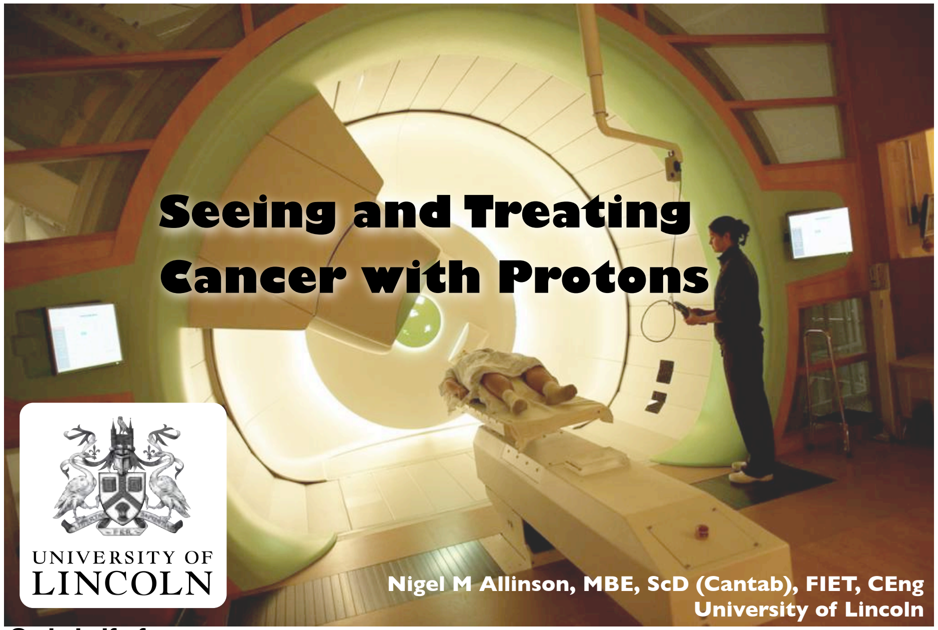


Seeing and Treating Cancer with Protons

UNIVERSITY OF LINCOLN

Nigel M Allinson, MBE, ScD (Cantab), FIET, CEng
University of Lincoln

On behalf of ...

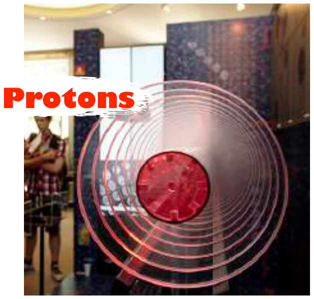
PRaVDA

PRaVDA

Seeing and Treating Cancer with Protons

- **University of Lincoln**
- University of Birmingham
- University of Liverpool
- University of Surrey
- University of Cape Town
- University of Warwick
- University Hospital Birmingham NHS Foundation Trust
- University Hospital Coventry and Warwickshire NHS Trust
- National Research Foundation (NRF) - iThemba LABS, SA
- United Lincolnshire Hospitals NHS Trust
- The Christie NHS Foundation Trust

- ISDI: Image Sensor Design and Innovation Ltd
- aSpect Systems GmbH
- Elekta AB (Publ)
- Advanced Oncotherapy Plc



Funded by
wellcome trust
Grant Number 098285

PRaVDA

PRaVDA

Seeing and Treating Cancer with Protons

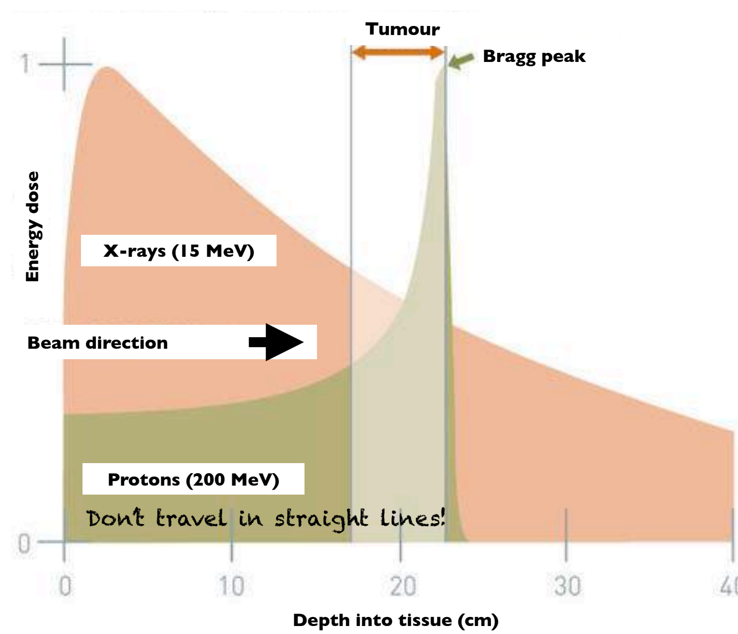
Funded: Wellcome Translational Grant
Duration: 3 years
Start date: Jan. 2013

Aim:
Develop an integrated instrument for Proton Therapy imaging, dosimetry, treatment monitoring and quality assurance.

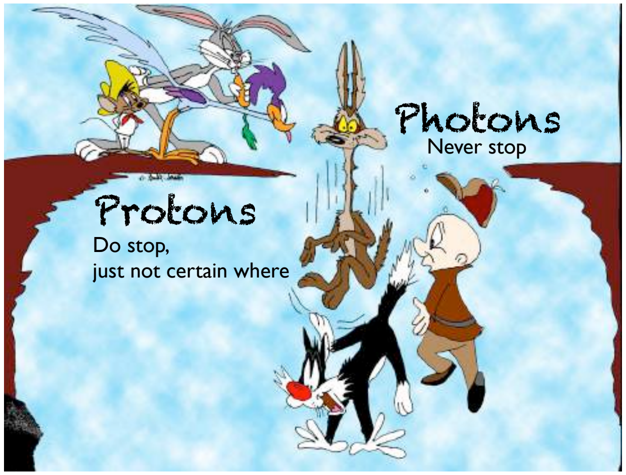
- **Proton Therapy**
- **Need for Proton CT**
- **PRaVDA overview**
- **Design decisions**
- **Way forward**

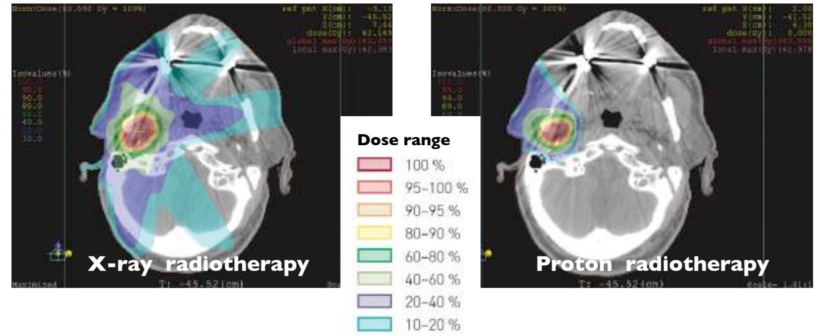
Note:
PRaVDA is a research tool

PRaVDA



PRaVDA





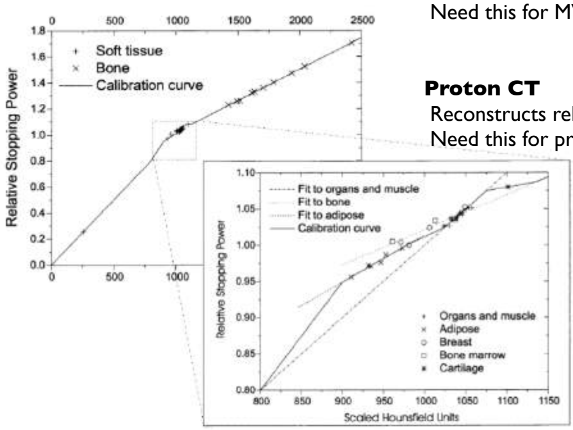
48 PT facilities worldwide are treating patients with proton therapy, with over 100,000 patients treated so far.

Number of centres is scheduled to double in the next eight years, with at least two new centres in the UK.

Proton beam rather than x-ray therapy is better for treating certain tumour types. Examples of where proton beam therapy can offer real benefits are:

- Tumours in the head and neck region
- Tumours near the spine or other critical organs
- Some types of brain tumours
- Some childhood cancers so the risk of second cancers later in life is greatly reduced.

CT in Proton Therapy Planning



X-ray CT
Reconstructs relative electron density
Need this for MV x-ray radiotherapy planning

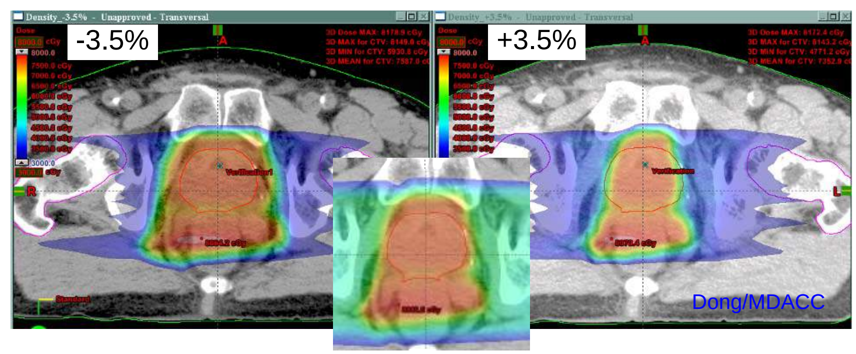
Proton CT
Reconstructs relative stopping power
Need this for proton radiotherapy planning

Main methods

- Simple look-up-table
- Stoichiometric calibration
- Dual-energy CT

"The values recommended in this study based on typical treatment sites and a small group of patients roughly agree with the commonly referenced value (**3.5%**) used for margin design."

M Yang, X Zhu, PC Park, U Titt, R Mohan, G Virshup, JE Clayton, L Dong,
"Comprehensive analysis of proton range uncertainties related to patient stopping-power-ratio estimation using the stoichiometric calibration" Phys. Med. Biol. 57 4095–4115 (2012)

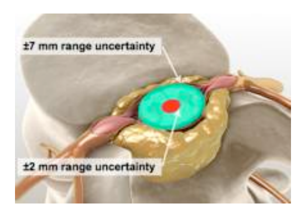


0% uncertainty

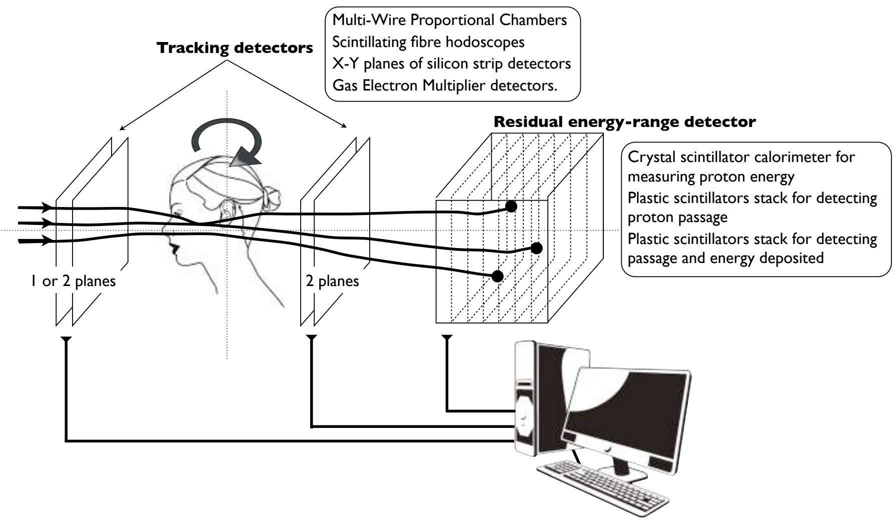
Current uncertainty in proton range is ~3.5%. If beam passes through 20 cm of tissue, then Bragg peak could be anywhere within +/- 7 mm. Can prohibit treatment of tumour adjacent to spinal cord

Aim to reduce proton range uncertainties to a ~1% – variation of +/- 2mm.

Simplified treatment plans – fewer beams; less possibility secondary cancers induced; and treatments will be shorter



Proton CT Technology



Summary of current and recent pRG/pCT prototypes

Group	Year of Ref.	Area [cm²]	Tracking tech. (# units)	RERD technology	Proton-rate [Hz]	PCT or pRG
PSI	2005	22.0x3.2	xy Sci-Fi (2)	Plastic scintillator telescope	1M*	pRG
LLU/UCSC /NIU	2013	17.4x9.0	xy SiSDs (4)	CsI(Tl) calorimeters	15k*	pCT
LLU/UCSC / CSUSB	2014	36.0x9.0	xy SiSDs (4)	Plastic scintillator hybrid telescope	2M*	pCT
AQUA	2013	30.0x30.0	xy GEMs (2)	Plastic scintillator telescope	1M*	pRG
PRIMA I	2014	5.1x5.1	xy SiSDs (4)	YAG:Ce calorimeters	10k*	pCT
PRIMA II	2014	20.0x5.0	xy SiSDs (4)	YAG:Ce calorimeters	1M	pCT
INFN/LN	2014	30x30	xy Sci-Fi (4)	x-y Sci-Fi	1M	pCT
NIU/FNAL	2014	24.0x20.0	xy Sci-Fi (4)	Plastic scintillator telescope	2M	pCT
Niigata U	2014	9.0x9.0	xy SiSDs (4)	NaI(Tl) calorimeter	30*	pCT
PRaVDA	2015	9.5 x 9.5	xuv SiSDs (4)	CMOS APS telescope	1M	pCT

G Poludniowski, N M Allinson, and P M Evans, *A review of proton radiography and tomography with application to proton therapy* (in press)

Summary of approximate design constraints

Calculations for the RERD are based on a proton with 13 cm range in water (135 MeV).

Design feature	Parameter	Value
Number of PSDs	N	4
PSD pitch	P	< 1 mm
PSD offsets	$\frac{PL}{\sqrt{6}D}$	< 1 mm
PSD thickness	$\frac{T}{X_0}$	< 0.005
RERD discretization (range-telescope)	S	< 5 mm water-equivalent
RERD energy resolution: (calorimeter)	R	< 0.7 MeV

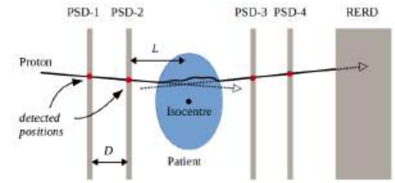
Offset between PSD units and to patient

The uncertainty in proton angle in a lateral dimension, based on spatial measurements in two idealized PSDs, can be estimated as: $\sqrt{2}\,\sigma_r / D$, where *D* is the separation in PSD modules. This ignores any effects due to the finite thickness of the PSDs. The projected spatial uncertainty, at a distance *L* is:

$$\sigma_{\theta L} = \frac{PL}{\sqrt{6}D}$$

where *D* is the separation in units. To control the precision of proton path reconstruction, the distances *L* and *D* must therefore be carefully considered. The distance *L* should be minimized and *D* kept sufficiently large (a few cm).

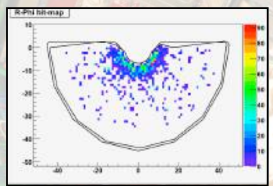
Practical considerations of avoiding collisions of the system with the patient and fitting the system in a treatment room limits the freedom of these choices.



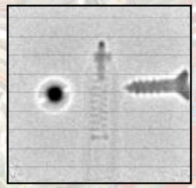
Our Approach

- Integrated instrument – QA, in-treatment monitoring, and proton CT
- Meet highest clinical needs and therapy workflows
- Capable of commercialisation
- Fully solid-state detectors
- Research platform to consider ALL aspects of proton therapy

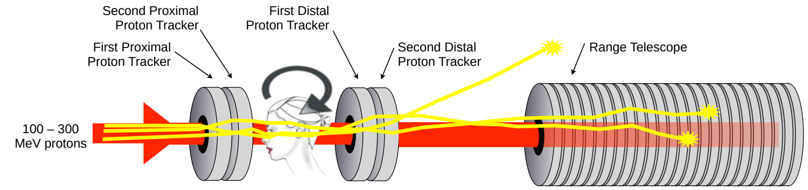
- Multiple Silicon Strip Detectors for tracking
- Multiple large-area CMOS imagers (APS) for residual energy determination



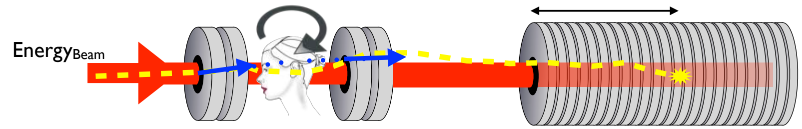
Liverpool demonstrated proton counting at Clatterbridge

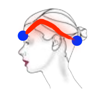

Dynamite (Rad hard wafer-scale CMOS) demonstrated proton imaging at therapy energies

"One of the most complex medical imaging instruments ever conceived"



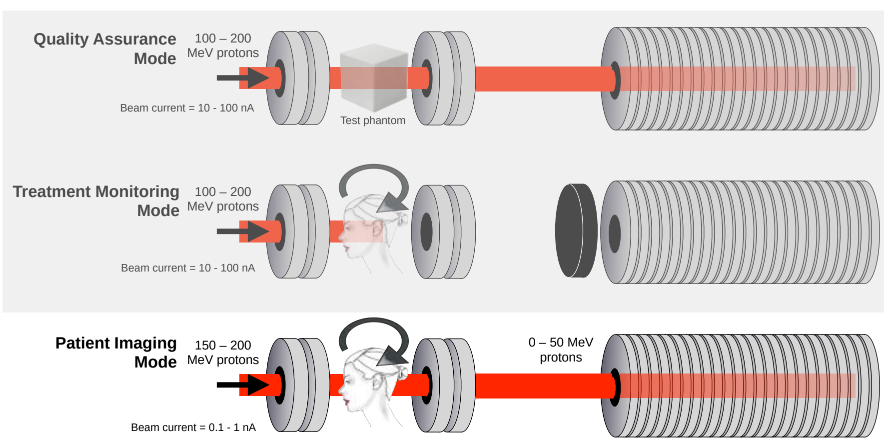
$Energy_{Absorbed} = Energy_{Beam} - Energy_{Residual}$ $Energy_{Residual} \propto Range$





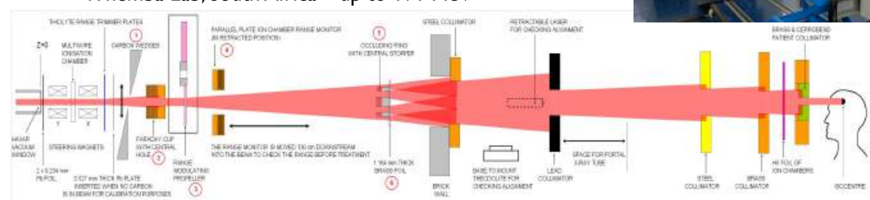
Entry position
Exit position
$Energy_{Absorbed}$
} Repeat millions of times!

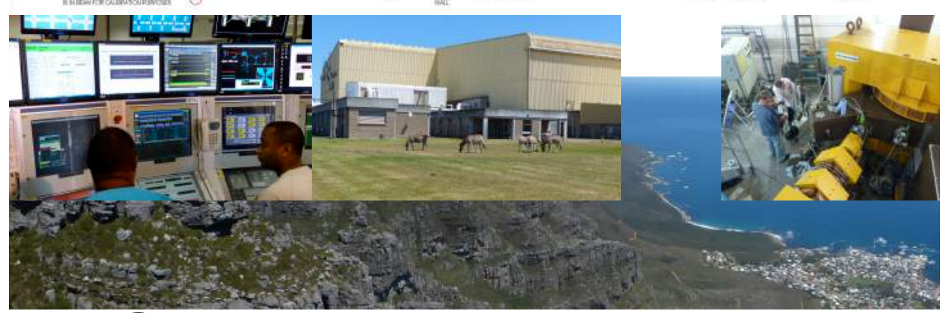
Operational Modes



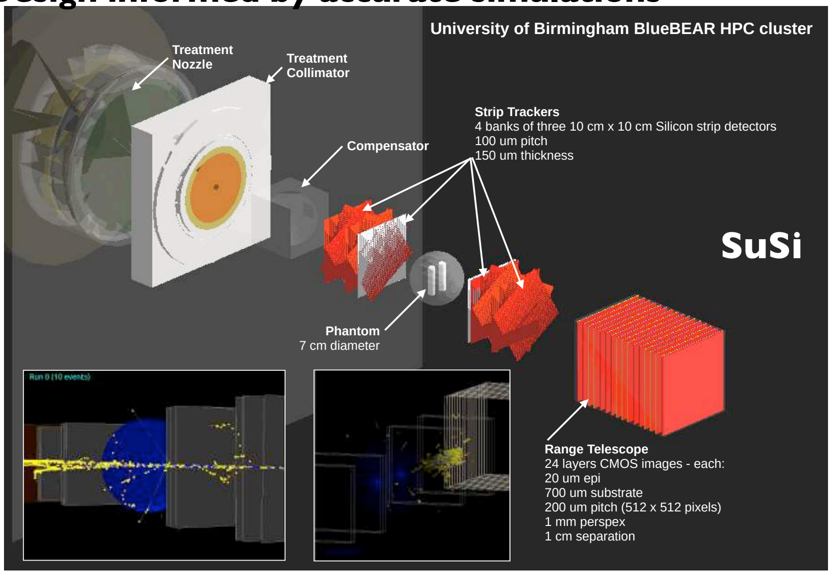
Available Proton Sources

- Birmingham Cyclotron Source – up to 36 MeV
- iThemba Lab, South Africa – up to 191 MeV

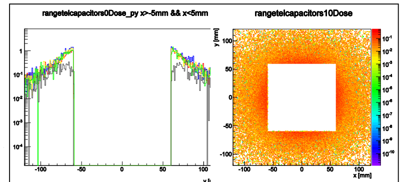




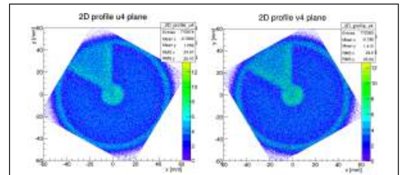
Design informed by accurate simulations



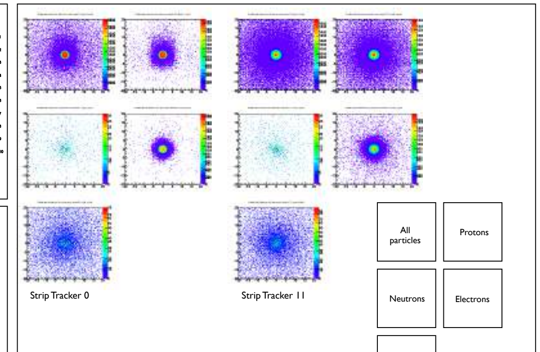
Geant4 model of PRaVDA instrument



Radiation exposure simulations

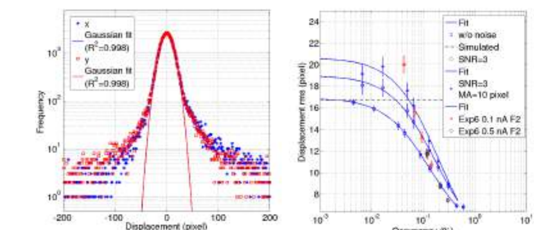


Strip detector resolution simulations



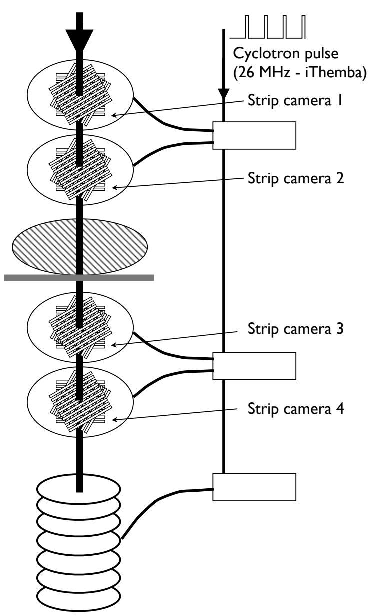
Strip detector -primary and secondary particle generation

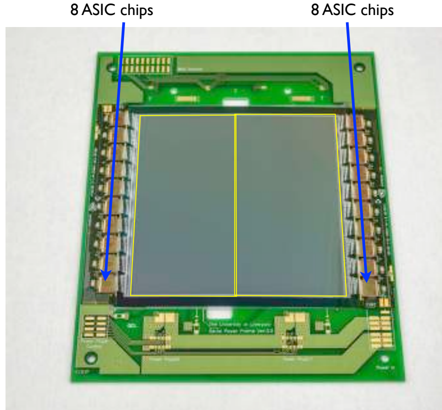
Examples of use of Geant4 model



Proton displacement in Range Telescope - comparison of theory and experiment

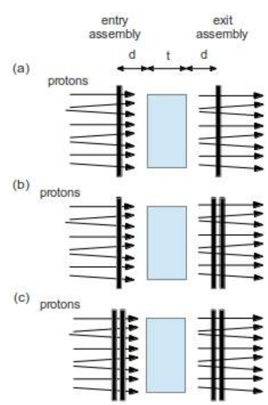
Strip Detectors

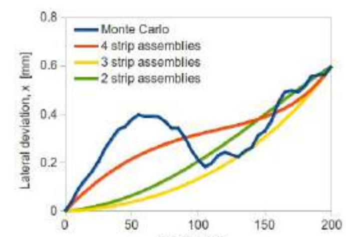




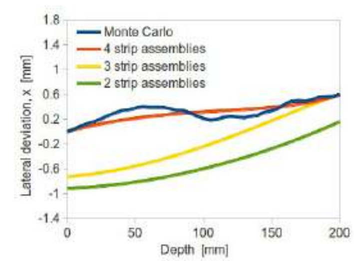
Double-ended 150μm thick n-in-p technology – 1024 strips at 90.8 um pitch

No. of strip cameras





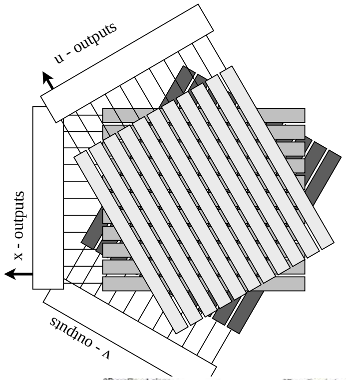
No offset of strips

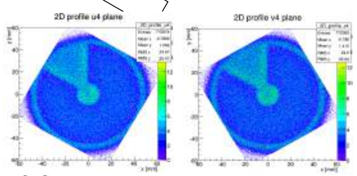


2 cm offset of strips

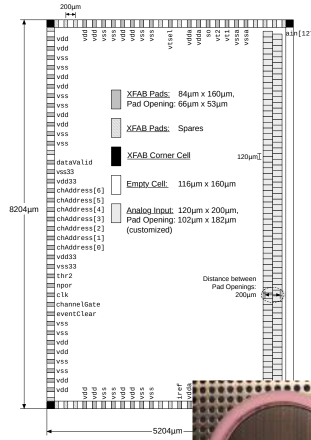
Strips per Camera

3 rotated strip assemblies per camera
Reduce ambiguities



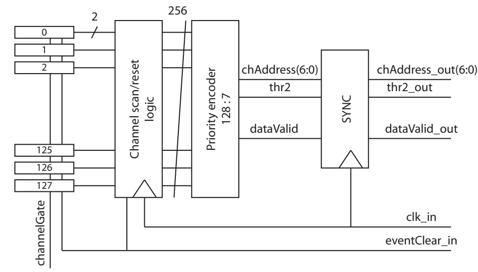


ASIC – Rhea



128 channels - 2 thresholds
(programmable at 6 bits)

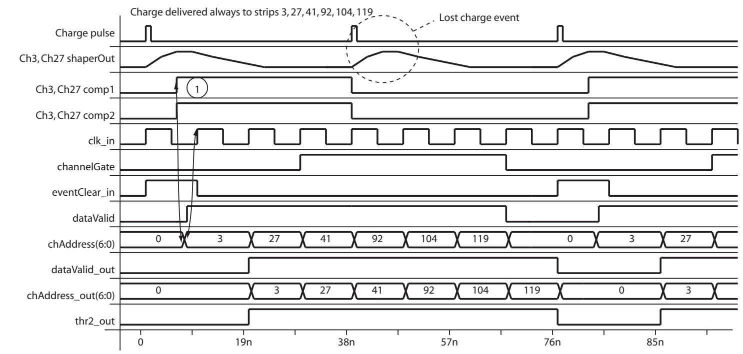
J.T. Taylor, et al., (2015), Proton tracking for medical imaging and dosimetry, *JINST* 10
doi:10.1088/1748-0221/10/02/C02015

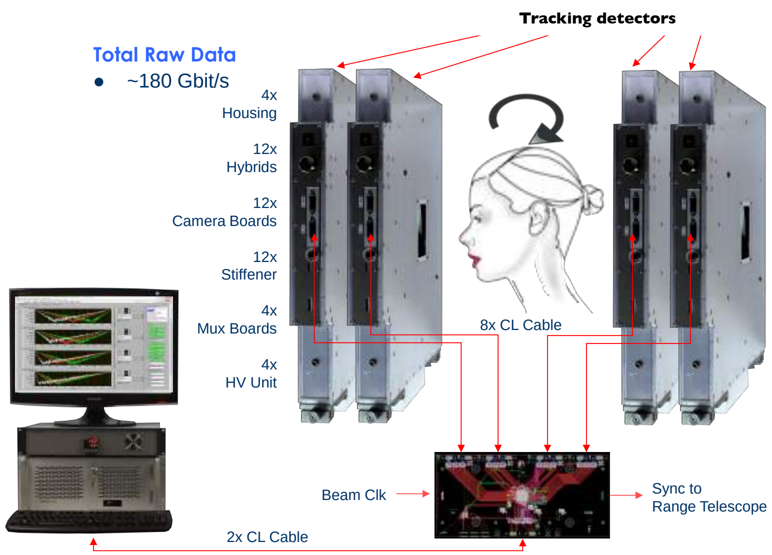


ASIC – Rhea

Imaging mode
Every proton detected

Treatment mode
Specified fraction of protons detected
Profile histograms to provide sufficient information for control feedback



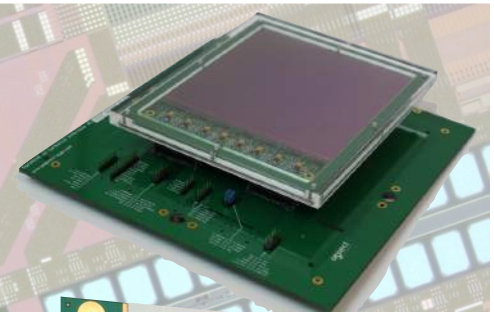


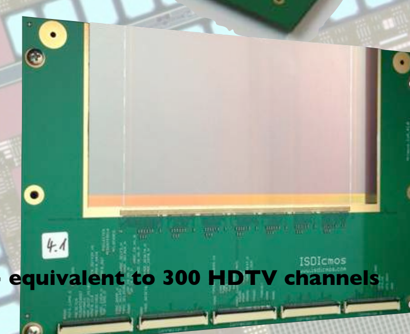
Range telescope

Measures the residual energy of the protons exiting the patient – consists of 24 layers of radiation-hardened CMOS imagers.

Same basic technology used in mobile phone cameras, except that ours are over 500 times larger and work 20 times faster.

Total imaging area is over 2.5 m^2 and enough Silicon to make over 22,000 iPhone cameras.



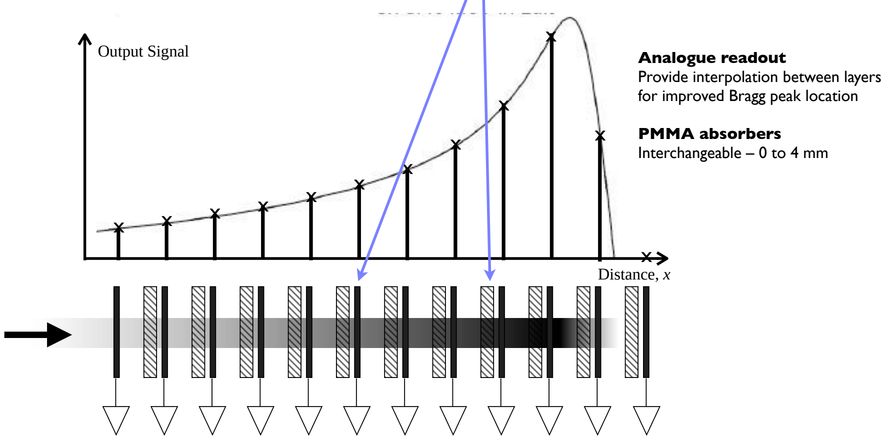


Collect data at 6 Gigabytes per second - equivalent to 300 HDTV channels

Range Telescope - *misnomer*

Measure exit energy of individual protons

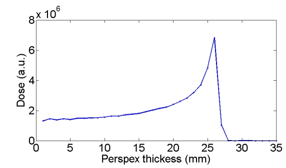
- **24 layers of large-area rad-hard CMOS imagers**
- **Interleaved changeable absorbers**

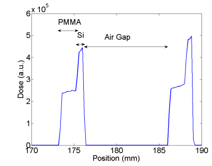


Analogue readout
Provide interpolation between layers for improved Bragg peak location

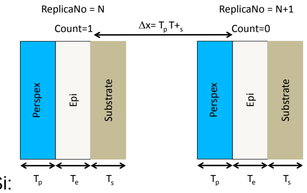
PMMA absorbers
Interchangeable – 0 to 4 mm

Range Telescope – how many layers?



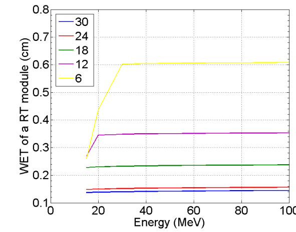


Energy loss in 700 um Si:
1.4 MeV @ 60 MeV
2.4 MeV @ 30 MeV



Intrinsic energy resolution:

- Absorber thickness (0 - 3 mm)
- Non-active thickness of Si (~700 um)



24 layers – Water Equivalent Thickness of ~1.5 mm

Range Telescope – Pixel size vs. Frame rate

Essentially: Smaller pixels – more discernible events/frame time

But: Longer frame time

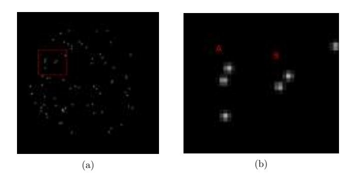


Figure 3: (a) A synthetic image (140 protons·cm^{-2}, 200x200 pixels, 50 μm pitch) and (b) a region-of-interest of the synthetic image at a larger magnification.

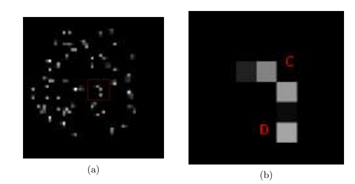
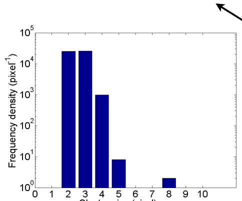
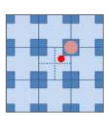


Figure 4: (a) A synthetic image (140 protons·cm^{-2}, 50x50 pixels, 200 μm pitch) and (b) a region-of-interest of the synthetic image at a larger magnification.

Simulations, plus experiments, plus final Proton CT specification = 200 um pixels and >1,000 fps

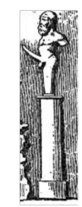


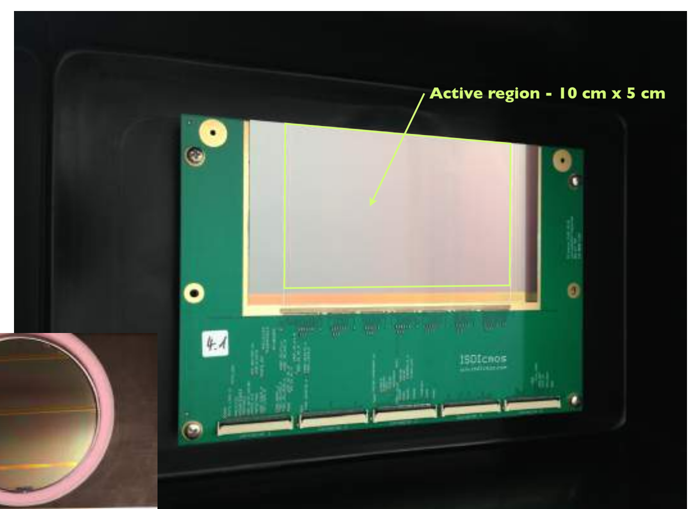
Average cluster size 2.5 pixels (50 um) - experimental at iThemba

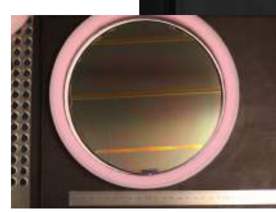


Charge sharing - charge cloud, diode placement

RT CMOS Imager – Priapus

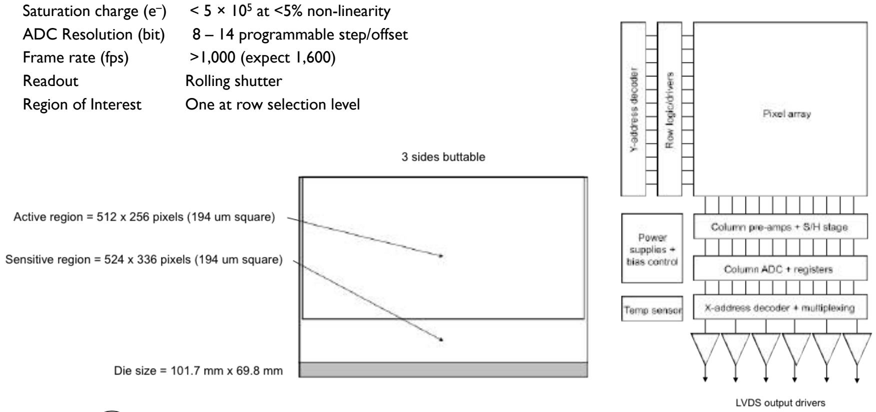






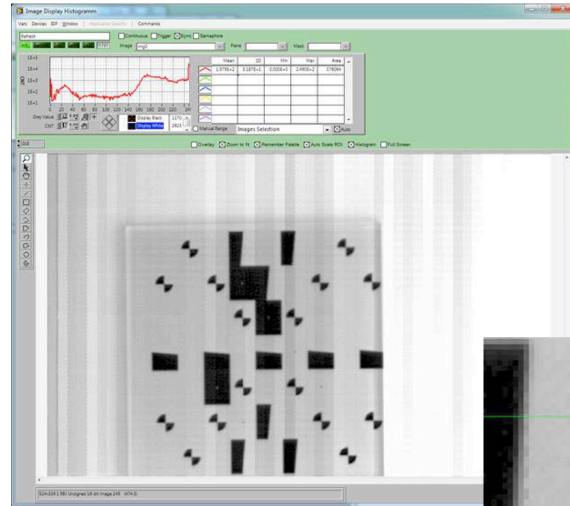
Priapus specification

Parameter	Value
Technology	0.35 um CMOS Active Pixel Sensor. Rad- hard pixels and on-chip analogue chains
Pixel pitch (um)	194
Active area (cm^2)	5 cm × 10 cm - three sides buttable (< 1 pixel loss)
Epitaxial thickness (um)	18
Noise floor (e$^-$)	~120
Saturation charge (e$^-$)	< 5 × 10^5 at <5% non-linearity
ADC Resolution (bit)	8 – 14 programmable step/offset
Frame rate (fps)	>1,000 (expect 1,600)
Readout	Rolling shutter
Region of Interest	One at row selection level

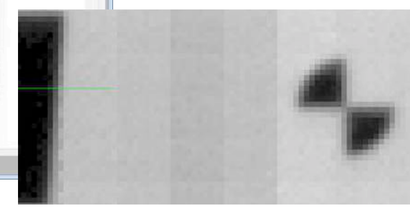


PRaVDA

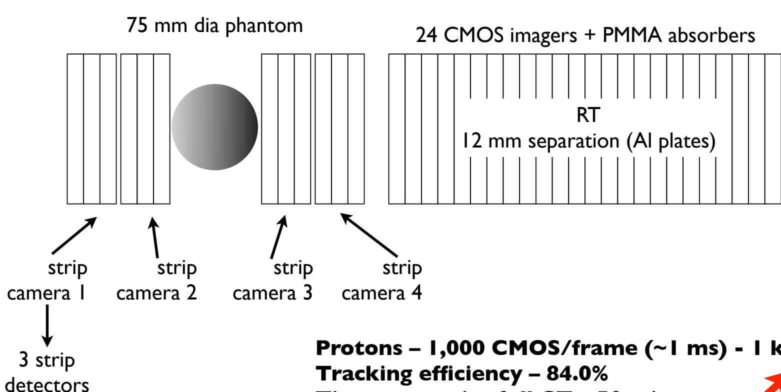
Priapus first image (totally raw)



8-bit image



PRaVDA



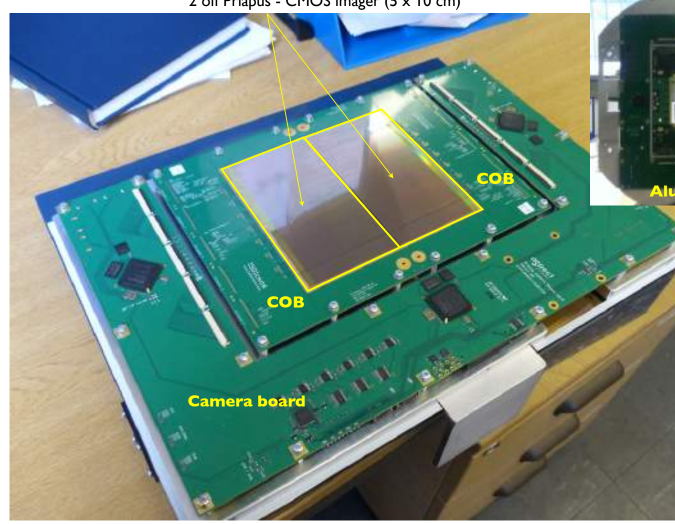
Protons – 1,000 CMOS/frame (~1 ms) - 1 kHz
Tracking efficiency – 84.0%
Time to acquire full CT – 50 min

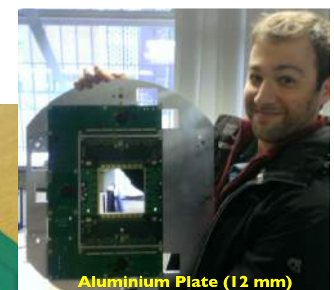
Strip detector "frame" – 104 MHz

PRaVDA

Range telescope slice

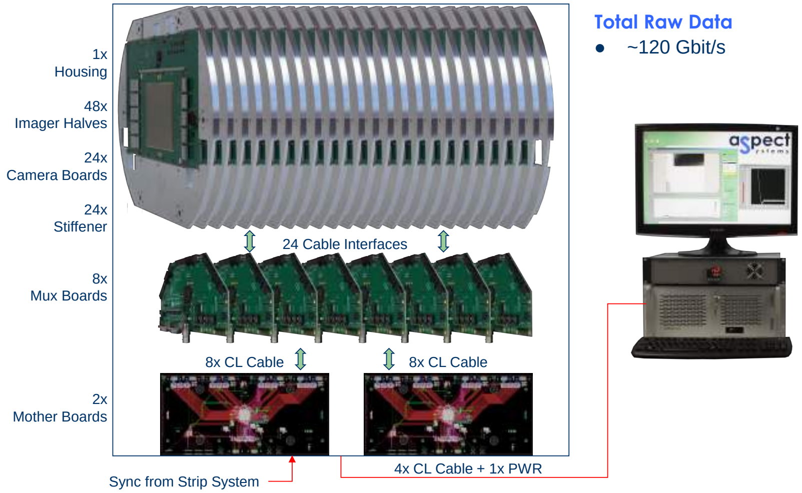
2 off Priapus - CMOS imager (5 x 10 cm)





Over 100 FPGAs
Data rate 6 GBytes/s

PRaVDA

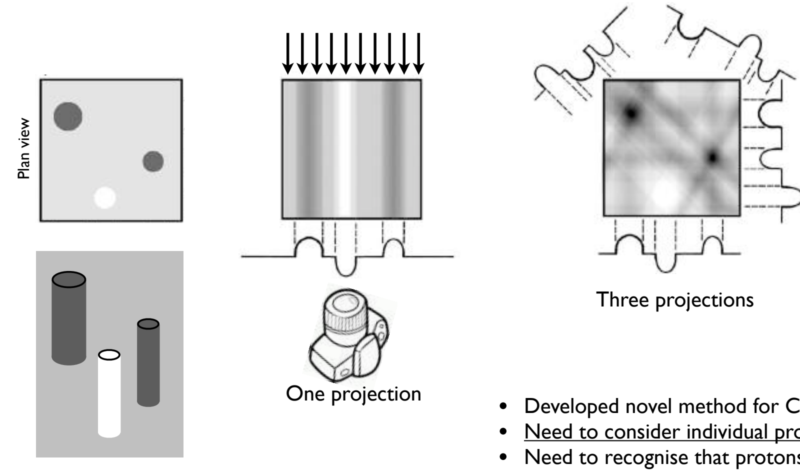


Total Raw Data

- ~120 Gbit/s

PROVDA

CT Reconstruction: Principles



- Developed novel method for CT
- Need to consider individual protons
- Need to recognise that protons don't travel in straight lines
- Need efficient and accurate method

PROVDA

Back projection then filtering

- Sampling ray-projections through a 2D slice (not necessarily uniformly)
- Backprojecting the ray-projections through a 2D reconstruction matrix
- Convolving (or filtering) this 2D matrix of data with a 2D kernel
- Repetition over a set of angles of orientation

FBP Advantages *(Standard Approach)*

1. Filtering operation in FBP is in 1D and therefore requires less computation and computer memory.
2. Analytic results for FBP convolution kernels are easier to obtain.
3. BPF approach has had issues with quantitative accuracy.

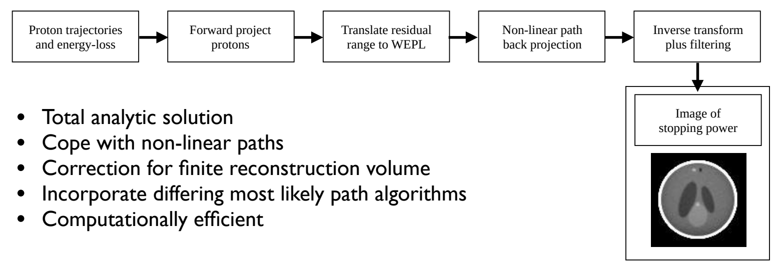
BPF Advantages

A. 1. is no longer a problem with increased computing power
B. Novel implementation overcomes 2. and 3.
C. BPF naturally deals with list-mode data (one particle at a time) without the need for binning and it can naturally accommodate non-linear ray-projection paths
D. Because the filtering operation occurs after the backprojection of each proton path onto a regular matrix in image space

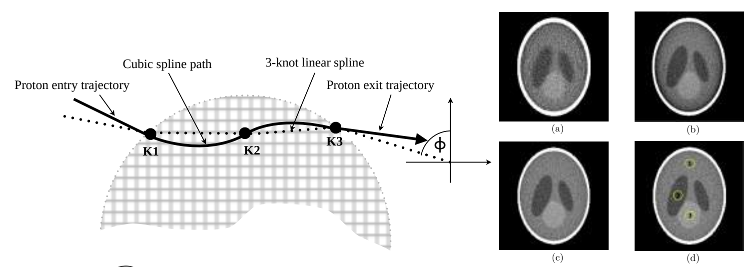
PROVDA

G Poludniowski, N M Allinson and P M Evans "Proton Computed Tomography reconstruction using a backprojection-then-filtering approach"

UK Patent Application Number **1413729.3**.



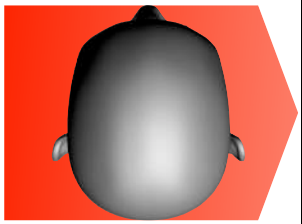
- Total analytic solution
- Cope with non-linear paths
- Correction for finite reconstruction volume
- Incorporate differing most likely path algorithms
- Computationally efficient

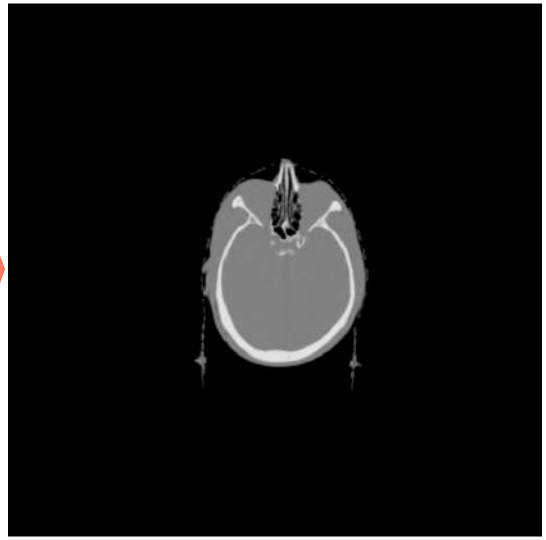


(a) FBP
(b) BPF - 0-knot
(c) BPF - 2-knot
(d) BPF - 9-knot

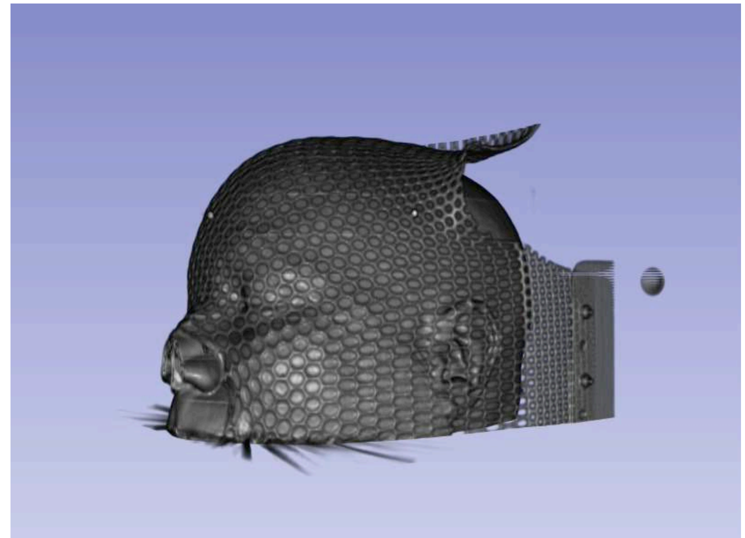
PROVDA

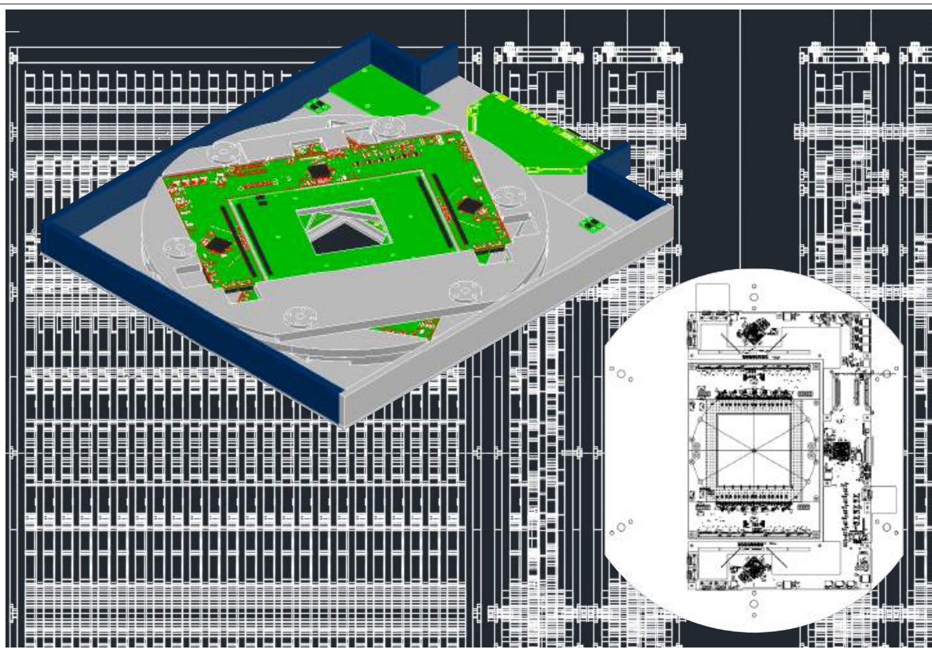
Proton CT - Single Slice Reconstruction

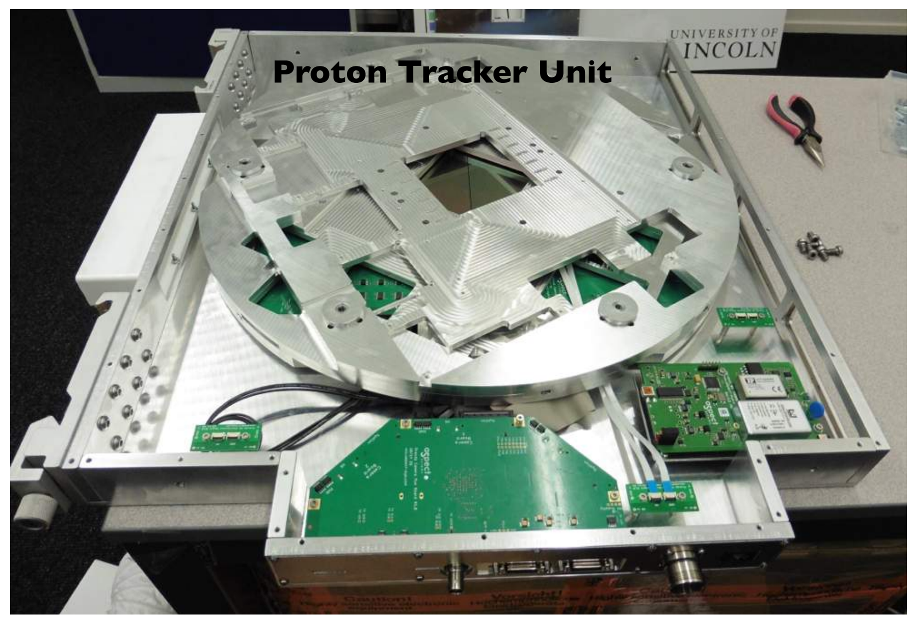




Combine all 180 images







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