Challenges to Demonstrating Efficacy When Translating Microwave Diagnostic Devices

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***Abstract*—Microwave interactions with biological tissues have been proposed and examined for medical diagnostics for over forty years, yet despite substantial academic and industrial interest, very few diagnostic devices are in clinical use. Drawing on evidence from the literature, several common challenges to clinical translation of microwave diagnostic devices are identified with a particular emphasis on clinical efficacy. This work highlights potential solutions and practical approaches from related fields to help bridge the translational gap.**

***Index Terms*—medical devices, biomedical microwaves, performance evaluation**

I. Introduction

The interactions of microwaves and biological tissues have been studied extensively over several decades for a variety of purposes including developing a basic scientific understanding of these interactions and their effects [1], the identification of safe limits for exposure to minimise risk [2], exploiting the effects for active treatments such as hyperthermia [3] and microwave ablation [4], and using both passive and active microwave devices for non-invasive imaging, screening, monitoring or diagnostic uses [5]. However, clinical adoption across these different areas has been variable with the exception of certain active treatments in ablation and hyperthermia.

Outside of treatment, microwave devices have been proposed and used with humans for a variety of potential clinical uses athough most extensively for breast cancer screening or breast cancer treatment monitoring. Other clinical applications in the literature are reviewed in detail in section IV and include stroke disambiguation, bone density estimation and lung monitoring and cancer detection. These can be broadly considered diagnostic applications as opposed to therapeutic applications, however, in many cases such as breast, there is a clear distinction between breast imaging with a goal to faithfully reconstruct the dielectric properties of the breast, asymptomatic screening seeking to identify patients requiring follow-up, diagnostics which is used to classify or distinguish suspicious findings and monitoring where changes to a known or suspected lesion are tracked. Furthermore, although commonly called microwave imaging, not all medical devices will reconstruct an image for analysis, although images are often preferred and easier to validate.

Microwave medical applications exploit the contrasts in dielectric properties of different tissues and the variations of electrical properties with disease, hydration and other factors to enable, among others, the focusing of microwave heating at tumour locations while minimising heat in healthy tissues or reconstructing of the dielectric properties of the region of interest. To understand and report the dielectric properties of tissue types, dielectric property characterisation studies based on single-ended coaxial probe measurements of excised animal tissues and complemented by measurements of excised human tissues from surgeries have been reported and many of these data are synthesises into large databases which are freely available [6]. In recent years, substantial work has been published to standardise and interpret these measurement, however, for most tissues, studies still report general averages with standard deviations to account for experimental error and variations between samples. In recent years, image-based techniques which infer properties from other imaging modalities such as MRI have been investigated and are seeing increasing usage as a state-of-the-art technique.

Initial investigations microwave medical technologies typically use existing literature values for dielectric properties and a series of models including simplified analytical modelling, computational anthropomorphic modelling and simplified and anthropomorphic experimental models to assess feasibility and identify the design inputs. In some rare cases, *in vitro*, *ex vivo* or *in vivo* pre-clinical models are also used. Both the dielectric properties values and the structure of the models comes from experimental studies of dielectric properties, anatomical understanding of the tissues of interest and image-based segmentation and analysis from other high-resolution modalities such as magnetic resonance imaging (MRI).

After basic feasibility is established, the majority of analytical, simulated, experimental and excised tissue studies are used to generate an initial estimate of efficacy in a broadly defined sense and to refine and guide hardware and algorithm development. Design of these test platforms is challenging due to a lack of information regarding the natural range of properties of healthy tissues compared to the natural range for diseased tissues, as well as substantial uncertainties regarding how these properties and ranges vary across individuals and with other factors such as gender, age, parity and clinical his-

tory [7]. Common test platforms include mostly "positive" test cases as it can be difficult to generate realistic, representative and diverse healthy, comparative cases. For many promising use cases, there can be similar issues with trial design to balance recruitment, throughout and primary outcomes.

In this work, a holistic view of microwave diagnostic device efficacy is presented to identify opportunities from the experience of devices which have progressed through various stages of clinical evaluation. All non-therapeutic uses of microwaves are considered under the term "diagnostic" except where there is a distinction between screening and diagnosis. Based on the experience of clinical trials and evaluation reported in the literature, the potential to refine and redesign modelling to improve predictive power and improve translation prospects is highlighted. Similarly, feasible pathways for early-stage clinical trials are discussed. Finally, sample clinical indications are reviewed and discussed.

The remainder of this work is structured as follows: section II examines the role of modelling in microwave diagnostic design and how to improve the predictive value of modelling; section III considers the requirements for early-stage trials to ensure later stages can demonstrate efficacy; promising applications and corresponding challenges are reviewed in section IV; perspectives on recent varied clinical studies are highlighted and discussed in section V; and finally, section VI concludes the paper.

II. Modelling

Modelling for microwave diagnostic devices can be categorised by how the electromagnetic fields are calculated:

- analytical: where closed-form solutions to the model exist;
- simulated: typically finite-difference time domain (FDTD) or finite-element model (FEM) iterative solutions to the environment;
- experimental where physical measurements of the environment are conducted, often with standard laboratory equipment such as vector network analyzers (VNAs).

Modelling can also be classified by the type of environment modelled:

- simplified: where unrealistic, simplified models are used to investigate theoretical limitations or to motivate specific design choices;
- anthropomorphic: seeking to model a realistic human environment, either specifically based on other imaging or using anatomical knowledge;
- validation: unrealistic models used to determine or validate equipment performance or criteria such as minimum resolution.

As very few analytical models exist, the majority of modelling uses simulated and experimental modelling. In recent years, a preference for experimental anthropomorphic models supported by simulated anthropomorphic models seems evident, with limited emphasis on simulated or experimental validation models. However, these models still have a clear role in supporting the findings of simulated and clinical studies, in identifying basic limits of performance of techniques, for quantifying the potential impact of variations and limitations of knowledge of dielectric properties on performance, and for validating system performance during trials.

For electromagnetic modelling in these frequency ranges and applications, biological tissues are broadly characterised into large and loosely defined categories such as skin, muscle, fat or the individual organ or tissue type. Furthermore, modelling regularly includes 'tumour' models but very infrequently are there models of different types of tumours (which may have different presentations), or of tumours with different extents of invasion into the local tissue. This second point is particularly important as studies have shown that within tumour regions, there exist both tumourous tissues and normal tissues, resulting in mixed dielectric properties [8], and as such including realistic dielectric properties for different tumours will impact the contrast and thus detectability. However, available data on properties for different tumour types and expected density of tumour cells for different cancers is exceedingly sparse.

Beyond diseased tissues, normal or healthy tissues also need to be modelled, as different normal tissue properties than expected can also result in lowered dielectric contrast between the background and target tissues, and lowered ability for detecting or imaging the target. Normal tissue properties can vary widely intra- and inter-individual; however, databases on these variations do not yet exist for most tissue types and data can be difficult to acquire. Additionally, for the vast majority of tissues, measurement campaign studies have not been large enough to provide indications of the magnitude or range of these variations. Despite these limitations, models should include expected variations in normal tissue properties, along with a realistic range of anatomical features relating to body shape or size and other factors which are not always well known.

Lastly, the overall set of models considered should be diverse and inclusive of the range of all expected presentations of the tumour target and all expected healthy variations in individuals. When limited types of models or scenarios are considered, the proposed technology is at risk of: failing in common clinical scenarios, not fully accounting for noise limits, and the prototype not being truly optimised for the proposed use. Several studies have indicated the potential impact of these variations on the expected efficacy of the device, as the magnitude of healthy variation may be as large as the effect size [9].

III. Early-stage Trial Design

The first-in-human (FIH) trials of microwave devices in general typically identify safety and comfort as the main primary outcome of the trials [10]. In nearly all published trials, patients overwhelmingly report that the devices are comfortable and there are no safety concerns. Supplementary primary outcomes typically attempt to estimate a form of

feasibility or efficacy from the same data, however, this can be extremely difficult for several reasons.

Firstly, as discussed, the preliminary modelling has limited predictive value due to the uncertainties in the models themselves. In the majority of clinical trials, it is also not possible to replicate the clinical trial case studies in simulation. The reference clinical history is normally gathered in a different orientation making it very difficult to register the case study with the clinical history. Clinical images may also have been taken at a different date than microwave measurements, which could also introduce the potential for tissue changes in between scan times (e.g., for women across the menstrual cycle [11], [12]).

Secondly, due to recruitment issues, patient populations typically have diverse disease, lack of healthy controls and often complicated or incomplete clinical histories. Subsequent trials are also difficult to design as recruitment is often limited to symptomatic clinics to ensure sufficient through-put.

Thirdly, systems in early-stage clinical trials typically are in early stages of technical development as well and have usually been evaluated with engineering-focused metrics such as binary detection or subjective or objective quality metrics without direct reference to the clinical indication [5]. However, depending on the role of the device in the patient pathway, more nuanced and sophisticated distinctions may be needed. For example, in screening, high confidence true negatives might be prioritised but in treatment response monitoring, exact size, location and shape of known lesions might be more important.

IV. Comparison of Proposed Clinical Applications

In this section, several proposed clinical applications under the microwave diagnostics umbrella are overviewed, including the challenges and potential advantages in conducting clinical studies for each.

A. Breast Health

Microwave medical technologies focusing on the breast have been by far the most commonly studied to date. Under diagnostic umbrella, clinical studies have been conducted on varied clinical use cases, including breast cancer screening and detection, cancer diagnosis, and breast health monitoring (e.g., [13]–[17]). Breast cancer treatment tracking has also been studied [18]. In general, the breast is an organ of particular interest since it is very easy to access and surround with antennas; breast cancer is the world's most prevalent cancer [19], so it is possible to readily identify study participants; and further, almost every country has regular breast cancer screening programs that involve multi-step diagnosis (e.g., mammogram, MRI or US, biopsy), so microwave technologies can be added with little overhead and reference comparators are available. However, for screening and diagnosis, existing competing technologies are very well established and function reasonably well in most cases.

Therefore, in order to demonstrate the clinical efficacy of proposed technologies, trials need to clearly differentiate between target clinical use cases (e.g., screening vs. diagnosis) as the patient populations studied and outcome indicators will differ. To this end, it is also important that studies refer to clinical outcomes so that the efficacy of the microwave prototypes can be compared to standard technologies. Common outcome indicators will also facilitate comparison between microwave prototypes of different designs. Lastly, due to the relative success of competing technologies (e.g., x-ray mammography, ultrasound, etc.), a large number of enrolled patients in a microwave trial would likely be needed to demonstrate significance in the outcomes, which makes such studies a time-consuming and expensive endeavour.

B. Brain Bleeds

Microwave technologies have also been proposed for detection and differentiation of stroke-type (particularly bleed discrimination) and for haemorrhage or traumatic brain injury detection. It is vital to detect bleeds in the brain rapidly so that treatment can commence in a timely manner, and, in the case of stroke, bleeds need to be excluded so that thrombolytic therapy can be delivered quickly. To this end, microwave technologies could provide an in-ambulance or in-clinic portable approach to rapid identification of bleeds, enabling proper patient triage.

Some clinical studies on both topics have been conducted (e.g., [20], [21]). In both cases, high sensitivity in bleed detection was able to be achieved, but at the cost of specificity. Because of the need to identify bleeds with certainty, near 100% sensitivity must be achievable, which is a significant challenge facing these technologies. Additionally, the stroke pathway is a particularly challenging landscape for conducting pilot studies and early trials, as time is of the essence and the existing protocols cannot typically be interfered with. Furthermore, stroke patients present to the hospital at unknown times and intervals, making staffing a study difficult (i.e., it's very difficult to be in the right place at exactly the right time frequently enough to attain a large enough study group). Other works have proposed microwave imaging for stroke monitoring (e.g., [22], which would avoid many of these challenges by removing the time pressure and uncertainty, along with the consequences of an incorrect diagnosis.

C. Bone Health

Microwave imaging has been proposed as an approach for assessing bone health, particularly in the context of injury recovery and osteoporosis screening [23], [24]. Like the breast, the heel bone (the typical proposed measurement site) is readily accessible and of small size enabling straightforward placement inside a surrounding microwave prototype. Screening of bone health is not typically a time-sensitive issue, so clinical trials of microwave prototypes may find an easier time recruiting participants than, e.g., for stroke trials. Competing technologies may also be limited, depending on the specific use case. However, osteoporosis screening, for example, is not as common and well established as breast cancer screening, so finding patients with disease and clinical records for reference may be challenging. Monitoring over

time may be of interest for bone, to evaluate changes in health after recovery or treatment, and may present an opportunity to fill a clinical gap in frequent, low-cost, and accessible monitoring.

On the technology side, permissible SAR exposure limits are also higher in the limbs than the head and trunk [25], which could enable safe use of higher incident powers and thereby higher amplitude scattered responses. Bone applications also present an unusual measurement and modelling challenge as bones are typically both solid and porous [26]. The standard techniques from other biological tissues are less effective in these circumstances and can be affected by preservation techniques.

D. Intra-abdominal Pressure

Monitoring of intra-abdominal pressure (IAP) through reflected microwave measurements has also been proposed with early pilot studies demonstrating potential correlations in microwave signals and IAP [27]. The proposed IAP technology, like other applications mentioned in Sections IV.A-C, is based on non-invasive sensing from the surface of the body. While the measurement itself is not invasive, its proposed use would be used during an invasive procedure (i.e., laproscopic surgery). IAP measurements are already commonly performed, providing a valuable reference for microwave measurements. However, microwave technology could fulfil a clinical need in the area, enabling the desired continuous monitoring which other technologies currently do not [27]. Conducting a trial on patients undergoing surgeries requires careful planning to integrate the microwave technology without interfering in surgical or monitoring procedures; however, the surgical timeframe is short and numerous measurements can be conducted over this timeframe, which allows for stability in microwave data (e.g., antennas not moving much over time) and tracking of changes over time, both of which are advantageous from the technical analysis perspective. The microwave measurement results are noted to likely depend on patients body mass index (BMI) and thus larger clinical studies should include patients with diverse BMI ranges.

V. Perspectives on Recent Clinical Trial Studies

In recent years, several interesting trials have been published. In this section, we briefly discuss trials from the two main categories of works: i) screening and detection; and ii) monitoring. While exhaustive review of all trial studies is not possible in this short paper, we highlight studies that facilitate understanding and comparison of clinical trial successes and issues as related to on-going translation of microwave technologies.

To facilitate the discussion, we refer to the PICOT format for formulating clinical research questions: P-Population, I-Intervention, C-Comparison (or Control), O-Outcome, T-Time period. Identification of these 5 points allows for a specific and clear study question, and enables selection of the best study design to answer such a question.

A. Screening and Detection

To date, numerous breast cancer screening prototypes have been used in clinical studies [5]. Recently, several impressively large studies have been undertaken (e.g., N=225 [28]; N=115 [17], N=103 [13]). In this subsection, a recent trial is highlighted which differs in the diversity of the population from the rest of the literature which is comprehensively reviewed several times including in [5], [10].

In [13], 103 breasts were scanned with their microwave screening prototype, from 58 patients. Out of these, 52 had no findings of clinical significance (i.e., normal breast), and 51 had a diverse range of clinical findings (including benign or malignant regions). The inclusion of normal breasts is highly valuable in assessing a screening technology. Both groups spanned a wide range of breast densities, as well. Radiological data was used as the reference diagnosis (mammogram/MRI/ultrasound). Custom features from the microwave measurements are designed that are used to predict the clinical outcome, with overall results shown in terms of sensitivity and specificity of detection. While promising, the custom features make it difficult to compare these results to the rest of the literature, however, the unusually diverse population is of substantial interest and the first published in this area.

B. Monitoring

Monitoring applications in particular could be very interesting clinical use cases for microwave technologies. As microwaves are safe for frequent and repeated scanning, relatively low-cost, and prototypes can be made quite portable, the potential for filling gaps in clinical pathways where no monitoring currently exists is substantial. Monitoring also allows for tracking changes in signals over time, which may allow anomalies to be detected more easily than from a single one-off scan.

A specific example of monitoring in a clinical study is neoadjuvant chemotherapy (NCT) monitoring during breast cancer treatment [18]. As mentioned above, there is currently no competing technology that regularly allows frequency or short-term monitoring during the neoadjuvant treatment phase. Early monitoring that could identify patients that are not responding well to treatment would be very useful in pivoting treatment strategies quickly, likely leading to improved patient outcomes in the long-term. For this clinical scenario, the patient population (breast cancer patients receiving NCT) and intervention (microwave imaging scan) are well-defined, and the time period is quite short (several scans over time periods of 4-6 months were conducted, but, responses at 1 month showed statistically significant differences between responding and non-/incomplete-responding patient groups). Through this timeframe, MRI scans were also conducted for comparison. The outcome was primarily an engineering perspective - changes in mean conductivity within a region of interest - however, it was linked to the key clinical outcome of patient response to treatment. Therefore, although this early pilot study had only a small number of patients

(N=8), it demonstrates a very clear possibility for microwave monitoring to fill a pressing clinical gap in this area.

Another, very different example, of a microwave monitoring study is for tracking of hydration status of athletes [29]. As the population is athletes, and not patients with a specific disease, study participants an are easily accessible and large portion of the general population. In this study (N=10), measurements were taken before an after an exercise session, on the forearm of the athletes. Urine specific gravity was also measured from a void in the morning before the session; however, validation of measurement data is challenging due to the lack of existing and usable technologies that provide relevant comparators. Despite this, trends were found between permittivity and body weight changes that track with water loss. Further investigation to understand the specificity of the permittivity changes with respect to hydration level is needed, as well as correspondence of the magnitude of the changes with hydration levels.

VI. Conclusions

Overall, microwave technologies for screening, detection, monitoring, and diagnosis of disease have demonstrated potential in identifying tumour presence, location, and tissue changes over time, through simulation and experimental studies, yet, their success in clinical usage still remains to be fully evaluated. Going forward, clinical research questions should be chosen strategically to enable quantitative assessment and comparison of clinical outcomes and measures with existing standard reference technologies. Additionally, although although breast cancer screening and detection applications remain the most studied to date, other applications and clinical use cases may more readily facilitate clinical studies and translation and should not be neglected.

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