Combined MRI and Optical Computed Tomography: Literature Review

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23/1/13

1 Introduction

2 Theory

2.1 Radon Transform

2.2 Filtered Backprojection

2.3 Refractive index matching

2.4 Common artefacts

Axis of rotation problems. Corrections suggested by many groups. Recently by Dong in 2012 [1] discuss method.

3 Dosimetry

3.1 Laser scanning configuration

One of the first reported optical computed tomography (OptCT) systems was developed in the area of gel dosimetry. Accurate 3-D measurement of dose delivery in radiotherapy is extremely important in developing safe treatment plans. Specialist polymer gels, such as BANG® [2], respond to irradiation with changes in optical attenuation and scattering properties. This makes them ideal for measuring 3-D dose distributions. Previously the irradiated gels were measured by MRI and x-ray CT however, these are expensive imaging modalities. In 1996, Gore and Maryanski published the first system for scanning polymer gels using optical computed tomography. [3] In later comparisons, OptCT has been found to be more precise, have reduced noise and smoother line profiles than MRI for gel dosimetry. [4]

Gore's system consisted of a He-Ne laser source and large area photodiode detector (see Figure 1). Translate-rotate acquisition was employed whereby the sample was rotated and projection data acquired by the photodiode over 360°. The smaller the angular steps between projections, the more accurate the reconstruction. [5] For a 2-D reconstruction, projections are acquired for multiple spots across a slice of the sample by translating the laser beam using mirrors. For 3-D information, the sample height had to be manually adjusted and many 2-D slices acquired. This meant scanning an entire sample took hours and lengthy scanning times are the chief disadvantage of the laser scanning method. Accuracy of 5% is reported and spatial resolution of 2mm, which is roughly the same as the laser beam width. [3]

The idea of OptCT scanning in dosimetry was quickly developed by other groups. Laser scanning set-ups were published in 1996 by Tarte *et al.*, [6] and Kelly *et al.* [REF] *Can't find the paper 1996 Kelly references in 1998 [7] Med Phys says it doesn't exist.* Kelly *et al.* claim to have independently developed their scanner which is very similar to that of Gore's. In in both Kelly's and Tarte's scanners, the sample is rotated and translated using a stage whereas Gore used mirrors to translate the laser spot across the sample.

A commercial laser scanning OptCT system, OCTOPUS™by MGS Research, Inc. (Madison, CT), is an extension of Gore's original set-up with the addition of a platform capable of vertical movement for automated slice-selection. [8] For a number of years it was the only commercially available system and has been characterised

by several groups. [8–11] According to Oldham, characterisation of OptCT systems should include checks on geometric distortion, accuracy of reconstruction, scatter artefacts and reflection and refraction artefacts. [12]

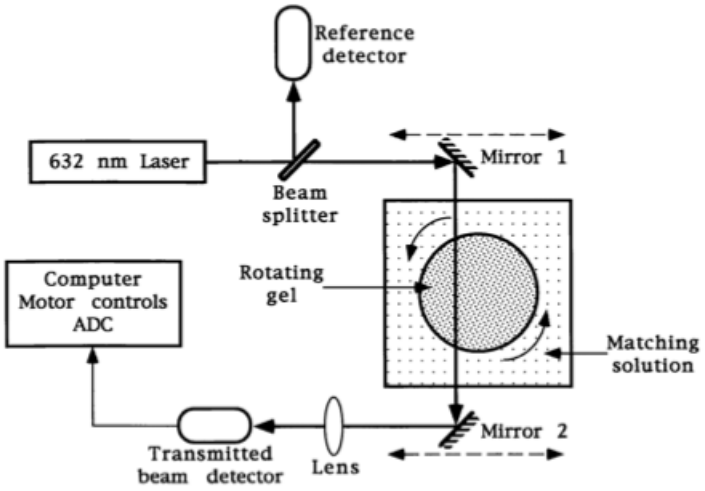


Figure 1: A first generation, Laser Scanning OptCT system developed by Gore. The sample is rotated and projections recorded at a number of angles. The mirrors scan the laser beam across the sample but movement in the vertical direction is by manual adjustment only (figure from [3]).

Laser scanning systems include a beam splitter before the sample to create a reference beam. Dividing projections by the reference intensity corrects for laser beam intensity fluctuations. [3]

Refraction and reflection at container walls are significant concerns for all configurations of dosimetry with OptCT. Generally, laser beams are incident on the gel container at a small angle, such as 5°, to avoid large reflection at the interface. In addition, the gel container is usually placed in a tank containing 'matching fluid' with a refractive index close to that of the gel. This prevents significant refraction as the light passes into the gel. Doran found through ray tracing simulations that the refractive index of the walls of the matching tank and gel container are not important compared to the gel and matching fluid. The optimum difference in refractive index between these two was calculated to be 0.0025 and not zero as originally thought. [13]

To maximise the dynamic range of the system, food dye is commonly added to the

matching fluid so both the refractive index and optical density of the matching fluid and gel are very similar. [14]

3.2 Pixelated detector based systems

In 1997 the first charge coupled device (CCD) camera based OptCT system was published by Tarte *et al.* which employed an incoherent white light source and CCD camera detection. [15] The advantage of a pixelated detector based system is that an entire 2-D projection can be imaged at once, potentially increasing the scanning speed by several orders of magnitude depending on the data through-put rate. Tarte's system used a divergent light source and diffusing screen to measure optical density in a thin gel section (see Figure 2).

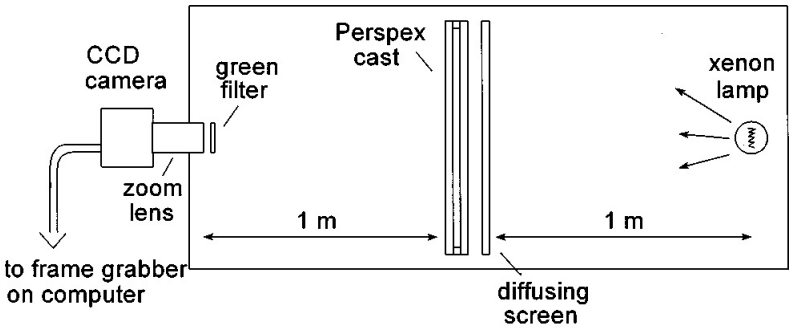


Figure 2: Diagram of the first CCD-based OptCT system, developed by Tarte *et al.* It uses divergent illumination from a white light source and CCD camera detection to record an entire 2D projection at once (figure from [15]).

The accuracy of Tarte's system was checked by comparison with the standard measure of dosimetry, the parallel plate ionisation chamber. It was found to be on average within 3% of the value from the ionisation chamber. [15] A comparison between Tarte's laser scanning and CCD set-ups found that they had similar spatial resolutions. The CCD method had improved speed of acquistion but suffered from consistently worse SNR as a photodiode detector can collect many more photons per 'pixel' than a CCD camera. [15]

Advances in technology have meant that high quality detectors are much more affordable. A cheaper alternative to very high quality CCD cameras is the CMOS

(Complementary Metal-Oxide-Semiconductor) detector which has the potential for higher resolution and dynamic range. [16] Using a higher quality detector would improve many OptCT systems in terms of scanning speed and reduced artefacts. [13,15]

Parallel beam configuration: One method to reconstruct 3-D images with a CCD or CMOS detector is to create a broad parallel beam. This allows the use of parallel reconstruction algorithms, very similar to those used for x-ray CT. Each 2-D projection image recorded corresponds to one row for every slice in the 3-D reconstruction sinogram. [16] Telecentric optics, in which the chief rays are parallel to the optical axis, are key in the design of this configuration. [17] Telecentric optics can be achieved either through a careful arrangement of a large converging lens before the sample and standard camera lens [13] (see Figure 3) or through an expensive telecentric lens [18]. The process of forming a parallel beam results in non-uniformities in the lightfield. This is compensated for by subtracting a 'correction' or 'open lightfield', image which is a projection taken with no sample in the tank. [13]

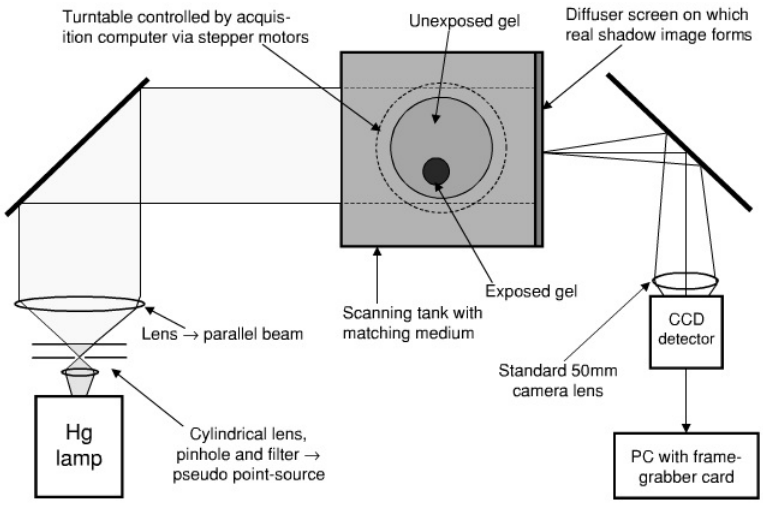


Figure 3: Diagram of a parallel beam OptCT system, developed by Doran *et al.* Telecentric optics create a parallel beam (figure from [13]).

Initial systems suffered from 'graininess' due to the unstable gain of cheap CCD cameras and granularity of the diffusing screen. [13] Doran *et al.* proposed some methods of correcting these problems. Oscillating the diffuser screen at high frequency "'smears' out the granularity" while randomly horizontally displacing the

CCD camera by a few pixels between acquisitions can reduce the effect of 'bad' pixels. [13] The parallel configuration appears to be more susceptible to schlieren artefacts caused by refractive index inhomogeneities in the sample. [19]

Cone beam configuration: Wolodzko *et al.* published the first cone beam OptCT system with CCD detection for gel dosimetry. [20] One advantage of this configuration is the optics for producing a cone beam are much simpler than those for producing accurate parallel beams. [16] However, the reconstruction is computationally more complex. [21] A commercial cone-beam system, Vista^{TM}by Modus Medical Devices Inc. (London, ON, Canada), is available and reviewed recently by Olding *et al.* [22]

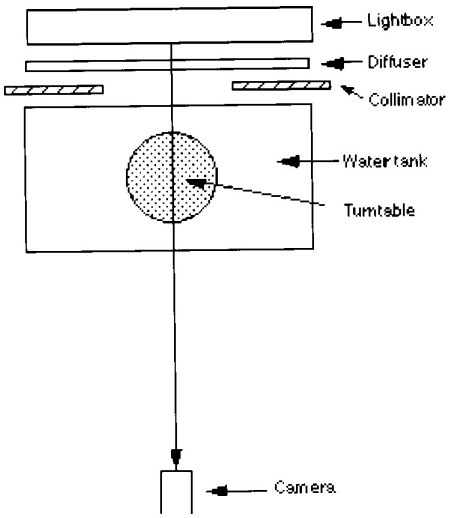


Figure 4: Cone-beam CCD configuration (figure from [20]).

When pixelated detectors are used, there appears to be more literature based on the parallel beam configuration than cone-beam. Although there has not been experimental comparison of the two Doran suggests that while cone-beam is usually somewhat cheaper due to simplified optics, modern parallel-beam systems have better scatter-rejection and may have fewer stray light problems. [16, 22, 23]

4 Tissue imaging

4.1 Optical Projection Tomography

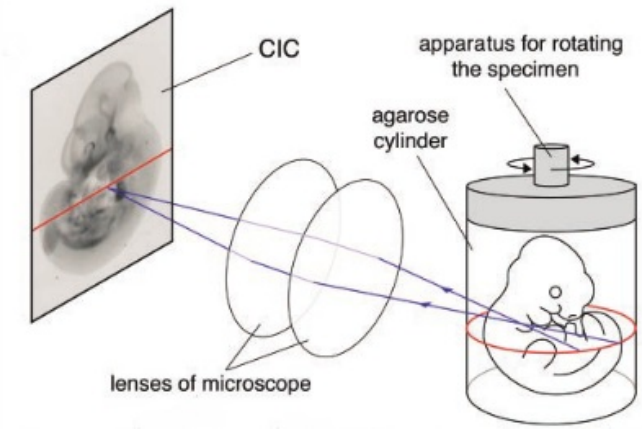
Another version of OptCT was developed by Sharpe *et al.* in the area of 3-D microscopy for gene expression studies. [24] Although this set-up in 2002 came after Gore's they are apparently independent and Sharpe named his technique Optical Projection Tomography (OPT).

Other techniques for 3-D microscopy include confocal microscopy which can image to a depth of about 1mm. [25] However, this is limited to fluorescent signals meaning many optical stains used routinely in histology would not work. Optical coherence tomography is another technique capable of micrometer-scale resolution. [26] However, its depth is limited to 2-3mm in tisse. Sharpe's OPT set-up could image much larger specimen, up to 15mm thick. [24] OPT is a projection based tomography technique, as the name implies, which means mathematical reconstruction is required. The other techniques mentioned give tomographic images by sectioning. [27] **Discuss**

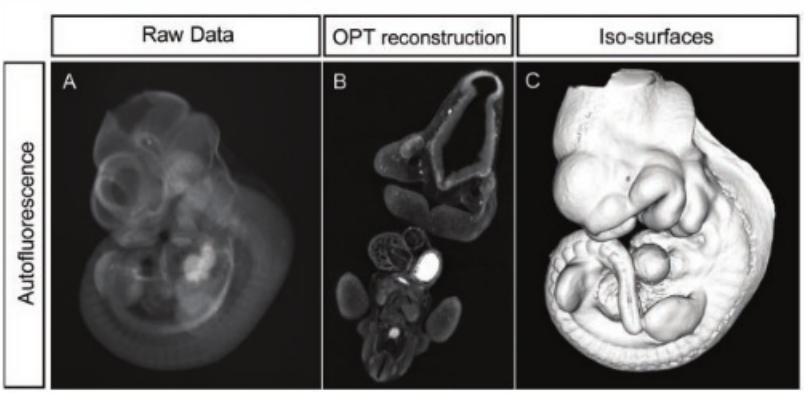
Sharpe's system includes a microscope to focus projections of a mouse embryo onto a camera imaging chip (CIC). Image-focusing optics are one difference between OPT and x-ray CT, which records shadows of the sample. Sharpe reports some impressive images (see Figure 5). Use of the microscope gives resolution of about 5-10μm meaning single-cell membranes, around 10μm thick, can be seen. [24] The axis of rotation is chosen so only half of the specimen is in focus at once which compensates for poor depth of focus.

To reduce scattering and refraction within the specimen it was immersed in Murray's Clear, also known as BABBs (1:2 mixture of benzyl alcohol and benzyl benzoate). BABBs works as an optical clearing agent (OCA) which reduces refraction by replacing fluid in a specimen. The OCA is chosen with a refractive index close to that of the solid structures in the specimen. See Section 5 for more detail on the clearing mechanism and possible agents. The result of clearing means that the light paths through the specimen can be approximated as parallel line integrals making high resolution reconstruction through back projection possible.

Sharpe - low NA optics.



(a) OPT setup



(b) Mouse images

Figure 5: Part (a) shows the optical setup for the first OPT system by Sharpe. CIC indicates the camera imaging chip. A microscope is used to focus. The specimen is set in agarose gel for stability. Part (b) shows some sample images from OPT scanning of a mouse embryo. The iso-surface shows contours linking all regions above a certain intensity. Both figures are adapted from [24]

Fauver 2005 [28] Single cell, $0.9\mu m$ resolution. Extended DOF, pseudoprojection. High NA lens scanned axially. 180° of data taken. Microcapillary, some cells injected into it. Rotation to sub-micron precision. Refractive index matching to 0.02. *Focal plane of high NA objective lens was scanned axially through the cell to create an extended depth of field image or pseudoprojection through incoherent superposition.* [28, 29] Not truly quantitative.

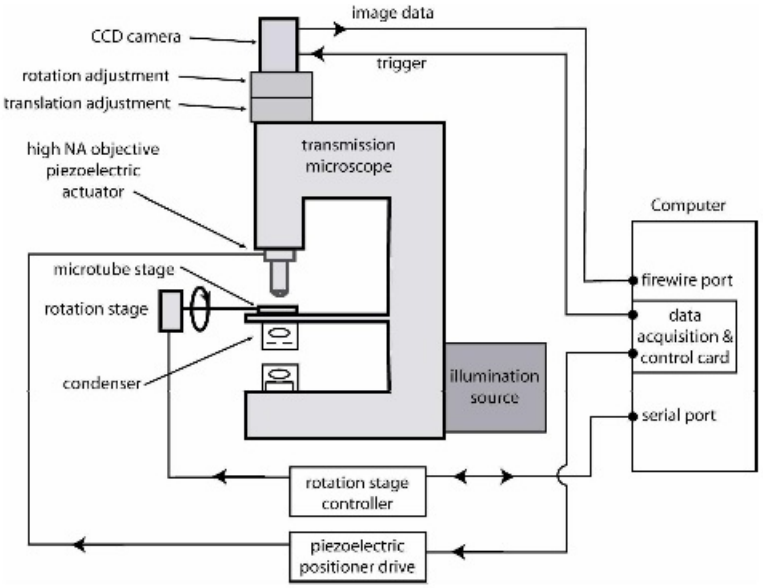


Figure 6: OPT microscope from [28]

They modified a conventional bright-field microscope with rotation stage and piezoelectric lens. See Figure 6 Extended DOF means all features have same focus from all viewing angles which is necessary for reconstruction.

Optimisation of optics for OPT by Wang in 2006 + 2007 [30,31] *Place an iris at the back focus of the objective lens to reduce divergence of projection from true parallel projection.* Resolution $40\mu m$ Fourier slice theorem requirements. 2007 is comparison of new iris system (described in 2006) with conventional system.

Live specimen OPT not a topic taken up by many other groups due to difficulties in keeping specimen alive, problems with OCA, can only image very small specimen anyway. [32] Boot and Sharpe 2008. Colas and Sharpe do live, time-lapse OPT in 2009, not particularly useful. Poor resolution due to lack of clearing [33]

Computational methods for improving reconstructions in OPT by Birk in 2011 [34]

4.2 Fluorescent OPT/emission OptCT

Oldham has dual set-up. However, it was not originally quantitative. Just pretty pictures. Steps by various groups to get quantitative information out of emission. What is the change to the set-up? [35] quantitative: [36]

Imperial group investigating Opt combined with FRET and FLIM. Define these and some uses for the combined modality. What physical/software changes needed for this imaging. FLIM OPT: [37], In vivo FLIM OPT [38].

5 Optical Clearing

6 Optical Staining

Sharpe 2002 stains for gene expression and limb bud growth.

Discuss which stains are relevant for cancer biomarkers. [39]

Being able to use optical stains is extremely useful for computer recognition of organs, can pick better thresholds. [27]

Soufan 2003 [40] gene expression during cardiac development. Highlights problem of whole-mount staining not working for all stains. Depends on size of specimen. Therefore, they took slices of embryo heart.

7 Recent Research

Time gated OPT Bassi 2010 [41]

CLAHE Hornblad 2011 [42]

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