Computational imaging driving precision medicine

Expert in medical image informatics, Dr Anant Madabhushi explains how research in computational imaging is vital to advance disease characterisation and personalisation of treatment

What are the objectives of your research on computational imaging?

Our work is primarily focused on the development and application of advanced computer vision, image analysis and machine learning tools for the examination and automated interpretation of medical imaging and digital pathology data. The creation of image-based prediction models will allow for better characterisation of disease risk, presence and extent.

The fundamental hypotheses underlying our approach are threefold. First, gene and expression profiles of the disease captured by molecular companion diagnostic assays manifest as unique phenotypic alterations that can be appreciated using standard haematoxylin and eosin stained images, as well as radiographic imaging. Second, image-based biomarkers of the disease contain information necessary to predict disease progression and response to therapy. Finally, computer vision algorithms are integral to the successful extraction of quantitative biomarkers from digitised histopathology and medical imaging.

Can you introduce the Center of Computational Imaging and Personalized Diagnostics (CCIPD)?

I established CCIPD at Case Western Reserve University in 2012, which now hosts 30 members, including faculty, administrative and research staff, scientific programmers, postdoctoral fellows, research associates, and graduate and undergraduate students.

CCIPD is involved in various different aspects of developing, evaluating and applying novel quantitative image analysis, computer vision, signal processing, segmentation, multi-modal co-registration tools, pattern recognition and machine learning tools for disease diagnosis, prognosis and theragnosis in the context of breast, prostate, lung, head and neck, and brain tumours. Our group is also exploring the utility of these methods in studying correlations of disease markers across multiple length scales and data modalities – from gene and protein expression, to spectroscopy, digital pathology and multi-parametric magnetic resonance imaging (MRI).

Would you describe your work as a collaborative endeavour?

CCIPD is a very close-knit group, which is reflected in the large number of joint authorship publications that we have published over the last few years. Situated in Cleveland, Ohio, USA, we are right next to two of the top medical centres in the country – University Hospitals and the Cleveland Clinic. In addition, CCIPD is all of five minutes walking distance from the Case Comprehensive Cancer Center, a top 20 ranked National Cancer Institute-designated cancer centre. Proximity to the medical centres provides unfettered access for CCIPD students, faculty and postdoctoral researchers to interact with our clinical collaborators in radiology, pathology, urology, radiation oncology and surgery.

This proximity also encourages our clinical collaborators to walk over to the centre, located in the Department of Biomedical Engineering, and participate in our research meetings. Students, faculty and postdoctoral fellows showcase their research updates from the past week and obtain input from other members in the group, as well as our clinical collaborators. CCIPD is also proud to be collaborating with a number of clinical and biomedical centres in the US, Europe, South America and Asia. Having a strong partnership with clinical input allows us to develop and apply highly innovative domain-specific tools to address key questions in disease diagnosis, prognosis and treatment response.

Have you faced any challenges during your investigations?

Like most academic research groups, we remain heavily dependent on grant funding. This is a challenge for research labs, both in the US and Europe. With the paucity of federal funds to conduct research, resources are stretched thin. While CCIPD has been fortunate to have a number of outstanding graduate students and postdoctoral fellows who have secured independent funding, the principal investigator and his faculty team have to dedicate a large portion of their time to writing and submitting grants.

Are there key outcomes from this project that you can currently share? How are your findings informing the research going forward?

Perhaps the biggest finding of our research to date has been the identification and validation of computer-based image biomarkers both associated and correlated with patient outcome and treatment response. In several papers, and in the context of different disease sites, our results demonstrate that image-derived features and measurements from pathology and radiographic imaging can strongly predict patient survival, treatment response and disease recurrence.

These tools need to be independently validated with data from large multi-site trials. This is exactly what we are pursuing currently. We are working with different cooperative oncology networks to obtain the digitised slides and associated radiographic scans of cancer patients from previously completed clinical trials. Having access to the digital image data along with associated patient outcome will allow us to test and validate our methods and approaches.
Researchers at the Center for Computational Imaging and Personalized Diagnostics at Case Western Reserve University are developing computational image analytic methods to identify subtle disease patterns that can help improve disease diagnosis, prognostication and treatment.

**Medical breakthroughs with sub-visual image computing**

**ACROSS THE SPECTRUM** of medicine and its related disciplines, the use of computers and sophisticated software is helping to unravel complicated medical enigmas, while improving and accelerating patient care processes. In the laboratory, these tools are used to support imaging, which is utilised to reveal the cellular and molecular mechanisms and interactions underlying a disease, while in the clinic, imaging assesses topographical anatomy and aids diagnosis.

Though images hold valuable information in the form of patterns and objects, human evaluation of them is largely subjective and lacks standardisation. The aim of computerised image analysis techniques is to convert image data into quantifiable, objective measurements by utilising morphological metrics, colour gradients and intensity markers, thus decreasing human-associated errors. These ‘sub-visual’ image metrics may inform a great deal about the risk profile of a disease, its aggressiveness and treatment outcome.

**A TARGETED APPROACH**

The Center for Computational Imaging and Personalized Diagnostics (CCIPD) at Case Western Reserve University in Ohio, USA, is one of the major hubs for innovative research in computational imaging for precision medicine. The biomedical researchers at CCIPD are dedicated to developing novel algorithms and applications to help with disease detection, diagnosis, treatment and prognosis of prostate, breast, lung, colorectal, oropharyngeal and brain cancers.

Director of CCIPD, Dr Anant Madabhushi, is working to advance image-guided interventions to better inform surgical procedures; develop digital pathology image analysis methods to determine the severity of disease; and optimise algorithms for computer-aided diagnosis and prognosis of disease. His aim is to squeeze out insights into disease behaviour and outcome from rigorous computational analysis of routinely acquired clinical, medical and pathological images that is possible via human interpretation alone.

**IMAGE-GUIDED INTERVENTIONS**

In developed countries, it is estimated that one in six men will be affected by prostate cancer – from which one in 36 will die. Unfortunately, a large number of men in the US with indolent or low risk prostate cancer undergo radical therapies such as surgery or radiation therapy.

Focal therapy is an emerging treatment modality for patients with localised prostate cancer. It offers a minimally invasive option that has significantly lower morbidity and fewer adverse symptoms such as urinary and sexual dysfunction, compared to surgery or radiation therapy. This therapy bridges the gap between aggressive treatment and watchful waiting.

Researchers at CCIPD, including Madabhushi and research faculty member Dr Satish Viswanath, are involved in conducting a clinical trial that employs advanced pattern recognition tools in conjunction with a focal treatment considered to be highly effective, known as laser interstitial thermal therapy (LITT). It offers a way of reducing the tumour size and destroying tissue with high-intensity laser energy.

More broadly, this strategy is also being explored for other diseases, such as brain tumours and epilepsy. “One of the major advantages enjoyed by LITT is its compatibility with magnetic resonance imaging (MRI), allowing for high resolution in vivo imaging to be used in LITT procedures,” Madabhushi states. Pattern recognition and computer vision tools can identify the target of interest via MRI, and then guide the laser probe, so that highly focused laser heat treatment can be applied directly to prostate tumour tissue. “LITT is uniquely suited for application and direct integration with MRI due to the use of non-electromagnetic energy and quartz fibres, which do not cause any disturbance during imaging,” he expands.

**DIGITAL PATHOLOGY**

Breast cancer is another area in which Madabhushi focuses his attention. It is an increasingly prevalent diagnosis worldwide. More specifically, 1 million women are diagnosed with oestrogen receptor (ER)-positive breast cancer each year. The hormone oestrogen binds to intracellular ERs, triggering a cascade of events leading to cell proliferation. If this proliferation is unhindered, cell mutations can occur.

Various prognostic criteria have been developed to distinguish cancerous tissues from normal ones, and to determine the level of differentiation of tumorous cells; for example, via grading of breast cancer morphology on haematoxylin and eosin (H&E) stained pathology images. Recently, scientists have demonstrated that there is a close relationship between tumour grade and prognosis. However, pathologic grade tends to suffer from significant inter-observer variability. Thus, determining the degree of tumour differentiation, accurately and reproducibly, especially with the current lack of automated image analysis tools, is a notable challenge for pathologists. Improvements, however, are in the pipeline: “Over the last decade, we have been developing advanced computerised digital pathology image analysis methods, enabling a detailed morphologic interrogation of the entire tumour landscape and its most invasive elements from a standard H&E slide,” Madabhushi explains. “This includes capturing nuclear orientation, texture, shape and architecture.” Due to the

Multimodal co-registration tools being developed in CCIPD allow the spatial mapping of disease extent from histopathology and immunohistochemically stained images onto in vivo radiographic images.
COMPUTATIONAL DIAGNOSTICS

‘Radiomics’ refers to the computerised extraction and analysis of various subtle mathematical features of tumour appearances from radiologic images obtained using technologies such as magnetic resonance imaging (MRI). The quantitative data collated can be used to construct models linking image characteristics to the molecular profile (genomic or proteomic) of the tumour, which can provide valuable diagnostic and prognostic disease insight in a non-invasive way.

More than 16,500 deaths are reported annually due to primary brain tumours. Though treatment options exist, there are serious risks. A common, potential long-term central nervous system complication of radiation therapy is radiation necrosis – a non-cancerous condition that manifests at the original tumour site. Distinguishing between radiation necrosis and recurrent tumours is difficult on standard MRIs, as their appearances are very similar. Patients could therefore be subjected to incorrect treatment, such as invasive biopsies and surgical resections, which can be life threatening.

Dr Anant Madabhushi and Dr Pallavi Tiwari – a research faculty member in CCIPD – are currently developing new radiomics tools for automated interpretation of brain MRIs and distinguishing radiation necrosis from recurrent cancer. “Computerised decision support tools, in conjunction with radiomic features, are increasingly being used to improve robustness and reproducibility of detection and diagnosis of cancer via imaging,” Madabhushi highlights.

rise in cancer incidence and enhancements in early diagnosis, distinguishing between patients with more and less aggressive disease would allow for de-escalation of therapy in patients with lower risk disease.

Madabhushi is also the co-Founder of Ibris Inc., a startup company focused on developing image-based assays for breast cancer prognosis. The Image-based Risk Score (IbRIS) predictor method is a computerised image analysis-based test used for measuring disease aggressiveness to evaluate disease outcome from digitised histopathology images. “IbRIS yields a continuous image-based risk score from the analysis of the breast cancer biopsy or surgical pathology images,” he states. “For patients with ER-positive breast cancer, a low risk score will suggest that hormonal therapy is sufficient, while adjuvant chemotherapy is required for high image-based risk scores.” This method would generate a more accurate capture of tumour heterogeneity and appearance, and would reduce the length of time between biopsy and diagnosis, thus providing a lower cost, non-destructive alternative to current expensive molecular assays.

NEW BEGINNINGS

These highly promising techniques demonstrate how computational image analysis can provide deeper disease insights than human analysis alone. Image-guided interventions could enable doctors to detect and eliminate diseases at their most curable stage. The exploding field of digital pathology is poised to provide indispensable tools for pathologists and oncologists, offering even faster and more accurate diagnosis, disease risk characterisation and treatment options.