ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

Pre-Clinical Micro-IMRT

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Apologies ….
Your meeting is about …

- High precision RT
- Intensity modulated RT

But clinical …

Why pre-clinical ?

Discovery/Validation of innovative 'biologically' motivated treatment strategies including radiation

Fundamental Cancer Biology → Pre-clinical validation (in 'vitro', in 'vivo') → Clinical Translation (Trials)

ICR The Institute of Cancer Research

CANCER RESEARCH UK

in partnership with

The ROYAL MARSDEN NHS Foundation Trust

The CCI at ICR – Advancing cancer therapy by pre-clinical research

CCI Vision

‘The Centre for Cancer Imaging is a leading edge preclinical research facility that brings together **multi-disciplinary research teams** with an ethos of **collaboration and innovation**. Its core purpose is to develop and implement state of the art **non-invasive imaging technologies** in order to support the discovery and development of **personalised cancer therapies** and ultimately deliver improved outcomes for cancer patients.’

The Building – 5 floors

Office Space

Labs: warm & cold chemistry; pathology; tissue culture; biochemistry; ultrasound ; photoaccoustic

Imaging: MRI and NMR; PET/SPECT; micro CT; small animal radiotherapy; hot chemistry

BSU: animal holding and procedure rooms

BSU: support services

Current research Teams

Topics

1) Multi-modality treatments

Combination of RT with
- Drugs (immunogenic agents)
- Hyperthermia, HIFU

2) New RT paradigms

- Micro beams
- High dose rate (Flash)

[redacted]

RT Technology ?

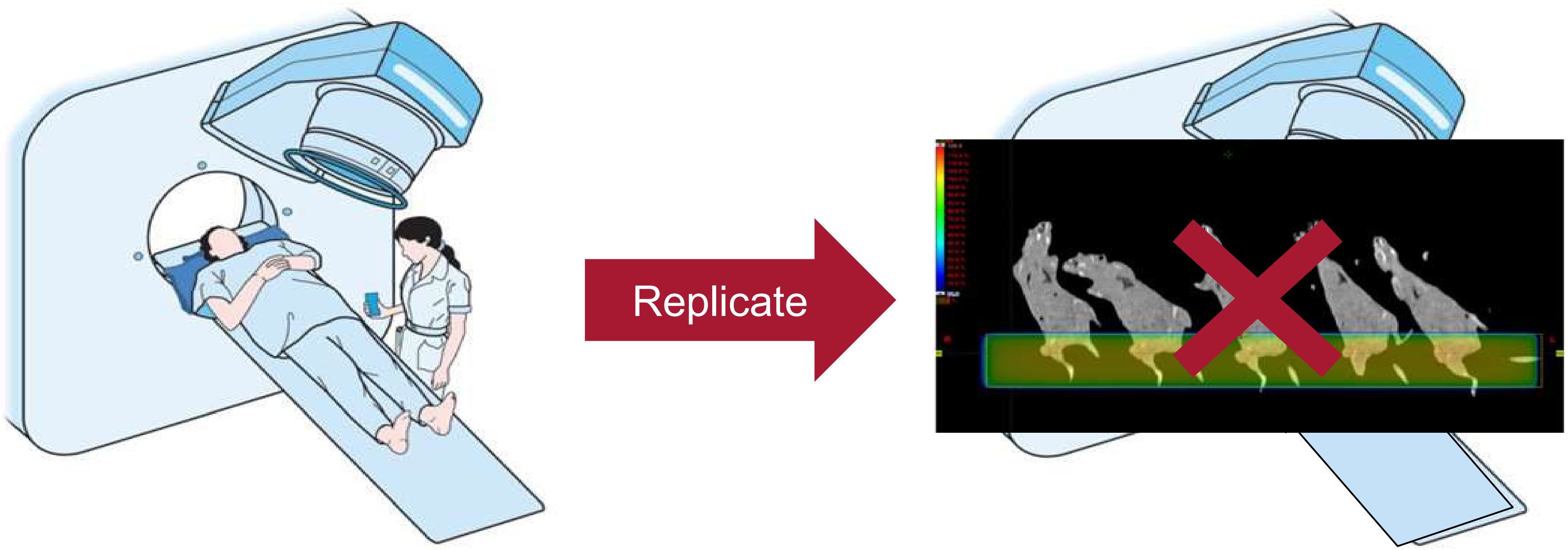
Micro-IMRT on the SARRP using the Motorized Variable Collimator

Anna Merle Reinhart, Simeon Nill, Uwe Oelfke

Overall aim

Dose response studies
TCP and NTCP
Fractionation

Combination treatments
New treatment techniques
…



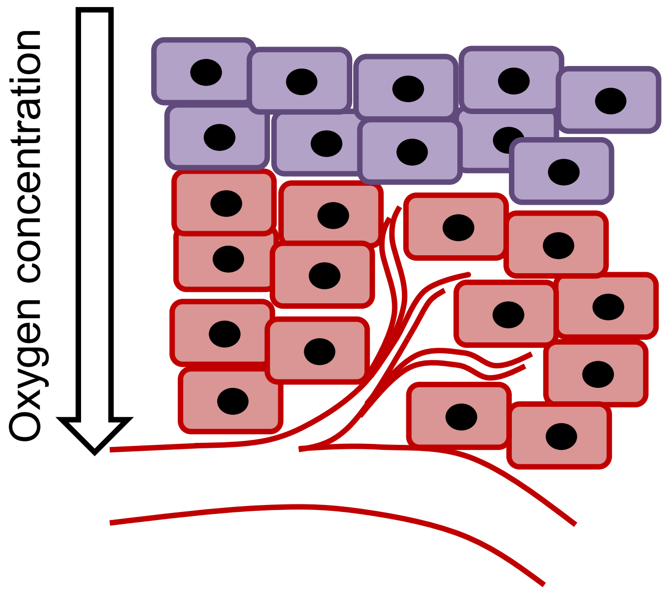
http://www.macmillan.org.uk/images/cancerinfo/cancertreatment/radiotherapy_treatment2010451x410.jpg

Why pre-clinical micro-IMRT ?

2 examples

Example 1: Hypoxia in radiotherapy

Hypoxia (low oxygen concentration) develops in tumours due to deficient vasculature.



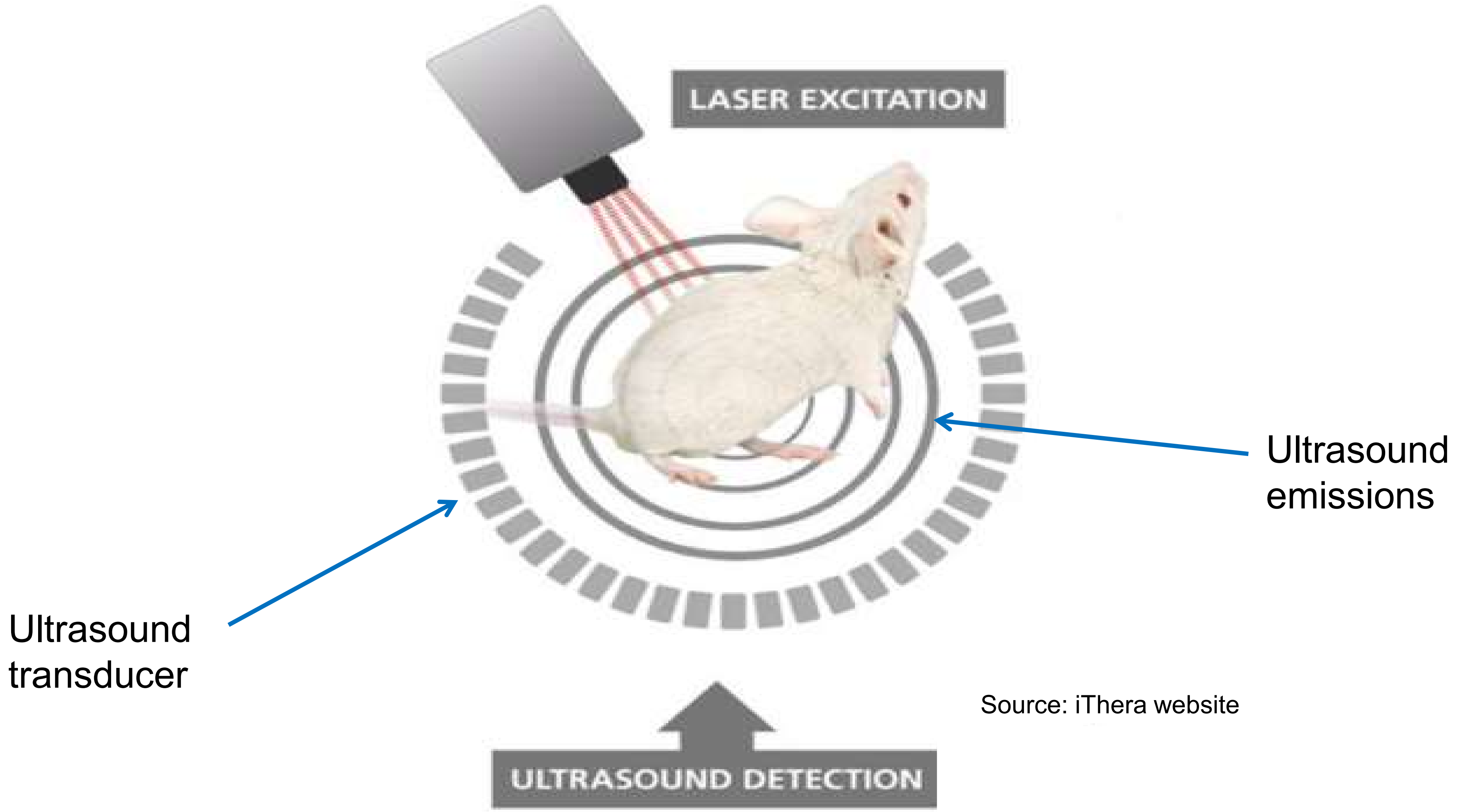
About radiotherapy

About 4 out of 10 people with cancer (40%) have radiotherapy as part of their treatment. Radiotherapy uses radiation to kill cancer cells.

Source: Cancer Research UK

Hypoxia results in RADIORESISTANCE!

Photoacoustic Imaging (PAI)



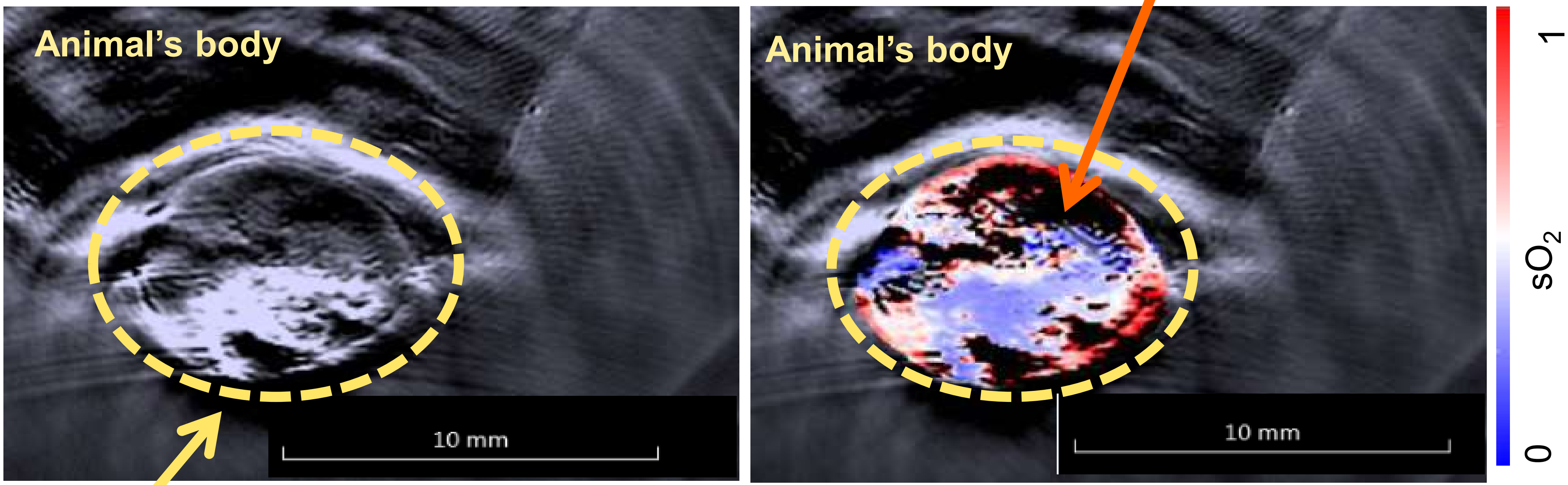
Source: iThera website

Light absorption in tissue produces ultrasound emissions!

Photoacoustic Imaging (PAI)

Black regions: haemoglobin below noise threshold

Example: subcutaneous tumour model in mouse flank



Tumour

$$sO_2 = \frac{HbO_2}{HbO_2 + Hb}$$

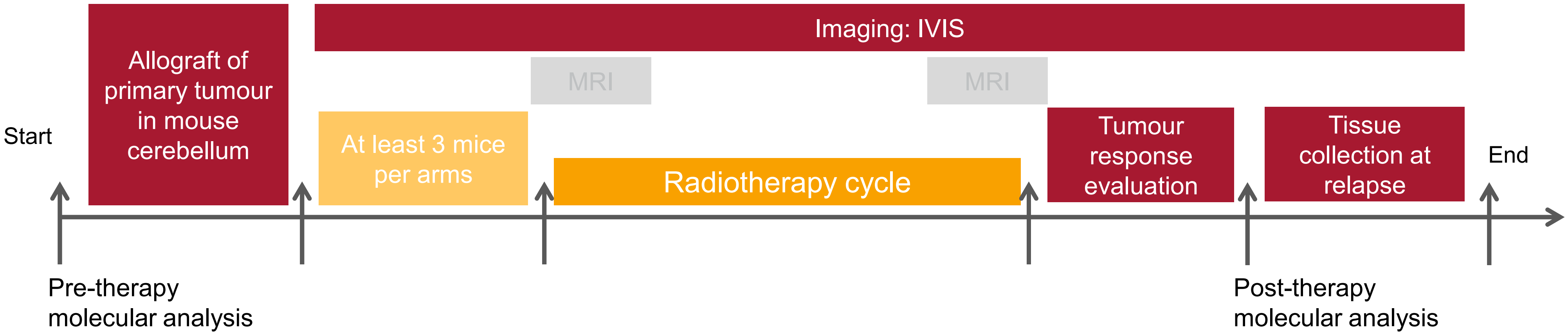
Total haemoglobin

Oxygen saturation

Eample 2: Pre-clinical RT of Medulloblastoma

Human treatment: Cranial/spinal irradiation
54 Gy in tumour bed
36Gy in spine
Schedule: 5 days on/2 days off cycle

Experimental design



ICR: Louis Chesler, Alaide Morcavallo, Karen Barker, Nikita Locket RMH: Henry Mandeville

Summary

- The current clinical pathway in which new agents are tested at recurrence is based on the premise that the recurrent tumour is biologically and genetically similar to the tumour at diagnosis

- Human diagnostic and post-therapy medulloblastoma (MB) demonstrated substantial genetic divergence after therapy

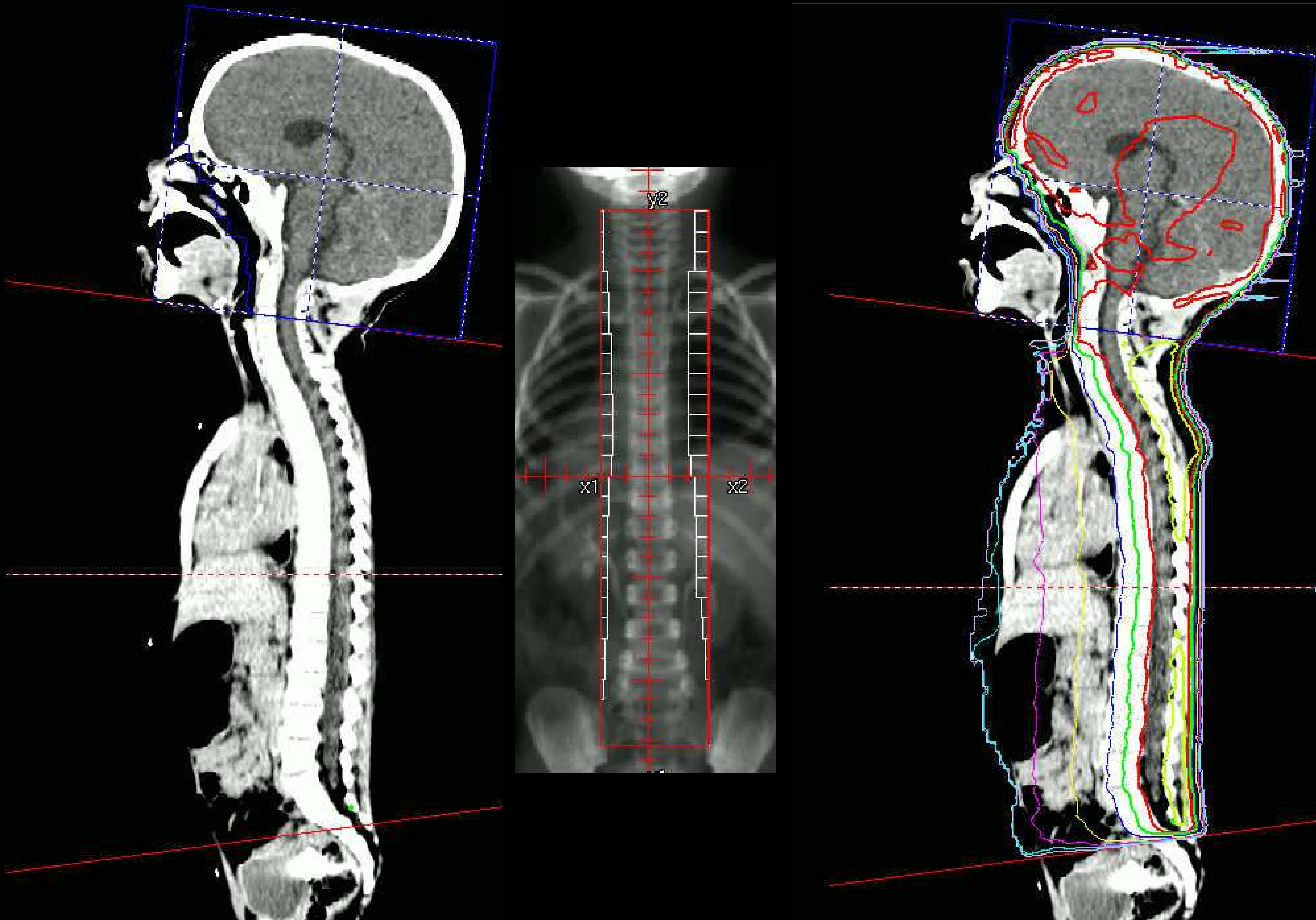
- The majority of basic and translational research on the biology of MB makes use models of MB that have not been exposed to prior anti-tumour therapies

- Current experimental models fail to model recurrent disease

- **AIMS: -** Targets identification at relapse stage
  - Preclinical brain tumour platform to test combinations of conventional and novel therapies in a manner that closely recapitulates clinic trials

  Methods:
  - GEMMs/Allograft representing higher-risk MB subgroups
  - Replicate human treatments in the GEMMs/Allograft

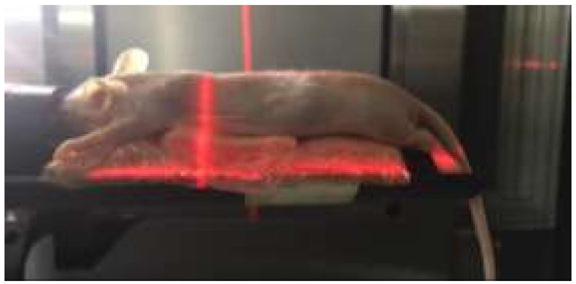
- **Outcome:**
  - Pre-clinical compound **efficacy** assessment
  - Suggest compounds for **clinical trials in relapse patients**


y2
x1
x2

SARRP irradiation parameters

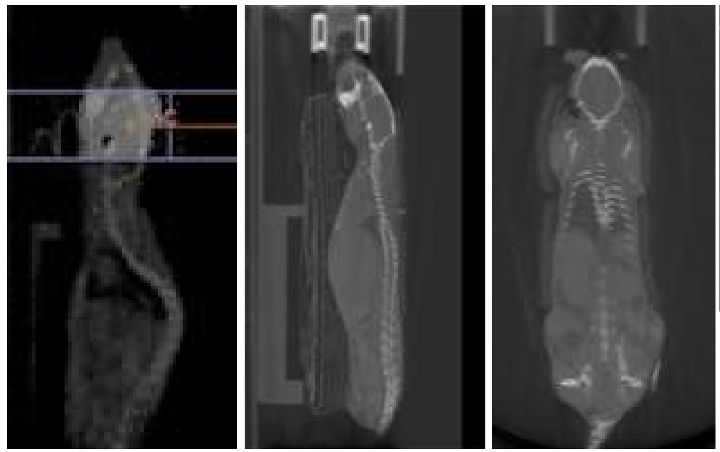
- Collimator: Motorized Variable Collimator
- Field shape and size: variable field radiation over a conformal arc
  - iso1-brain: 13mm X 4-5mm
  - iso2-neck: 11mm X 4mm
  - Iso3-spine: 44mm X 4mm

1) Positioning

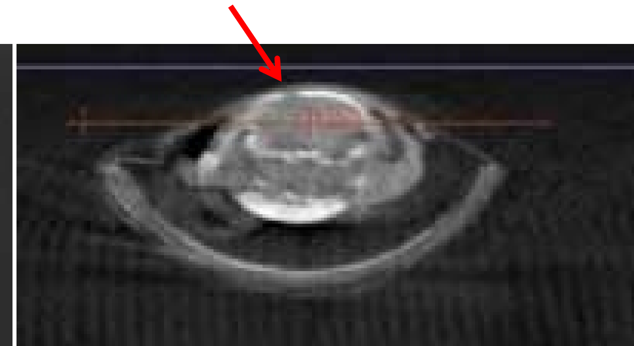


Handmade bed, 3d printed on going

2) Cone beam computed tomography



Spine alignment



Tumour site identification (based on site of injection)

ICR: Alaide Morcavallo, Nikita Locket
Xstrahl: Amanda Tulk, Sara Chiblac

Small animal precision irradiators SARRP

Precision irradiation

- 225 kVp x-ray tube
- 360° gantry
- Fixed size collimators
- Variable Jaws

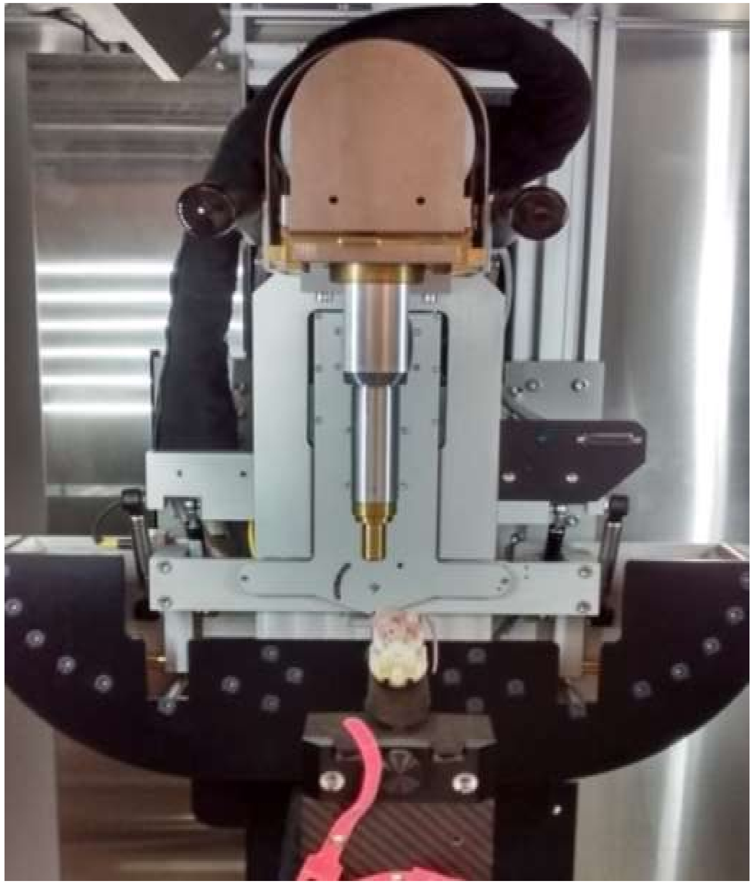
On-board CBCT

Robotic couch

Treatment planning system Muriplan

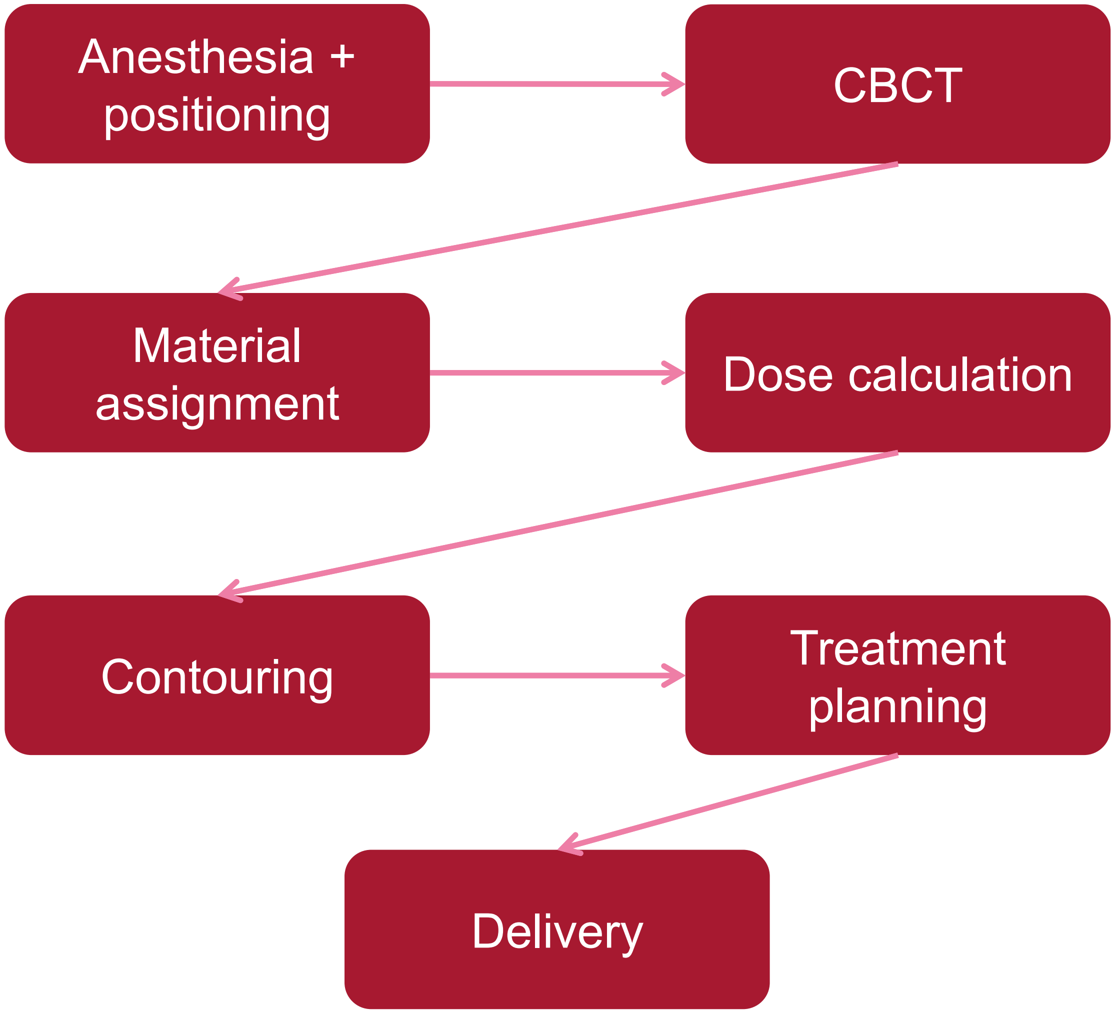
http://www.meditron.ch/radiation-therapy/media/com_hikashop/upload/sarrp600x600.jpg

Standard SMART with the SARRP

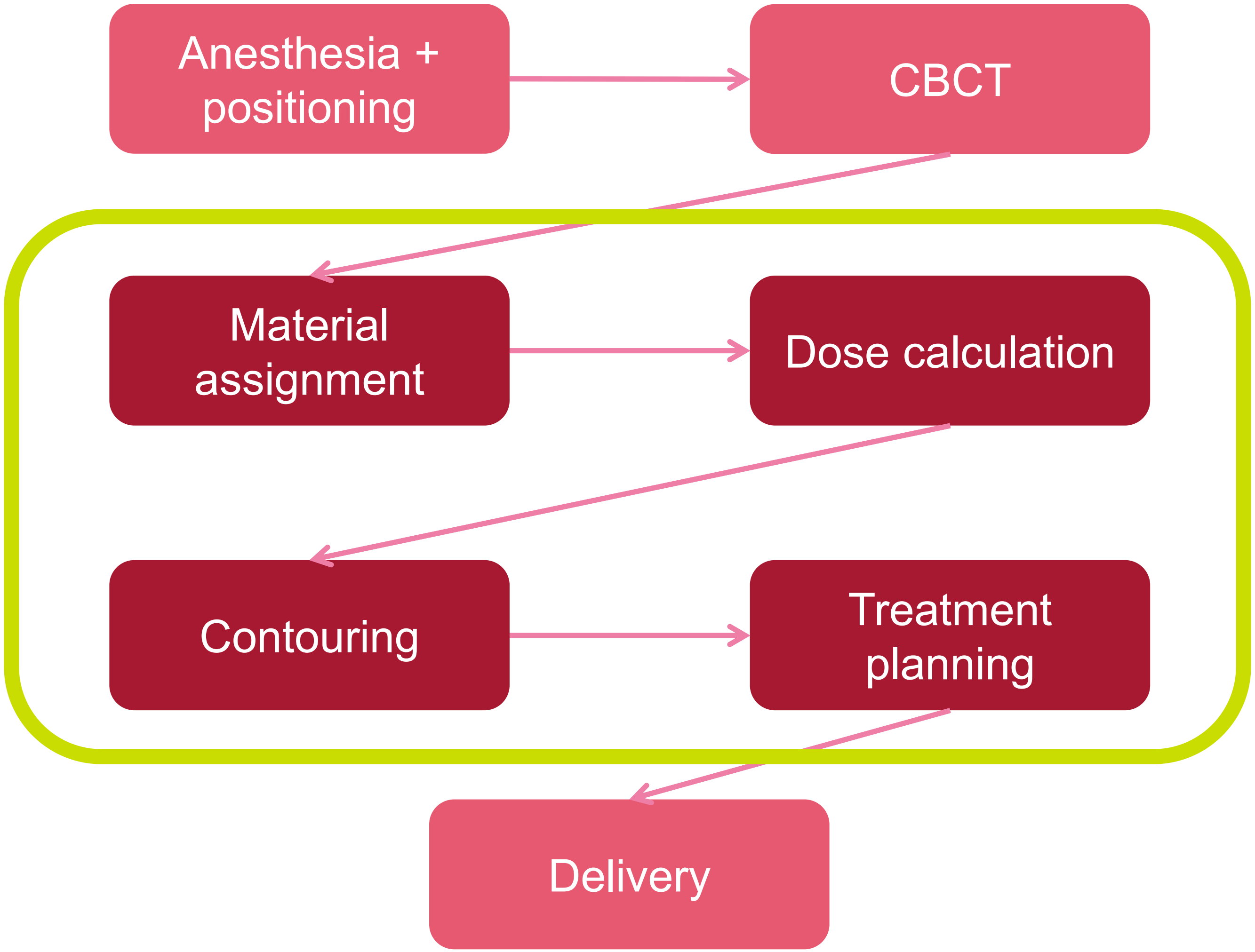


- Mice irradiated in a small animal radiation platform (SARRP®, Xstrahl, Camberley, UK).
- 10x10 mm^2 square collimator
- 0^o and 180^o beams.

µIMRT on the SARRP
Workflow



µIMRT on the SARRP
Workflow



Material assignment

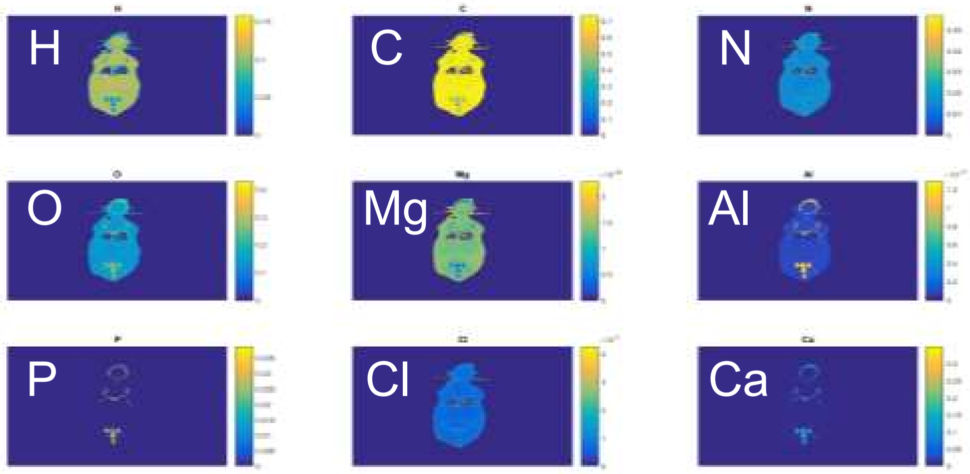
CBCT ➔ elemental composition

Schneider et al., 1999

- Stoichiometric calibration
- 5 HU windows
- Interpolation between 2 out of 7 base materials

DECT

- Current work
- Principal component analysis
- Shallow neural network to find weights



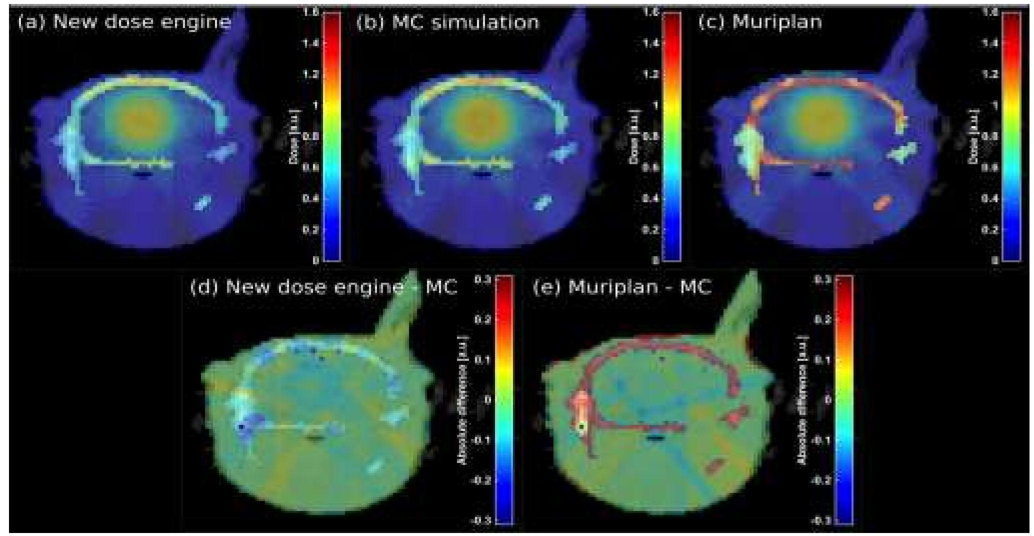
Dose calculation

Superposition-convolution with a twist:

1. TERMA for 6 energies:
2. Primary dose = $f_E \times$ TERMA(E)
3. Scatter dose for 60 kernels: 6 energies x 10 materials: TERMA(E,M) * Kernel(E,M)

$$D_{total} = D_{primary} + D_{scatter}$$

Calculation time (5 beams): 18.4 s




SMALL ANIMAL IGRT SPECIAL FEATURE: FULL PAPER

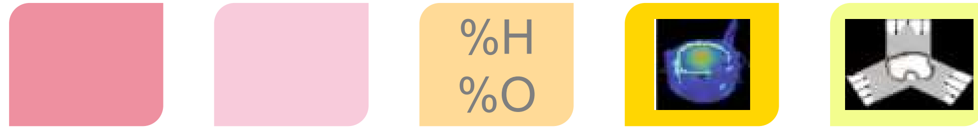
A kernel-based dose calculation algorithm for kV photon beams with explicit handling of energy and material dependencies

ANNA MERLE REINHART, MSc, MARTIN F FAST, PhD, PETER ZIEGENHEIN, PhD, SIMEON NILL, PhD and UWE OELFKE, PhD

Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK

Address correspondence to: Ms Anna Merle Reinhart

Dose engine



Superposition-convolution with a twist:

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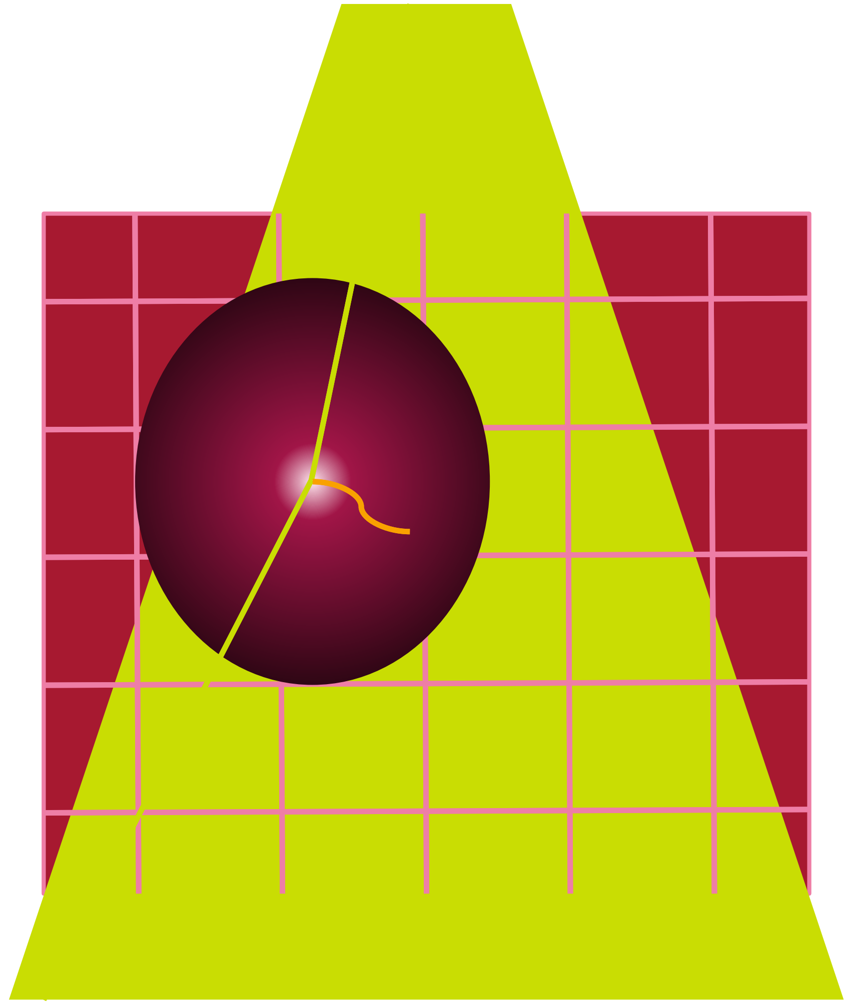
$$D_{total} = D_{primary} + D_{scatter}$$



TPS
D_{ij} approach

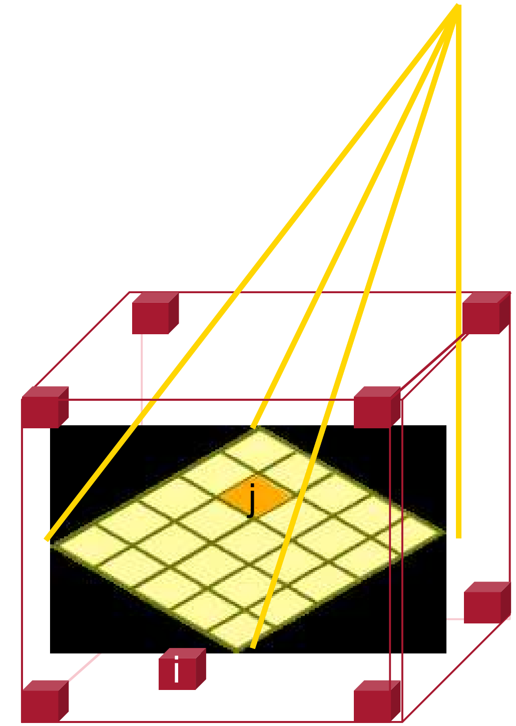
Dose-influence matrix D_{ij}

- Split beam into bixel
- Calculate dose to every voxel i for each bixel j

$$d_i = \sum_j w_j \cdot D_{ij}$$

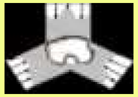
D_{ij} matrix calculated with kernel dose engine

Optimization to find weights w_j



Implementation

%H
%O



- Multi-core CPU environment
- Highly parallel calculation

Test case	Mean calculation time [s]	
	New dose engine	Muriplan
256^3 water cube, $(1mm)^2$ beam	4.1 ± 0.0	5.5 ± 0.0
256^3 water cube, $(5mm)^2$ beam	5.2 ± 0.2	5.4 ± 0.2
256^3 water cube, $(10mm)^2$ beam	7.9 ± 0.1	5.5 ± 0.2
$128^2 \times 326$ mouse CBCT, 5 $(3mm)^2$ beams	18.0 ± 0.3	18.4 ± 0.2

Treatment planning for the SARRP

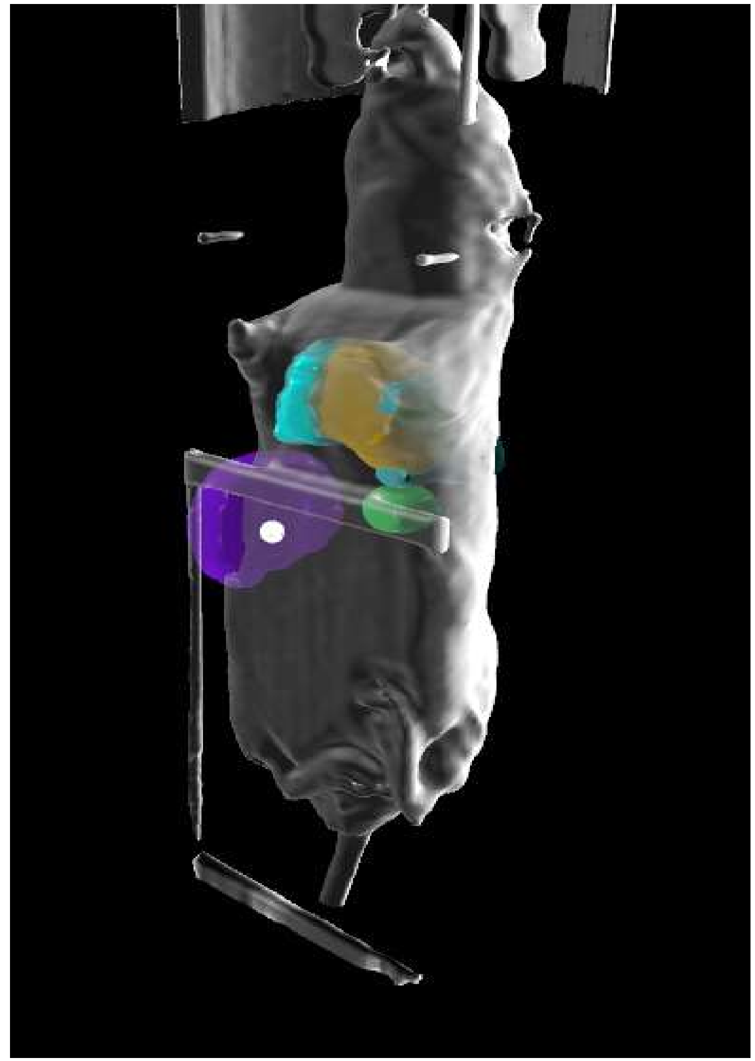
CBCT from the SARRP

➔ Contouring

Dose calculation with our new dose engine

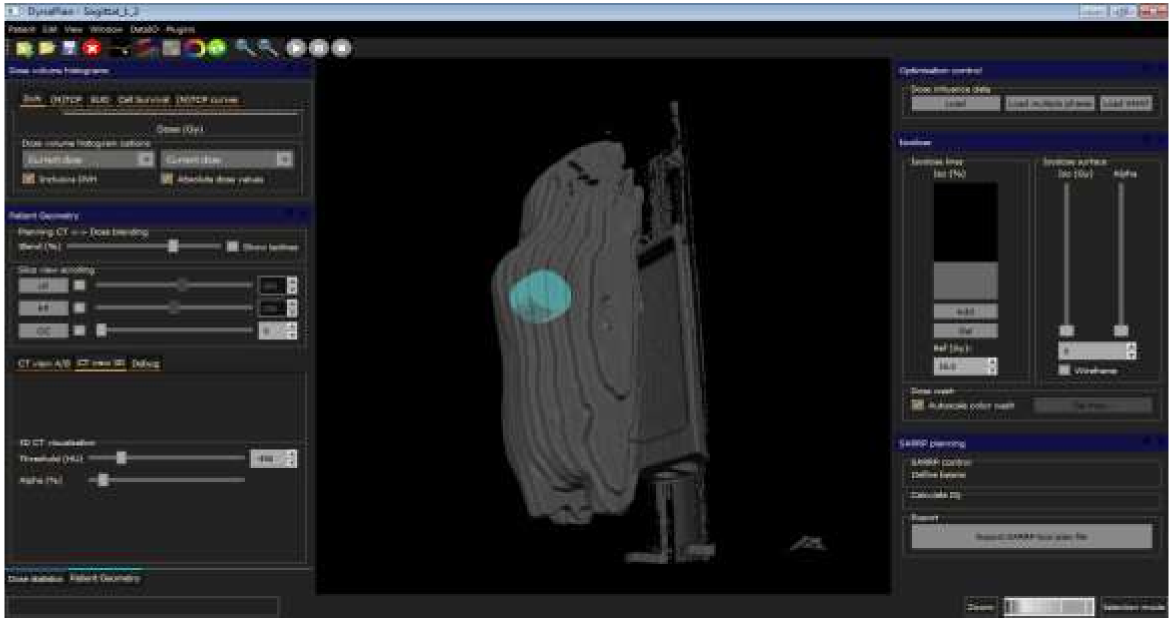
➔ Dij matrices

Planning in Dynaplan



Treatment planning system

Based on in-house system Dynaplan



Dij-based fluence optimisation

- Quadratic cost function
- Quasi-Newton optimisation

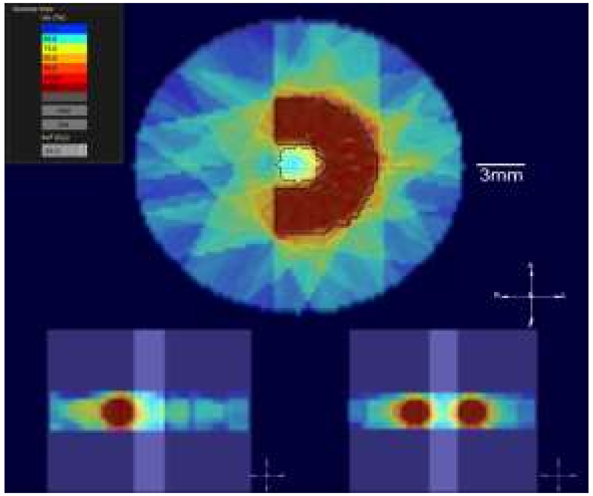
Ultra-fast multi-core CPU implementation

- Optimisation in seconds

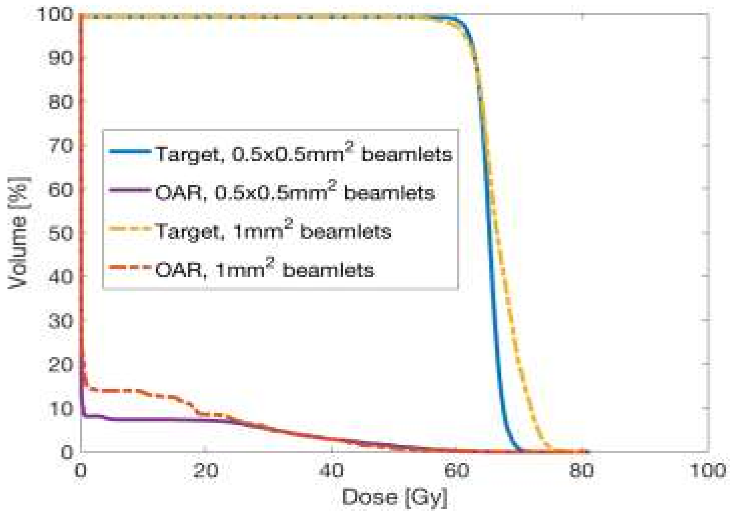
Treatment planning

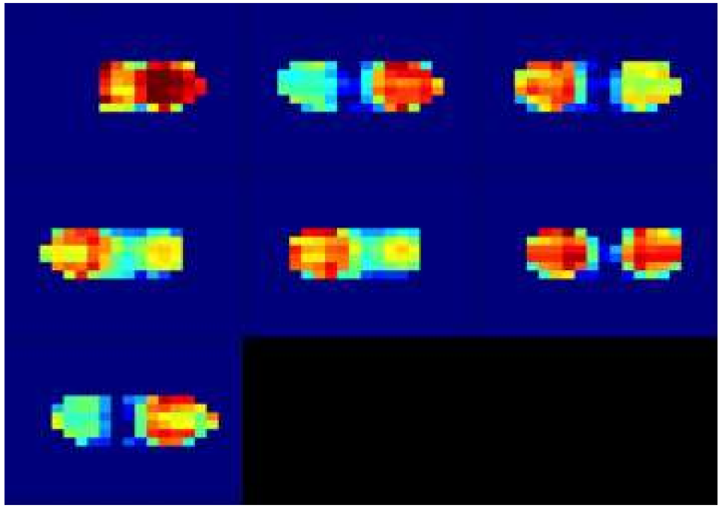
Horseshoe phantom

- 7 equidistant, co-planar beams
- Maximal field 1cm^2
- 0.5x0.5mm^2 or 1x1mm^2 beamlets



0.5mm



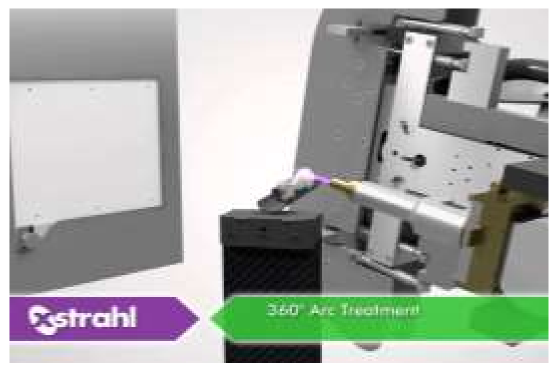


Delivery techniques

Jaw-only IMRT

- Rectangular fields
- Variable size

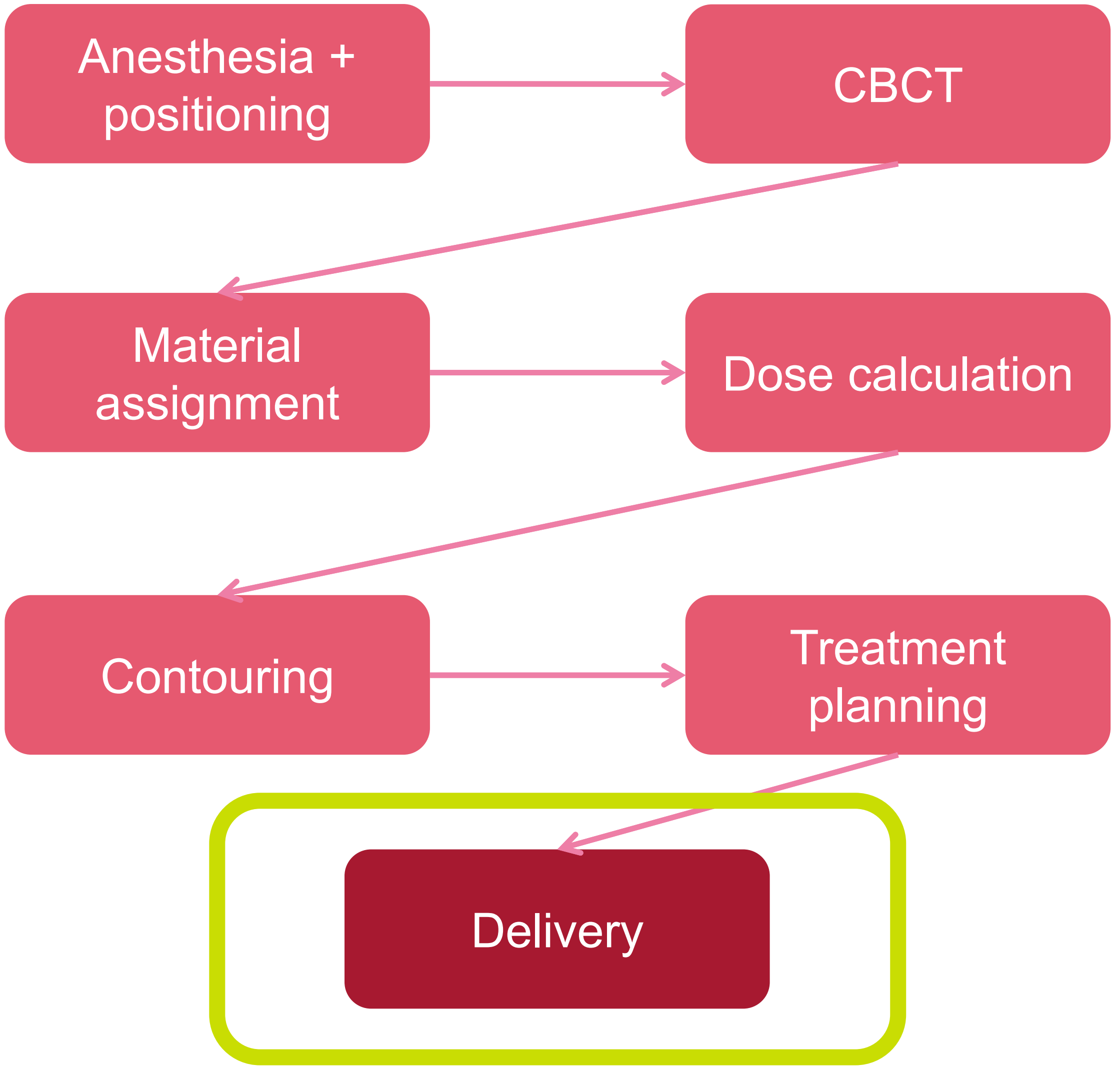
- Superposition of rectangles
- Couch motion



rwinc.com/manufacturing-industries/

www.xstrahl.com/media/117852/VC-Web.jpg

μIMRT on the SARRP
Workflow



Delivery
Jaw only IMRT

XStrahl's Motorized Variable Collimator (MVC):

- 2 sets of focused, orthogonal tungsten jaws
- Field sizes: 1x1mm^2 to 80x40mm^2

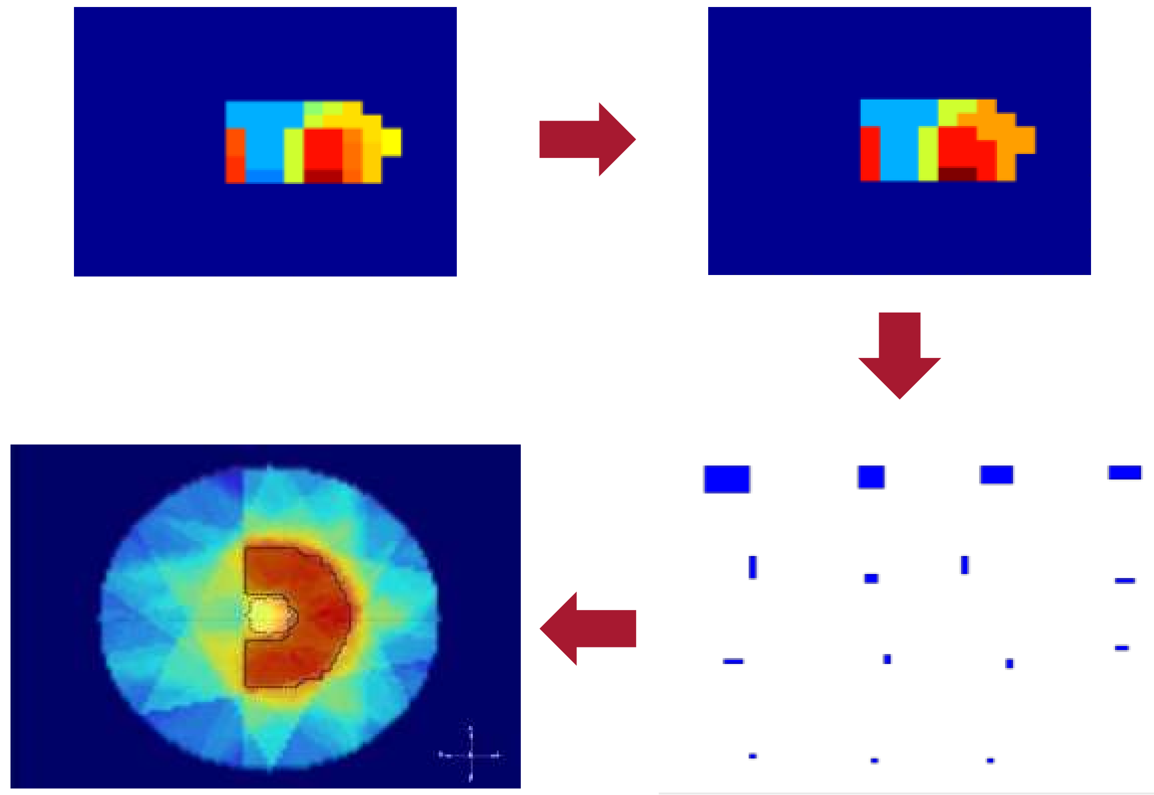
➔ Jaw only IMRT
➔ Superposition of rectangular fields

Sequencing

Jaw-only IMRT

- Variable rectangles

- Simplify fluence as $\Sigma 2^n$
- Heuristic approach based on maximal rectangle size



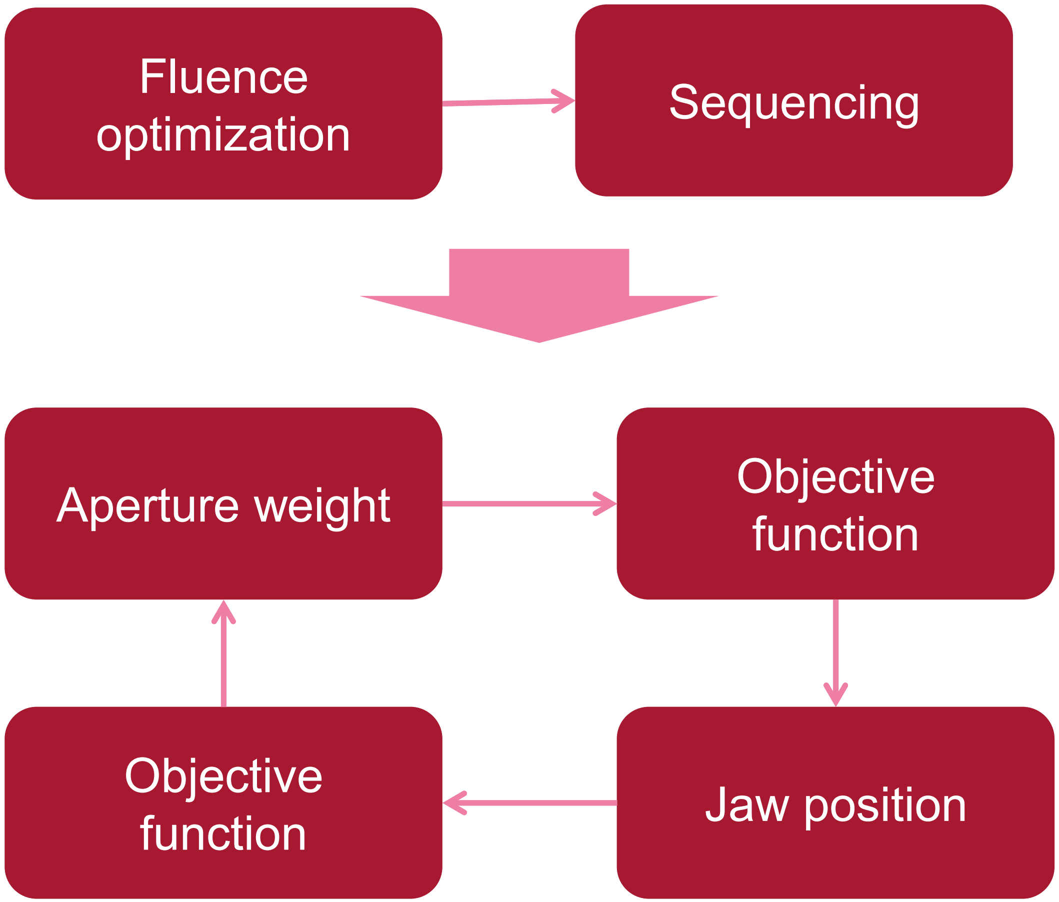
Direct aperture optimization

Initial solution:

- Fluence optimization
- Sequencing

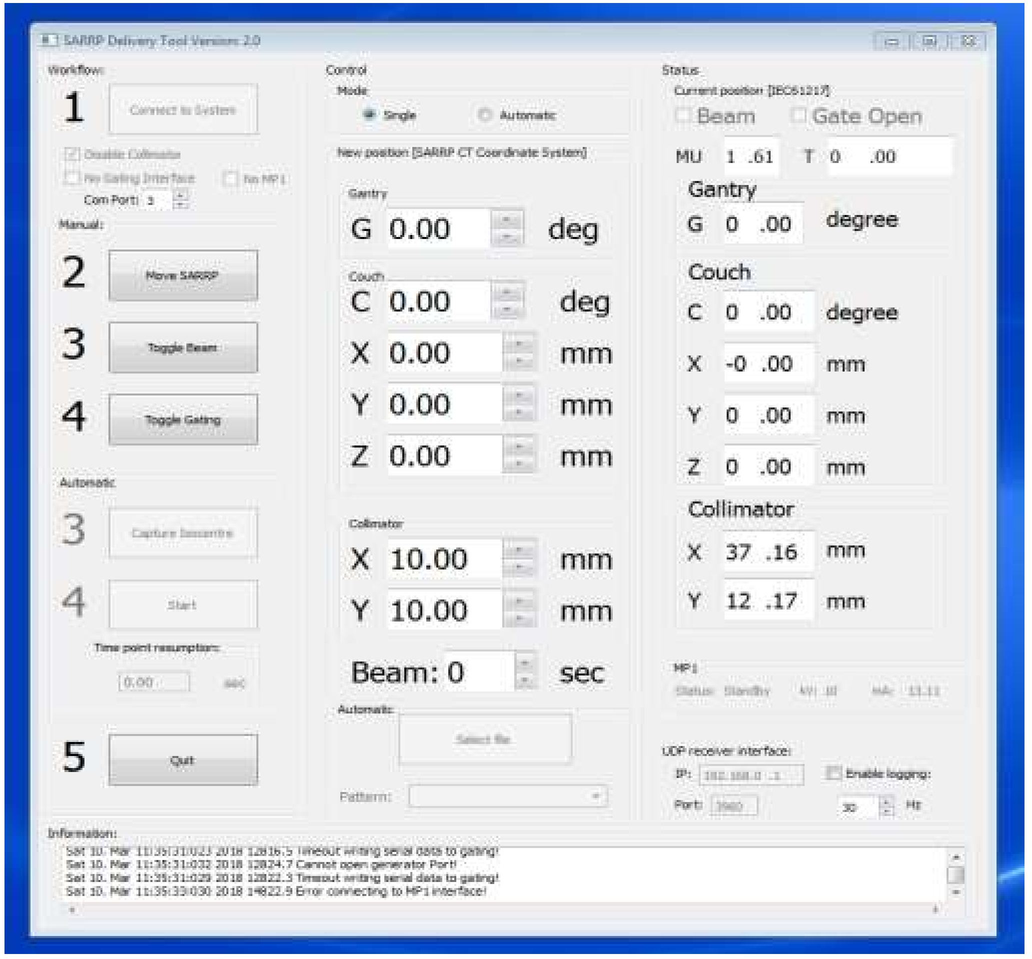
Gradient-based optimization loop:

- Aperture weight
- Aperture size



Delivery

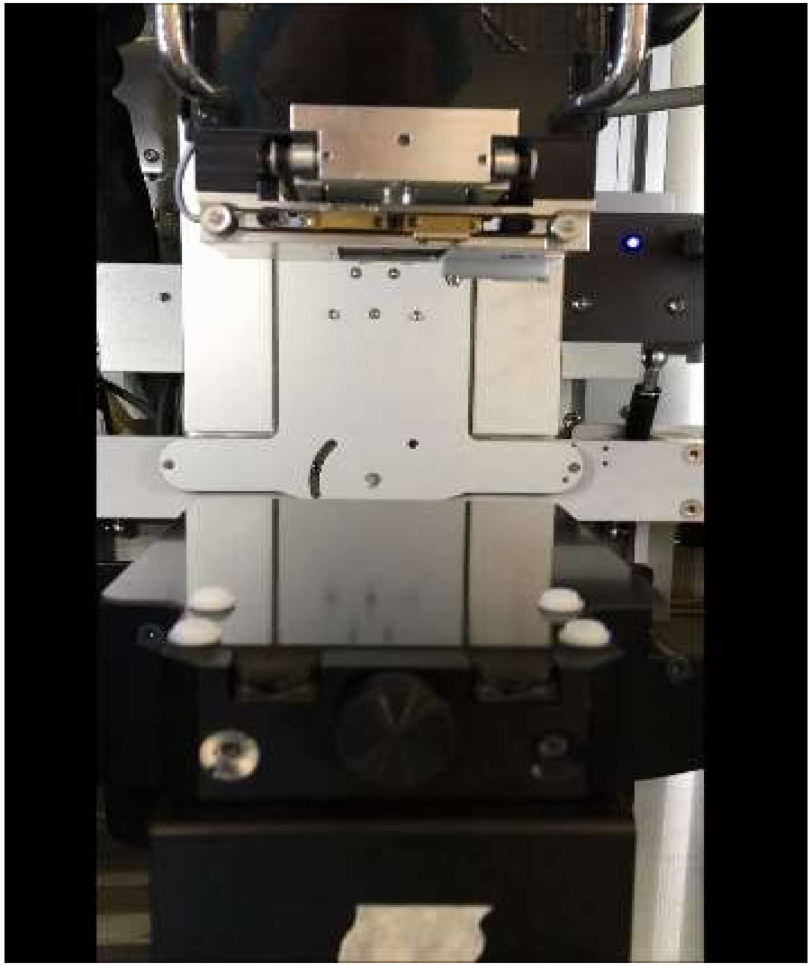
- Couch movement for asymmetric fields
- Gating system to stop beam between segments
- Control software: stage, gating system and beam
- Fully automated delivery



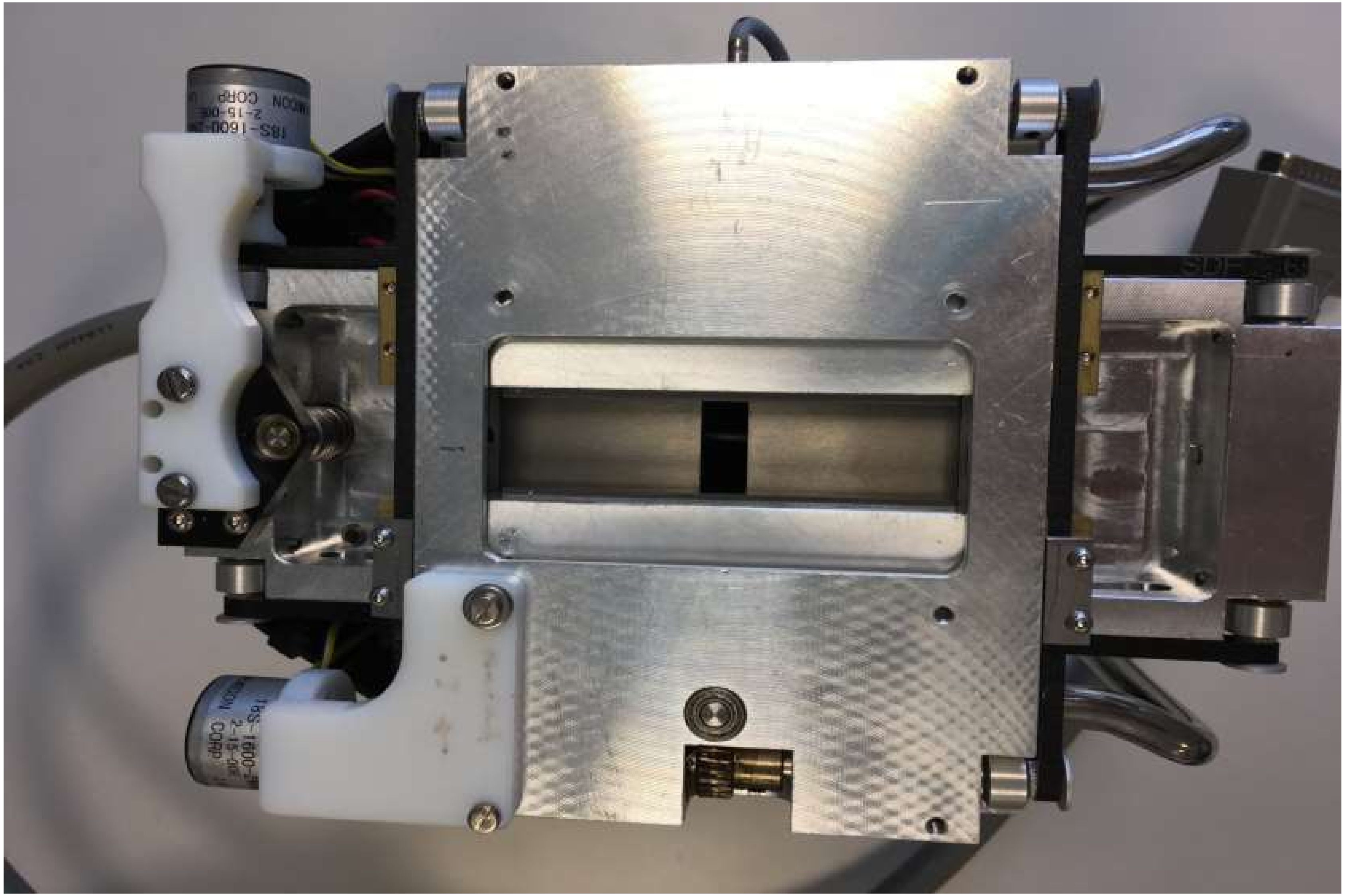
SARRP: Degrees of freedom dose delivery

Jaws Collimator
(Symmetric fields)

‘Robotic’ Couch
(Asymmetric field location)



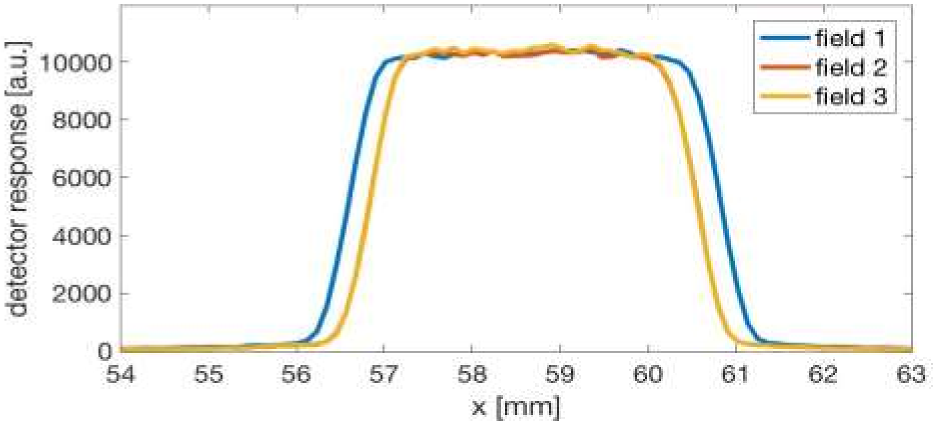
SARRP: MVC

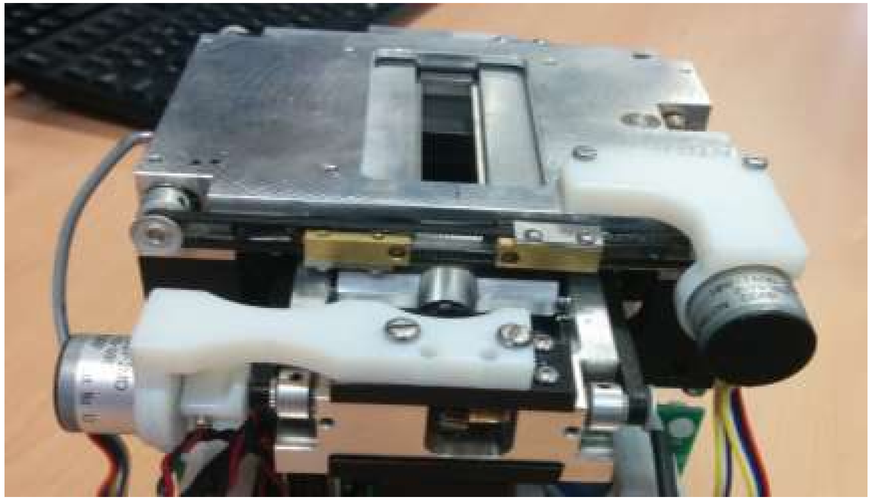


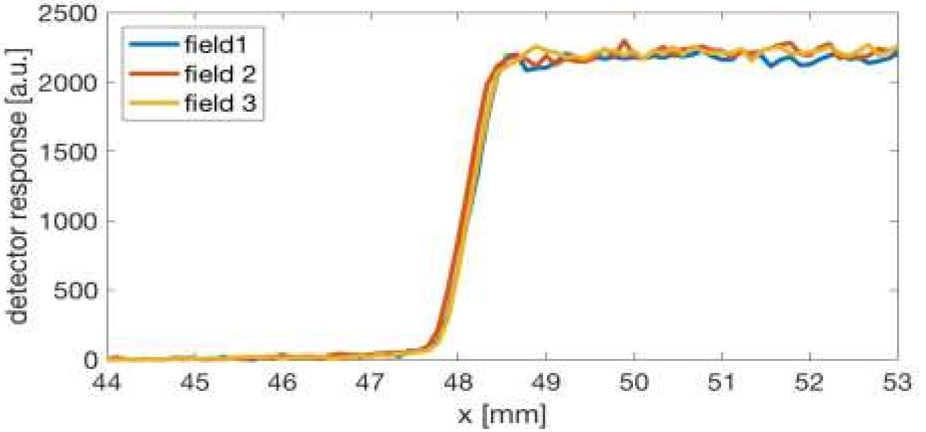
Collimator problem: jaw positioning accuracy

- Repeatability within 0.4mm
- Delivery of 1x1mm^2 fields

- Added encoders
- Repeatability within 0.1mm

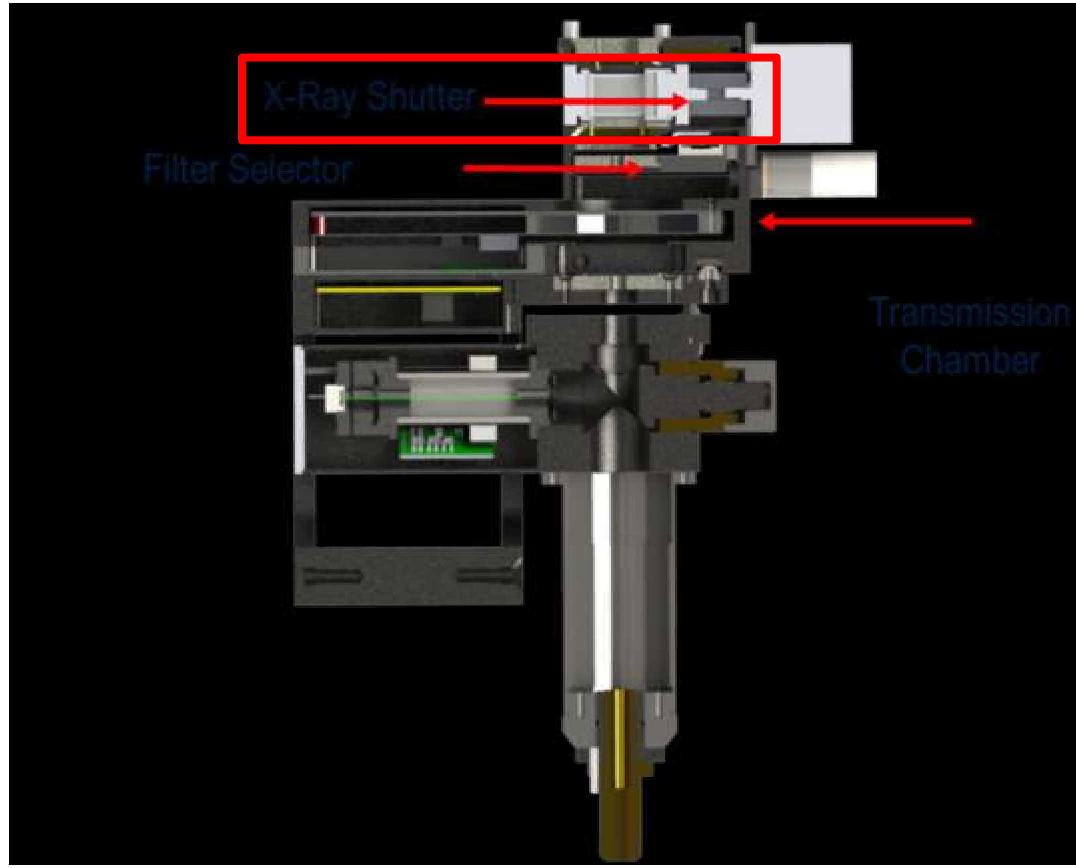






Shutter for gated dose delivery

Beam On/Off



Courtesy of Xstrahl and B. Voinovic

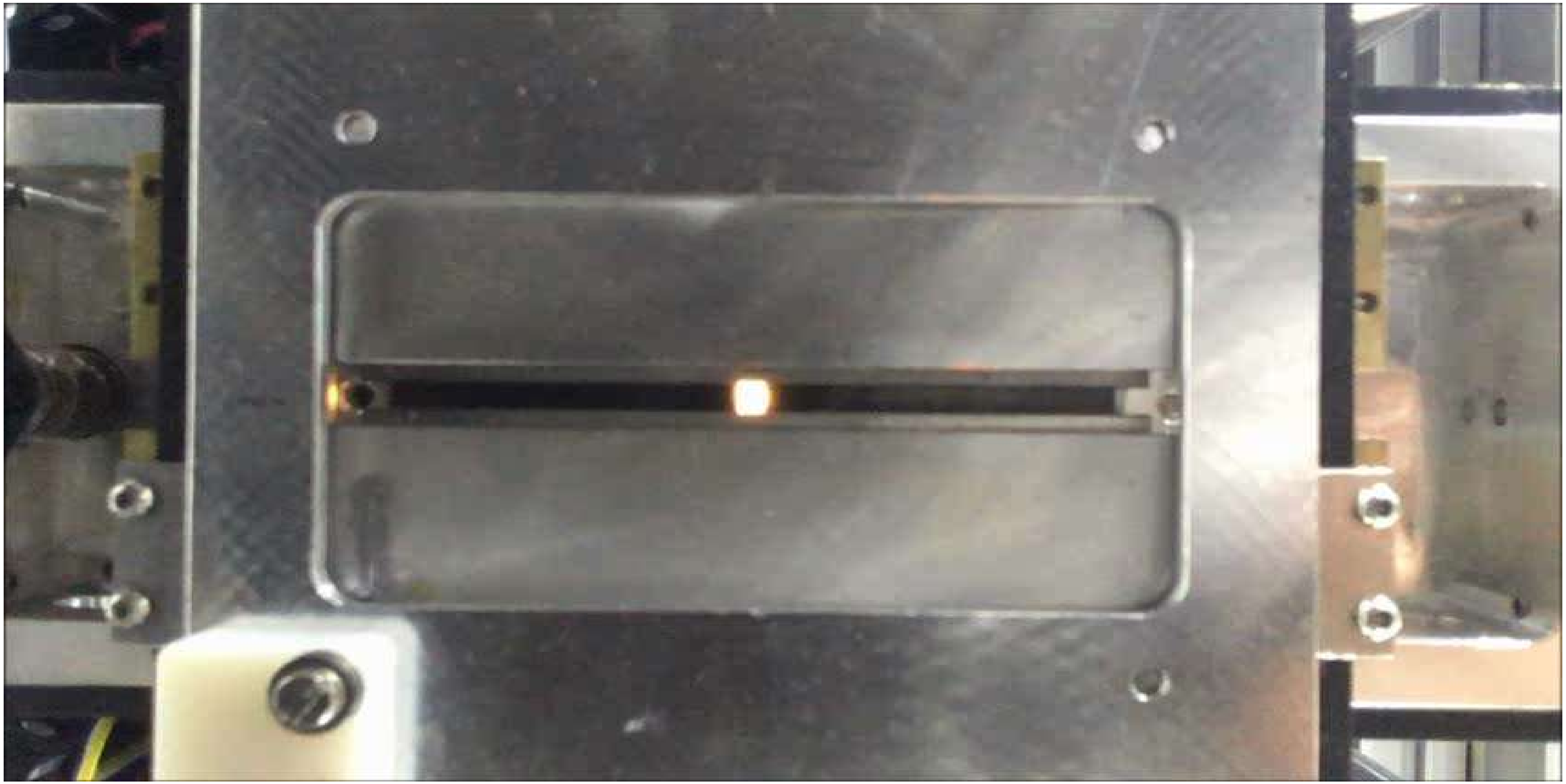
Thermal sensor for animal temperature monitoring

- Optional feedback loop to warming pad*

Transmission ion chamber for dose verification

Shutter for dose beam control

SARRP: Automated delivery (Mouse view)



Speed up (4x)

Feasibility test

Preliminary base data:

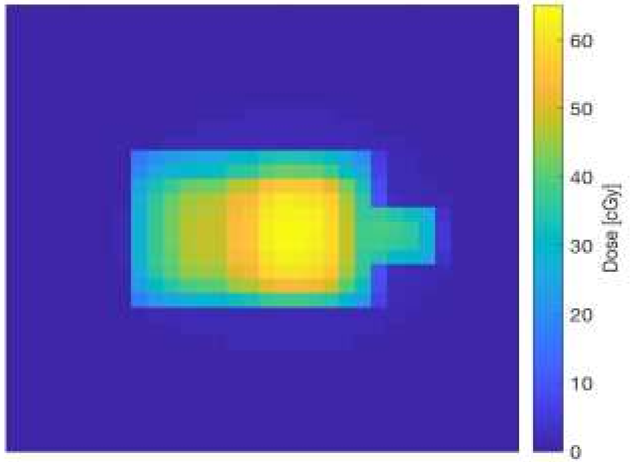
- Output factors for 10 field sizes

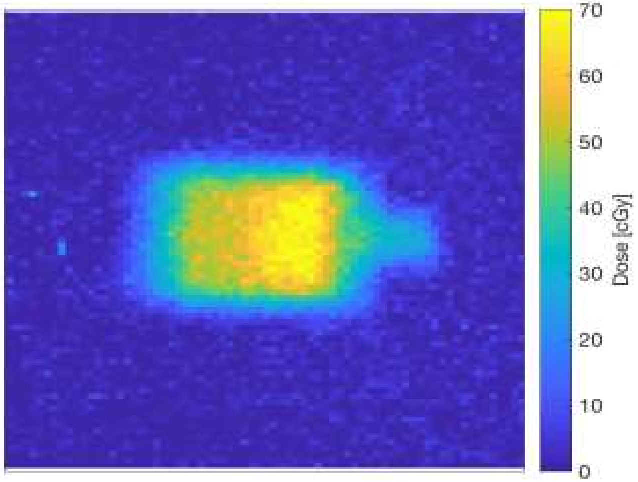
Head model:

- Analytic head model
- Raytracing through collimator

Irradiation time:

- 8Gy
- 5-12 min depending on number of shapes





Outlook
Commissioning

Full commissioning of the system:

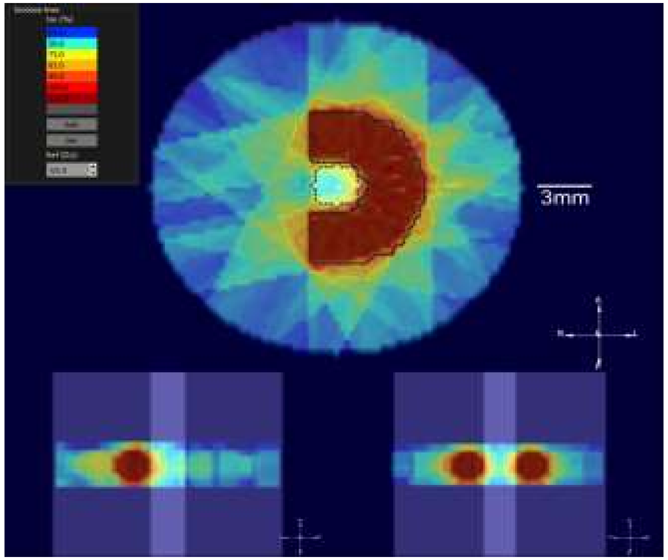
- Depth dose profiles
- Output for various field sizes and SSDs
- Collimator validation

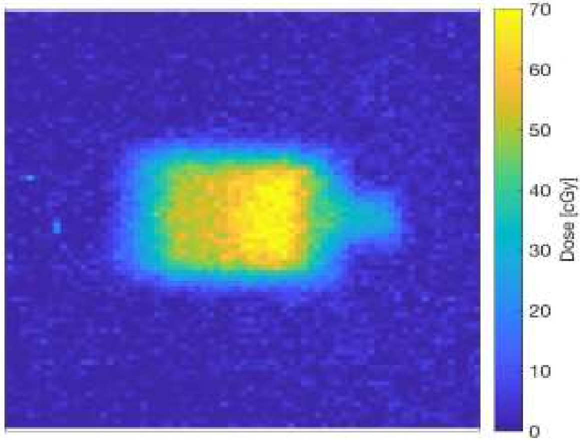
µIMRT on the SARRP
Summary

µIMRT delivery

- Delivery with the MVC
- Superposition of rectangles
- Direct aperture optimization

➔ Full commissioning of the system





- Microbeam therapy ?

Who performs micro-beam therapy?

Nobody

How does it work?

We don’t know

What is it good for?

We don’t know

What is micro-beam therapy?

The begining of MRT

An unexpected observation

1959

Tolerance of Mouse-Brain Tissue to High-Energy Deuterons

Abstract. A striking relationship between the size of the impact area of a deuteron beam and the threshold dose for a radiogenic lesion has been noted. The dose required to produce a threshold lesion in mouse brain increases from 30,000 rad with a beam 1000 μ in diameter to 1.1×10^6 rad with a beam 25 μ in diameter.

While investigating the effect of extraterrestrial heavy ion beams on astronauts the astonishing little effect of microbeams on tissue was found.

W Zeman, H J Curtis, E L Gebhard, and W Haymaker. Science, 1959.

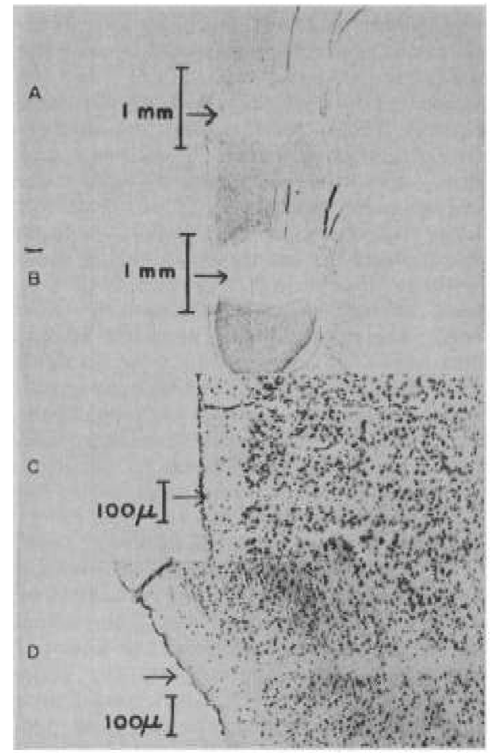
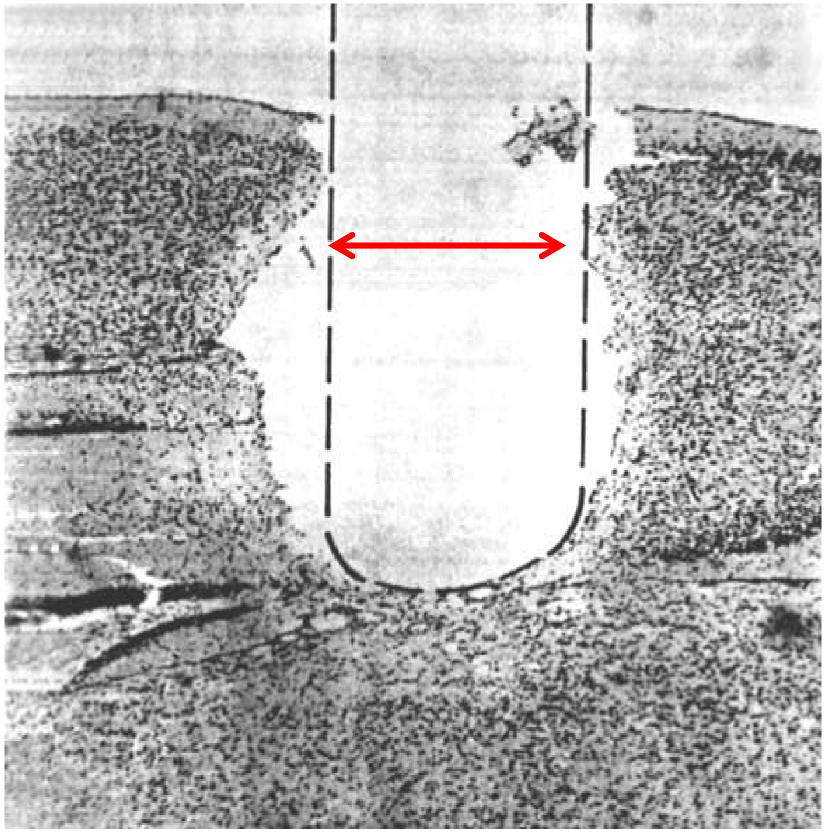


Fig. 1. Frontal sections of visual cortex of mice irradiated with deuteron beams. The arrows indicate the direction of the beam. (A) 1-mm beam, 30,000 rad, 24-day survival; (B) 1-mm beam, 60,000 rad, 24-day survival; (C) 0.025-mm beam, 1.1×10^6 rad, 6-day survival; (D) 0.025-mm beam, 1.1×10^6 rad, 48-day survival.

The dose volume effect

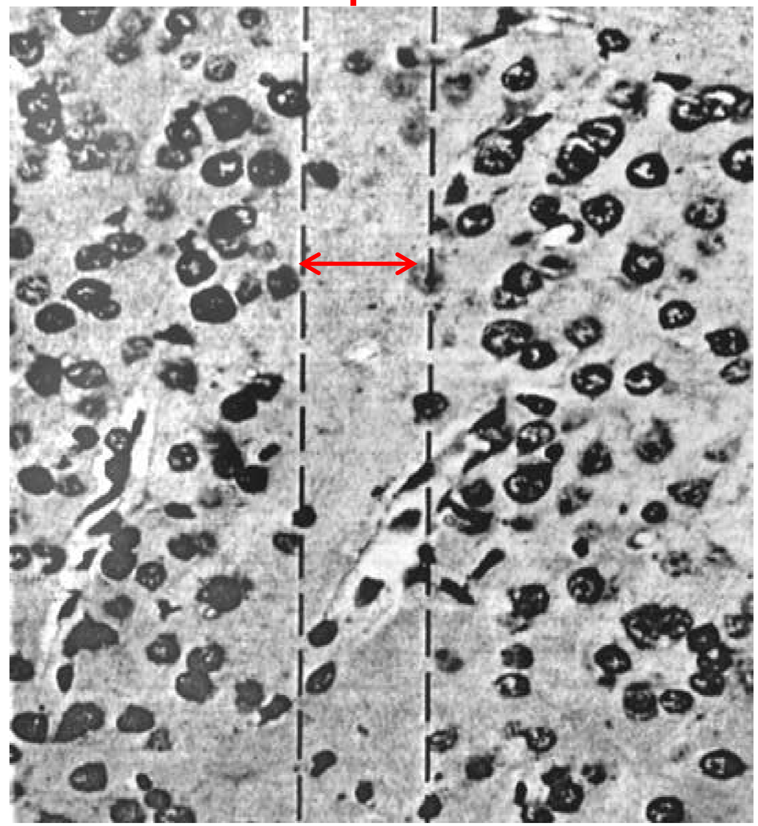
140Gy

1mm



4000Gy

25µm



22 MeV Deuteron beam; cerebral cortex of mice

Zeman et al, Radiat Res 15, 496,1961

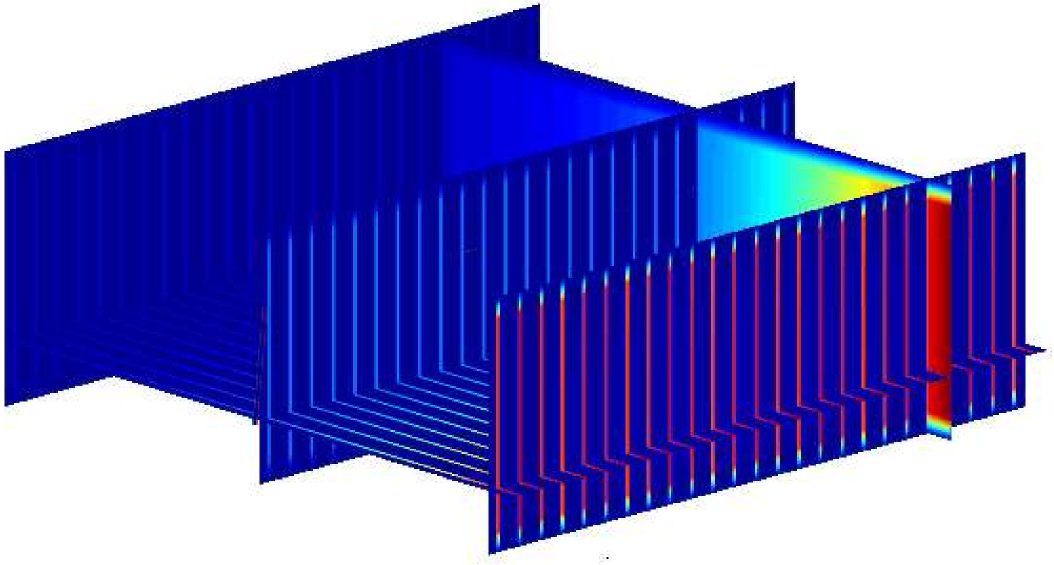
Courtesy of EBK

The begining of MRT

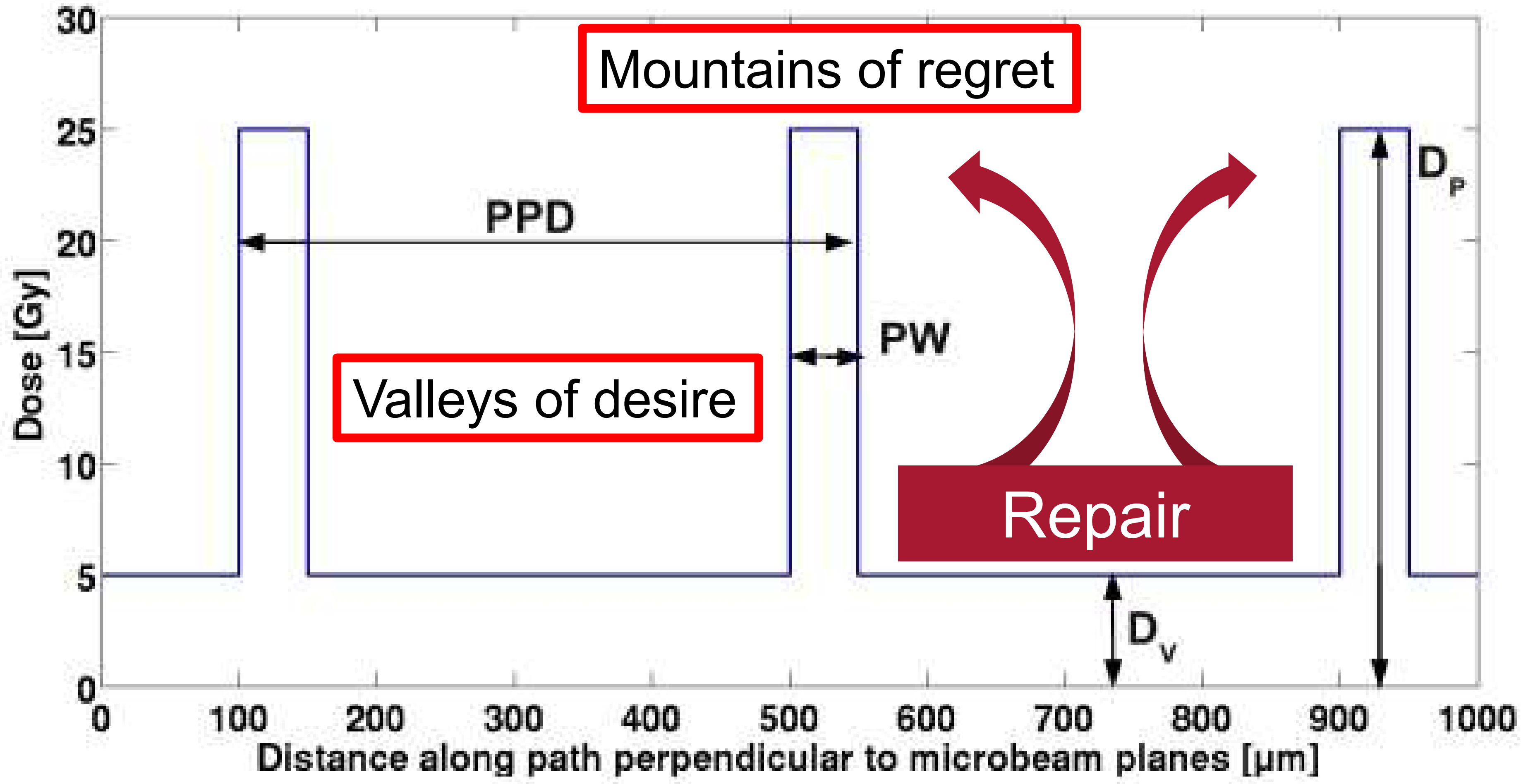
Generation of Microbeams

Creation of microbeams with synchrotron radiation (= photon beams):

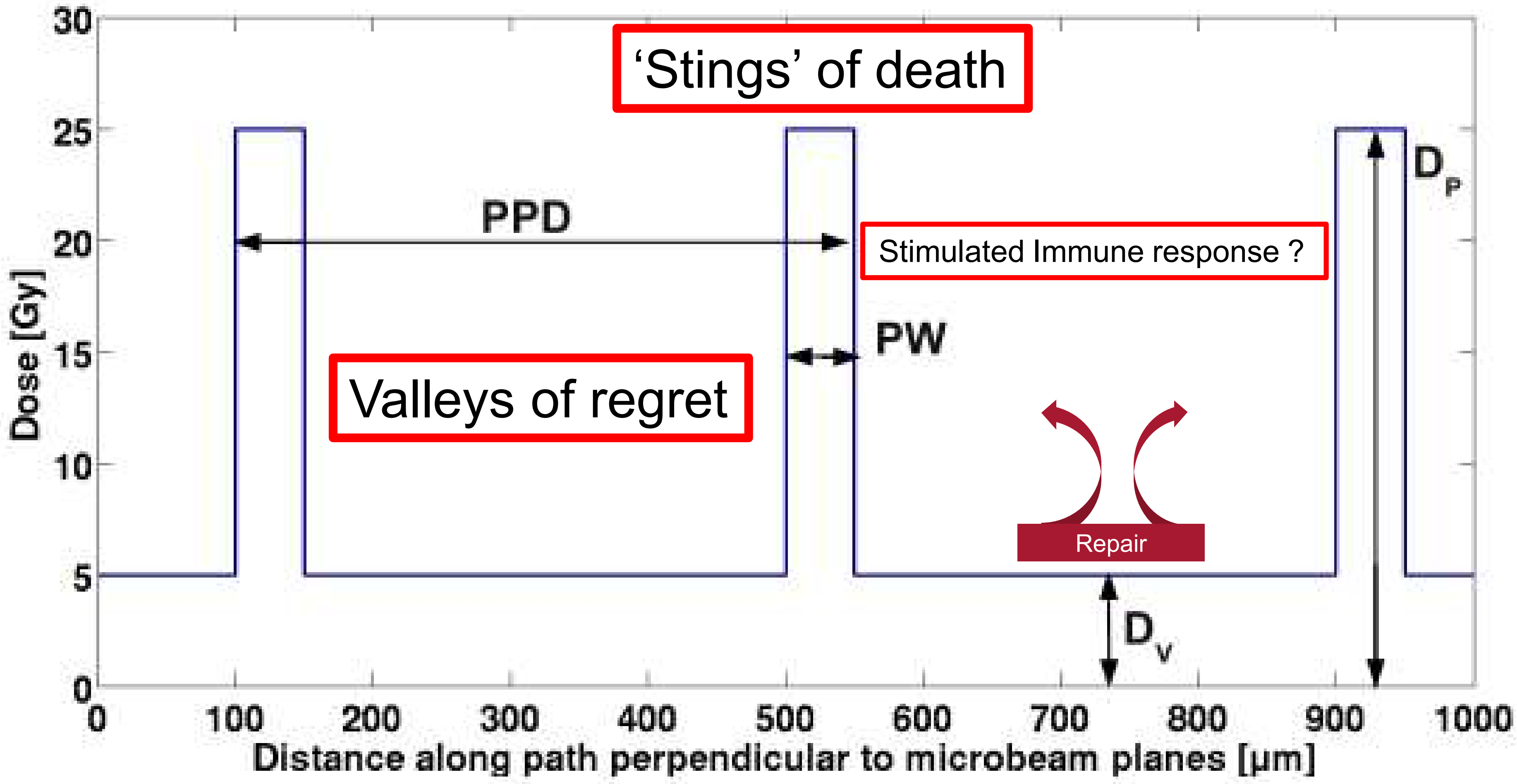
- 25-75 µm wide beams
- 100-400 µm distance (ctc)
- dose rate 16,000 Gy/s
- photon energy 40-150 keV
- even in 15 cm water depth dose gradients remain sharp



The normal tissue perspective



Our ‘tumour’ perspective



Cervical spinal cord in rats

MRT mode

≈ 11 mm

No paralysis: MRT< 500 Gy !!!

vertical microplanar beams, width 26 µm, beam spacing 210 µm
Length of spinal cord irradiated ≈ 11 mm
Entrance doses: from 1248 Gy to 156 Gy

J.A. Laissue , S. Bartzsch, H. Blattmann, , Elke Bräuer-Krisch, A. Bravin, D. Dalléry, V. Djonov, A. L. Hanson, J.W. Hopewell, B. Kaser-Hotz, J. Keyriläinen, P. Laissue, M. Miura, R. Serduc, A. E. Siegbahn, D. N. Slatkin "Response of the rat spinal cord exposed to X-ray microbeams" Radiother Oncol 106, 1 (2013) 106-11

Courtesy of EBK

MRT and interaction with the vasculary network

- Severe damage of immature and small blood vessels – no repair
- Much reduced damage at mature blood vessel systems – repair
- Tumour blood vessel networks are more immature – differential enhanced damage when compared to normal tissue
- MRT seems to ‘open’ the blood brain barrier ‘significantly’ – increased time window for efficient drug delivery

A compact microbeam source at the ICR

Accurate alignment is important

A preclinical microbeam facility with a conventional x-ray tube

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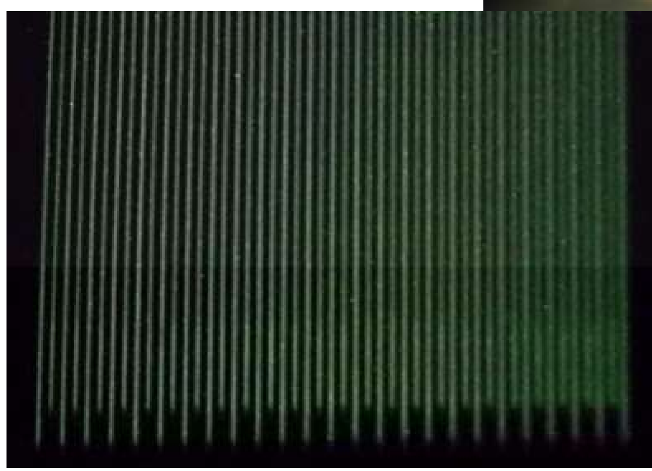
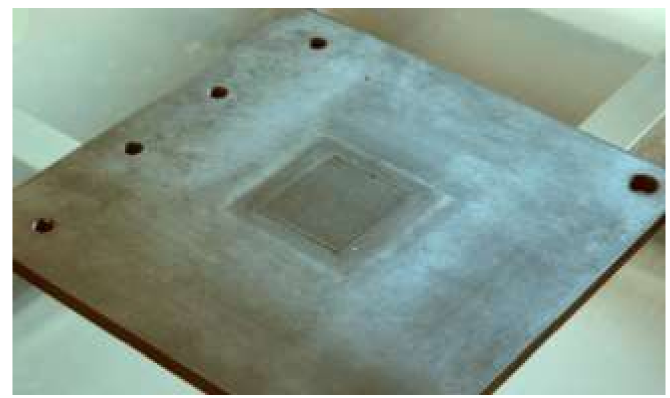
PVDR = 20



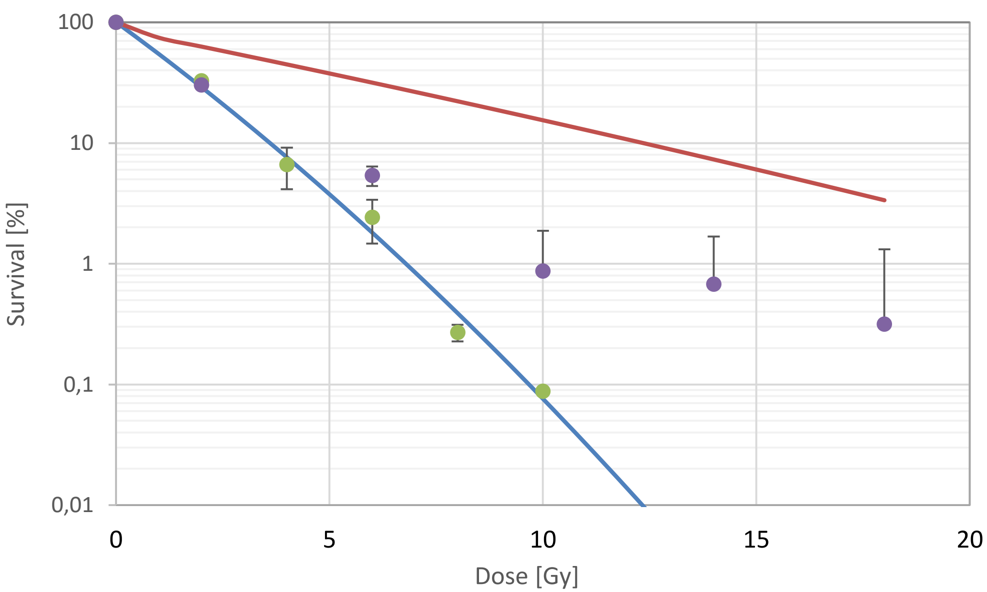


Reduced survival of cancer cells following microbeam irradiation

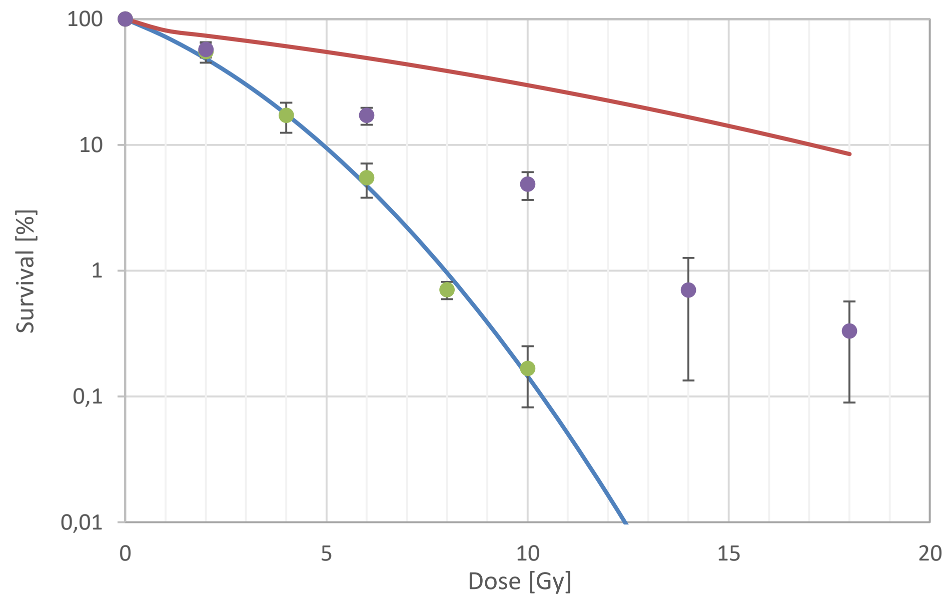
Clonogenic survival data following broad beam irradiation was fitted to a linear quadratic model

From this, survival following microbeam irradiation was predicted, assuming no communication between cells in the peaks or in the valley

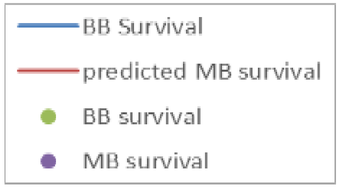
Actual microbeam survival data was then plotted



NCL-H23

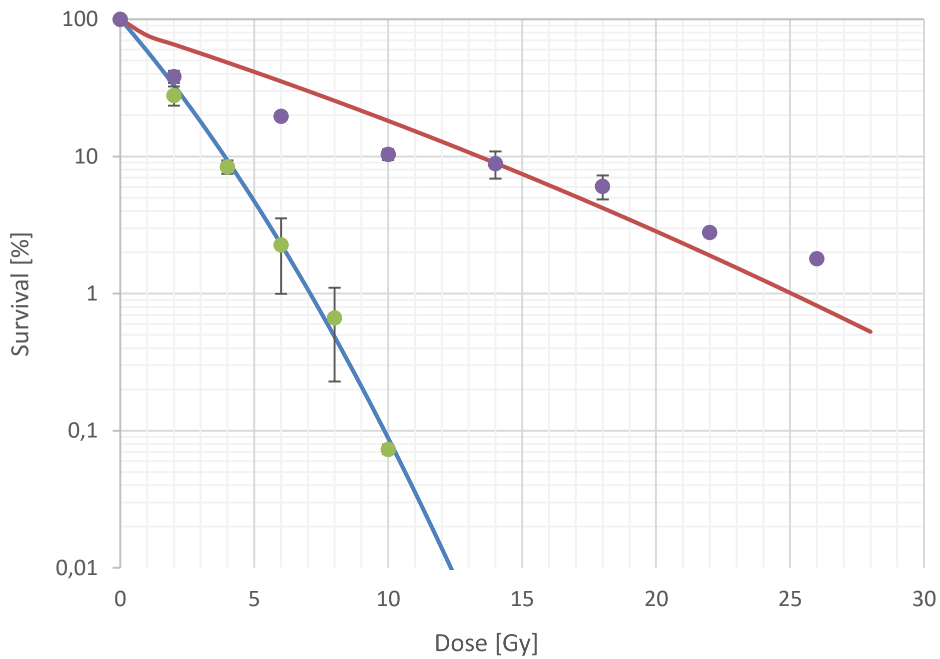


A549

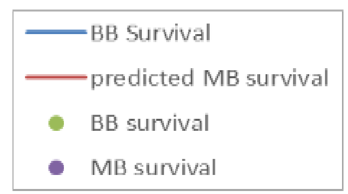


This suggests that there is communication between cells

Clonogenic survival of normal cells following MRT was greater than predicted



MRC-5



this suggests communication between cells does not affect normal cell survival following microbeam irradiation.

Biological effects – Microbeams or high dose rate ?
MRT vs 'FLASH'

OC-0039 Unique sparing of spatial memory in mice after whole brain irradiation with dose rates above 100Gy/s

K. Petersson[1], P. Montay-Gruel[2], M. Jaccard[1], G. Boivin[2], J. Germond[1], B. Petit[2], F. Bochud[1], C. Bailat[1], J. Bourhis[2], M. Vozenin[2]
[1]Lausanne University Hospital, Institute of Radiation Physics IRA, Lausanne, Switzerland
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RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

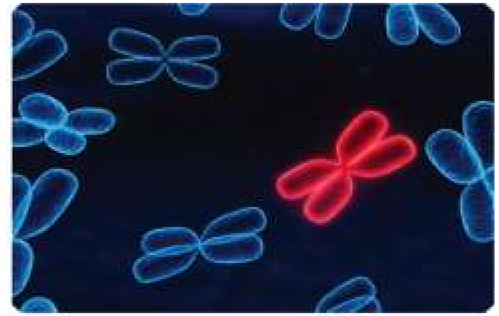
Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5†] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

In vitro studies suggested that sub-millisecond pulses of radiation elicit less genomic instability than continuous, protracted irradiation at the same total dose. To determine the potential of ultrahigh dose-rate irradiation in radiotherapy, we investigated lung fibrogenesis in C57BL/6J mice exposed either to short pulses (≤500 ms) of radiation delivered at ultrahigh dose rate (≥40 Gy/s, FLASH) or to conventional dose-rate irradiation (≤0.03 Gy/s, CONV) in single doses. The growth of human HBCx-12A and HEp-2 tumor xenografts in nude mice and syngeneic TC-1 Luc$^+$

ICR

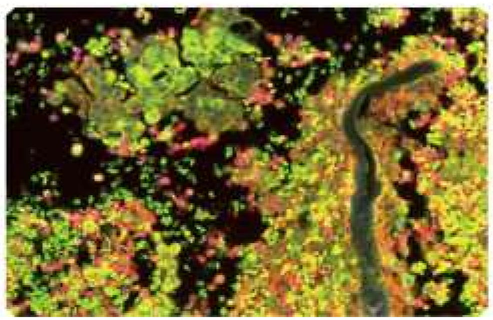
Unrivalled track record

ICR The Institute of Cancer Research



Making the discoveries that defeat cancer

ICR



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