Report on data user requirements for dielectric / thermal data and metadata

MyWAVE Working Group 3

Authors:

Giuseppe Ruvio

Martin O'Halloran

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Dielectric and thermal data and metadata

European citizens are rapidly approaching a very significant demographic cross-road: an increasingly aging population, suffering from a wide range of non-communicable diseases, will push European healthcare services to their limit over the next 60 years. Citizens aged 65 years or over will account for 28.7 % of the EU-28's population by 2080, compared with 18.9 % in 2016, and the non-communicable diseases suffered by older citizens will impose the greatest economic burden on global health. Adding to this, the share of the European population of working age is expected to decline steadily through until 2050. Within these economic constraints, it will not be possible for European states to raise their health spending in line with population ageing; instead European states will be required to maximise the impact of their available budgets by developing new low-cost diagnostic and therapeutic modalities, and streamlining their translation into the public health space. One of the most promising areas of medtech development in recent years is novel electromagnetic (EM) medical devices, and this work has been led by European researchers. However, uncertainty in the dielectric and thermal properties of tissue is currently severely restricting this potential of the sector.

Within the context of an aging population in Europe and an exponential growth in healthcare costs, EM therapeutics and diagnostic technologies (also called "theranostics") provide a very attractive solution, since they are low cost, non-ionising and largely non-invasive. EM imaging ranges from low-frequency Electrical Impedance Tomography (EIT) to high-frequency Microwave Imaging (MWI). EIT systems have been developed for a wide range of clinical applications from lung-function monitoring to brain, breast and cervix imaging, with a number of commercial systems now available[1]. MWI uses higher frequencies than EIT (typically in the GHz range), and therefore produces higher-resolution images at shallower tissue depths. MWI has mainly been targeted at breast and neuro-imaging applications. Based on the low-cost nature of MWI systems, and the fact they are completely non-invasive and non-ionising, European companies are now beginning to commercialise the technology.

From a myWave therapeutic perspective, EM fields are used to treat a wide variety of diseases, ranging from cancer to Parkinson's disease, and from epilepsy to depression. The frequencies employed range from less than 1 Hz to greater than 1 GHz, with the treatment mechanism matched to different physical phenomena at the various frequency bands. At low frequency, neuro-modulation and neuro-rehabilitation devices operate in the range of 0.5 Hz – 1 kHz. These recently-developed devices target clinical conditions by carefully modulating electrical signals within the body. Neuro-modulation is currently being used to treat Parkinson's disease,

dystonia and essential tremor[1]. Recently, it is also being studied as a novel non-invasive method to treat epilepsy[7] and obesity[2] and to relieve depression[3] and pain[4].
At higher frequencies (MHz range), EM fields are used to treat cancerous tumours that are resistant to standard treatments. Medium-frequency hyperthermia (HT) devices alter the temperature in the body to just above a normal physiological level to sensitize tumour cells, making the cancerous tissue much more susceptible to chemotherapy and radiotherapy. Targeted HT has been demonstrated to be particularly effective in the treatment of cervical cancer, breast cancer, cancers of the head and neck and sarcoma in adults[5],[6], and germ cell tumours in young children[7]. Radiofrequency ablation (RFA) and microwave ablation (MWA) are two promising treatments for liver, kidney and lung cancer[8],[9]. Both methods cause the direct coagulation of disease, and the high frequencies allow for high selectivity in terms of targeting the cancerous tissue while protecting the surrounding healthy tissue. MWA is a more emerging technology, with the focus on further increasing the targeted heating volume while protecting surrounding healthy tissue. Irreversible Electroporation (IRE) is also gaining significant interest in recent years, as a technology that could provide the same therapeutic benefit as thermal ablation, without the thermal tissue scarring. Overall, each of these therapeutic techniques has shown very significant promise, with the real potential to be applied to an even wider range of clinical applications. The low cost and largely non-invasive nature of the therapeutic technologies make them an attractive prospect for further investment, particularly in the context of an aging European society, and ever-increasing health care costs.
Underpinning the development of all these technologies is the need for good knowledge of the underlying dielectric and thermal properties of human tissue. These properties can be incorporated into highly accurate computational models, and the generated preliminary data can be used to assess the technical risk of the proposed medical device or treatment[10]. Without knowledge of the dielectric or thermal properties, engineers would instead be forced to develop a prototype system and complete costly pilot patient studies to gather the same preliminary data**.** Very few medical device companies (in particular European SMEs) can afford the cost of such a preliminary clinical study, and therefore in situations where dielectric data is missing or there is uncertainty as to the true value, new medical device development is stagnating.

While the dielectric properties of biological tissue have been examined for decades[11], the majority of the studies have been narrow in focus, resulting in a somewhat incomplete dielectric landscape. In efforts to address EM dosimetry (safety) concerns, the dielectric properties of healthy tissue in the radio-frequency (RF) and microwave (MW) were the subject of many historical studies[12]. This focus on dosimetry defined the experimental approach, including the tissue selection, measurement method, and frequency range, amongst many other experimental parameters. These studies have been incorporated into dielectric repositories, and over time

have become the *defacto* standard for EM modelling and therefore EM medical device development. Gaps in these repositories (thermal and dielectric) act as a clear barrier to EM medical device development and provide a certain motivation for the re-examination of these critical tissue properties.

Hyperthermic treatments

EM-based hyperthermic have been used for decades in clinical practice to deliver controlled electromagnetic energy into targeted tissues or body regions and address several indications. While different treatments use different frequencies and leverage on different induced physical phenomena, they are all modelled and designed around a thorough physical characterisation of the targeted complex biological tissue including a dielectric and thermal description.

The following sections list those hyperthermic treatments that have been adopted in the clinical environment including both more established and emerging techniques.

Hyperthermia

Hyperthermia, one of the oldest forms of cancer treatment involves selective heating of tumour tissues to temperatures ranging between 39 and 45 °C. Recent developments based on the thermo-radiobiological rationale of hyperthermia indicate it to be a potent radio- and chemo-sensitizer. This has been further corroborated through positive clinical outcomes in various tumour sites using thermo-radiotherapy or thermo-radiochemotherapy approaches. Moreover, being devoid of any additional significant toxicity, hyperthermia has been safely used with low or moderate doses of reirradiation for retreatment of previously treated and recurrent tumours, resulting in significant tumour regression[10]. Hyperthermia treatments are currently delivered across a broad range of configurations and applicators to better adapt to the anatomy of the treated body part.

The table below summarises different hyperthermia typologies together with corresponding clinical indications.

Treatment typology	**Clinical indications**
Superficial Hyperthermia (SHT)	Breast and superficial tumours

Deep Hyperthermia (DHT)	Breast and cervix tumours
Interstitial Hyperthermia (ISHT)	Head, neck, pelvis and cervix tumours
Intravesical Hyperthermia (IVHT)	Bladder tumours
Intracavitary Hyperthermia (ICHT)	Head, neck and rectum tumours

A dielectric and thermal characterisation of the irradiated region is fundamental to identify the specificity of the diseased tissue against the interfacing healthy region. Moreover, within large tumour masses a specific contrast may be also characterised between a more necrotic core and a perfused periphery. On one hand this characterisation informs the design of the system and in particular of the applicator and the focal mechanism. But it also enables a more accurate pre-treatment planning which is a fundamental requirement of the clinician and key to clinical acceptance and market success.

Tissue metadata is required to combine dielectric and thermal data together with fundamental information of the measurement protocol and full description of the sample processing. Given the different dielectric and thermal profile of healthy and diseased tissues, datasets are needed from a large number of tumour samples possibly including large masses with necrotic cores. This can be achieved from ex vivo tissue samples excised during surgical procedures or in vivo samples from animal models embedding controlled tumour growth.

Radiofrequency Ablation (RFA)

Radiofrequency ablation is a medical procedure in which part of the electrical conduction system of the dysfunctional targeted tissue is ablated using the heat generated from medium frequency alternating current (in the range of 350–500 kHz). Radiofrequency current does not directly stimulate nerves or heart muscle and can therefore often be used without the need for general anaesthetic enabling procedures in the outpatient setting, using either local anaesthetics or conscious sedation anaesthesia.

In monopolar RF ablation, the patient is part of a closed-loop circuit that includes an RF generator, an electrode needle, and a large dispersive electrode (ground pads). An alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the electrode, since the tissue ions attempt to follow the changes in direction of the alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode[13] [14].

The thermal damage caused by RF heating is dependent on both the tissue temperature achieved and the duration of heating. Heating of tissue at 50–55°C for 4–6 min produces irreversible cellular damage. At temperatures between 60°C and 100°C near immediate protein coagulation is induced, with irreversible damage to mitochondrial and cytosolic enzymes as well as nucleic acid-histone protein complexes[15].

RFA has grown over the last three decades in parallel with interventional cardiology and oncology. The table below summarizes the numerous clinical indications treated with RFA.

RFA modality	**Clinical indications**
More common percutaneous treatments	Liver, kidney, bone, thyroid and lung tumours
More common endoscopic treatments	Atrial Flutter (Afl), Atrial Fibrillation (AF), Supraventricular Tachycardia (SVT), Atrial Tachycardia, Multifocal Atrial Tachycardia (MAT) and some types of ventricular arrhythmia; varicose veins, Barrett's oesophagus, uterine fibroids
Emerging laparascopic/endoscopic treatments	lung, pancreas, bile duct tumours, renal sympathetic denervation
Superficial	Aesthetics dermatology

A thorough knowledge of the dielectric properties of targeted and surrounding tissue is fundamental to inform the design of the applicator and more importantly to assist the pre-treatment planning providing suitable power/time settings for the desired ablation. Moreover, as RFA is highly vulnerable to the presence of blood vessels and airways acting as heat-sink, a thermal characterisation of targeted tissues is paramount. As more complex operating scenarios are proposed for RFA, more importance has been given to the availability of reliable metadata incorporating dielectric/thermal properties together with information on the measurement protocol and tissue processing. Larger sets are required for tissues with high perfusion and heterogeneity like in the lung. Additionally, as during the ablation process a dramatic irreversible tissue change occurs (i.e. dehydration, coagulation), data should be achieved at several time-points of the treatment.

Microwave Ablation (MWA)

Microwave ablation is a fast-growing hyperthermic treatment option for unresectable malignancies. From pioneering percutaneous microwave applicators to treat liver lesions, nowadays more suitable clinical indications are emerging. The spread of microwave ablation applicators in clinical practice is growing alongside with the requirement for minimally-invasive procedures.

Microwave radiation manifests as high-frequency electromagnetic wave which induces frictional heating from its interaction with polar molecules[16]. Water molecules present polarity due to the hydrogen side of the molecule carrying a positive charge and the oxygen side carrying a negative charge. When microwave radiation is applied to water molecules, rapid oscillations (between two and five billion times) occur to align the molecules with the oscillating microwave field. The induced rotation at molecular level generates heat. For properly controlled power/duration settings of the microwave radiation, the induced heat generation leads to cell death through coagulation necrosis, which is instantaneous and continue until the radiation is stopped. Another minor mechanism of heat generation is due to ionic polarization which occurs when ions move in response to the applied microwave electric field. The ionic polarization causes collision with other ions, converting kinetic energy into heat. However, the heat component generated by this mechanism is mitigated by intra-tissue attenuation. Soft tissues present high water content and respond well to microwave radiation. When soft tissue interacts to an intense microwave field that generates heating corresponding to local

temperatures of 50–55 °C for 4–6 min, irreversible cellular damage occurs. At temperatures between 60 and 100 °C nearly immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100–110 °C, tissue vaporizes and carbonizes.

Thermal ablation of solid tumours is defined as the direct application of therapies based on temperature-induced coagulation to achieve complete tumour destruction. Although its principle has been known for more than 100 years[17], microwave coagulation was only introduced in the early 1980s to achieve haemostasis along the plane of transection during hepatic resection, but rapidly expanded into the area of tissue necrosis to treat unresectable hepatic malignancies[18]. Nowadays, clinical practice has been witnessing a rapid expansion into image-guided minimally invasive microwave ablation (MWA) techniques to destroy focal tumours in multiple organ sites [19], [20].

The local interstitial deployment of microwave radiation inside a targeted tissue for ablation purposes is performed by using needle-shaped antennas mainly operating at 2.45 GHz. The treatment is more commonly delivered percutaneously and is today an established treatment modality for liver, kidney, thyroid and bone tumours. But it is also used to treat lung tumours for the large inoperable patient population. However, emerging interventions in laparoscopic or endoscopic settings are also proposed to facilitate access in more remote hidden regions (e.g. pancreas, bile duct, adrenal glands tumours, and polyps in the gastrointestinal tract) and/or to prevent pneumothorax while treating lung cancer.

Dielectric and thermal characterisation of the targeted tissue and its proximal region inform the design of the MWA applicator to ensure impedance matching and optimum power delivery across all tissue stages during ablation. Moreover, dielectric and thermal properties data are fundamental to enable pre-treatment planning in terms of suitable power and time settings for the desired ablation zone. This is currently based on charts obtained from testing in ex vivo animal samples. Limitations of this approach are significant due to the divergence between the targeted diseased and perfused tissue and the ex vivo healthy animal sample. The lung is a particularly difficult scenario because of its heterogeneity and the sharper dielectric contrast between healthy and tumour tissue.

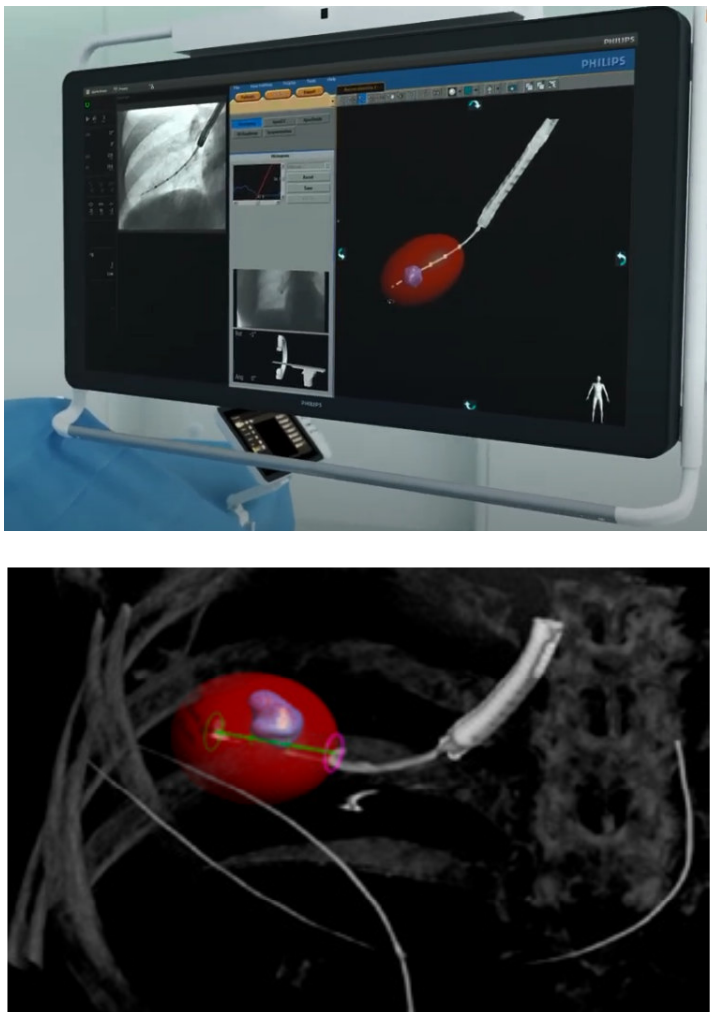

Figure 1. Philips Azurion Lung suite integrating ablation charts into Cone-Beam Computed Tomography (CBCT) and Fluoroscopy Imaging [21].

Improved metadata sets integrating dielectric/thermal measurements together with protocol and complete tissue description are required for both healthy and diseased tissues. Larger sets are required for tissues with high heterogeneity like in the lung. Additionally, as during the ablation process a dramatic irreversible tissue change occurs (i.e. dehydration, coagulation), data should be achieved at several time-points of the treatment. Suitable metadata will finally mitigate the requirement of sophisticated imaging machinery like CBCT.

Electroporation/Pulse Electric Fields

Irreversible Electroporation involves applying a strong external electric field to cells to increase transmembrane potential (voltage) and induce the formation of permeable pores in the cell

membrane. This membrane provides the structure to cells and is composed of two layers of lipid molecules. This membrane regulates intra and extracellular solute transport within the cell. In a stable static situation, the cell has a negative charge distribution on the inner surface of the membrane and a positive charge on the outer surface of this membrane. If we apply a large external electric field to a cell, the DC current passes around the cell rather than through it. This means the current density outside the cell is larger than the current density inside the cell, and creates a large potential difference between the inside and outside of the cell membrane. If the potential difference becomes large enough, the cell membrane starts to break down/rearrange itself and nano-scale holes are created in the cell membrane. Since the membrane self is now breached, the cell itself must work very hard to maintain normal transmembrane ionic differences (e.g. normal voltage difference between inside and outside the cell membrane).

If the external electric field is reduced, the nano-scale pore in the cell will close and the cell with return to normal function (Reversible electroporation); however, if the electric field is maintained for a sufficient amount of time the ionic pumps in the cell are unable to compensate for the sheer number of ions passing through the breached cell membrane, the cell becomes energy depleted. The cell will eventually die and will be later mopped up by the immune system later (Irreversible electroporation).

It is unclear from the literature if apoptosis or necrosis play the key role in IRE-induced cell destruction. This difference is important since apoptosis induces innate cellular regeneration and requires less time for tissue healing and recovery than necrosis. Additionally, apoptosis causes less fibrosis in the ablated area than necrosis, which would help prevent further damage to ablated organs. Encouragingly recent studies have identified apoptosis biomarkers in IRE-ablated tissue.

Electroporation can be achieved using direct current (static or pulsed), AC current, or a combination of both. There is no consensus on the exact threshold electric field required for IRE, but the recommended values of the field strength range from approximately 200 to 1000V/cm. Some researchers have examined the question of the required electric field threshold under ideal conditions (bipolar electrodes into dry cardiac tissue – dry tissue used to remove the issue of conduction through the blood). These studies have estimated a minimum delivered threshold field strength of 268V/cm required for IRE, assuming a tissue impedance of circa 160 Ω cm . The general approach, requirements and clinical risks associated with each energy delivery approach are described in the figure below.

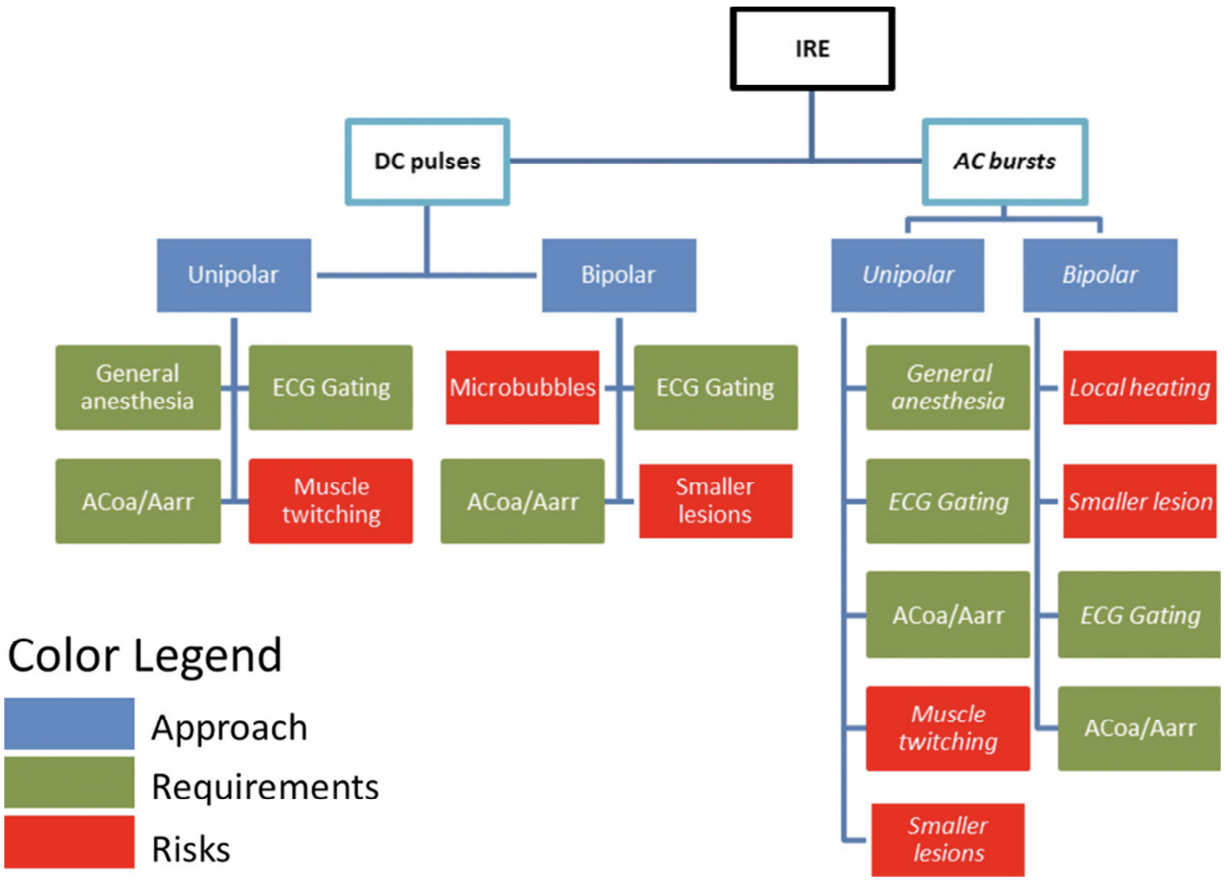

Figure 2. General approach, requirements and clinical risks associated with each energy delivery.

Electroporation is gaining significant momentum from industry since it provides an exciting non-thermal alternative to both microwave and RF ablation. Industry is particularly interested in Irreversible Electroporation (IRE) for cardiac ablation for the treatment of Atrial Fibrillation. The advantage of IRE is it provides the same therapeutic effect without the scarring associated with thermal ablation. The risk of clot formation with thermal ablation is also reduced. Electroporation can be delivered at field strengths >300V/cm, and can involve either DC or AC. AC provides the extra benefit of reducing the risk of unwanted cardiac muscle contraction during the ablation procedure. The area can be summarised with the key points below:

- Move of many MNEs to the use of non-thermal therapies for cardiac ablation, with a particular focus on Irreversible electroporation (IRE).
- IRE also being used clinically for oncology drug delivery.
- Dielectric/Electrical properties of tissue required to predict E-Field distribution in-vivo.

- Localised dielectric property information required (e.g. separation of organs into distinct regions, such as the dielectric properties of the pulmonary veins of the heart (rather than global average values for the heart tissue or vein tissue).
- Need knowledge of average dielectric values plus standard deviation (both within patients and between patients). This data can be used to test the robustness of the solution.
- Thermal properties required to ensure IRE temperatures do not exceed clinically-acceptable threshold of 5-10 degrees °C.

Dielectric & thermal data and metadata centres in the MyWAVE network

The table below summurises the tissue testing capabilities of dielectric and thermal properties within the MyWAVE Action. Although we are aware that more Action members have been working trying to implement more testing facilities and protocols, the table helps to map out the laboratories where tissue testing is already a well-established part of current research activities.

Summary of Dielectric & thermal data and metadata centres in the MyWAVE network											
Institution	**Tissue type**	**Animal samples**	**Human samples**	**Normal tissue**	**Diseased tissue**	**Ablated tissue**	**Dielectric measurements (bandwidth, technique/tool)**	**Dielectric measurements during hyperthermia**	**Dielectric measurements during ablation**	**Thermal properties measurements**	**Protocol in place for destructive tests (like ablation) on excised human tissue**
Erasmus MC[1] (NL)	Breast	Y	Y	Y	Y	N	4MHz - 3 GHz, open-ended coaxial probe DAK-12	Y	N	Y	N
	Blood	Y	Y	Y	N	N	4MHz - 3 GHz, open-ended coaxial probe DAK-12	N	N	Y	N
	Lung	Y	Y	Y	Y	N	4MHz - 3 GHz, open-ended coaxial probe DAK-12	N	N	Y	N
	Muscle	Y	Y	Y	Y	N	4MHz - 3 GHz, open-ended coaxial probe DAK-12	Y	N	Y	N
	Fat	Y	Y	Y	Y	N	4MHz - 3 GHz, open-ended coaxial probe DAK-12	Y	N	Y	N
University of Malta (MT)	Lung	Y	Y	Y	N	Y	500-50 GHz, Slim probe	N	Y	N	In progress
	Liver	Y	Y	Y	N	N/A	500-50 GHz, Slim probe	Y[2]	N/A	N/A	N/A
	Blood	N	Y	Y	N	N	500-50 GHz, Slim probe	N	Y	Y	N
	Red blood cells	N	Y	Y	N	N	500-50 GHz, Slim probe	N	N	N	N
	Plasma	N	Y	Y	N	N	500-50 GHz, Slim probe	N	N	N	N
	Muscle	Y	Y	Y	N	N	500-50 GHz, Slim probe	N	N	N	N
	Fat	Y	N	Y	N	N	500-50 GHz, Slim probe	N	N	N	N

[1] Available Equipment: 1.5T MRI scanner; TEMPOS thermal property analyzer, equipped with SH-3 and KS-3 sensor; Schmid & Partner Engineering DAK-12 Probe

[2] Temperature-dependent measurements of the complex permittivity were performed using heating methods that do not involve a Hyperthermia or Ablation system. Measurements were conducted from 23 °C up to 70 °C. Dielectric measurements between 500 MHz and 50 GHz.

	Grey matter	Y	N	Y	N	N	500-50 GHz, Slim probe	N	N	N	N
	Kidney	Y	Y	Y	N	N	500-50 GHz, Slim probe	N	N	N	N
Public Health England (UK)	All	Y (Rodents) Bigger animals on demand if ethically approved	N	Y	Some Tumours	N	VNA #1 covering 40 MHz-20 GHz VNA#2 covering 10MHz-43.5 GHz Coaxial Probes with and without flange ranging from 1.6 to 10 mm[3]	Y	Y	N	Y[4]
University of Pavia (IT)	Breast	Y (ex-vivo/in-vivo)	Y (ex-vivo)	Y (ex-vivo)	Y (ex-vivo/in-vivo)	N	0.5-50 GHz, Coaxial probe at room temperature	N	N	N	N
National University of Ireland Galway (IE)	Blood	N	Y	N/A	N/A	N/A	0.5 – 20 GHz Slim probe Room temperature	N/A	N/A	N	N/A
	Bone	N	Y	N	Y	N	0.5 – 8.5 GHz Slim probe Room temperature	N	N	Y	N
	Kidney	Y	Y	Y	N	Y	0.5 – 20 GHz Slim probe Room temperature	N	N	Y	N
	Heart	Y	N	Y	N	N	0.5 – 20 GHz Slim probe Room temperature	N	N	Y	N
	Liver	Y	N	Y	N	Y	0.5 – 20 GHz Slim probe Room temperature	N	N	Y	N
	Breast	N	Y	Y	Y	N	0.5 – 20 GHz Slim probe Room temperature	N	N	N	N
	Adrenal gland	Y	Y	Y	Y	N	0.5 – 20 GHz Slim probe	N	N	N	N

[3] Temperture range: -5 to 90 °C

[4] Standards and Uncertainty protocol in place

							Room temperature				
	Bladder	Y	N	Y	N	N	0.5 – 20 GHz Slim probe Room temperature	N	N	N	N
	Brain	Y	N	Y	N	N	0.5 – 20 GHz Slim probe Room temperature	N	N	N	N
	Pancreas	Y	N	Y	N	N	0.5 – 20 GHz Slim probe Room temperature	N	N	N	N
	Thymus	Y	N	Y	N	N	0.5 – 20 GHz Slim probe Room temperature	N	N	N	N
	Lung	Y	Y	Y	Y	N	0-20 GHz, Slim probe	N	Y	Y	N
	Parathyroid	N	Y	Y	Y	N	0.5 – 8.5 GHz Slim probe Room temperature	N	N	N	N
ENEA – La Sapienza (IT)	Liver	Y	N	Y	N	Y	500 MHz - 4 GHz, Slim probe @2450 MHz up to 100 °C	N	Y	Y	Y

Conclusions

A complete and systematic dielectric and thermal characterisation is fundamental to inform the design of medical devices and finally improve the safety and the efficacy of hyperthermic treatments.
The MyWAVE Action is enabling collaboration across members to share testing facilities and know-how and promote technology transfer to commercialisation initiatives.

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