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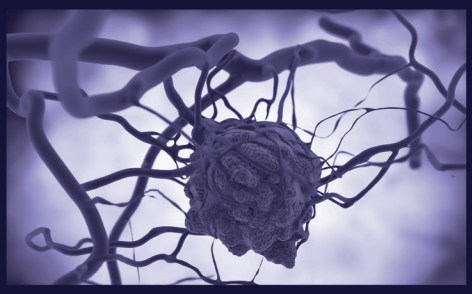
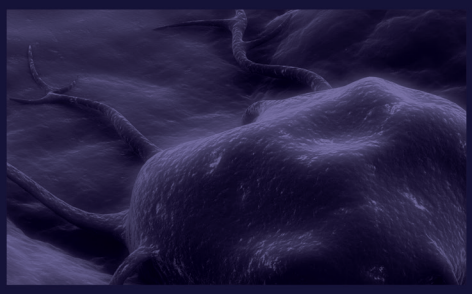
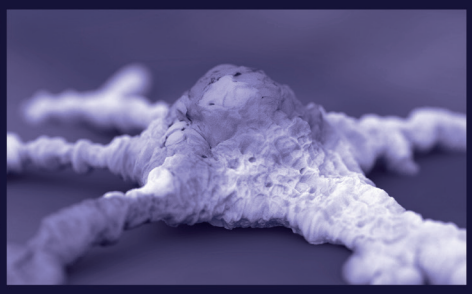
Published in:
International Innovation

Publication date:
2014

Citation for published version (APA):
Zwiggelaar, R., Denton, E. R. E., & Strange, H. (2014). Modelling cancer risk. *International Innovation*, *165*, 73-75. http://www.internationalinnovation.com/modelling-cancer-risk/

Modelling cancer risk



Professors Reyer Zwiggelaar and **Erika Denton**, and **Dr Harry Strange** are creating groundbreaking new models of cancer risk. Here, they discuss the challenges they face and the collaborations they participate in that contribute to the constant improvement of their work

Professor Zwiggelaar, could you provide a brief outline of your research career? How did you first become involved in computer science?

My PhD was related to optical signal processing and, during my first postdoctoral position at the Silsoe Research Institute, UK, I switched to computer-based signal/image processing, with some applications in the clinical domain. During my second postdoctoral position at the University of Manchester, I worked exclusively on medical image analysis, mainly mammography. During subsequent faculty positions at the University of Portsmouth and the University of East Anglia, I developed broader medical image analysis and computer vision work across a range of application areas. In the medical domain this covered breast, prostate, lung and brain cancers, and analysis of associated images (radiology, blood, cells), while in other areas this covered the analysis of plants, crops, faces, biometrics and chronic obstructive pulmonary disease. I am currently a professor at the Department of Computer Science at Aberystwyth University.

How can the effectiveness of cancer screening be increased using computer-aided diagnosis (CAD) prompting systems?

There are a number of aspects where contributions are made. Most of the time, prompting systems are used as a second opinion and, in effect, contribute to the early detection of abnormalities; sometimes early signs are missed or deemed normal, in which case a prompt might alert the clinical expert. The same could happen when the CAD system does not indicate an area where the expert was suspecting something. The second way in which a CAD system can contribute is in the classification of an abnormality as malignant, which is likely to affect the number of biopsies taken and the direct effect this has on the patient.

How do you develop the methodology for statistical models? What are the benefits of using a model-based approach in your research?

Statistical modelling relies on the distinction between abnormal and normal regions, and in having enough examples of all the different classes. In effect, the methodology involves obtaining a model based on a distinct set of examples. If the models are specific enough, they can be used to distinguish between unseen cases.

The biggest benefit of such model-based approaches is that the results tend to be within the anatomical expected variations and are realistic. Modelling can be restricted to cover only a limited range of variation from the training data. It also provides a probabilistic approach that makes classification easier, and can be used to generate examples, that are realistic and can teach us about cancer development.

What are the biggest challenges involved in evaluating and improving the understanding and assessment of medical images?

The evaluation tends to involve large numbers of cases, which are similar to clinical trials. In many of the application areas we work in, one of the biggest problems is obtaining reliable ground truth data at a detailed enough level. For example, we might know that there is cancer in a prostate, but be unsure of its precise location and rely on experts to outline the relevant region.

How important is collaboration to your line of research?

It is essential, especially with clinical experts. Professor Erika Denton from the University of East Anglia is a longstanding collaborator with whom we have been working for almost 15 years. She provides ground truth data for creating models, is involved in design discussions and plays a major role in evaluation aspects.

From a computer science point of view, we collaborate both within Aberystwyth and abroad; the University of Girona, Spain, and the University of Pennsylvania, USA, are longstanding collaborators.

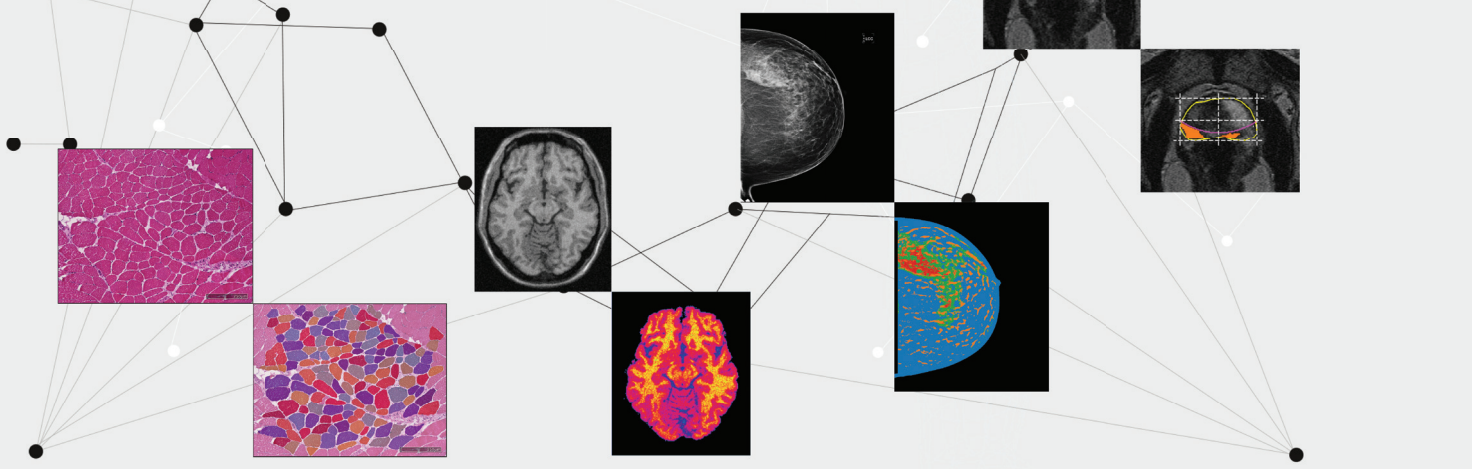
How do you see your research developing in the future?

There always seems to be room for improvement. In breast cancer for example, computer-aided detection is getting close to the performance of clinical experts, but the classification is an area where significant improvements can be made. Classification could try to investigate links between complex appearance and biopsy data.

This research has the potential to develop towards applications, especially in the classification of mammographic and prostate abnormalities, mammographic risk assessment and the analysis of blood and cell images. Our research tends to be an interaction between basic research, specific application areas and translation to clinical end-users.

PROFESSORS REYER ZWIGGELAAR, ERIKA DENTON & DR HARRY STRANGE

Computer-aided diagnosis



Cancer diagnosis based on imaging is subject to variability in the observer's definition of health. Research at **Aberystwyth University**, UK, has produced an array of computer-aided diagnostic tools to aid the understanding of medical images

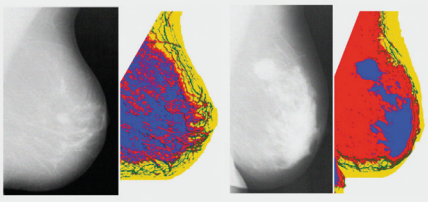
OVER 25 MILLION people around the world are living with cancer, with more than 11 million new diagnoses every year. Catching cancer early can significantly improve a patient's chance of survival as the tumours are smaller, less likely to have spread and therefore easier to treat.

Cancers are mostly detected by physicians using imaging techniques such as magnetic resonance imaging (MRI), X-rays or ultrasound. The results can often be difficult to interpret, partly due to the natural variation in patients and because individual physicians will read the images slightly differently using subjective criteria, leading to both false negative and false positive outcomes. To address this problem, Professor Reyer Zwiggelaar from Aberystwyth University, UK, is working alongside his colleague Dr Harry Strange and collaborator, Professor Erika Denton, from Norfolk and Norwich University Hospital. Together, they have developed a set of promising new computer-aided diagnosis tools that could revolutionise the detection of a range of cancers, including breast, brain and prostate.

HIGHLIGHTING BREAST CANCER RISK

Each year, over 2 million women in the UK are screened for breast cancer using a mammogram, with around 16,500 tumours detected. As the risk of breast cancer is strongly linked to age, all women between the ages of 50 and 70 are invited for screening every three years. Physicians can recommend more frequent screening when an individual has a higher risk of disease, which is currently determined based on their lifestyle and family history. At present, Zwiggelaar's research is working towards an improved understanding of a variety of biological and clinical risk factors within an individual's breast tissue that could better inform the risk assessment process.

Automated image analysis means all patients are subject to the same criteria for cancer risk

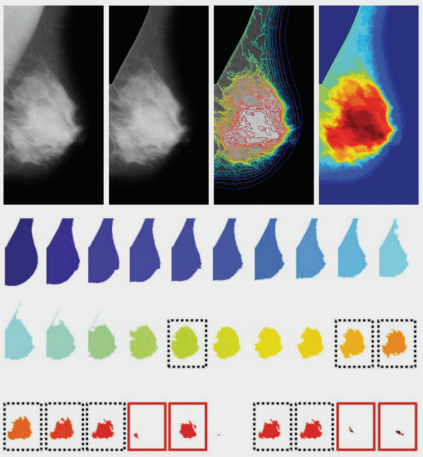


Anatomical tissue segmentation results to indicate mammographic density and risk.

Breast tissue density is known to be an important risk factor for cancer; individuals with denser breast tissue are up to five times more likely to develop a tumour, and the mammogram screen is less likely to discover an abnormality because the surrounding dense tissue obscures its detection. The distribution of dense fibroglandular tissue is therefore important for assessing cancer risk. The effectiveness of using these factors in risk assessments, however, is limited by the variation between physicians in their classification of the density and distribution of the fibroglandular tissue, as different observers will have different opinions of what constitutes 'dense'. To address this issue, Zwiggelaar and his team have developed automated image analysis software that eliminates observer variability and highlights patients who are more at risk.

AUTOMATED ABNORMALITY DETECTION

Closely related is the detection of mammographic abnormalities. "We aimed to model the normal representation of the breast and detect any deviation from that as the probability of abnormality," explains Zwiggelaar. He created a computer model that automatically processes mammogram images, calculating the density, segmentation and textures of the tissues, which enables the identification of abnormalities



Topographic-based breast density segmentation.

associated with breast cancer. "We developed this approach based on a technique borrowed from facial analysis, which exploits the variation in the shape and contrast of masses across a large dataset," elaborates Zwiggelaar. This automated image analysis means all patients are subjected to the same criteria for breast cancer risk, providing the physician with an objective second opinion that could prevent the unnecessary worry of a false positive diagnosis or a potentially life-threatening false negative.

Mammographic images are very useful but are only able to provide a projection image of the 3D breast structure. An alternative screen called tomosynthesis overcomes this issue by subjecting the patient to several small X-rays at different orientations to build up a 3D representation of the breast tissue. This affords the observer access to, and therefore a deeper understanding of, the anatomical tissue structures. One such feature are linear structures which, while they can represent normal tissue architecture such as milk ducts or blood vessels, can also reveal abnormal structures. "Spiculated lesions tend to be malignant and have a distinct pattern of radiating linear structures associated with them," reveals Zwiggelaar. "There can also be a central mass-like structure." It is difficult to tell using a mammogram whether or not the linear structures are spiculated lesions, so Zwiggelaar and his team have created computer-aided diagnosis models using 3D tomosynthesis to reveal their true structure: "Our techniques are capable of detecting the location and orientation of linear structures, and also provide an indication of the associated anatomical structures in a cross-section," he enthuses. This will help physicians to distinguish between normal and abnormal linear structures.

TARGETING PROSTATE CANCER BIOPSIES

Around 40,000 men in the UK are diagnosed with prostate cancer every year, which is predicted to become the UK's most common cancer by 2030. Rectal exams are often used to detect tumours in combination with assessing the amount of prostate-specific antigen in the blood, which increases when the prostate is inflamed or has cancer. Imaging techniques such as transrectal ultrasound and MRI can be used to evaluate a tumour's volume and invasiveness into neighbouring tissues, identifying patients at an advanced stage of cancer. Interobserver variation is a problem with the use of these imaging methods, which has led Zwiggelaar to spend several years developing computer-aided diagnostic tools for prostate cancer that can determine tissue segmentation and tumour confinement in the organ.

One of his team's most recent efforts was to improve the targeting of biopsies performed to assess the invasiveness of a tumour. Typically, biopsied tissue is taken from the prostate at random locations; however, this approach can miss the cancerous tissue, leading to an underestimate of tumour aggression and disease severity in half of all cases. Zwiggelaar's group designed a computer-aided diagnostic tool aimed at the prostate peripheral zone, from which 80-85 per cent of prostate cancers arise. The tool divides the MRI images of the peripheral zone into four subregions and uses the difference in greyscale and contrast to determine the most cancerous of the sections. This technique can be used to perform fewer and more accurately targeted biopsies for the patient and obtain a better understanding of their cancer.

BLOOD INDICATORS OF BRAIN CANCER

Glioblastoma multiforme is the most aggressive type of brain cancer and can be very difficult to remove safely. Tumours require their own blood supply to grow and Zwiggelaar has identified tumour vasculature as a promising method of assessing their biological features. The researchers used stable xenon computed tomography (CT) to investigate the vasculature of glioblastomas. The patient undergoes a CT scan whilst simultaneously inhaling xenon gas – the amount of xenon diffusing into the brain correlates to blood flow. The image is processed into a blood flow map, for which Zwiggelaar has developed a method to assess two important biological features; neurological necrosis and vascularity. In glioblastomas, tumour vasculature is not able to give adequate tissue perfusion, so a reduced blood flow is indicative of a higher level of cancer angiogenesis. It is also possible to determine the amount of neurological tissue still remaining within the tumour, if any, which is vital for a preoperative assessment of the maximum amount of tumour that is safe to remove without damaging healthy brain tissue.

CONTINUOUS IMPROVEMENT

The contributions that Zwiggelaar has made to the field of automated medical imaging analysis are indicative of his constant drive to improve. The computer-aided diagnostic tools he has already developed have a high degree of accuracy, but he is keen to ensure that they are useful in a clinical setting to guide cancer risk assessments, diagnosis and classification in an objective and precise way in the future.

INTELLIGENCE

IMAGING TECHNIQUES FOR IMPROVED DIAGNOSIS FOR BREAST, BRAIN, BLOOD AND PROSTATE CANCER

OBJECTIVES

To assist radiologists (and other clinical experts) in their understanding and assessment of medical images by using advanced computer modelling techniques.

KEY COLLABORATORS

Andrew Maidment; **Predrag Bakic**, University of Pennsylvania, USA

Robert Marti; **Joan Marti**; **Arnau Oliver**; **Jordi Freixenet**, University of Girona, Spain

Paul Malcolm; **Stuart Williams**, Norfolk and Norwich University Hospital, UK

Fangjun Luan; **Zhili Chen**, Shenyang Jianzhu University, China

Ashwini Kshirsagar, Hologic Inc., USA

FUNDING

National Institute for Social Care and Health Research

China Scholarship Council

Wales Office of Research and Development for Health and Social Care

Spanish Ministry of Education and Science

Biotechnology and Biological Sciences Research Council

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REYER ZWIGGELAAR received the Ir. Degree in Applied Physics from the State University Groningen, Netherlands, in 1989, and his PhD in Electronic and Electrical Engineering from University College London, UK, in 1993. He is currently Professor at the Department of Computer Science, Aberystwyth University, UK, and the author or co-author of more than 200 conference and journal papers. Zwiggelaar's current research interests include medical image understanding, particularly focusing on mammographic and prostate data, pattern recognition, statistical methods, topological data analysis, texture-based segmentation and feature-detection techniques.

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