninvasive and inexpensive. It requires neither fluorescent nor radioactive labels, nor ionizing or other radiation. MWR can be used in early drug discovery as well as preclinical and clinical studies.

Introduction

The first microwave radiometers were launched on satellites in the 1970s to measure sea surface temperature [1], among other applications for climate and weather remote monitoring. In 1975, Barrett and Myers [2] showed that using a microwave radiometer to identify temperature abnormalities of internal tissue noninvasively could help to detect breast cancer. Subsequently, several studies have confirmed the effectiveness of microwave radiometry in revealing tissue pathologies [3–7]. The term 'internal temperature' is more commonly used by medical professionals in the medical literature, whereas physicists use 'brightness' temperature. Bones, fatty tissue, breast tissue and other organs have a different depth of measurement. Muscles and skin have a high moisture content and a shallower depth.

Currently, in biomedicine, infrared radiation (IR) and microwave radiation are being used for temperature measurements. The main difference between them is the ability to measure either the skin temperature (IR can penetrate only several millimeters deep) or internal tissue temperature (microwaves can record to a depth of 2–6 cm). In recent years, there has been growing interest in microwave radiometry (MWR; see Glossary) technology. There are multiple medical applications targeting the breast [8], brain [9–15], carotid artery [16–20], brown adipose tissue (BAT) activity [21], rheumatoid arthritis [22], joints [23], synovial inflammation [24], veins [25], vesicoureteral reflux [26], the urogenital system [27], back pain [28,29] and diabetic foot [30]. Use of this method in preclinical research has been demonstrated in mice [31]. So far, everyone is convinced that all the heated bodies, and really all the bodies that surround us, emit electromagnetic waves in the microwave range. So, everything around us emits a noise signal where power is proportional

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GLOSSARY

Passive medical microwave radiometry a method of measuring the intensity of intrinsic electromagnetic emission from biological objects in 1–10 Ghz range (organs, tissues, cells, enzymes and other proteins).
Internal (deep) temperature microwave emission power (W) from human body or other biological objects converted to temperature in degrees using Plank's equation.
Skin temperature temperature of the human body measured in infrared spectrum.
Thermal asymmetry a deep or skin temperature difference between left and right organs (breast, kidney, lungs, legs, arms or tissues of organs on left and right side of the human body or specific tissue or organ).

to the temperature. In the microwave range, the power of thermal radiation is linearly correlated to body temperature (Eq. 1).

$$P = k \times Tbr \times \Delta f \quad \text{(Eq.1)}$$

where P is noise power at the output antenna; Tbr is brightness temperature; k is the Boltzmann constant; and Δf is receiver bandwidth. However, recent studies show that, in many cases, non-thermal radiation of living systems in the microwave range also takes place. To better understand the nature of the phenomena several *in vitro* experiments on cell lines [32], enzymes [33,34] and proteins [35,37] were performed. Commercially available equipment: RTM-01-RES (http://www.mmwr.co.uk) (Fig. 1), has been developed for early diagnosis of cancer and other diseases [8,9,28]. Technical details about different types of sensors and antennae have been reported [38–46].

Breast tissue

Breast cancer diagnostics is the most explored application of MWR technology – by visualization and analysis of left and right breast deep and skin temperature (Fig. 2). Nine points on each breast, two axillary points and two reference points should be measured. Each measurement takes 5–7 s (Fig. 3). Microwave emission asymmetry between the left and right breast, and difference between skin (infrared) and internal (microwave) temperature, is used for diagnostics. Thermal asymmetry <0.5 °C indicates a normal state. Larger values could indicate pathology and increases >1 °C could indicate malignant tumors. Hot areas of a breast could indicate inflammation or acute or chronic malignant growth, whereas cold areas of the breast could be caused by adipose involution, local anemia, scars and fibrosis, lipoma or a cyst.

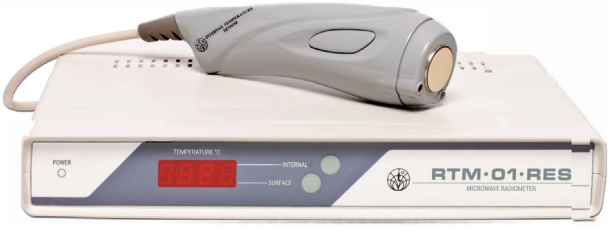

FIGURE 1
The RTM-01-RES device. The device and antenna for human body deep and skin temperature measurements.

The method has ~92 ± 5% sensitivity and ~80 ± 5% specificity for breast cancer detection [8]. This effect could be explained by the Warburg effect and/or other changes in metabolic and signaling pathways [47–49]. By measuring the temperature of specific areas of breast tissue, MWR has a potential role in diagnosis, prognosis and monitoring that has not been widely explored. The technology is safe, easy to apply and is painless. There are already good diagnostic tools for breast lumps. MWR has the added potential to provide more than just a diagnosis and it should be able to provide information on the rate of vascularity of cancer and correlate the rate of proliferation. Changes in internal temperature in a cancer should occur early in treatment, before clinical signs of response are apparent. If we can show that this device can successfully predict response, this will allow early prediction of response in individual patients and would have enormous clinical benefit. Deep tumor temperature changes could be used as an indicator of aggressiveness, precede structural changes and correlate with microvessel density.

Brain

The level of intrinsic radiation of tissues in the microwave range is only 10^{-12} W; and processing such a weak signal is rather complicated. Nevertheless, use of MWR has made it possible to show that regions with thermal anomalies are formed over some areas of the brain in patients with traumatic brain injuries (TBIs). It can also be used to detect regions with a growing tumor and complications after stroke during the process of therapeutic hypothermia [10,11]. Validation of MWR has been performed in animal experiments, in which implanted induction heat sensors were compared with MWR values. In addition, in neurosurgical patients with implanted thermal sensors, recorded temperatures were compared with MRI data. A satisfactory agreement of the data (±0.23 °C) was obtained, which made it possible to conduct a large study of temperature heterogeneity of the brain in healthy individuals, athletes with lung trachea arthrosis and patients with ischemic stroke [9]. Subsequently, a large study of the temperature heterogeneity of the brain in healthy individuals and patients with ischemic stroke was carried out [10]. The results of measuring temperature in stroke patients using magnetic resonance spectroscopy were controversial [50]. Several mechanisms of microwave emission and temperature increase in some areas after brain damage have been proposed. According to current thinking, in concussion or other damage to the brain a rapid internal induction of immune factors occurs. Thus, a neurometabolic cascade develops, which causes the clinical manifestations [10].

Another hypothesis is that microwave emission is caused by albumin and other protein denaturation [35]. Hypoalbuminemia in acute stroke patients is associated with increased mortality and morbidity. A study of 750 patients with acute cerebral infarction found hypoalbuminemia, defined as serum albumin level <35 g/l, in 45.5% of patients. The authors found that low serum albumin was associated with poor prognosis in acute ischemic stroke patients and concluded that serum albumin could be used as a rapid, simple and inexpensive treatment. Currently, the albumin decrease index (ADI) is measured using electrophoresis, which is time and labor intensive. Using MWR to monitor albumin denaturation in damaged brain *in vivo* would allow doctors to assess ADI instantly and to choose appropriate therapies. MWR can also be

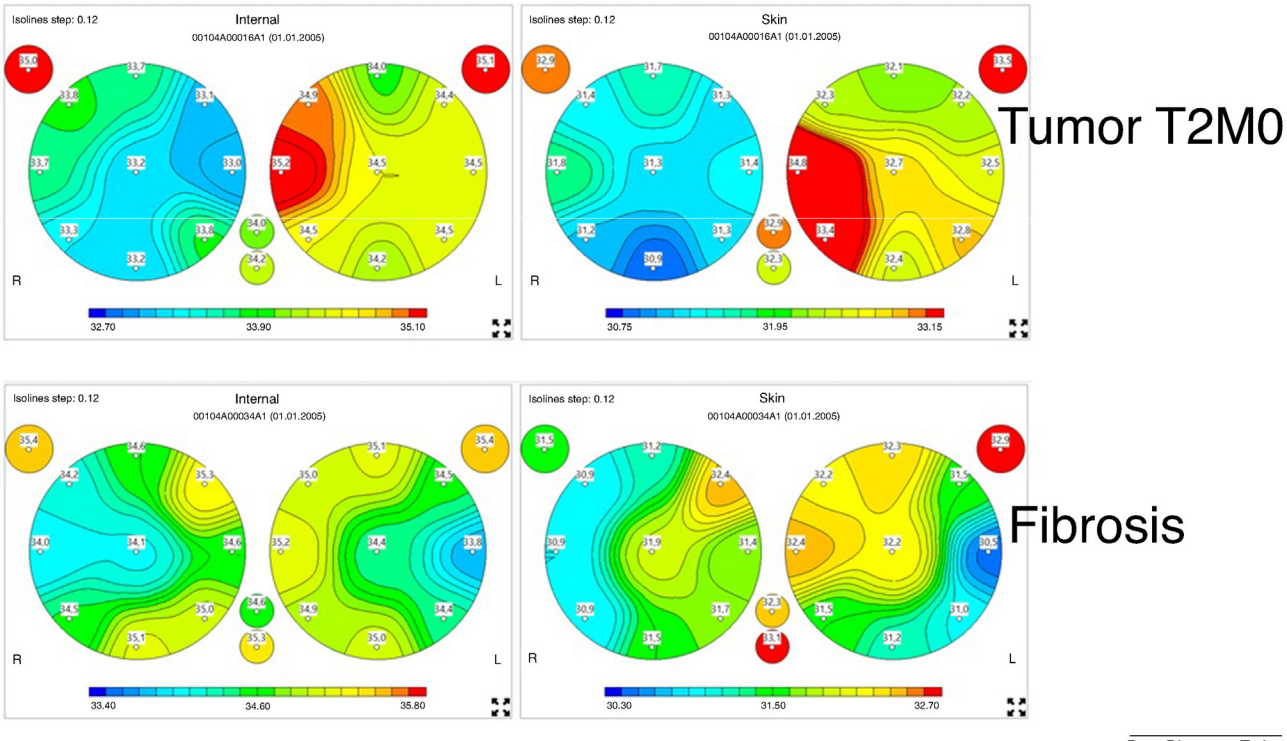

FIGURE 2

Visualization of microwave emission using RTM-01-RES. Deep and skin temperature field. Red color indicates increase of temperature (tumor was confirmed by biopsy in right breast). Green color indicates normal state. Blue color indicates deep temperature decrease as a result of clinically confirmed fibrosis.

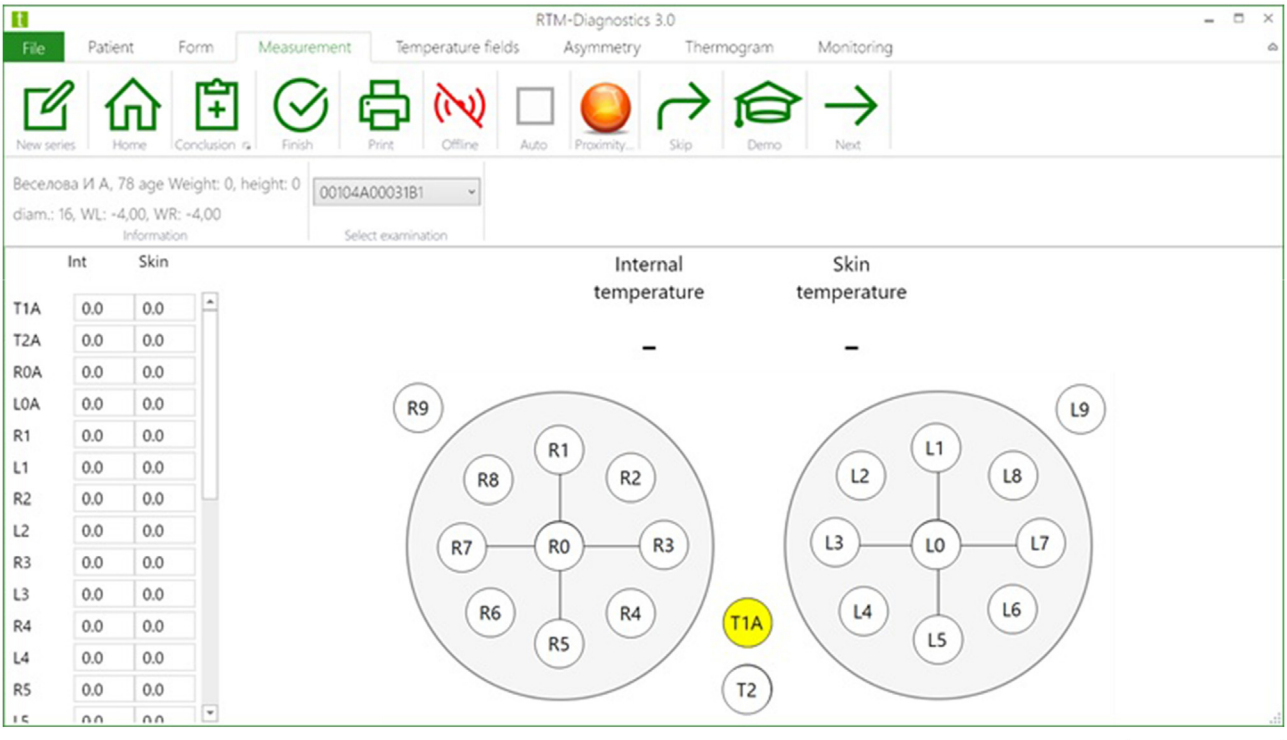

FIGURE 3

Specialized software. Eight points on the left breast (L1–L8) and eight points on the right breast (R1–R8), and four reference points to measure (L9, R9, T1A, T2).

used to monitor albumin degradation after therapeutic intervention [51–53]. Overall, MWR could be used to monitor the course of therapy, determine the extent of brain damage, calculate optimal dosage and type of therapeutic intervention and monitor hypothermia and hyperthermia therapies.

Noninvasive carotid artery

Atherosclerosis of the internal carotid artery is an important cause of disabling ischemic stroke and therefore constitutes a major medical, social and economic issue; although advances in vascular imaging modalities allow to stratify patients based on 'high risk' indications and there is increasing evidence that inflammation is a key factor in the initiation, progression and destabilization of plaques. MWR is used to measure the level of inflammation in carotid arteries [16,17]. In a recent study [18], 300 patients from three centers with significant coronary artery disease were included in this study. Both carotid arteries were measured using ultrasound and MWR for at least 2 years. Temperature difference (ΔT) was defined as maximal minus minimal deep temperature along each carotid artery. Fatty plaques exhibited higher internal temperature heterogeneity compared with mixed and calcified plaques. In recent publications [19,20] it was shown that MWR could contribute significantly to primary and secondary prevention of stroke.

Back pain

Pain is highly subjective in nature. The measurement of intensity is primarily dependent on patient sensation. The correlation between the pain syndrome and the results of MWR was reported in the diagnosis of muscular-joint disorders of cervicogenic headache [29]. In the area of the projection of back pain, the temperature of deep structures, in comparison with other areas, could be elevated, reduced or normal. So, back pain syndromes can be assessed by MWR. This enables more-precise diagnosis including localization of pain and discrimination of its intensity. It was shown that temperature increases with low-back pain (LBP) severity and MWR allows the objective assessment of the magnitude of clinical symptoms [28]. Recently, clinical studies of 48 LBP patients showed that internal temperature is highest in patients with LBP who report the most severe pain and in whom MWR was performed within the first week after the patient experienced an exacerbation. It was shown that MWR allows an objective assessment of the magnitude of clinical symptoms in patients with LBP and that the method shows promise for measuring the severity of pain and for predicting the duration of exacerbation and time for recovery [28].

Venous thrombosis

There are multiple publications and patents on this disease [25]. The MWR measurements are conducted at 12 points for >100 patients. The temperature is sequentially measured at symmetrical points on the posterior surface of the legs of the patient in the supine position and standing with a surface infrared sensor and a deep microwave sensor. The diagnosis is made on the following criteria: the axial gradient of deep temperatures is reduced in a standing position and is absent in a prone position; decrease and absence of an axial gradient of deep temperatures associated with an increase in deep temperature along the medial surface of the lower leg in the middle and lower third sensitivity 100% and specificity 81.3% [25]. It was shown that MWR can be used for early-stage diagnosis of acute thrombosis and to observe the dynamics of the inflammatory process.

Diabetic foot

Diagnosis of vascular involvement in diabetic foot ulceration (DFU) remains challenging. A proof-of-concept, multicenter feasibility study of MWR for noninvasive differential diagnosis of arterial disease in diabetic patients with suspected critical limb ischemia (CLI) in subjects with DFU was carried out. Eighty participants [30] were divided into four groups (group N: normal control subjects; group DN: participants with diabetes and verified neuropathic ulcers without vascular involvement; group DC: participants with diabetes and CLI and group NDC: participants with CLI without diabetes). Vascular disease was confirmed with angiography. The mean deep tissue temperatures at various predetermined foot sites were measured. Temperatures recorded in the vicinity of the foot ulcers of participants with diabetes and CLI were similar to those with CLI without diabetes but significantly lower than in subjects with neuropathic ulcers without vascular involvement and normal controls (group DC: 29.30 ± 1.89 °C vs group NDC: 29.18 ± 1.78 °C vs group N: 33.01 ± 0.45 °C vs group DN: 33.39 ± 1.37 °C). According to receiver operating characteristic (ROC) analysis, cut-off temperature value to diagnose CLI was 31.8 °C, with a sensitivity of 100% and specificity of 88.37%. Tissue temperatures in the vicinity of the ulcers were significantly lower in participants with CLI, with or without diabetes, compared with nonischemic controls.

Brown adipose tissue

Recently, MWR technology was used to monitor BAT activity and identify therapies for diabetes, metabolic syndrome, obesity and aging [54,55]. It was shown that activation of BAT is a powerful remedy to ameliorate hyperlipidemia and protect from atherosclerosis [56]; and that brown fat activation reduces triglyceride and low-density lipoprotein (LDL) levels and attenuates diet-induced atherosclerosis progression. The mean radiometry result collected during BAT maximization was 33.2 ± 1.5 °C at points designated as active and 32.7 ± 1.3 °C at points designated as inactive. It was shown that MWR could be used to detect active BAT without a radiotracer injection, and noninvasively [21].

Urology

MWR was used to determine the microwave emission at nine points for the left and right kidney in the upper, intermediate and lower segments, which increases the sensitivity diagnosis of pathology [27]. First, MWR tests were performed in 30 healthy individuals and then in 86 patients with acute pyelonephritis. Healthy volunteers demonstrated the absence of thermal asymmetry, the temperatures of the kidneys differ with $34 \pm <0.3$°C. This temperature was considered as the physiological normal. In acute nonobstructive pyelonephritis, the thermal asymmetry average is 0.9°C; or 1.5°C among patients with acute obstructive pyelonephritis. These data provide evidence of MWR value at the early stages of the inflammatory process in renal tissue, when ultrasound has not yet detected structural changes in the renal parenchyma (only 64%). There were similar results in studies of 93

patients with acute nonobstructive pyelonephritis: 55 with acute obstructive, 19 with acute purulent and 140 without urological disease. The increase in deep temperature in acute purulent obstructive pyelonephritis was >1.3°C and in acute obstructive pyelonephritis it was 0.9–1.3 °C. In healthy individuals the difference between the kidneys was <0.3 °C. For prostate mean temperatures in the suprapubic area in patients with acute prostatitis it was 37.1 ± 0.2 °C, for prostate abscess it was 38.0 ± 0.3 °C and for prostate cancer it was 36.4 ±0.2 °C. Healthy individuals in the older age group have decreased deep temperature in the perineal area from 36.4 ±0.2 °C (age 18–25 years) to 36.0 ±0.2 °C (age 66–75 years). Studies show that MWR could be used for diagnostics in different forms of acute pyelonephritis, renal colic and acute inflammatory diseases of the prostate [27].

Whole-body scan

The biological aging markers [57] were revealed in the form of MWR thermal asymmetry in the projection zones of the following organs: the thyroid gland eight points; the liver 18 points; the kidneys nine points on each side; the spine (along the median and paravertebral lines in the cervical and thoracolumbar sections) 48 points; knee and hip joints nine points on each side. An average temperature was obtained for each zone. The average deep temperature, taken as a standard, was compared with the temperature at each point in the zone. When the value of the indicator was 0.6–1.0°C a dysfunctional type of thermal asymmetry was determined. The method enables identification of individuals with an accelerated rate of aging and the individualization of therapeutic measures in this group of patients.

Preclinical applications

A special antenna was designed for preclinical studies to acquire fundamentally new information about the processes of metabolism, perfusion (microcirculation) and cellular kinetics in malignancies in animal models [31].

Cell line applications

Microwave emission (brightness temperature) of a suspension of cells of follicular carcinoma of the thyroid gland during necrosis was monitored. It was shown that, when necrosis occurs in a cell suspension, the microwave emission increases, whereas the IR temperature does not change in the infrared range [32]. It was shown that cell necrosis could lead to a non-equilibrium state of the medium, expressed in a change in the microwave emission ratio. The authors hypothesized that the effect can be associated with the restructuring of the intracellular and intercellular cells. Cell necrosis in the microwave and infrared range can be monitored and used to control the dynamics of necrosis.

In vitro applications

Using smaller microwave antennae with the USB powered sensor RTM-01-RES and a specialized antenna (Fig. 4), a microwave emission change of 1.5–2 °C for aqueous albumin solution was found during its thermal denaturation. In addition, protein denaturation kinetics were determined [33]. The same phenomena were observed during chemical denaturation of egg white, which is well-known to contain 10% protein including albumin. The 2 °C increase of microwave emission was observed during the first 20 s after alcohol addition, whereas infrared temperature rose much slower, taking minutes [36].

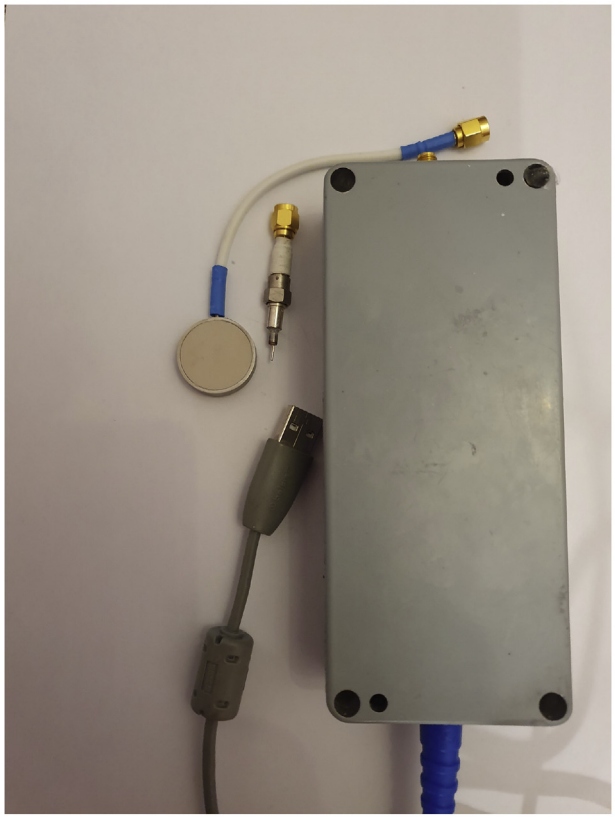

FIGURE 4

Microwave passive antennae (disk and wire) for *in vitro* and cell culture experiments. The microwave sensor with USB connection to a laptop.

Microwave emission has been observed as well – in the process of hydroxylation of enzyme CYP102 A1 [34]. The 0.5–2 °C increase within 10–20 s in multi-pulse mode follows the addition of co-substrate NADPH (0.2 mM) to the system containing lauric acid (0.5 mM), and enzyme 10^{-10} to 10^{-8} M. A single-pulse mode (synchronized pulse radiation) at 10^{-6} M concentration of enzyme was observed. This effect could be explained using biomaser hypothesis. Also, the synchronized pulsed radiation could indicate the generation of qubits in a biological system [34]. The similar 0.5 °C microwave emission increase in passive mode and 2 °C in excitation mode was observed in a solution of horseradish peroxidase (HRP). Luminol (10^{-3} M) was added to the solution of HRP (10^{-6} M) and oxidization of the H_2O_2 substrate (10^{-4} M) within 20 s in excitation mode has been observed [33].

Each HRP and CYP102 A1 reaction is accompanied by the fluctuation of the protein globule with approximately the same amplitude (in the order of 0.08 nm). The microwave emission effect could be explained by rotational transitions of molecules and ions excited during catalysis (OH^-, H_2O and H_2O_2) in GHz (the change in the ratio between para- and ortho-isomers of H_2O in GHz), with increased mobility of the protein globule during the catalytic reaction [33,34].

MWR does not require any isotopes or fluorescent labels. It is simple and low-cost in comparison with calorimeters and optical

spectrometers and provides new opportunities for R&D studies. Measurements can be recorded every 4 s and time series data can be analyzed, which is very important for enzyme kinetics studies. The method could be particularly useful in enzymatic and metabolic research, and for inhibitor screening. Microwave emission could be used as a direct readout to measure enzyme–substrate binding and inhibition effects. Further experiments with changing substrate and inhibitor concentrations are required to calibrate the method for particular biochemical systems. It is possible to determine kinetic parameters of biochemical processes. So, the method could be used to obtain data for modeling of biochemical reaction and quantitative dynamics modeling of cells, tissues and organs.

AI for microwave radiometry: big data

Large volumes of microwave data can be generated inexpensively in comparison with other temperature measurements. An expert system has been developed to analyze these data [58,59] and, recently, AI deep learning has been applied to provide advice regarding the diagnosis of breast cancer. The dataset consists of 363 pairs of mammary glands of which 77 are classified as healthy or low risk (labeled as class 0) and 286 classified as potentially cancerous or high risk (labeled as class 1). The Deep Neural Networks (DNN) was able to obtain a G-mean loss of 0.2843, accuracy of 0.7703, sensitivity of 0.8103 and specificity of 0.625. The prediction will be increased when more data will be used in a training set. A human annotated dataset >2000 healthy and diseased breasts is under construction. Recently, we initiated a worldwide initiative to collect MWR data from patients and healthy people.

Concluding remarks

It was shown that MWR has many advantages compared with IR thermography (IRT). MWR is not as expensive as fMRI. It benefits from passive sensors, a lack of radiation, no side-effects and high sensitivity. It can detect pathologies deep in the human body at an early stage and visualize and analyze results with advisory diagnostics software. It does not require any consumables. MWR could be considered the 'poor people's fMRI'. This is a reason why MWR is very popular in developing countries but not in the West.

We have demonstrated that MWR can be used at all stages of the pharmaceutical R&D process, and as a rapid and cost-effective clinical diagnostic, as well as to monitor effects of therapies. As a companion diagnostic tool, MWR can increase the informativeness of existing X-ray and ultrasound diagnostics at the early stages of diseases. The high-resolution data obtained could be used for systems biology, quantitative systems pharmacology and deep neural network models to make predictions. Such models could be used for preclinical research, clinical trials, better diagnostics and monitoring effects of treatment.

Recently, the FDA issued a warning that IRT cannot be used as a diagnostic tool for breast cancer, because IR can only measure skin temperature [60]. MWR is an alternative technology that could be used for breast cancer diagnostics and screening programs from childhood. The technology is currently popular among traditional and holistic medicine practitioners, as well as beauty salon professionals. With the proven hardware, associated AI software and more clinical evidence we expect MWR will be used worldwide in the near future. More clinical studies and collaboration between academia and the pharma industry are required in different therapeutic areas.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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