Oncological image analysis:

medical and molecular image analysis

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Abstract

This paper summarises the work we have been doing on joint projects with GE Healthcare on colorectal and liver cancer, and with Siemens Molecular Imaging on dynamic PET. First, we recall the salient facts about cancer and oncological image analysis. Then we introduce some of the work that we have done on analysing clinical MRI images of colorectal and liver cancer, specifically the detection of lymph nodes and segmentation of the circumferential resection margin. In the second part of the paper, we shift attention to the complementary aspect of molecular image analysis, illustrating our approach with some recent work on: tumour acidosis, tumour hypoxia, and multiply drug resistant tumours.

1. Introduction

Cancer is, after heart disease, one of the major causes of death in the developed world. Cancer statistics make grim reading. One in three people in developed countries will be diagnosed with cancer during their lifetime. The worldwide incidence (number of new cases) is currently 10 million, a figure that is expected to double over the next 15-20 years. It is estimated that over 550,000 people died of cancer in the USA alone in 2002. For women, the incidence of breast cancer is 31% (so that one woman in 9 will be diagnosed during her life), followed by lung (12%) and colorectal (12%). For men, the leading cancer is of the prostate (30%), followed by the lung (14%) and colorectum (11%). Colorectal cancer most often metastasises to the liver or pelvis, both with poor prognosis. The first part of this paper concentrates on colorectal and liver cancer, the two cancers which have been the major focus of our work over the past two years, primarily on a project carried out jointly with GE Healthcare.

Cancer is the collective name for a group of probably more than one hundred diseases that are characterised, following the pioneering work of Hanahan and Weinberg (Cell 100, 2000) by one or more of the six hallmarks of cancer[1]:

1. Growth signal autonomy
2. evasion of growth inhibitory signals
3. evasion of apoptosis

[1] Lauren Pecorino, Molecular Biology of Cancer, Oxford University Press, 2005

Medical Imaging 2007: Image Processing, edited by Josien P. W. Pluim, Joseph M. Reinhardt,
Proc. of SPIE Vol. 6512, 65121E, (2007) · 1605-7422/07/$18 · doi: 10.1117/12.718033

4. unlimited replicative potential
5. angiogenesis
6. invasion and metastasis

Cancers vary considerably according to the site in the body – for example, in the extent of local perfusion (blood supply) necessary to sustain the unregulated growth, the consumption of oxygen (and attendant hypoxia), the control of pH, etc. The second part of the paper reviews some of the mathematical/computational models we have developed for tumour hypoxia and its imaging using PET, tumour acidosis, and multiply drug-resistant tumours.

Cancer is costly in financial as well as human terms. For example, in 2001 the cost of cancer treatment in the USA alone for breast cancer were $7Bn and for colorectal cancer $6.5Bn.

It is not all bad news, however. There have been massive advances over the past 30 years, partly due to improved understanding of the molecular biology of cancer – and to the introduction of the drugs such as 5FU, Tamoxifen, Herceptin, … which have resulted from that understanding; and partly also from our rapidly advancing ability to image the body noninvasively. Section 2 sets out some of the the difficulties of image analysis applied to cancer.
The combination of image analysis and the massive advances that we have seen over the past 50 years in molecular biology have led to the development of molecular image analysis, to which we return in Section 4.

2. Image analysis applied to cancer

It should be clearly understood that no single imaging "modality": computed tomography (CT), MRI and its variants, PET, Spect, ultrasound, MEG, EIT, … deliver the information that supports a definitive detection, diagnosis, or patient management decision in all cases. Increasingly, images are combined ("fused") as an identikit of the tumour is built up from a set of images. The Table below merely hints at the range of aspects of a tumour and the corresponding images that can be used to detect that aspect.

Aspect of the tumour	Most appropriate imaging modality
Cancer tissue is radiologically dense, microcalcifications	Mammography
Cancer tissue is biomechanically dense	Ultrasound
Angiogenesis	ceMRI, more recently BOLD MRI
Cancers have massively elevated need for food, eg glucose	FDG-PET, SPECT
Cancer cells divide rapidly	FLT-PET
Cancers are most dangerous when they metastasise	Whole body PET

Cancers can control their local acidity (pH)	ce-MRI with pH-sensitive & pH-insensitive Gd-DTPA
Cancers grow hypoxically	PET + nitroimidazoles (FMISO, FAZA, FETNIM), Cu-ASTM, …

In summary, oncological image analysis is intrinsically hard because:

1. the images vary enormously, not least because the anatomy and physiology of people vary enormously.
2. image formation is not an exact science and so different radiographers (US: technologists) will acquire quite different images of the same patient. There is a strong analogy to film-based photography, where one can vary the film, exposure time, aperture, focus, … to yield a wide variety of images of the same scene; radiographers have even more choices to make!
3. medical images have less spatial (and temporal) resolution than one ideally needs. For example, it would be ideal to detect tumours when they are just 1-2mm in dimension, for then the probability of metastasis is extremely low; but this defeats the resolution of PET and many MRI examinations.
4. medical images have substantially poorer signal-to-noise ratio than modern visual CCD images – typically by a factor of 10. Note that the noise of many kinds of medical image is not well modelled by parametric distributions such as Parzen windows, so that we have developed a non-parametric estimator of the probability density function of image regions of images, explicitly recognising that they are band-limited and critically-sampled. The paper by Joshi in these proceedings explains the idea.
5. the images are complex, textured, noisy, and often have low spatial resolution
6. the objects to be detected, for example cancers, often have complex shapes and poor contrast relative to their surrounds
7. disease processes are often subtle, so that it is difficult to differentiate benign conditions (for example, a fibroadenoma) from a malignant condition (for example, an adenocarcinoma). A corollary is that precise definitions of "normality" are not available

Evidently, oncological image analysis is difficult, yet to be accepted and used by clinicians, image analysis systems have to be reliable, accurate and robust almost always. A clinician's confidence in a piece of software grows slowly; one stupid result (eg presenting the heart as a region of interest in dce MRI of the breast) will instantly undermine that confidence. How can performance at that high level possibly be achieved on such complex and variable images? A recurrent theme in our work over the past 20 years is the range of models that needs to be developed:

1. ***Models of image formation***: we have developed models of the passage of x-rays through breast tissue as the basis for algorithms for mammographic image analysis; pharmacokinetic models of Gd contrast agent take-up for dynamic contrast enhanced MRI; and now we have developed models of dynamic PET.
2. ***anatomy***: segmenting the colorectum and finding the mesorectal fascia, in the case of colorectal cancer, requires knowledge of the colorectal anatomy as it appears in MRI (and of the T_1, T_2 at each image location)

3. ***physiology***: we illustrate the mobilisation of physiological knowledge in the cases of: tumour segmentation in dce MRI and FDG-PET, and to constrain non-rigid registration of pre- and post-chemotherapy images of the colorectum

The next section briefly overviews our recent work on colorectal and liver cancer image analysis.

3. Colorectal and liver cancer

Over the past year we have worked closely with GE Healthcare on colorectal and liver cancer, as a paradigm example of integrated systems biology, which studies the disease from DNA and proteomics through to surgical decision making. Our particular contributions have been on MRI image analysis of the colorectum and liver, on molecular image analysis models (see the next section), and a software system for information integration (see section 5). Note that we group colorectal and liver cancer because the primary metastasis of colorectal cancer is (via the portal vein) to the liver. A large proportion of liver tumours are, in fact, secondary cancers whose primary site was the colorectum.

The primary imaging modality used for the detection, diagnosis and for staging colorectal cancer is MRI. Specifically, the clinical protocol typically comprises axial small field of view T2 weighted MR images (TE = 90ms, TR = 3500-5000ms, α = 90deg, slice thickness = 3mm) acquired using a 1.5T MRI machine. Our datasets are 3-D, each comprising 512 x 512 x 25 voxels of size 1mm x 1mm x 3mm (though we have an increasing number of data sets with voxels of size 0.78 mm x 0.78 mm x 3mm). The datasets acquired at our site have (until a recent upgrade) exhibited a substantial bias field, with a particularly bright artefact near the coccyx and extending over several MR slices. There is a diversity of tissue classes in colorectal MR images, and several of them have substantial texture.

To date, our work has concentrated on:

1. Segmentation of the colorectum and mesorectum (see Bond 2005, 2006). This builds a representation of the colorectum and surrounding mesorectum (in which the key sentinel lymph nodes are to be found) based on a model of the MRI signal values of the hip bones and colorectum, and a model of the anatomy.
2. Detection and assessment of lymph nodes (Bond 2006, Kim 2007). This is essential to down-staging a tumour.
3. detection of the boundary of the mesorectum, which is necessary to determine the circumferential resection margin, hence the likely outcome of surgery. This step mobilises our non-parametric representation of probability density functions, together with a level set segmentation algorithm based on the monogenic signal (Bond, Joshi, Petroudi, and Brady 2007). We present some more detail on this below.
4. non-rigid registration of MR images of the colorectum pre- and post-chemotherapy (Bond 2006), enabling a quantitative assessment of tumour change. This mobilises a model of the anatomy and of the physiological changes wrought by chemotherapy.

5. compensation for unpredictable breath-holds in contrast-enhanced imaging of the liver (Noterdaeme 2007)
6. non-invasive assessment of tumour ablation in high-intensity focussed ultrasound (Noterdaeme 2007)
7. a model of cancer growth that we have developed, linking tumour morphology to aggressivity of tumour growth, and ultimately to the DNA mutations of the components of the heterogeneous tumour (Matthew Kelly, 2007).
8. for dynamic contrast-enhanced MRI: segmentation, registration (motion compensation), and simultaneous segmentation and registration (Hua 2005, Lo 2006)

Currently, apart from chemoradiotherapy (used in 65% of cases), surgery is the only curative therapy. Local excision surgery continues to gain acceptance slowly; generally, surgery is by "total" resection of the mesorectum (TMR). This is often quite traumatic surgery, frequently necessitating use of a stoma post-surgery. Clinicians consider very carefully the likely success of surgery before proceeding. Evidently, it is doubly traumatic for the patient to undergo such radical surgery, then to have a recurrence of cancer (often within 6-12 months) or to discover that the chemoradiotherapy had already rendered surgery unnecessary. One of the major reasons for poor outcome following a TRM is the presence of affected lymph nodes too close to the surgical boundary. The circumferential resection margin (CRM) is "defined" as the shortest distance from an affected lymph node to the mesorectal fascia. It has been proposed that the TRM be planned so that the CRM is at least 1mm, or, if this is not possible, that the surgical option be dismissed. To this end, one influential study proposed that "thin section" MRI (typically, meaning voxels of size 0.78 mm x 0.78 mm x 3mm) be used to estimate the CRM. At first sight, this appears to be a straightforward application of image analysis. However: (1) it assumes that all affected lymph nodes have been detected and their often small sizes estimated accurately (incorporating partial volume estimation) as noted above, in this paper we assume that this has been done; (2) that the bounding surface of the mesorectum (the MF) has been located completely and accurately; and (3) that the CRM estimation has taken due account of the MRI spatial sampling and the relative orientation of MRI slices to the local axial direction of the colorectum/mesorectum. We have recently shown how to combine anatomical knowledge (to initialise estimation of the MF) with a level set method based on a non-parametric representation of the distribution of intensities inside the putative MF. Uncertainty in the position of the MF is estimated at each boundary location. One of the challenges that need to be overcome is the substantial variation in the appearance in the image of the MF as one moves along its contour. To this end, we have incorporated the monogenic signal into the estimated position of the MF, and to provide a model of uncertainty in localisation.

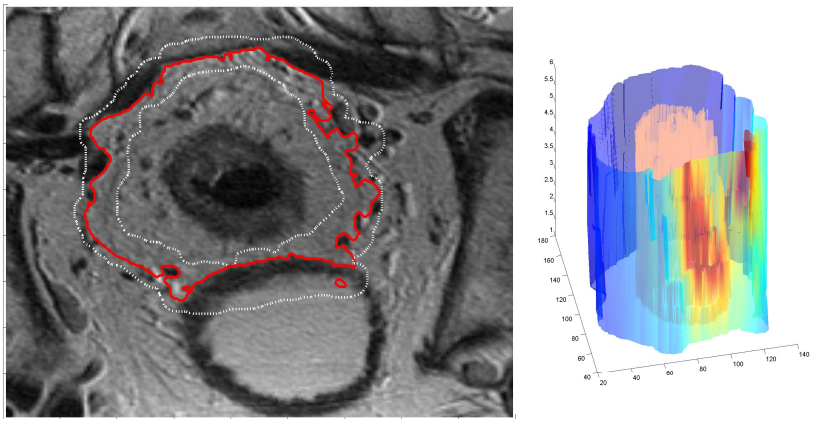

Figure 1: left: the minimum and maximum displacements from the optimal MF; right: the CRM color coded.

Figure 1 shows the minimum and maximum displacements from the optimally placed MF. The figure at right is a display of the circumferential resection margin.

4. Molecular Oncological Image Analysis

In the fourth part of the talk, we shift attention to the complementary aspect of molecular image analysis, illustrating the approach with some of our recent work on: tumour acidosis, hypoxia, metastasis, and heterogeneity. We show the role that an advanced PET simulator can play in developing algorithms. This is a rapidly growing topic and references will be provided. The book edited by Mike Phelps *PET: Molecular Imaging and its Biological Applications* is a good starting point. We show examples of our work to date on molecular image analysis for cancer:

1. ***Tumour acidosis***: My student Kieran Smallbone has developed a mathematical model of the way in which a tumour actively controls its pH environment. This comprises a cellular automaton model of cell-cell interaction, and a mean field partial differential equation formulation at a larger scale. The model offers new therapeutic alternatives for chemotherapy, and provides an alternative explanation of quiescent cell cycling. The model has been validated against pH sensitive/pH insensitive Gd MRI images. The work has been published in several papers in J. Math. Biol.

2.

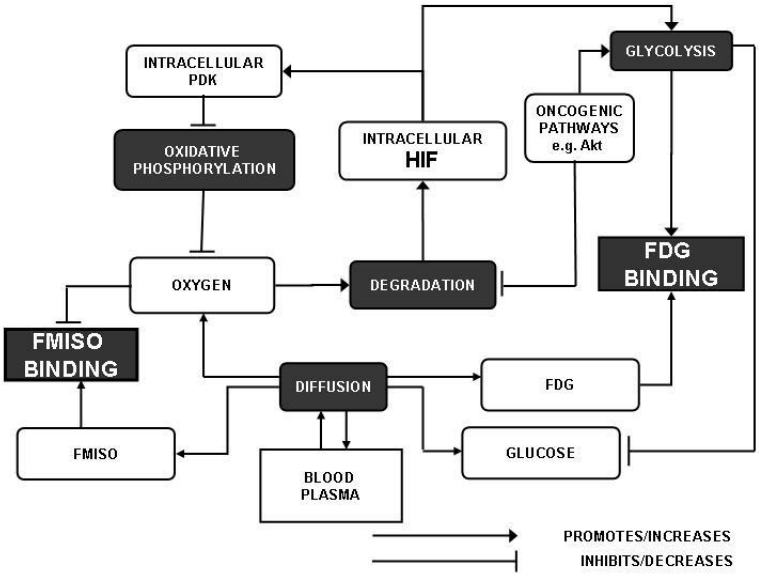

Figure 2: A schematic of the hypoxia model – refer to text for details. The model is expressed computationally as a set of coupled partial differential equations.

2. ***Tumour hypoxia***: My graduate student Cat(herine) Kelly has developed a mathematical model for tumour hypoxia, work that is at the interface between medical imaging and systems biology. A characteristic of the model is the use of a probability density representation of vascularity. From the reaction-diffusion model of hypoxia, we have predicted, initially for F-MISO, hypoxia islands and time-activity curves (TACs) which correlate closely with experimental findings. Our model has been developed so that other hypoxia markers can be substituted straightforwardly for F-MISO, including Cu-ATSM, but perhaps more interestingly the other nitrimidazoles you mention. More interestingly, we have developed a refinement of the model that predicts the interaction between hypoxia and the glycolytic phenotype. Our work has lead to the development of a model describing the relationship between the local environment and metabolic state of a cell, and the uptake of two PET tracers; the hypoxia-specific Fmiso and FDG, conventionally a marker of glucose metabolism, whose binding has been linked to hypoxia.

The model, a schematic of which is presented in Figure 2, is based on a realistic representation of the physical delivery process, combined with a systems biology representation of the factors influencing the cellular metabolic response to hypoxic stress, via both the Hypoxia-Inducible Factor 1 (HIF), and also the oncogenic Akt pathway, believed to be a key promoter of the Warburg Effect. In the model, nutrients and tracers may diffuse through a network of 'cells', being metabolised or bound, depending on local environmental conditions and the metabolic state of each cell.

Our model is successful in reproducing both the hypoxia-dependent binding of both tracers, as reported in the literature (Figure 3). However, the model also highlights the conflicting effects of oncogenic factors on image *contrast*.

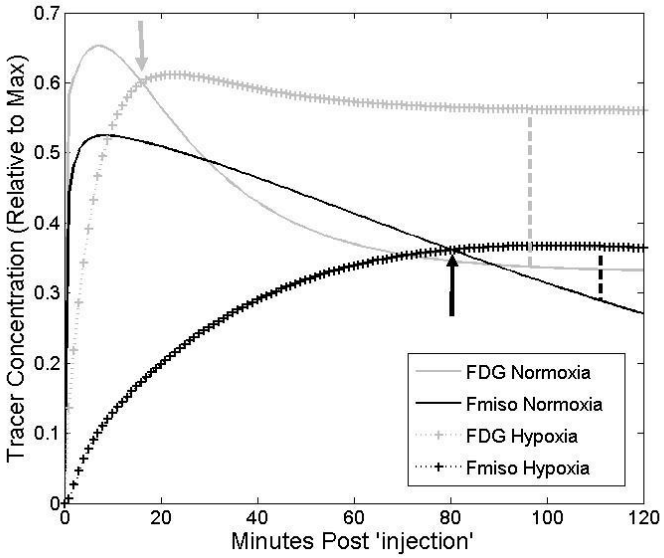

Figure 3: predictions from the model presented in outline form in Figure 2 for normoxic and hypoxic tumours for the FDG and FMISO radiochemicals. See text for more details.

From an imaging perspective, a hypoxic tracer must demonstrate contrast (i.e. differential binding) between hypoxic and normoxic tissue. Our results indicate that we can predict the hypoxic:normoxic contrast of tracers under a variety of physical and genetic conditions. Specifically, we have reproduced the image contrast observed in the literature, for a number of tracer and oxygenation combinations, and predicted a reduction in contrast elicited by oncogenic contributions. These predictions provide a tool for identifying and designing molecular cell biology experiments.

Initial Validation

Cell Biology

To test the model hypothesis that hypoxic:normoxic contrast is compromised by the expression of oncogenic factors, we are currently designing molecular cell biology experiments, to be conducted at the Weatherall Institute of Molecular Medicine.

Multicellular Tumour Spheroids grown from cancer cell lines are to be modified to express high or low levels of the oncogenic factor, Akt. The uptake of FDG and an analogue of Fmiso, pimonidazole, will be used to determine any changes in contrast between hypoxic and normoxic regions of the MTS.

3. ***Dynamic PET***: My students David Schottlander (Siemens Molecular Imaging), Andy McLennan, and I have developed a method for reconstructing and analyzing dynamic PET data. We begin with a method for regional quantification and then develop a parametric list-mode reconstruction algorithm. This has been extended to a regional parametric list-mode reconstruction algorithm. One part of this work has been the installation of the SORTEO PET simulator in the Medical Vision Laboratory, running on a 20 node (each a dual processor) cluster. This has enabled us to test algorithms for dynamic PET over a wide range of parametric conditions prior to application to human/small animal data.

4. ***Relating microscopy images to PET tumour data***: My student Bobby Ali has also worked extensively on PET SORTEO, and has developed a PETParams website which provides parametric values for a range of radiochemicals and published experiments (we found that the values of the parameters of compartmental models varied widely, often by two orders of magnitude). Each compartmental model has its parameters associated with it, and hyperlinked to PubMed references in which the model appeared. We also have access to a time series of images following the uptake and efflux of ZnATSM. We can capture snapshots of several cells at various time points, and we are using image analysis methods to generate an ensemble average of intra-cell probes at each time point. This work is being done in association with Professor Ruth Muschel and the GCI. The eventual aim of the work is to simulate heterogeneous tumours in human and mouse digital phantoms, relating the ZnATSM-analogue CuATSM TACs to those generated by PET-SORTEO.

5. My student Bobby Ali has begun to model multiply drug-resistant tumours, specifically the key role that lysosomes play in defending the cell nucleus from attack by chemotherapy agents.

5. Information integration: the *MDTSuite*

The following diagram sketches the complex set of "patient journeys" that arise in the patient management of cancer. The important messages are (i) that image analysis does not exist in isolation of the many other considerations that need to be taken into account in cancer, so developing (for example) a neural network intended for CAD does not necessarily contribute to clinical practice; and (ii) that image analysis is only one piece of the whole system that needs to be constructed. The paper by Matthew Kelly and Mark Austin shows examples of the MDT Suite software that we have developed to support the weekly multi-disciplinary team meeting for patient management, and which comprises surgeons, radiologists, clinical pharmacologists, oncologists, epidemiologists, etc. This is shown in skeletal form in the following Figure.

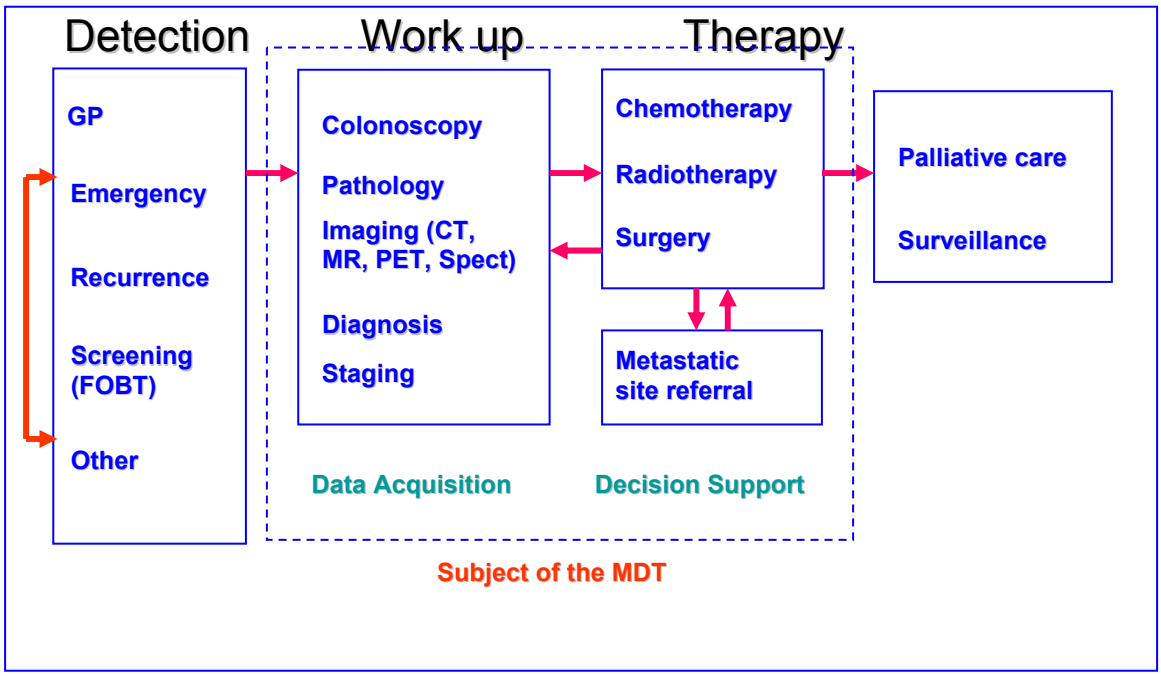

Figure 4: the set of "patient journeys" for colorectal cancer. The multidimensional team meeting decision support system addresses the two central panels.

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