QA of absorbed dose and RBE in contemporary radiotherapy

Professor Anatoly B.Rozenfeld



ARDENT, 29th September, 2014, Germany

Acknowledgement

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- **SPA BIT** CMRP exclusive semiconductor foundry
- ICCC: Illawarra Cancer Care Centre, Wollongong
- This work will be impossible without large number of PhD students at CMRP who are essentially contributing to all results.

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Introduction

- Advanced radiotherapy techniques such as IMRT, SRS, Helical TomoTherapy and VMAT produce radiation dose maps with high dose modulation and tight gradients.
- Difficulties in the dosimetric verification of these new complex treatment methods using existing dosimeters has led to the need for a new generation of fast responding real time dosimeters with submillimetre precision.
- Silicon Radiation Detection Systems (SRDS), designed, fabricated and prototyped by the CMRP were developed to address these needs
- Most of them is spin off from HEP radiation detectors for fundamental research.



Centre for Medical Radiation Physics University of Wollongong

5 Faculties, 22,000 students, Technology Park, IHMRI, Wollongong Hospital (ICCC) and 3 more hospitals associated







Meet the CMRP team



Prof Anatoly Rozenfeld Founder and Director



Dr George Takacs



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Prof Peter Metcalfe





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Outline

- Semiconductor Dosimetry in RT

 Diodes Design and its Applications in IMRT,SRS,Tomo
 Dose Magnifying Glass

 - Magic Plate
 - MOSFET, MOSkin Design and its Applications
 Skin Dosimetry in Radiotherapy
 Brachytherapy Applications
 IMRT and 3D CRT Applications
- 2D Si High Spatial Resolution Dosimetry

 Movable targets QA dosimetry
 Medipix-Eye plaque QA
- Electronic Dosimetry in MRT and Hadron Therapy
 Si microdosimetry (example)
 Micron resolution detectors
- Conclusion



Accidents in Radiotherapy

SFR Business Team, marque du groupe SFR, est à destination des entreprises. Détails et co

Mise à jour (FIGA	RO •fr	ACTUALITÉ	ÉCONOMI	E CULTU
INFO					DÉBATS
> Politique	> International	> Environnement	> Sciences	> Auto	> Figaro
> Société	> Médias	> Tech et Web	> Santé	> Météo	Vos réa
Exemples : Médias, Présidentielle, Auto, Golf, Immobilier				Rechercher dans le Fig	

EN CE MOMENT : Crise de la dette > JMJ > Affaires DSK > Primaire PS > Guerre en Libye

Radiothérapie à Epinal : un cinquième patient est mort

Un homme de 84 ans, qui faisait partie des 24 patients surirradiés à l'hôpital d'Epinal, est mort il y a une quinzaine de jours. L'information, révélée par Le Parisien, a été confirmée par Patrick Colombel, le directeur par intérim de l'établissement, qui reste prudent sur les causes du décès : "on ne sait pas s'il est lié à l'accident de radiothérapie ou non", car il était âgé et atteint d'un cancer.

Date: November 2004 Location: Lyon, France Type of event: radiotherapy overexposure Description: A patient receiving treatment by radiotherapy was overexposed due to confusion over units used in defining the body surface to be irradiated.





New technology required for QA in real

time

- More than 90 cases documented
- Affects brachytherapy, external beam radiotherapy and CT scanning
- Affects developed and developing countries

•Radiation technology for cancer treatment became very conformal and very complex and more rely upon computer control.

•Large gap between delivery technology and QA





Magic Plate



Arc Gantry Modulation

- Arc Gantry Modulation
- "Volumetric Modulated Arc Therapy"
- (VMAT)





Beams Eye View



Current IMRT & VMAT verification

- Fluence
 - DAVID system
 - IBA compass



In phantom

- 2D arrays (Delta4, ArcCheck)
- MapCheck



Exit fluence

• EPID

Venkataraman, S., et al. (2009) Physics



SRS Arc delivery: In phantom dose measurement

- 2D detectors array plane
- Spatial resolution5mm is poor
- New solution by CMRP





2D High T-S Resolution MP512 and DMG OCTA Dosimetes

- Bulk silicon substrate
- M512 matrix: 512 individual channels in a monolithic sensor, s-resolution 2mm, t-0.1ms
- **DMG OCTA:** 8 linear radial arrays, s-resolution 0.32 mm, t=0.1ms, shifted 45 deg.





1D and 2D High T-S Resolution Dosimetes

a)sDMG-serial DMG: SR 0.2mm

b)MP M512 matrix: 512

0.3x0.3mm2 detectors in a

monolithic sensor, SR: 2mm

c)DMG OCTA: 512 0.02x0.5mm2

detectors in 8 linear radial arrays,

SR: 0.32 mm

d)DMG DUO: 512 0.02x0.5mm2

detectors in 8 linear radial arrays,

SR: 0.2 mm



Applications:

- In phantom QA: small static and movable targets
- In Vivo real time QA: Transition mode upstream of the patient



SRS Small field dosimetry with M512



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- -Beam energy: 6 MV
- Depth: 10 cm
- SSD: 90 cm (isocentre)

SRS : In phantom dose calculation with CMRP MP M512





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QA Dosimetry for Motion Adaptive Therapy



4D image of lung tumour in motion



DMLC tracking of tumour in motion



Serial Dose Magnifying Glass - Setup



- Experimental setup geometry illustrated for sDMG measurements.
- Beam aligned between detector chips to acquire penumbral region for 3x3cm² field size.

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 For 1x1cm² field size, the beam is aligned to the centre of a single detector chip.

Motion – Clinical Lung Trace

- Clinical lung trace generated by Varian Calypso Motion Tracking system.
- Motion in x & y coordinates only



Royal North Shore Hospital (RNSH)

- MagicPlate 512 (MP512) or sDMG placed upon Scandidos Hexamotion movable phantom.
- Lung motion pattern from 4D CT lung library





MP512 - sDMG

- AFE data acquisition (DAQ) system.
- The acquisition of data by the system is triggered; integration dose pulseby-dose pulse.



- sDMG in a phantom and connected to DAQ QA placed on a LINAC cauch.



sDMG Measurement – 1x1cm² Field Size



- 'Motion' and 'No Motion' measurements are shown.
- Illustrating the instantaneous and cumulative effects of clinical lung motion upon the position of a 1x1cm² beam.
- 'Clinical Lung Trace' loaded into Hexamotion phantom and engaged for single acquisition of 'Motion' data.



sDMG Measurement – 1x1cm² Field Size

- sDMG placed at 1.5cm depth in solid water upon Hexamotion phantom and aligned to single DMG detector.
- Acquisition of 200MU of 1x1cm² beam repeated with and without motion supplied by phantom.
- Numerical investigation of integral dose measured by detector yields
 0.66% difference between area under 'Motion' and 'No Motion' curves.



Preliminary Results - sDMG

 Conducted radiation hardness testing and percentage depth dose measurements.



Dose Rate QA in VMAT OOMU/min

600MU/min





Pulse by pulse DAQ – TI-AFE



Channel 0 response visualised as a function of time after acquisition.



Transient characteristic of individual LINAC

% vs t(ms) - ch0



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High Dose Rate (HDR) Brachytherapy







Accidents in High Dose Rate (HDR) Brachytherapy

The ICRP publication 97 states that "More than 500 HDR accidents (including one death) have been reported along the entire chain of procedures from source packing to delivery of dose... many accidents could have been prevented if staff had had functional monitoring equipment and paid attention to the results." (2011)



HDR Brachytherapy Quality Assurance



- Treatment Plan consists of:
 - Patient Geometries
 - Dose at relevant points
 - Catheters for treatment
 - Dwell Positions
 - Dwell Times
- Impossible to test every plan with its own system, but with a generic system of fixed geometry and catheter position, possible to assess treatment parameters

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Magic Plate - BrachyPix Concept



- Reconstruction of dose planned from TPS onto the CMRP Smart Phantom - Magic Plate sandwiched between planar HDR catheters within solid water
- Real time error analysis of: timing pattern of source dwellings, source positions and total dose based on detector response
- Pre-treatment Quality Assurance of HDR afterloader + In-vivo evaluation



BrachyPix Smart Phantom



- Portable Brachy Pix phantom
 - Three 30x30x1 cm³ Perspex slabs screwed together.
- Top and bottom slabs have grooves for up to 10 catheters each.
- Magic Plate inserted within middle slab.
- 13.5 cm solid water placed on both sides of Brachy*Pix*.
 - Full scattering conditions.



Results - Source Positioning

- Experimental Magic Plate at depth 6 mm from source within solid water, source steps in at 2.5 mm step sizes, dwell time 2 seconds.
- Differences in calculated and expected positions are no more than 0.3 mm. Errors are based on two standard deviations and are seen to be a maximum of 0.8 mm, but an average of 0.3 mm. Variations with depths up to 30 mm have seen to be no more than 1 mm.
- Dwell times are all measured to be 2 seconds.



HDR Average Speed Measurement

- The HDR source moves extremely fast between dwell points (~ 50 cm/s) to minimise dose delivered while the source is in transit.
- Using the CMRP fast electrometer, which can measure the charge generated within the diode at 1 MHz, it is possible to estimate the average speed of the HDR source at varying dwell distances.

N14-195 Poster



BrachyPix software toolkit

- C++ software has been developed for BrachyPix. It is capable of:
 - Performing the full measurement and saving for later viewing.
 - Full plan analysis of dwell positions and dwell times



In Vivo QA in HDR barchythearpy



BMP512 is embed in a couch and placed below prostate. TRUS probe stepper frame is fixed on a couch making rigid alignment with a BMP512.


Conclusions

- Dual purpose MP Detector array
- Demonstrated ability to verify IMRT dose
 - In phantom
 - In transmission mode
- On going/future development
 - Monte Carlo simulation to predict transmission mode signal.
 - Inclinometer real time angular information
 - FPGA-USB readout system
- New prototype has 512 detectors



MEDIPIX in Radiation Therapy





BrachyView : QA Concept in RT

Firstly introduced and patented by CMRP

In Body Imaging for advanced QA in brachytherapy for

prostate cancer treatment



Concept

- Seed localisation uncertainty causes dosimetric complications
 - Prostate mobility
 - Seed twisting
 - Brachy needle placement errors
- Intraoperative dynamic dose planning
 - Fuse with existing ultrasound technology
- New in-body ultra-functional probe:
 - Ultrasound, radiation source and CT imaging captured real-time
 - Possibility to introduce fast, online seed position imaging using seeds themselves as radiation source
- Applications:
 - Seed positioning in tumour
 - Real-time CT imaging of implants



Current Technology – TRUS



 Result
 Seed misplacement errors
 Urethral and rectal toxicity: 40% cases
 No real-time planning option available



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Example: C-arm Fluoroscopy

- Obtain plane image of seeds without positioning relevant to anatomy
- Similar goal of registering TRUS and fluoroscopic images (technically difficult to perform)
- Post-implant dosimetry: impossible to change seed position
- Disadvantage: not true 'realtime', planar image only (no anatomy), cumbersome and expensive equipment



Figure 1: C-arm X-ray unit used in the study, the offset between the position of the centre of rotation and the X-ray beam central axis is illustrated. (FID - focus to -image intensifier distance) Ravindran, Lewis et al 2006



Tomography in PiPB



Fig. 1. Transverse CT image of implanted prostate: (a) without contoured prostate; (b) with prostate contoure

- Because the quality of the proce postimplantation computed tomc dosimetric outcomes only becom reviewing the postimplantation C for a flawed implant requires an a
 - Zelefsky, 2011

is an essential component of nly method of assessing the ate and normal surrounding post-implant and nue to improve permanent an effective treatment for



Figure 1. Patient with implanted needles in extended lithotomy position with CBCT imager in place.

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Medipix device:

Single particle counting pixel detector

- Planar pixellated detector (Si, GaAs, CdTe, thickness: 300mm)
- Bump-bonded to Medipix readout chip
- Pixels in one single Medipix2: 256 x 256
- Pixel size: 55 x 55 µm²
- Area: 15 x 15 mm²



BrachyView: Pinhole Application

- In-vivo detector plane integrated into TRUS probe
- Use seeds themselves as source of imaging radiation
- Seed position reconstruction via 'camera obscura' concept
 - Using lead pinhole collimator, reconstructions have been found to be within 0.5-1mm of expected positions
- Real-time, intraoperative treatment planning seed positioning possible during implant procedure





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Soft tissue diagnostic imaging

- Feasibility studies completed to investigate the applicability of TimePix for soft tissue imaging
- Well-known device for distinguishing materials of similar composition (plexiglass, water, acrylic materials)
- Delineation of prostate soft tissue, lesions, urethra etc



HDR BrachyView Probe: Ir-192 Source Tracking



Pinhole imaging Experiment: Result

- Source placed 40mm above the collimator
- Real dwelling time:1.7s
- Aquisition time: 0.5s/frame
- The video presents every 3 frames





Seeds localisation: CT vs BrachyView

- Prostate phantom with 20 seeds was scanned on CT
- Each CT slice corresponds to
 0.8 mm thickness, which allowed higher accuracy than the typical
 2 mm thick slice used for patients
- Two datasets:
 - 1. TimePix 2D maps
 - 2. Full CT scan as a reference





CT-BrachyView: image fusion

- Co-register the 3D coordinates to obtain full information for seed location in phantom
- 3D combined view of CT DICOM and BrachyView in 3DSlicer (standard freeware license software for DICOM visualisation)







3D Silicon Microdosimetry



Proton and Heavy Ion Therapy

$$\begin{array}{l} \text{Protons \& carbol} \\ \text{Bethe Formula} \\ \text{Dose conforma} \end{array} \quad -\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2\beta^2}{I\cdot(1-\beta^2)}\right) - \beta^2\right] \end{array}$$

The cancerous tumors are removed most efficiently by the ion radiation as it had been previously (1946) recognized by **R. Wilson.** [Radiological use of fast protons. Radiology 47:487-91, 1946].



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Different: biological effectiveness

Heavy Ion Therapy



- Secondary nuclear fragments
- Secondary neutrons





Ionization by proton and ¹²C ion



¹²C ion in contrast to proton is producing clustered damage of DNA (i.e. many DSBs)



Local Effect Model (LEM) :cell damage by ions

Dose-deposition pattern of individual ions depends on **ion type and energy**

Biological effectiveness of ions depends on this pattern



Spectral composition of the beam (Z,E) and LQM for low LET radiation are input for calculations of biological dose (cell survival)



Cell damage by Gamma and Heavy Ions radiation

sparsely ionising



mainly indirect DNA damage

relative biological effectiveness: RBE_v=1 Average RBE_{protons}= 1.1

densely ionising



mainly direct clustered DNA damage irreparable DNA breaks

Increase of biological effectiveness RBE_{carbon}= 2-4 → Radioresistant tumours!

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PRINCIPLES OF LOCAL EFFECT MODEL (LEM)



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Microdosimetry and Dose Equivalent

Microdosimetry

- $\circ\,$ Assumes the weighting factor is related to the energy deposited in the cell nucleus: $\epsilon\,$
- Measure this for each particle that crosses detector
- Formulate dose distribution: d(ε)
- Integrate with weighting factor to give **Dose Equivalent** : $H = \int Q(\varepsilon) d(\varepsilon) d\varepsilon$
- Dose Equivalent can be used to predict biological effect of radiation
- We require detectors with dimensions commensurate with cell nuclei



RBE₁₀

$$\bar{y}_f = \int_0^\infty y f(y) dy \qquad \bar{y}_d = \frac{1}{\bar{y}_f} \int_0^\infty y^2 f(y) dy = \int_0^\infty y d(y) dy.$$
$$y^* = \frac{y_0^2 \int_0^\infty \left(1 - \exp\left(-\frac{y^2}{y_0^2}\right)\right) f(y) dy}{\int_0^\infty y f(y) dy}$$
$$S = \exp\left[-\alpha D - \beta D^2\right] \qquad \alpha = \alpha_0 + \frac{\beta}{\rho \pi r_d^2} y^*$$

$$RBE_{10} = \frac{2\beta D_{10,R}}{\sqrt{\alpha^2 - 4\beta \ln(0.1)} - \alpha},$$

- α_o= 0.13 Gy⁻¹; β= 0.05 Gy⁻²; r_d = 0.42 μm is radius of sub cellular domain in MK model
- Where D_{10,R} = 5Gy is 10% survival of 200 kVp X rays for HSG cells



Relative Biological Effectiveness (RBE)



[1] O. Jäkel et al Technology in Cancer Research & Treatment, ISSN 1533-0346, Volume 2, Number 5, October (2003)
[2] O. Steinsträter et al "Mapping of RBE-weighted doses between HIMAC- and LEM-based treatment planning systems"
[3] N. Matsufuji et al Specification of Carbon ion dose at NIRS, JRS 2007.

HIMAC (Japan)

- Passive beam and starts using scanning beam
- RBE values are derived from in vitro experimental data in conjunction with clinical neutron experience

• RBE estimation at HIMAC is independent of the tumor type

GSI (Germany)

- Scanning beam
- RBE values for planning were estimated using Local Effect Model – LEM)
- RBE estimation are based on photon dose response curves under the cell lines



HIMAC Heavy Ion Therapy facility



http://www.nirs.go.jp/ENG/research/charged_particle/index.shtml



3D Mesa "Bridge" Microdosimeter



A schematic of the design of SOI bridge microdosimeter. a) 3D view, b) A cross-section of the microdosimeter behind the silicon bridge.

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3D Mesa "Bridge" Microdosimeter (Results)





Experiment at HIMAC, Japan, May 2014



NEW PROPOSED DESIGN 3D MICRODOSIMETERS DEVELOPED BY CMRP



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 PMMA medium is filled around the sensitive volumes to produce tissue equivalent medium in order to avoid generation of secondary particles from Si

Experiment for ultra-thin 3D detector with 290 MeV/u ¹²C ion at HIMAC, 2014



(a) Ultra-thin 3Ddetectorconnected topreamplifier andelectronics

AMPTER



(b) The detector is fabricated using 3D technology in 3.5 k Ω .cm n-SOI active layer followed by a thinning process which removed the 300 μ m supporting wafer.

[L. Tran et al, 2014 "Ultra-thin 3D detector: Charge collection study and application for microdosimetry".]

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Experiment for Ultra-thin 3D detector with 290 MeV/u ¹²C ion at **HIMAC, 2014**



Ultra-thin 3D detector



DMG: high spatial resolution dosimetry





Single DMG 128 channels, pitch 0.2 mm Total length 28 mm

Serial DMG 256 channels, pitch 0.2 mm Total length 56mm



Heavy Ion Therapy - Carbon-12

10cm

10cm

Beam

Brass

Brass

- Experiments undertaken at National Institute of Radiological Sciences (NIRS), HIMAC facility in Chiba.
- Irradiation of Serial Dose Magnifying Glass (sDMG) with C-12 beam of energy 290 MeV/u.
- Studies performed:
 - Depth profile:
 - 1. Spread-Out Bragg Peak (SOBP60mm)
 - 2. Pristine Bragg Peak (PBP)
 - Penumbral study for SOBP60mm

Electronics



Various depths in PMMA

TOP VIEW



Gantry

Heavy Ion Therapy – Pristine Bragg Peak

Depth (mm)

Depth (mm)



Heavy Ion Therapy – Pristine Bragg Peak



 Residual energy, E_R, for various depths in PMMA, D, reconstructed from detector measurements and compared to Monte Carlo simulation

Depth in PMMA (mm), (+/- 1 mm)	Reconstructed Residual Energy, <i>E_R</i> (MeV/U), (+/-3MeV/U)	Simulated Residual Energy (MeV/U), (+/-0.1%)
98	118	121
85	143	147
60	186	190
50	203	206

Simulated E₀=275 MeV/U compared to reconstructed E₀ calculated from measured residual energies, E_R:

 $E_0 = (274 + - 1) \text{ MeV/U}$





Heavy Ion Therapy – Penumbral Study


Heavy Ion Therapy – Penumbral Study





Conclusion

- Semiconductor dosimeters small and real time
- High spatial resolution and skin equivalent
- Good for RT and Diagnostic Radiology
- Multiple detector redundancy
- Future of Semiconductor Dosimetry:
 - System on a Chip (detector, reader, WiHi)
 - 3D MEMS structure with well defined Q collection volume
 - Nanodosimetry –track structure measuremenst
 - Spectroscopy dosimetry –no need for TE material



MMND & IPCT 2014

Sheraton Mirage, Port Douglas, Australia October, 20th-25th, 2014

Chair: Prof Anatoly Rosenfeld CMRP, Australia Co-Chair: Prof Paolo Colautti INFN-Laboratori Nazional Dr Josh Yamada Memorial Sloan Kettering Cancer Centre | USA Dr Joseph Bucci St George CCC I Australia







MMND-IPCT 2014 Invited Speakers











Dr Josh Yamada Prof Pat Kupelian Prof Carl Rossi Prof Hiroshi Tsuji Prof Morten Høyer MSKCC UCLA San Diego PT NIRS HIT Arthur Uni, Denmark



Milan

Prof Mack Roach Prof Hsiao-Ming Dr Mauro UCSF Lu, MGH Carrara National CC

Dr Michael Scholz, GSI

Prof Reinhard Schulte, LLU



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Thank you for your attention!



