An introduction to medical imaging and radiotherapy: Current status and future directions I

Dr Colin Baker

Head of Radiotherapy Physics
Royal Berkshire NHS Foundation Trust
Overview – Lecture 1

- Principles of radiotherapy & radiobiological modelling
- Historic & conventional treatment modalities
- Anatomical & functional imaging, CT, MR, SPECT, PET
- Dose painting & functional avoidance
Overview – Lecture 2

- Radiation transport for radiotherapy planning
- Plan optimisation
- On-treatment imaging & verification
- Future directions
Principles of Radiotherapy

- Use of ionising radiation to destroy tumour cells
- Direct and indirect damage to DNA
- Single (SSB) and double-strand (DSB) breaks
- Generally assume normal cells are better able to repair ‘sub-lethal damage’
- Maximise tumour cell kill over normal tissue damage & toxicity
Factors in radiation response: The 5 R’s

Radiosensitivity - Varies between cell types

Repair - Of sub-lethal damage, capability varies between cell types, time period of ~6 hours

Repopulation - Particularly for tumours and ‘early reacting’ normal tissues

Reoxygenation - Of hypoxic regions of tumour, increasing radiosensitivity

Redistribution - Radiosensitivity varies with cell cycle phase, cells in a resistant phase at one fraction may be more sensitive in future fractions
Repair and fractionation

If radiation delivery is divided into fractions separated in time, sufficient for the repair of sub-lethal damage, the initial shape of the single-dose curve is repeated.

\[
SF = e^{-\alpha d - \beta d^2}
\]
\[
SF^n = e^{-n\alpha d (1+\beta d/\alpha)}
\]

The shape of these curves is described by the linear-quadratic (LQ) model.

Parameters \( \alpha \) and \( \beta \) determine the shape of the curve for a specific cell line.
Tumour Control Probability (TCP)

The probability that no tumour clonogens survive, $P(0)$, is the tumour control probability:

$$TCP = P(0) = e^{-N}$$

Where $N$ is the average number of tumour clonogens remaining, estimated from the LQ model (here ignoring tumour repopulation):

$$N = V_{CTV} \rho_c \exp \left[ -\alpha n d \left( 1 + \frac{\beta}{\alpha} d \right) \right]$$
Normal tissue complication probability (NTCP)

Modelling normal tissue response is more challenging; tissues are generally partially irradiated – volume dependence

May often have multiple end-points for each organ

How does cell kill relate to organ function?

17/08/2017
Tissue architecture

Assume functional sub-units (FSUs), each of which performs the organ's basic function e.g. lung alveoli, kidney nephrons.

Each FSU contains stem cells, each of which is capable of regenerating the FSU.

Complications (toxicities) are a result of failure to repopulate FSUs due to stem cell killing.

The arrangement of FSUs (serial or parallel) reflects the organ’s volume dependence.

Källman et al 1992
Optimising dose prescription

PFS and CI (rectal and urinary) for prostate radiotherapy

Points represent clinically observed outcomes for varying dose and/or fractionation

Minimise normal tissue toxicity by optimising fractionation (and avoidance!)

17/08/2017
Radiotherapy treatment modalities

- kV & MV photon beams (50 to 300 kV, 6 to 20 MV)
- Electrons 4 to 20 MeV (conventional), up to 250 MeV (VHEE)
- Protons (60 to 250 MeV)
- Neutrons (fast, 60MV)
- BNCT (epithermal)
- Carbon ions (to 450 MeV/u)
- Pions (100 MeV)

Dose profiles for various particle beams in water (beam widths $r = 0.5$ cm)
Clinical comparisons – multiple beams & directions

Schüler et al 2017
MV Photons (& electrons)

1. (Photon) collimators
2. Monitor (ionisation) chamber
3. Carousel (photon flattening filter / electron scattering foils)
4. Bending system
5. Photon target
6. Accelerating waveguide
7. Electron gun
Protons

\[ D(z) = \sum_{i=0}^{N} w_i D_i(z) = \sum_{i=0}^{N} w_i D_0(z + t_i) \]
MD Anderson Proton Therapy Centre

Treatment Rooms
1. Passive Scattering
2. Passive Scattering
3. Pencil Beam Scanning
4. Passive Scattering
   - Large Field
   - Eye Treatment

[Smith 2009]
Paediatric cancers

MD Anderson
10 craniopharyngioma patients
(4-17 years)

[Boehling 2012]
Head & Neck cancers

Paul Scherer Institute
10 patients with stage T2-T4 oropharyngeal cancer

PTV1 (black)
PTV2 (white)
1 - parotid

[Van der Water 2011]
Lung cancer
MD Anderson
Stage IIIB (advanced) NSCLC

[Zhang et al 2010]

63Gy IMRT escalated to 80Gy IMPT
Carbon ions

- Dose tail due to nuclear fragments
- Greater relative biological effectiveness (RBE)
- Energies up to 450 MeV/u required
Boron Neutron Capture Therapy (BNCT)

- Preferentially load tumour with boron
- Irradiate with uniform neutron fluence
- Emitted $\alpha$ particle and Li ion have very high LET, very short range; dose is concentrated within the tumour
Imaging for radiotherapy

3D & 4D x-ray CT
MRI

- Head & neck
- Brain
- Pelvis

fMRI
PET (/CT)

Spatial variation in function in addition to anatomy

healthyscientist.blogspot.co.uk

Konert et al 2015
# Function tracers

<table>
<thead>
<tr>
<th>Function</th>
<th>Tracer</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose metabolism</td>
<td>$^{18}$F-FDG Fluorodeoxyglucose</td>
<td>Tumour detection &amp; treatment response</td>
</tr>
<tr>
<td>Proliferation</td>
<td>$^{18}$F-FLT Fluorothymidine</td>
<td>Tumour detection &amp; treatment response</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>$^{18}$F-MISO Fluoromisonidazole, $^{18}$F-FAZA Fluoroazomycin, $^{64}$Cu-ATSM methylthiosemicarbazone</td>
<td>Identification of hypoxic regions for potential dose-painting</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>$^{11}$C-Choline</td>
<td>Prostate cancer</td>
</tr>
</tbody>
</table>
SPECT (/CT)

Typically using $^{99m}\text{Tc}(140\text{ keV})$ combined with appropriate pharmaceuticals

- Bone imaging
- Brain perfusion imaging
- Heart perfusion imaging
- Lung perfusion & ventilation imaging
Dose painting via functional imaging: Prostate

- a. T2 weighted MRI
- b. Diffusion Contrast Enhanced MRI
- c. Diffusion Weighted MRI
- d. Ultrasound-guided (targeted) biopsy
- e. $^{18}$F Choline PET
- Identify areas of high tumour activity
- Boost radiation dose to these regions
- Improved tumour control for similar toxicity

<table>
<thead>
<tr>
<th></th>
<th>TCP (%)</th>
<th>NTCP (%)</th>
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</thead>
<tbody>
<tr>
<td>Conventional plan</td>
<td>75.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Dose-painted</td>
<td>85.6</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Dose sparing via functional imaging: Lung

- Perfusion (Q) and/or ventilation (V) imaging indicates regions of functioning lung
- Preferentially spare these lung regions during plan optimisation

$^{99m}$Tc MAA Perfusion SPECT/CT (CCC)
Ventilation SPECT:
$^{81m}$Kr or Technegas

4D-CT ventilation ‘for free’ from planning 4D-CT
[Castillo et al 2010]

$^{3}$He MRI ventilation
[Ireland et al 2007]
Functional lung sparing

- Conventional (whole lung – GTV)
- Functionally optimised (50%)
Lecture 1 summary

• Radiotherapy is an optimisation problem in maximising tumour control (eradication) for minimised toxicity to normal tissues that impact on a patient’s quality of life.

• The majority of radiotherapy is currently delivered using MeV photons (6 to 20MV spectra), with the remainder comprising MeV electrons, protons and carbon ions.

• Medical imaging is increasingly contributing to radiotherapy advances, providing both anatomical and functional information for improved optimisation and evaluation of treatment response.
An introduction to medical imaging and radiotherapy: Current status and future directions II

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Overview – Lecture 2

• Radiation transport for radiotherapy planning
• Plan optimisation
• On-treatment imaging & verification
• Future directions
Radiation transport

Dose (energy deposition) calculation in radiotherapy requires an accuracy of c. 1% with spatial resolution of c. 1mm³

Monte Carlo simulation

Simulate individual particle tracks by sampling interactions according to appropriate cross-sections

‘Score’ energy deposited at each step, repeat ‘histories’ until desired statistical accuracy is achieved.

10 MeV photons (green) incident on water slab. Secondary electrons (red) and positrons (blue)
Modelling of electron source required, to match measured beam characteristics to within appropriate tolerances (~1% local dose)

Typically pre-compute for generic geometry, creating a *phase-space file*, containing details of position, direction and energy of each particle.
• Typically ~ $10^9$ initial particles tracked though the patient to achieve statistical accuracy in dose deposited ~1%

• Full account of tissue inhomogeneities, secondary electrons explicitly tracked; accurate in lung, bone and at interfaces

• Computationally expensive, but ideal for distributed computing, GPU

• Generally only practical for ‘final’ dose calculation, not iterative steps during optimisation
Superposition / convolution

Pre-calculated (via Monte Carlo) dose kernel, $K_v$, represents the dose deposited at $(x,y,z)$ from interactions of primary photons, $\psi$, at $(x',y',z')$.

Suppose we have $n$ surface positions and $m$ depths, the dose at $(x,y,z)$ is then:

$$D(x, y, z) = \sum_{j=1}^{m} \sum_{i=1}^{n} \psi(x_i', y_i', z_j') \times K_v(x_i', y_i', z_j' : x, y, z)$$

Computationally much faster than full Monte Carlo
‘Collapsed Cone’ algorithms

Superposition over all irradiated voxels to each point of calculation is time-consuming. The collapsed-cone approximation allows faster calculation by discretising angles.

- The energy transported within each cone is ‘collapsed’ onto the cone axis and transported along to points (B), taking inhomogeneity into account.
- Energy from A that in reality contributes to B’ is deposited at B instead and vice-versa.

[Ahnesjö & Aspradakis 1999]
Pencil-beam superposition

Simplify the voxel superposition by summing dose from \( n \) ‘beamlets’ within the irradiated area.

Contribution from beamlet at \((x',y')\) to point \((x,y,z)\) is given by a pre-calculated (typically via Monte Carlo) dose kernel, \( K_{pb} \).

Faster again than voxel superposition / convolution, however fails to account for electronic disequilibrium
Algorithm test case: Lung inhomogeneity

- 30x30x20cm phantom, with lung inhomogeneity (relative density 0.3) on one side
- Compare convolution/superposition algorithms with Monte Carlo simulation (MCNPX) for clinical spectra

Note broadened penumbra (increased secondary electron range)
Pencil-beam (PB) algorithm fails to account for penumbral broadening and outward scatter in small fields.
Radiotherapy plan optimisation

Increasingly ‘inverse-planned’

Cost function, \( F(\vec{b}) \), minimised according to goals and constraints:

\[
F(\vec{b}) = \sum_i \left( u[D_{Pmin} - d_i(\vec{b})]^2_+ + w[d_i(\vec{b}) - D_{Pmax}]^2_+ + \cdots \right)
\]

\( \vec{b} \) = beam element
\( d_i \) = dose in voxel \( i \)
\( u, w \) = weighting factors
\( D_{Pmin} \) = prescribed minimum dose
\( D_{Pmax} \) = prescribed maximum dose

\( [x]_+ = \begin{cases} x & \text{if } x > 0 \\ 0 & \text{if } x \leq 0 \end{cases} \)
On-treatment imaging

3D CT/CBCT

medicalphysicsweb.org

2D MRI
Gated planning 4D CT

Gated on-treatment 4D CBCT
Treatment verification: Photons

\[ D_p = \varphi_p \otimes K_D \]

\[ D_I = \varphi_I \otimes K_I \]

\[ D_m = \varphi'_p \otimes K_D \]

\[ \varphi_m = D_m \otimes^{-1} K_I \]

PerFRACTION, Sun Nuclear
Proton therapy verification

Single field **Photons, Protons**
Clinical dose distributions

Radiotherapy is only effective if it’s delivered to the intended place…

Van der Water 2011
Small proportion of nuclear interactions resulting in radioactive nuclei & excited nuclear states:

- Positron emitters; PET
- Prompt-gamma emissions; ~2-10 MeV
PG emissions

<table>
<thead>
<tr>
<th>Target</th>
<th>Daughter</th>
<th>PG (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{12}\text{C}$</td>
<td>$^{12}\text{C}$</td>
<td>4.44</td>
</tr>
<tr>
<td>$^{11}\text{C}$</td>
<td>$^{16}\text{O}$</td>
<td>6.13</td>
</tr>
<tr>
<td>$^{16}\text{O}$</td>
<td>$^{16}\text{O}$</td>
<td>6.92</td>
</tr>
<tr>
<td>$^{15}\text{N}$</td>
<td>$^{14}\text{N}$</td>
<td>5.27</td>
</tr>
</tbody>
</table>

Wong 2015
Radiation dose and PG correlation

$^{12}$C 4.44 MeV PG & Dose deposition

$^{16}$O 6.13 MeV PG & Dose deposition

Wong 2015
PG Imaging

Compton camera

\[ E_{\gamma} = e_1 + e_2 \]
\[ E_{\gamma'} = e_2 \]

A Gutierrez
Future directions in radiotherapy

- On-treatment MR imaging, intra-fraction imaging & monitoring
- On-treatment (real-time) planning (fast registration and optimisation)
- Increasing availability of proton therapy
- Increased use of functional imaging (PET, fMRI) in dose painting and avoidance of functional normal tissue
- Improved outcome modelling, data and image driven
- Advanced adaptive planning over the course of radiotherapy, due to anatomical changes and treatment response
- Availability of other ions, He, C
- *Very high energy electron beams (VHEE)*
- *Grid therapy*
- *Ultra high dose-rate delivery (FLASH)*
Why VHEE?

Advances in linear accelerator technology are making c. 250 MeV electron beams accessible & affordable.

200MeV electrons on 30cm water
Dose Delivery With Focussed Electron Beams

- Our recent simulation studies indicate focussed VHEE can achieve better dose deposition than proton beams
- Focussed VHEE beams reduce entrance dose
- Increased dose rate to cancerous tissue

In patient treatment a superposition of several peaks — Spread-out Bragg Peak (SOBP) — is used to cover larger areas.

Strongly focussed wide ($r = 5 - 10$ cm) VHEE beams compared with mono-energetic and spread-out Bragg peaks.
Grid radiotherapy

- Deliver dose in spatially separated ‘micro’ or ‘mini’ beams
- Greater sparing of overlying normal tissue, recovery occurs in the spacing between beams

Dosimetric evaluation of new approaches in GRID therapy using nonconventional radiation sources

I. Martínez-Rovira
Laboratoire d’Imagerie et Modélisation en Neurobiologie et Cancérologie (IMNC), Centre National de la Recherche Scientifique (CNRS), Campus universitaire, Bât. 440, 1er étage—15 rue Georges Clemenceau, Orsay cedex 91406, France

G. Fois
Dipartimento di Fisica, Università degli Studi di Cagliari, Strada provinciale Monserrato Sestu km 0.700, Monserrato, Cagliari 09042, Italy

Y. Prezado
Laboratoire d’Imagerie et Modélisation en Neurobiologie et Cancérologie (IMNC), Centre National de la Recherche Scientifique (CNRS), Campus universitaire, Bât. 440, 1er étage—15 rue Georges Clemenceau, Orsay cedex 91406, France
‘FLASH’ therapy

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

Pierre Montay-Gruel, Kristoffer Petersson, Maud Jaccard, Gaël Boivin, Jean-François Germond, Benoit Petit, Raphaël Doenlen, Vincent Favaudon, François Bochud, Claude Bailat, Jean Bourhis, Marie-Catherine Vozzenin

*Department of Radiation Oncology/DUZ/CHUV, Lausanne University Hospital, Switzerland; **Institut Curie, INSERM U1021/CNRS UMR3347, Université Paris-Saclay, Orsay, France; 

Institute of Radiation Physics (IRA), Lausanne University Hospital; and Faculty of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Switzerland

3,000,000 cGy/min [~0.2ms]

600 cGy/min [~2min]
Electromagnetic steering/scanning optics

Fixed annular gantry & integrated imaging system

Steerable high-energy electron beam

Compact high-gradient electron linac

Vacuum window

Treatment table

Pluridirectional High-Energy Agile Scanning Electron Radiotherapy (PHASER)
Summary

• Accurate radiation transport algorithms for radiotherapy planning are available, however speed requirements are still challenging for plan optimisation.

• Treatment verification through on-treatment imaging and dosimetry is essential.

• Verification methods are established for photon radiotherapy, promising approaches for proton therapy are being developed.

• Focussed VHEE, Grid and FLASH therapy are at an early stage of development but are potential competitors for proton therapy.