Models for Cancer Imaging

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Cancer in Europe 2012

- New cases: 3.45M, deaths: 1.75M
- Cases
  - Breast: 474,000 (deaths: 131,000)
  - Colorectal: 447,000 (deaths: 215,000)
  - Lung: 411,000 (deaths: 353,000)

Projections 2030

UK lifetime risk of getting cancer will be 47% by 2020 (44% in 2012)

By 2020, 38% will survive cancer to die of another cause (35% in 2012)
Breast cancer incidence

- In developed countries, 1 in 8 women will get breast cancer at some point
- 23% of all cancers in women – projected to rise to 29% by 2030
- Peak incidence is women over 60

- In developing countries, including BRIC, numbers are rising rapidly, already 500,000 cases in 2008
- Reasons: increasing urbanisation, changes in lifestyle
- Impacting particularly on younger women

Early detection + chemo/radio/conservative surgery + risk analysis is transforming morbidity
Mammography: Image Parameter Dependence

29kVp 128mAs

RW: 35%
ES: 50%

28kVp 67mAs

RW: 40%
ES: 25%
First technological capability: need for quantitative analysis in mammography

Two of the UK’s most experienced breast radiologists each examined the two mammograms shown, to estimate the percentage of dense tissue – a key risk factor for breast cancer.

BK estimated 25%; TLS estimated 40%.

But it is the same breast, left imaged 2X right.

Image intensity relates to anatomy in a very complex way, making quantitative image analysis a hard problem.

Starting 1994, with Ralph Highnam, I have invented a sequence of solutions to this problem:

• $h_{int}(x)$ – a quantitative representation of the image intensity at pixel $x$ as the amount of non-fat (interesting) tissue at $x$;

• Volpara density – a fast, relative physics model developed by Matakina Ltd.

* SMF = Standard Mammogram Form
First, a tiny bit of physics: Beer’s Law

\[ \text{Fluence } I \]

\[ \text{attenuation } \mu_1 \]

\[ \text{Fluence } I e^{-h\mu} \]

\[ \text{Fluence } Ie^{-(\mu_2 h_2 + \mu_1 (h_{1a} + h_{1b}))} \]

Note that the exiting fluence is the same irrespective of where, vertically, the block of attenuation \( \mu_2 \) is.

Mammography is fundamentally projective: though digital breast tomosynthesis is changing that…
A model of mammographic image formation

Device $\rightarrow$ X-ray photon fluence model

Energy that reaches the imaging sensor:

$$E^{\text{imp}}(\mathbf{x}) = \phi(V_t, \mathbf{x}) A_p t_s \int_0^{E_{\text{max}}} N_0^{\text{rel}}(V_t, \varepsilon) G(\varepsilon) D(\varepsilon) \exp^{-\mu_{\text{lucite}}(\varepsilon) h_{\text{plate}}} \exp^{-h_{\mu}(\varepsilon)} d\varepsilon$$
Highnam & Brady’s $h_{\text{int}}$ model

The literature tells us* that you cannot distinguish stromal tissue and tumours on the basis of their x-ray attenuations ➔ two kinds of tissue: fat & “interesting”. If the compression between the plates is $H$ cm, then at any given pixel $x$, we have $H = h_{\text{fat}}(x) + h_{\text{int}}(x)$

Our job is to find $h_{\text{int}}(x)$ for every voxel $x$. We know $H$ and the tube parameters.

What can we find from the equation of photon fluence?:

$$E^{\text{imp}}(x) = \phi(V, x) A_p t_s \int_0^{E_{\text{max}}} N_{\text{rel}}^t(V, \varepsilon) G(\varepsilon) D(\varepsilon) \exp^{-\mu_{\text{lucite}}(\varepsilon) h_{\text{plate}}} \exp^{-h\mu(\varepsilon)} \, d\varepsilon$$

We measure this

We know all this stuff

Compression plates – we know that too

The bit we don’t know!

$$h\mu(\varepsilon) = h_{\text{int}}\mu_{\text{int}}(\varepsilon) + h_{\text{fat}}\mu_{\text{fat}}(\varepsilon)$$

$$= h_{\text{int}}(\mu_{\text{int}}(\varepsilon) - \mu_{\text{fat}}(\varepsilon)) + H\mu_{\text{fat}}(\varepsilon)$$

* It may be wrong 😊
Volume-based Density Measurement

Volumetric Breast Density = \frac{\text{Volume of "interesting" tissue}}{\text{Volume of the breast}}
We have to know all those calibration parameters for Highnam and Brady’s method to work. We can guess at lots of them... BUT

Suppose we knew a region of the breast that was *entirely* fat... We could then use this as a “reference”

\[ h_d(x) = \frac{\ln \left( \frac{I_{\text{obs}}(x)}{I_{\text{fat}}} \right)}{\mu_{\text{fat}} - \mu_{\text{dense}}} \]

We need accurate breast inner/outer boundary segmentation .... We use phase congruency
Why is Breast Density Important?

• 40% of women have dense breasts

• Mammography is only 48% effective in dense breasts, compared to 98% in fatty breasts
  – This is why mammography gets criticised

• Dense breasts are 4-6 more times more likely to develop cancer than fatty breasts

• Breast density is a more significant risk factor than having a mother and sister with breast cancer

• Cancer recurrence is four times more likely in women with dense breasts

• 35+ Years of research with very large number of published papers have documented the importance and difficulty associated with classification of breast density
Current Breast Density Classifications

BI-RADS®: The American College of Radiology (ACR) has published a set of criteria which radiologist’s use to categorize their opinion of the absence or likelihood of disease. Within that criteria is also a visually-assessed BI-RADS breast density category (an area-based breast density assessment method). Those categories are:

Category 1 — The breast is almost entirely fat (<25% glandular).

Category 2 — There are scattered fibroglandular densities (approximately 25-50% glandular).

Category 3 — The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% – 75% glandular).

Category 4 — The breast tissue is extremely dense. This may lower the sensitivity of mammography (>76% glandular).

These are commonly called the BI-RADS breast composition categories. Radiologists in the US should record every woman’s breast density using the BI-RADS scheme.
Volume-based Methods for Density Measurement

Approximately 2,000,000 mammograms processed over past 12 months
Volume-based Methods for Density Measurement

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Approximately 2,000,000 mammograms processed over past 12 months
Woman has a mammogram. A patient stratification tool, such as Volpara breast density score, is immediately available.

The patient can decide on supplementary screening before she leaves the clinic.

Options for supplementary screening include:
- Breast ultrasound
- Breast MRI
Why do we need contrast agent?

No abnormal tissue visible
Contrast Agent Uptake Profiles

- Malignant to benign distinction is improved using concentration based analysis.
Gradient Echo Signal Model

• Use Bloch equation to describe signal for a gradient echo pulse sequence (for example)

\[
S = g \rho e^{-\frac{TE}{T_2^*}} \sin \alpha \left( \frac{1 - e^{-\frac{TR}{T_1}}}{1 - \cos \alpha e^{-\frac{TR}{T_1}}} \right)
\]

• Add effects of contrast agent (\(T_1\) & \(T_2\) alteration).

\[
S(C_t) = g \rho e^{-TE\left(\frac{1}{T_2^*} + R_2C_t\right)} \sin \alpha \left( \frac{1 - e^{-TR\left(\frac{1}{T_1} + R_1C_t\right)}}{1 - \cos \alpha e^{-TR\left(\frac{1}{T_1} + R_1C_t\right)}} \right)
\]

\(TE, T_2^*, T_1\) are fixed for any given voxel;
\(g, \rho\) depend on the particular machine, and are unknown
The only things we can vary are: \(\alpha, TR\)
In practice, vary \(\alpha\)
Measuring effect of chemotherapy

Pre- and post-chemotherapy
Percentage increase in intensity at right

Pre- and post-chemotherapy $\Delta T_1$ at left
(non-rigid) registration and pre- and post-chemotherapy, from $\Delta T_1$

Armitage, Brady and Behrenbruch, Medical Image Analysis (2005)
Colorectal cancer dceMRI: motion

Original data
Simultaneous estimation of motion parameters and PK parameters

DCE image set

Estimate & correct motion

Estimate PK parameters at each voxel

There are numerous ways in which this cycle can be developed mathematically and implemented in an efficient algorithm. The simplest is expectation-maximisation...though there are several others
Model-based Registration and Parameter Estimation (MoRPE)

Input: Baseline image + DCE-MRI scan

Initialize $\theta$ (by curve-fits), and $T$ (= 0), and generate the ‘predicted dataset’.

Evaluate: Cost Function $= -\log(P(T, \theta | Y, X_0, \sigma))$}

Minimize Cost Function w.r.t. PK parameters $\theta$ and motion parameters $T$.

Repeat until convergence, or for $t$ iterations

Update $T$ and $\theta$

Output final deformation parameters $T$ and final PK parameters $\theta$. 

M Bhushan et al. MICCAI’11, ISMRM’12
Motion correction of dceMRI volumes for colorectal cancer
In this case, the signal change and motion were simulated. ( ----- )

The simultaneous algorithm:

Two standard similarity criteria for deformable registration:
Motion correction: Differences in $K_{\text{trans}}$ distributions before & after therapy

No discrimination for non-responder/responder case using conventional normalised cross-correlation (NCC) registration

Increase in perfusion for responder vs no change in non-responder case using MoRPE (PK model-based registration)

M Bhushan et al. MICCAI'11, ISMRM'12
The importance of motion correction

Without Motion Correction

Motion correction using our algorithm

discrimination between responders & non-responders is not possible without motion correction

Statistically significant* discrimination between responders & non-responders

We use the Komogorov-Smirnov test, KS

*M Bhushan et al. MICCAI'11, ISMRM'12
What can currently cure cancer?

Professor Sir Mike Richards, NCRI 2011

Surgery, 49%

Radiotherapy, 40%

Chemotherapy, 11%

Can we define biological processes that regulate or are markers of the responsiveness of tumours?

Can agents that target these processes be taken into the clinic to alter outcome?
Hanahan and Weinberg Hallmarks of Cancer

- EGFR inhibitors
  - Sustaining proliferative signaling
- Cyclin-dependent kinase inhibitors
  - Evading growth suppressors
- Immune activating anti-CTLA4 mAb
- Aerobic glycolysis inhibitors
  - Deregulating cellular energetics
- Proapoptotic BH3 mimetics
  - Resisting cell death
  - Genome instability & mutation
- PARP inhibitors
  - Inducing angiogenesis
  - Activating invasion & metastasis
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met
  - Avoiding immune destruction
  - Enabling replicative immortality
  - Tumor-promoting inflammation
  - Selective anti-inflammatory drugs
  - Telomerase Inhibitors
An early example: Melanoma*

40-60% of patients with melanoma have activating mutations of BRAF – a proto-oncogene that makes a protein B-RAF, which is involved in signalling in cells related to cell growth.

PLX4032 (Vemurafenib) is an inhibitor of BRAF kinase.

Vemurafenib targets the RAS-RAF1-MEK-ERK pathway.

*Strictly: Chronic Mylogenous Leukaemia
Man, 38 years old with a BRAF-mutant melanoma

PET fluorodeoxyglucose (FDG) image
PET imaging shows the impact of Vemurafenib

Before and two weeks after initiating PLX4032
“This is one of the best examples I’ve ever seen of science triumphing over disease.” Brian Druker
Conclusion
....cancer is agile.. It rapidly learns to mutate to accommodate a new therapy.....

This is a salutary lesson ... but it is not all such bad news....
Cancers don’t just develop as aberrant processes within a cell, rather by a complex series of interactions with the cells in their neighbourhood, that form the normal epithelia.

In normal tissue, these form the basement membrane.

Tumour angiogenesis has many similarities to normal wound healing …
A picture of wound healing....

Pathway model
Above, left: normal; right chaotic (tumour is black)

Another rendition of chaotic & leaky neovasculature

normal tissue  tumor
Imaging angiogenesis: many targets!

**Growth Factors and Receptors**
- **VEGF A-D**
- PIGF
- VEGF-R1-3
- PDGF/PDGFBRs
- FGF/FGFRs
- Neuropilin receptors

**Extracellular Matrix Proteins**
- Vitronectin
- Fibronectins
- Collagens
- Laminins
- Fibrin
- Thrombospondin

**Adhesion Molecules**
- **Integrins**
  - Cadherins
  - VCAM
  - Ig SF

**Proteinases**
- MMP2 and 9
- TIMPs
- uPA, tPA
- uPAR

**Maturation and guidance factors**
- Angiopoietins
- Ephrins
- Wnt
- Notch/DLL
- Semaphorins/Collapsins
- Robo-4

**Signalling Molecules**
- MAPK
- Raf Ras
- PKA
- Cdc42
- PKB
- COX-2

**Transcription Factors**
- HIFs
- NFkB
- PROX-1
- FOX
- Hox

 Courtesy Dr. Neel Patel, Oxford
Integrins 'integrate' signals from the extracellular matrix (ECM) to the intracellular cytoskeleton in focal adhesions.

In particular, the integrin αvβ3 mediates the migration of endothelial cells through the basement membrane during blood-vessel formation. It binds to peptides containing the amino-acid sequence RGD*.

* Arginine-Glycine-Aspartic acid

18F-RGD PET-CT image of small renal tumours

Courtesy Dr. Neel Patel, Oxford
VEGF for inhibition of angiogenesis

Vascular Endothelial Growth Factors
VEGF A-D are signalling proteins

Cellular response through the tyrosine kinase receptors (the VEGFR 1-3) on the cell surface

Courtesy Dr. Neel Patel, Oxford
A range of related targets
Imaging Avastin bound to SPECT emitter $^{124I}$
Biodistribution & immunohistochemistry

Biodistribution of $^{111}$In-bevacizumab in FaDu xenograft bearing Balb/c nude mice

%ID/g

- Tumour
- Blood
- Muscle
- Skin
- Stomach
- Small intestine
- Large intestine
- Fat
- Spleen
- Tail
- Liver
- Kidneys
- Heart
- Lungs

VEGF
Avastin
Autoradiograph

Courtesy Dr. Neel Patel, Oxford
(Liver) tumour shape pre-chemotherapy
Liver tumour shape post-chemotherapy, 9 months later
pre-ablation, another 3 months later
Tumour Growth Model

- Early tumour masses are often approximately spherical and grow as spheres. Mathematical models treat this case.
- They can sprout additional spheres (this corresponds, biologically, to clonal expansion)
- Heterogeneous tumours with multiple clonal centres may demonstrate variations in response to therapy (i.e. resistant clones)
- Can we relate morphological changes, determined from images, to underlying cancer growth processes?

recent examples from the Churchill

The shape of the resected specimen

We conjecture that shape and shape changes encode the evolution, mutations, and severity of a tumour

Olivier Noterdaeme, Dr. Matt Kelly, Mike Brady, and numerous clinicians
The tumour growth model gives a plausible account of tumour morphology; but the key question remains: do the successively sprouted clonal centres correspond to increasingly severe mutations of the original tumour DNA?

More precisely, we conjecture that the genomes of samples within a spheroid will show minor variation; but that the genomes of samples from different spheroids will have substantial variation.

Noterdaeme, Kelly & Brady 2008
Pre-resection CT (6 slices shown)

3D model of tumour

DNA extraction (proteinase K digestion & purification).

Nuffield Department of Clinical Laboratory Sciences

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<th>SampleID</th>
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<th>labelling yield [µg]</th>
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array Comparative Genomic Hybridization (aCGH), NimbleGen, Iceland

385,000 probes of a sample 17.4mm x 13mm \( \Rightarrow \) 6270 base pairs analysed

This shows the amplification of each of the genes in each of the chromosomes of the particular DNA sample – in this case from the turquoise spheroid

Noterdaeme, Kelly & Brady 2008
Log2 intensity ratios as a function of chromosome position for 7 hybridisations.

Horizontal axis is chromosome number; vertical axis is log intensity ratio – higher values show amplification of a particular chromosome = significant changes of the DNA sequence in the genes that make up the chromosome.

312 and 313 are from the same spheroid, and show similar amplification of chromosomes 2, 7, 10

318, 319 are both from another spheroid and show similar amplification of chromosomes 7, 8, 10, 14, and 20

More importantly, note that the amplification pattern is different for the two spheroids – this finding is repeated for all distinct spheroids.

We have linked developing tumour shape to increasing DNA mutations
So what?


Disease **progression** $\equiv$ increase by at least 20% in *longest linear dimension*

Disease **response** $\equiv$ decrease by at least 30% in *longest linear dimension*

Otherwise, disease is considered to be **stable**

According to RECIST, stable disease

According to our model, the tumour has shown some response (green) *but there is evidence of aggressive growth in a new spheroid*