ICR The Institute of Cancer Research

Imperial College London

Cancer Research Centre of Excellence: **PhD Studentship Project**

| Project Title<br>**Ultrasound backscatter assessment of tumour response to radiotherapy using finite element model-based attenuation and diffraction corrections.** | |
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| **Pre-requisites of applicants** | First or upper-second class honours degree (Bsc or Msci) in Physics, Mechanical Engineering, Bioengineering or Computational Physics. |

**Project outline**

***This proposal develops and uses powerful numerical modeling tools, originally developed for Non-Destructive Evaluation of advanced industrial materials, for the development of a clinical ultrasound imaging technique for the determination of early tumour response to radiotherapy.***

Approximately 50% of patients receive radiotherapy (RT) as part of their treatment for cancer. We know that patient outcomes can vary for a variety of reasons but we are currently unable to identify which patients will respond well, or poorly, to radiotherapy. Early assessment of tumour response, i.e. within the first two weeks, will enable clinicians to adapt treatment according to the individual[1]. For example, determination of radiation resistance, or no response, may identify the need for the integration of other treatment modalities, such as

radiosensitisers, which may improve patient outcomes.

Ultrasound backscatter characteristics (UBC) measured using ultrasound backscatter spectroscopy (UBS) can be used to evaluate the size and density of microstructural tissue components that scatter ultrasound but are too small to be resolved, such as tumour cell density and extracellular matrix and microvascular structure. UBS can detect morphological changes in tissue at the cellular level, which has application for identifying disease[2] and indicating tissue damage, such as cell death caused by RT[3]. The potential for using UBS to monitor tumour response to RT has been demonstrated both *in vitro* and *in vivo*[4]. The Imaging for RT Adaptation Team at ICR is developing 3-dimensional UBS for the purpose of evaluating the response of head and neck cancer and cervical cancer to RT.

UBCs are principally derived from spectral analysis of the ultrasound backscattered signal, which is strongly influenced by ultrasound attenuation and diffraction by tissues. Corrections for attenuation and diffraction are typically made by comparison of the tissue UBS signal to the UBS signal from a reference material acquired using the same equipment and imaging parameters.[5] This technique relies on the assumption that the properties of tissues are phantom-like, i.e., they are uniform and have similar ultrasound scattering properties to the phantom. In reality, tissues are rarely homogenous and contain multi-scale scattering components whose spatial distributions are unique to the patient. As a consequence, subtle changes in overlying tissues result in differences in the UBS signal limiting the accuracy of UBS to characterise cancer.[5] This is a particular problem in deeper-seated tumors, which have more overlying tissues through which the ultrasound must penetrate, limiting a potentially powerful technique to a handful of superficial cancer sites. One solution is an experimental attenuation and diffraction correction measured in the subject, which could be considered a gold standard. However, this requires the use of a motion controller to control the ultrasound probe position and a large water stand-off, which is not practical in a clinical environment as it would require the patient to be partially submerged.

We propose to devise a patient–specific model-based correction method for attenuation and diffraction. During a course of RT the patient receives repeat imaging. They will typically receive Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) for RT planning, and repeat cone-beam CT (CBCT) during treatment. We propose to use these multi-modality datasets to model the propagation of ultrasound through the patient anatomy to predict the attenuation and diffraction of ultrasound. The use of patient-specific model-based corrections has never been explored before and the opportunity arises, in part, due to this frequent longitudinal multi-modality patient imaging, which is unique to RT.

Accurate modeling of acoustic waves in matter is a computationally intensive activity, which places practical limitations on model size and complexity. The Non-destructive Evaluation (NDE) Team at IC has developed Pogo, an elastodynamic finite element solver which can be used to solve wave propagation problems in solid media. Pogo is enabling very large models to be run at very high speed, thanks to an optimised implementation on a graphics processor (GPU) platform. The IC team is using it to perform some important advanced modelling for the first time, such as simulations of wave propagation in granular materials with spatial representation at grain scale. This is transforming NDE studies in such materials. This proposed project will benefit from this step change in capability applied to wave propagation in tissues.

We will develop meshed patient-specific models from CT and MR images to input into Pogo to derive attenuation and diffraction corrections, which can be applied to UBS data. Initially, the current capabilities of Pogo will be assessed to evaluate the performance for this application; for example, at present, Pogo does not accurately capture propagation through viscous media, so strategies to address that with the current package will be developed along with testing approaches which could be implemented in the full package to better suit

medical applications.

**Translational potential:** This PhD project will evolve alongside preclinical and clinical studies of 3D UBS for tumour response of head and neck cancer (HNC) to RT. The student will have the opportunity to acquire UBS data preclinically and clinically (healthy volunteers) to develop and validate their work. This proposal will focuses on HNC and explore opportunities in transperineal ultrasound imaging of prostate cancer during RT and neoadjuvant RT of breast cancer. The successful implementation of model-based patient-specific attenuation and diffraction correction will benefit early assessment of radiotherapy and other therapies, such as targeted-drug therapy, as well as other areas of cancer research, such as ultrasound guidance of biopsies or surgery.

**Feasibility**

This PhD focuses on the development of novel computational methods, building on on-going work at IC. The student will initially be based within the NDE team at Imperial and will work alongside others with expertise in numerical modelling. Experimental validation of the models will be supported by staff and students at ICR who will be conducting similar experiments. The team at ICR have two laboratories dedicated to phantom based and animal experiments. Volunteer studies will be subject to ethics approval. The team at ICR have experience in the design and execution of clinical studies and acquisition of ethics approval.

Project is divided into 4 distinct phases, the latter phases building on the knowledge gained in earlier phases. This will be the first time numerical modelling is used to generate ultrasound attenuation and diffraction corrections, and therefore we expect each phase of this work to be of significant interest to the medical physics and imaging community, and therefore highly publishable. High calibre-student are expected to apply: this multi-disciplinary project offers the opportunity for the student to develop their own intellectual contribution to Pogo, to gain lab-based and preclinical experimental skills and to obtain and work with clinical and histopathological data.

**Multidisciplinarity**

This project uses Pogo software and the modelling and mechanical engineering expertise of the non-destructive evaluation (NDE) team at IC. Huthwaite and Lowe and the NDE team are already progressing the development of technologies to evaluate polycrystalline materials, routinely applying numerical methods to solve complex inverse problems to reconstruct images of metallic and composite industrial parts. Huthwaite and Lowe will supervise the deployment of Pogo to create representative models and simulate the ultrasound wave propagation in soft tissues.

Harris and Bamber will support the development of the model providing guidance and training in the acquisition of experimental data for model development, testing and, ultimately, clinical validation. They will help develop the phantoms and experiments required to both characterise the clinical ultrasound scanner for model input and to test the model. Harris is currently developing preclinical and clinical evaluation of 3D backscatter ultrasound for assessment of tumour response. Within this programme the student will have the opportunity to test the new implementation of Pogo *in vivo* in HNC tumour models.

Harrington is a Consultant Clinical Oncologist and runs the Targeted Therapy team at the ICR. Harrington's lab has previously run successful trials of MRI and PET imaging in HNC which correlated radiological response to tumour histopathology in patients with involved neck lymph nodes. Harrington and his lab will provide support and advice on clinical studies, tumour models and histopathological surrogates of tumour response to RT.

- Year 1: (IC 70%, ICR 30%) student will develop knowledge of advanced ultrasound engineering and FEM at IC and attend the Radiotherapy and Medical Imaging course, and the Perspectives in Cancer Research on-line course at ICR. The student will learn to operate medical research ultrasound equipment and acquire phantom data to incorporate new physics (e.g., viscosity) into Pogo. The focus of the first year will be convergence testing of simple experimental versus simulated scenarios.
- Year 2: (IC 70%, ICR 30%) The student will develop meshing techniques to build complex models of using CT and MR images of phantoms and *ex vivo* tissues. The model will be used to simulate the backscattered ultrasound signal received at the individual transducer elements and compare this with experimental ultrasound signals.
- Year 3: (IC 30%, ICR 70%) The student will devise and perform preclinical experiments in HNC to demonstrate improvement in UBS assessment of tumour response to RT. UBS assessment of the necrotic fraction of the total tumour volume will be performed through varying amounts of attenuating tissues which have been imaged using preclinical MR and CBCT. The actual necrotic fraction will be evaluated using histopathology.
- Year 4: (IC 30%, ICR 70%) Conduct experiments of UBS to evaluate the size and density of microstructural tissue components in the neck lymph nodes and breast tissues of healthy volunteers using model-based (derived from MRI of the volunteer) and experimental attenuation and diffraction corrections. Ultrasound scatter size and number density, determined using UBS with model-based, reference phantom and experimental corrections, will be compared. Neck and breast tissues are chosen as it is possible to measure experimental corrections in these sites without submerging the patient.

**Literature references**

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2. Feleppa, E.J., C.R. Porter, J. Ketterling, P. Lee, S. Dasgupta, S. Urban, and A. Kalisz, *Recent developments in tissue-type imaging (TTI) for planning and monitoring treatment of prostate cancer.* Ultrason Imaging, 2004. **26**(3): p. 163-72.
3. Lee, J., R. Karshafian, N. Papanicolau, A. Giles, M.C. Kolios, and G.J. Czarnota, *Quantitative ultrasound for the monitoring of novel microbubble and ultrasound radiosensitization.* Ultrasound Med Biol, 2012. **38**(7): p. 1212-21.
4. Czarnota, G., W. Chu, A. Giles, and M. Kolios, *Ultrasound imaging and spectrosocopy of cancer radiation therapy effects.* Cancer Research, 2007. **67**(9 Supplement): p. 5484-5484.
5. Yao, L.X., Zagzebski, J.A. and Madsen, E.L., 1990. Backscatter coefficient measurements using a reference phantom to extract depth-dependent instrumentation factors. *Ultrasonic imaging*, *12*(1), pp.58-70.