Relative Biological Efficiency of Antiprotons

The AD-4 ACE Experiment

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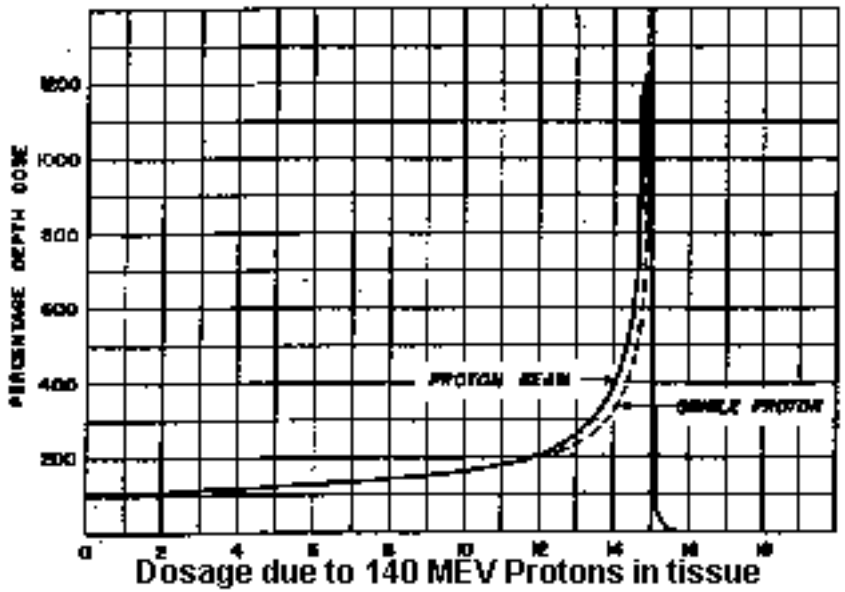
- **Introduction and historical background**
- **Phase I – Biological Effective Dose Ratio (BEDR)**
  Summary of results
- **Phase II – Relative Biological Efficiency (RBE)**
  Experimental Methods
  Biology meets Physics – Problems and Issues
  Data Analysis and Error Discussions
  Final Results
- **Summary Missing items?**
  Future tasks?
  Lessons learned?

Historical Background

- **Heavy Charged Particles proposed for cancer treatment by Robert Wilson in 1946**
  (R R Wilson; Radiology 47 (1946) pp. 487 – 491)



"Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest."

"The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays."

Wilson already includes all essential elements: Straggling in target, ionization density, relative biological effectiveness, and the benefits and dangers of using heavier particles.

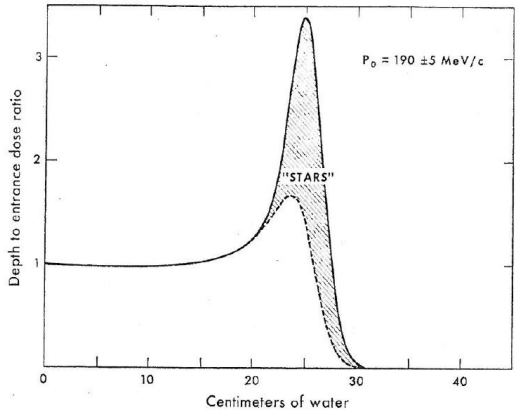
Initial work at Berkeley laid foundation for cancer treatment with heavy ions (C, Ne, Ar), but only proton treatment survived the funding cuts by NSF and NIH.

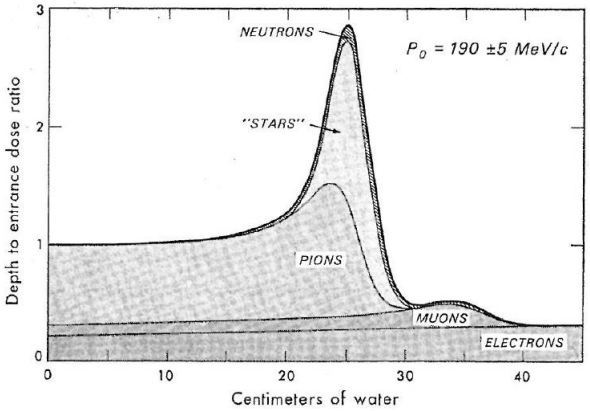
Luckily two post docs involved in the work at Berkeley (G. Kraft and H. Tsujii) took the knowledge home to Europe and Japan allowing the development of carbon ion therapy.

Historical Background II

More exotic particles were proposed early on:

Pion Therapy was established at Los Alamos, SIN, and TRIUMF. Enhancements in therapeutical efficiency was expected due to annihilation of pions (Star formation). Pion Therapy eventually faded away due to poor spatial conformity of high dose region.





LANL: 227 patients 1974 – 81
SIN: 126 patients 1982 - 84
TRIUMF: 1982 - 85 randomized trials of pions versus photons

S.B. Curtis and M.R. Raju;
Rad. Res. 34 (1968) 239-255

Antiproton Therapy was first proposed in 1984 by L. Gray and T. Kalogeropoulos: High concentration of dose around annihilation vertex predicted. (Rad. Res. 97 (1984) 246-252).

A. Sullivan, CERN: Measured relative energy deposition antiproton to proton: ONLY 30 MeV of 1.9 GeV deposited in target – BUT THAT's FACTOR OF TWO

The birth of AD-4 ACE

Letter of Intent I-225 submitted August 2002
Proposal PS-324 submitted October 2002 and accepted February 2003.

MINUTES OF THE 162nd MEETING OF THE RESEARCH BOARD:
6. REPORTS AND MATTERS ARISING FROM THE SPSC MEETING OF 14 JANUARY 2003:

K. Königsmann reported on the recent meeting of the SPSC. He first discussed proposal P324, to study the biological effectiveness of antiprotons for cancer treatment [12]. The experiment involves exposing cells to the antiproton beam from the AD, and measuring their survival fraction as a function of the position in the target. …….

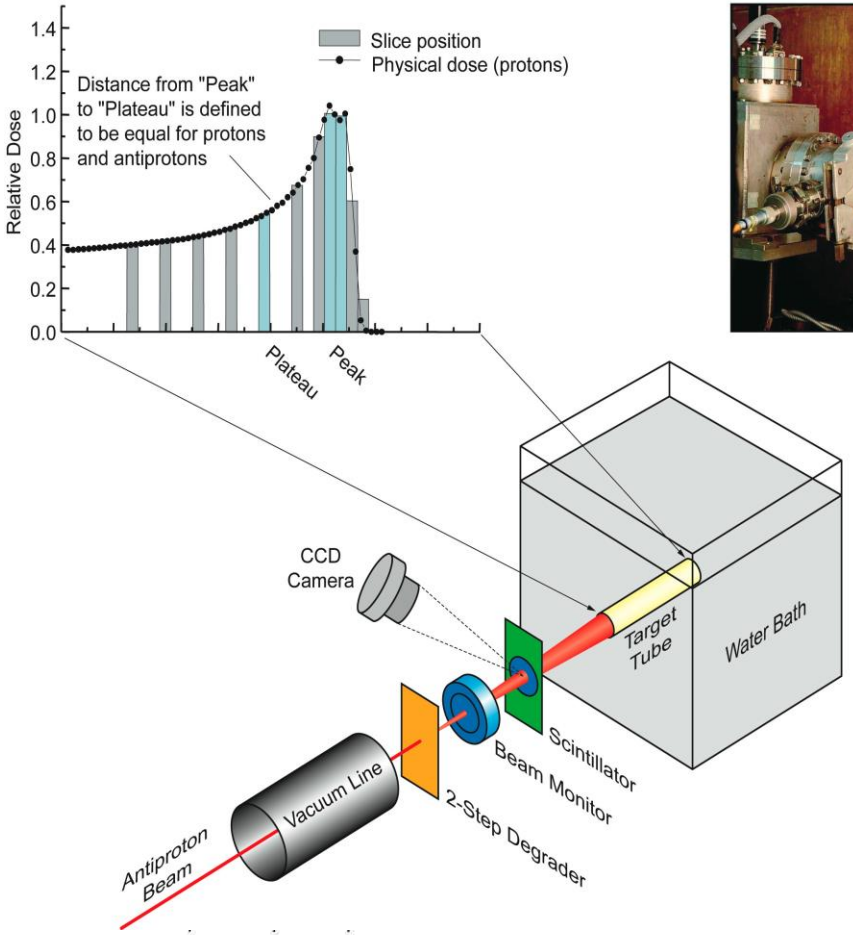
The Research Board approved the experiment for 9 shifts…….The experiment is to be known as AD-4.

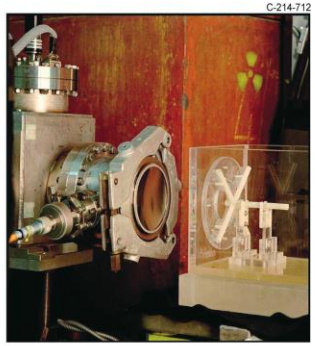
AD-4 ran at 46.7 MeV for 17 individual shifts between June 2003 and November 2004.

- No absolute dosimetry of antiproton beam
- Measured relative biological effect Peak-to-Plateau compared to protons (BEDR)

We have produced the first measurements of the biological consequences of antiproton irradiation. These data **substantiate theoretical predictions of the biological effects of antiproton annihilation within the Bragg peak**, and suggest antiprotons warrant further investigation. “Antiprotons are 4x times more powerful in killing cancer cells.”

AD-4 ACE Phase I





INGREDIENTS:

- V-79 Chinese Hamster cells embedded in gelatin
- Antiproton beam from AD (46.7 MeV)

METHOD:

- Irradiate cells for prescribed fluencies to give dose values where survival in the peak is between 0 and 90 %
- Slice samples, dissolve gel, incubate cells, and look for number of colonies

ANALYSIS:

- Study survival vs. dose in peak and plateau and compare to protons (and carbon ions)

AD-4 ACE Phase I - Results

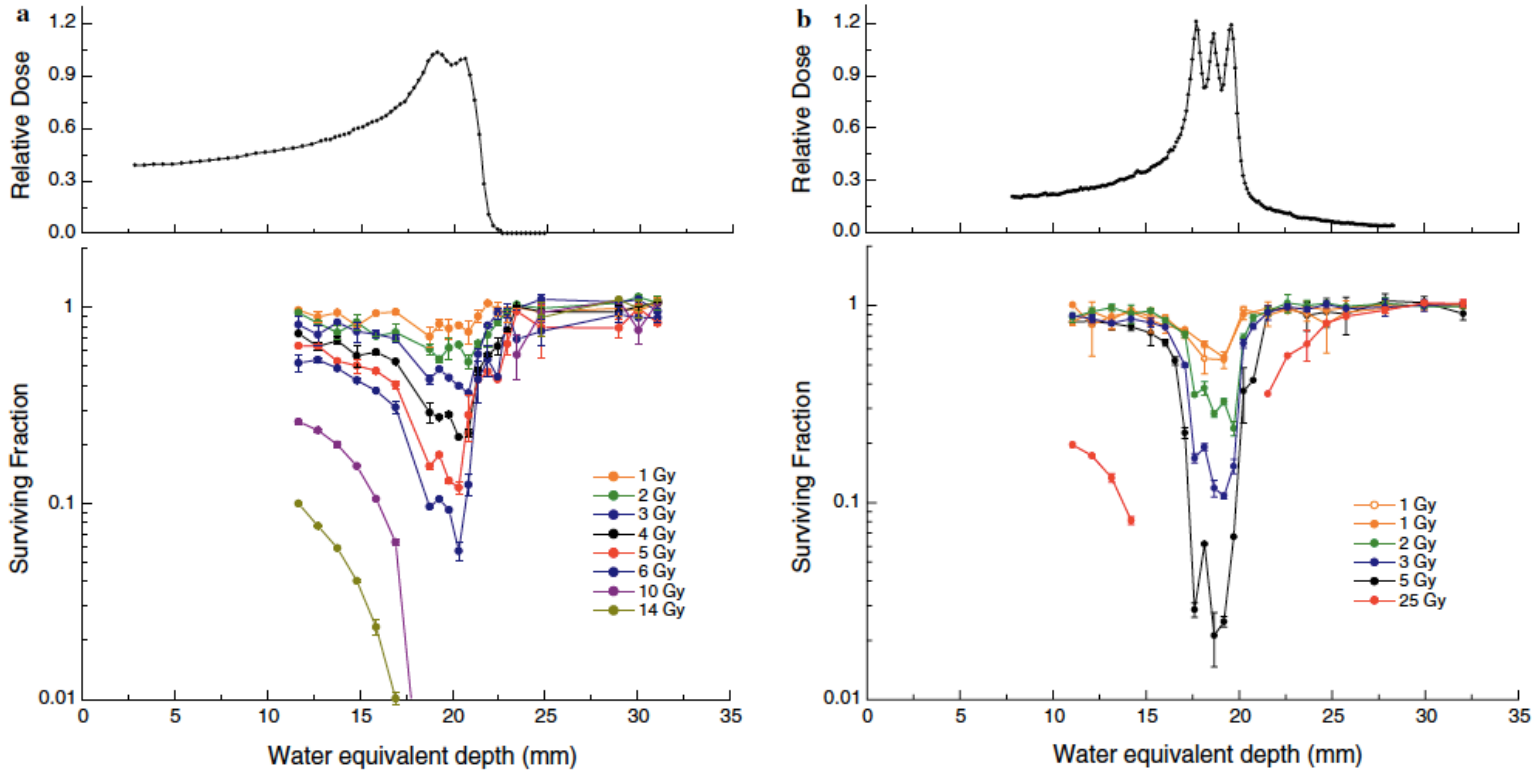
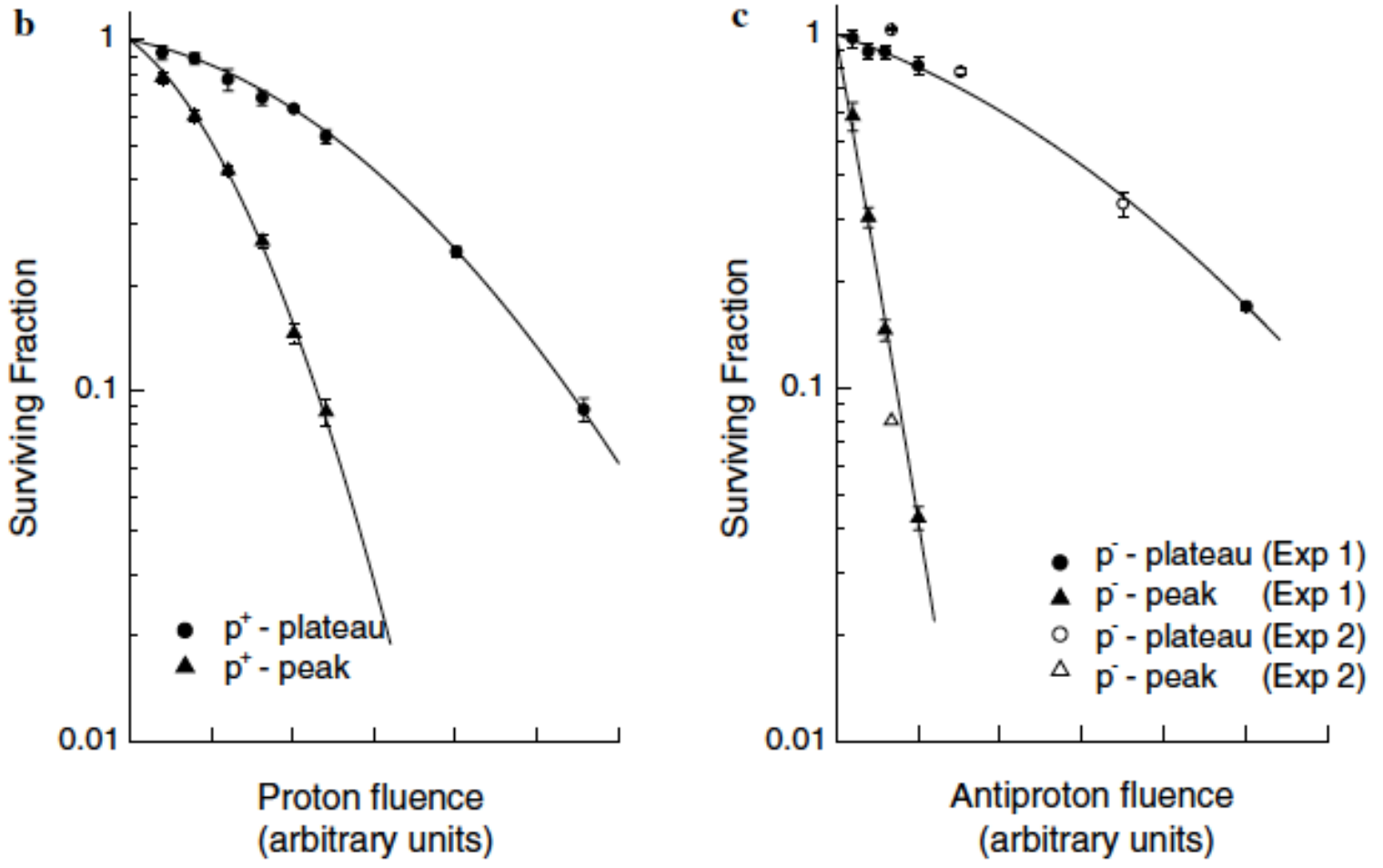


Fig. 4. Clonogenic survival response to antiprotons and protons. The clonogenic survival of V79-WNRE cells is plotted as a function of water equivalent depth along the axis of the proton beam (a) and antiproton beam (b). Survival was measured in 20 individual gel slices after proton irradiation and in 23 slices after antiproton irradiation in individual tubes irradiated with a range of peak doses. Each line represents a single tube irradiated with the measured proton (a) or estimated antiproton (b) dose to the SOBP. For reference, the physical dose profiles are shown in the upper frames.

From: M.H. Holzscheiter et al. / Radiotherapy and Oncology 81 (2006) 233–242

AD-4 ACE Phase I - Results



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AD-4 ACE Phase II

Goals:

Build clinically relevant Spread Out Bragg Peak (SOBP)
Penetration in Target ≈ 10 cm/Width of SOBP ≈ 1 cm.

Include absolute Dosimetry in order to measure Relative Biological Efficiency (RBE)
which then can be used for dose planning excercises.

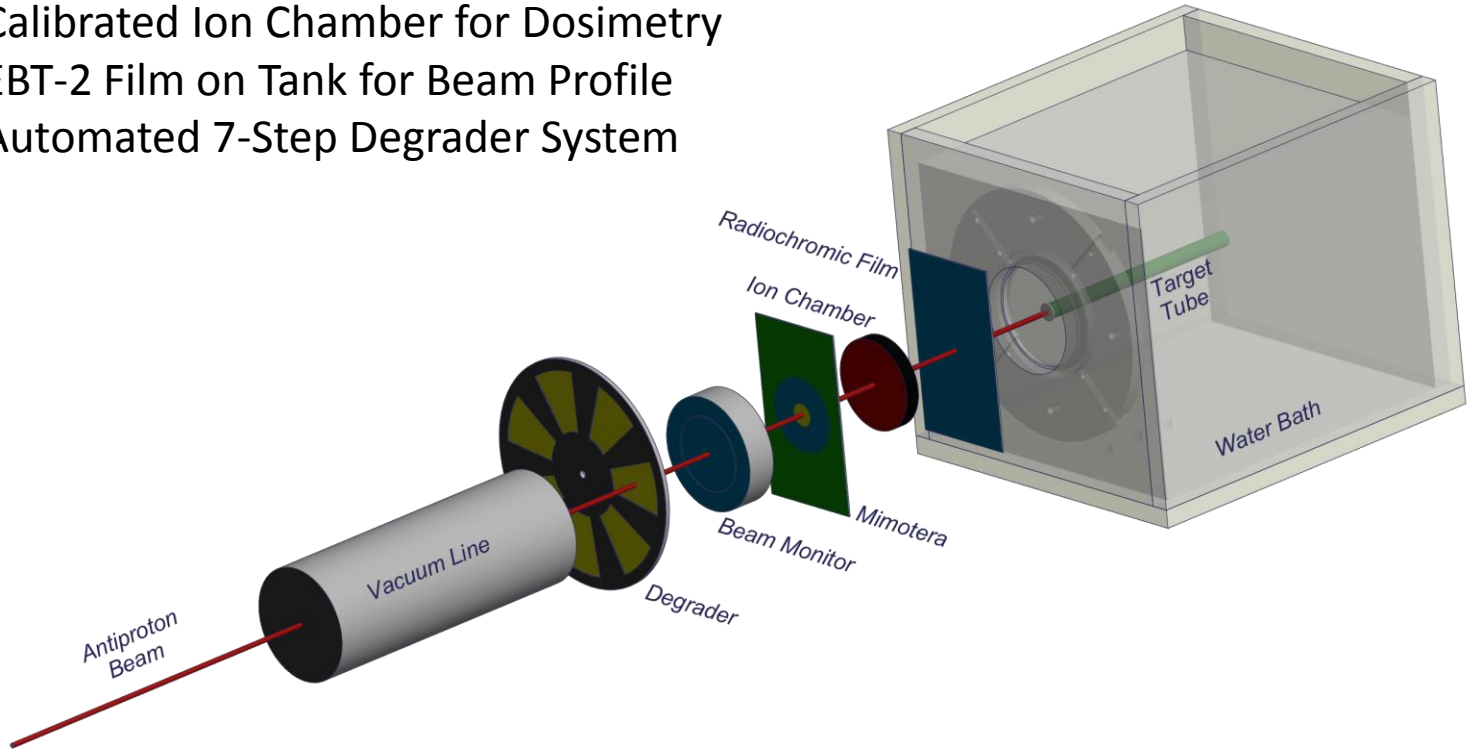
Requirements to AD:

Increase beam energy to 500 MeV/c (126 MeV kinetic)

Resulting in fewer but longer shifts due to more difficult switch-over of accelerator

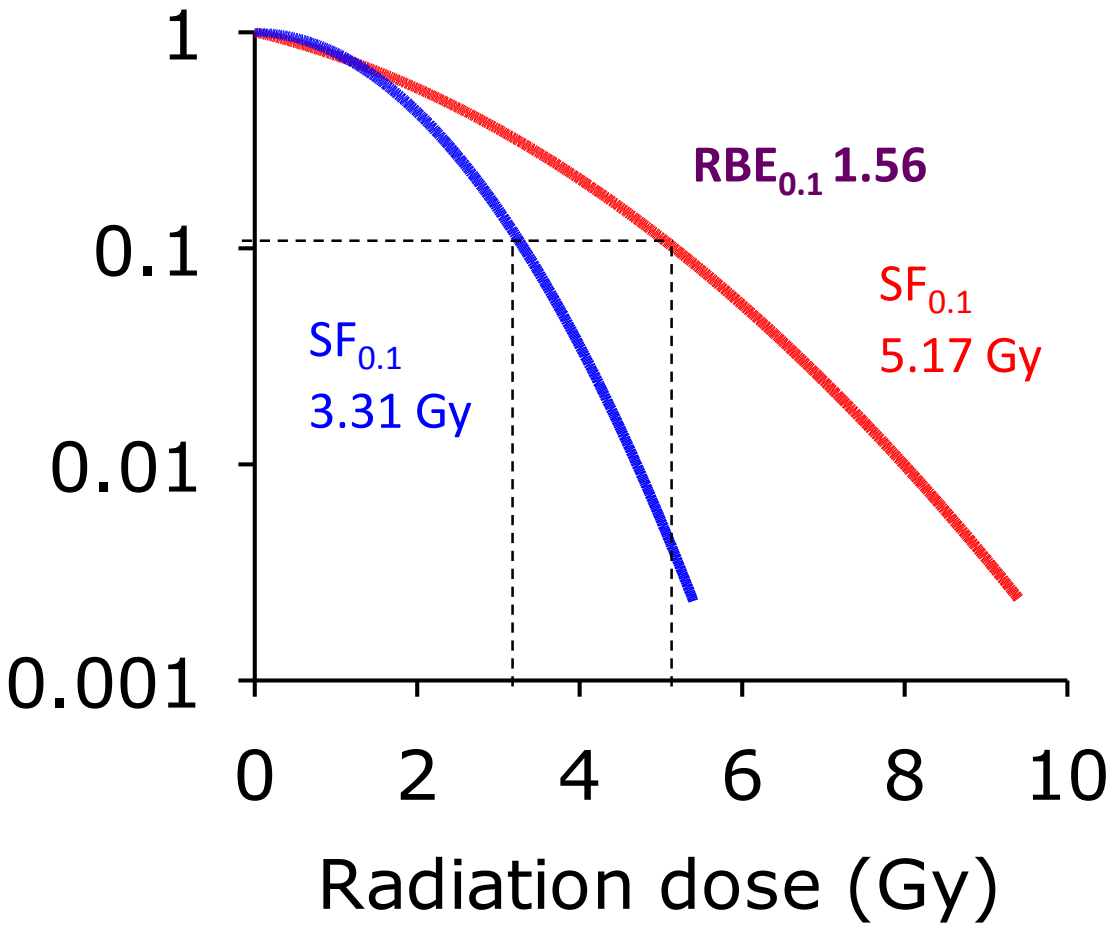
AD-4 ACE Phase II – Experimental Set-Up

Minor, but essential, changes:
Mimotera for shot-by-shot beam monitoring
Calibrated Ion Chamber for Dosimetry
EBT-2 Film on Tank for Beam Profile
Automated 7-Step Degrader System



Relative Biological Effect

= ratio of DOSE of reference radiation to dose of test radiation producing same BIOLOGICAL EFFECT



Measuring RBE requires Dose and Biological Effect

Biological Effect:

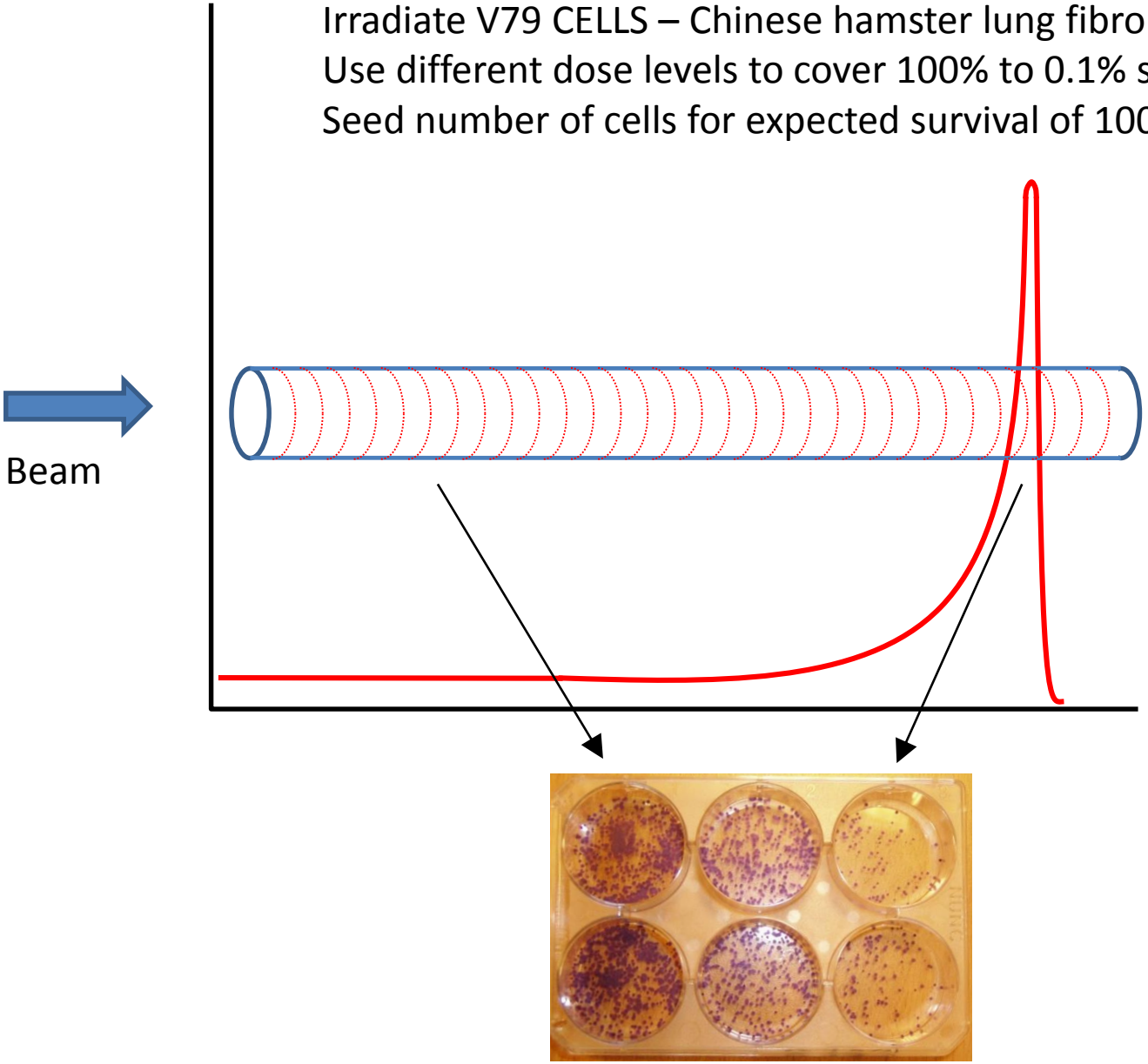
- Embed cells in gelatin matrix inside 6 mm diameter tube
- Irradiate with different fluences of antiprotons (various doses)
- Extract gelatin from tube and take 2 mm slices at several positions
- Disolve slices and seed number of cells determined by predicted survival in growth medium
- Incubate for 5 – 6 days
- Stain cells and count number of colonies ➔ extract survival fraction

Monte Carlo Assisted Dosimetry:

- Determine number of antiprotons entering experimental set-up
- Measure beam spot and position at entrance to target tank
- Estimate beam divergence (*0 mrad/source distance 200 cm*)
- Build model of experimental set-up in FLUKA
- Transport 5 million primaries through FLUKA
- Rerun using +/- sigma for parameters with know errors
- Study systematic errors due to arbitrary assumptions

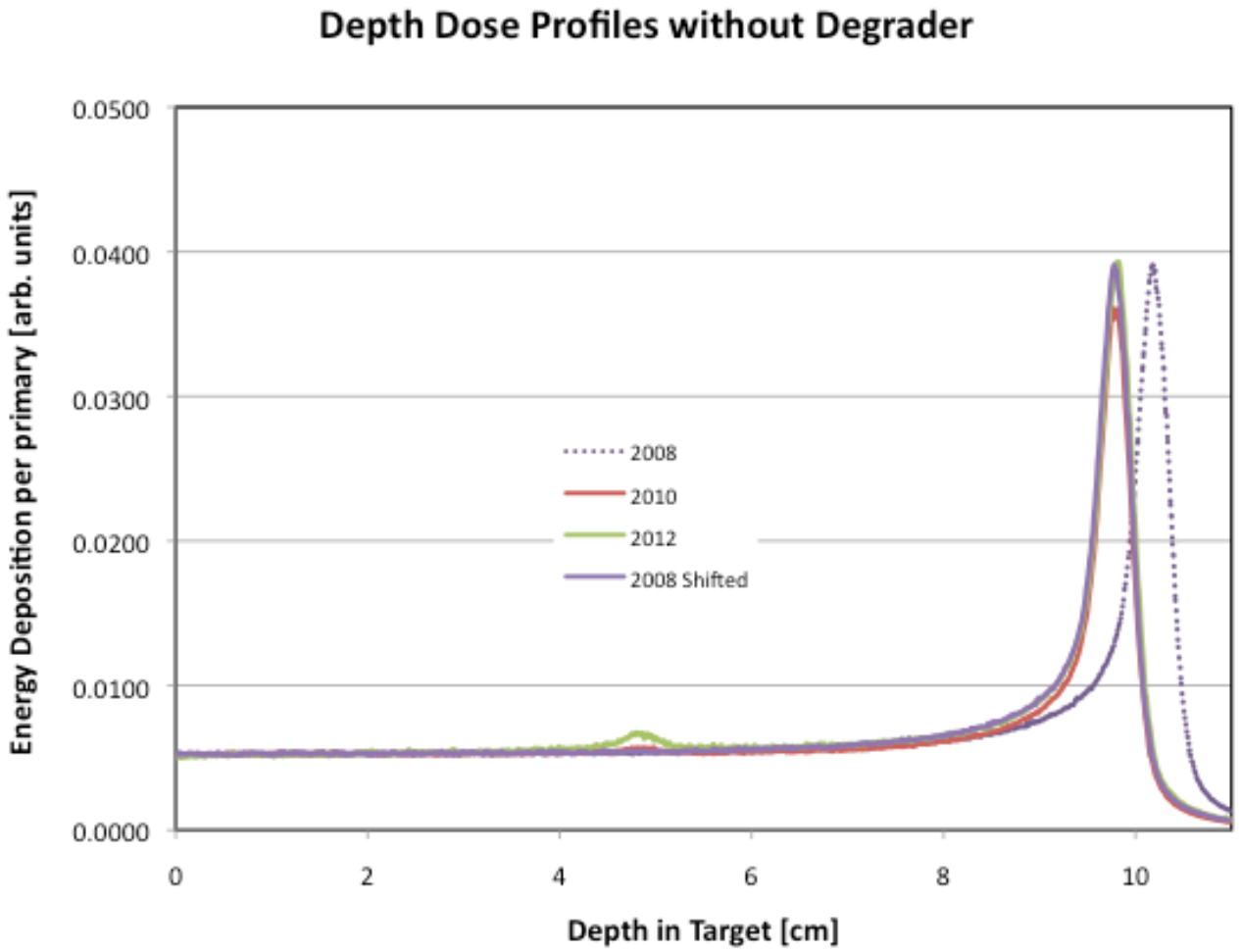
Biological Effect - The tube approach

Irradiate V79 CELLS – Chinese hamster lung fibroblasts
Use different dose levels to cover 100% to 0.1% survival
Seed number of cells for expected survival of 100 cells



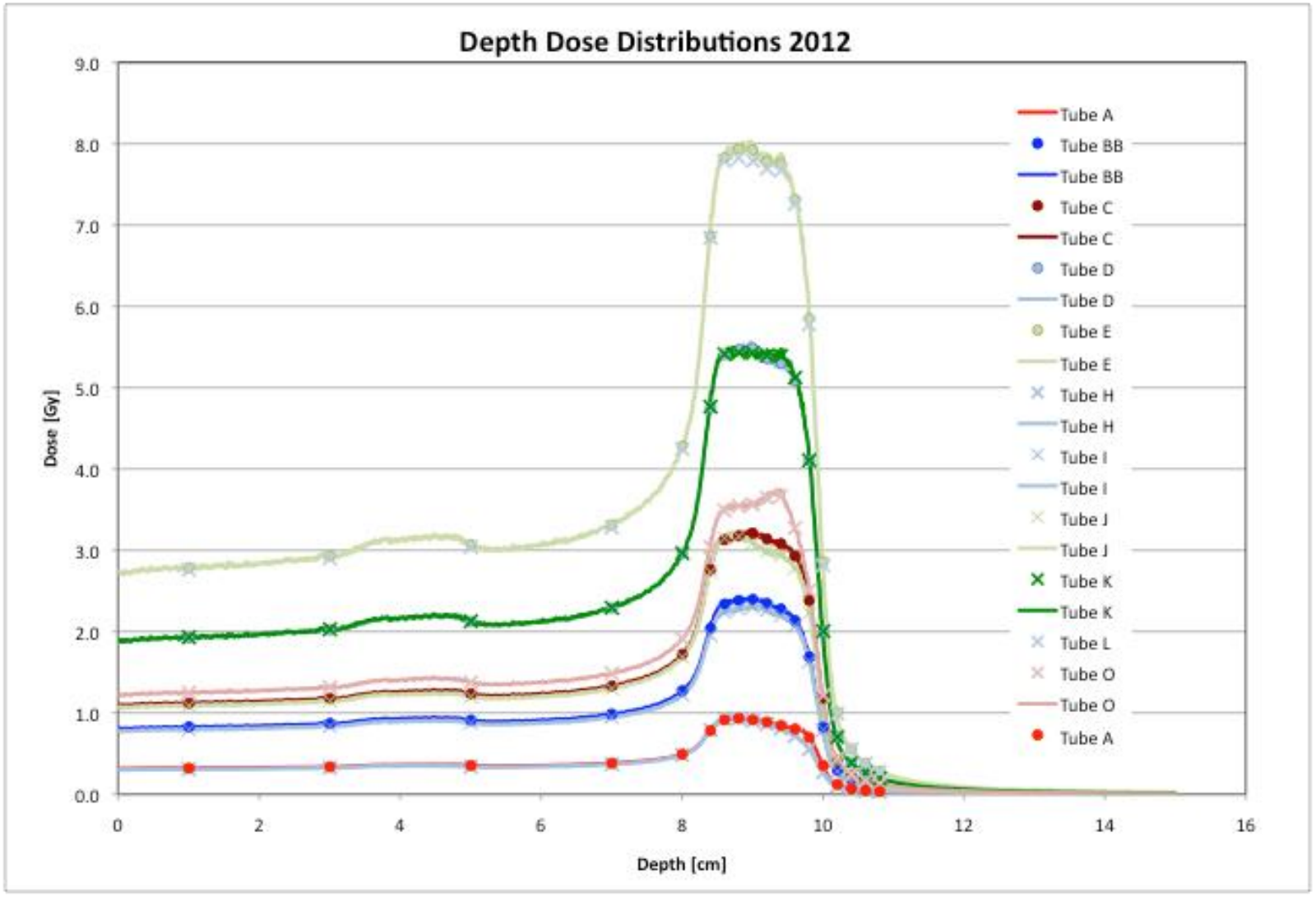
The tube approach – not a trivial task

Monte Carlo Assisted Dosimetry

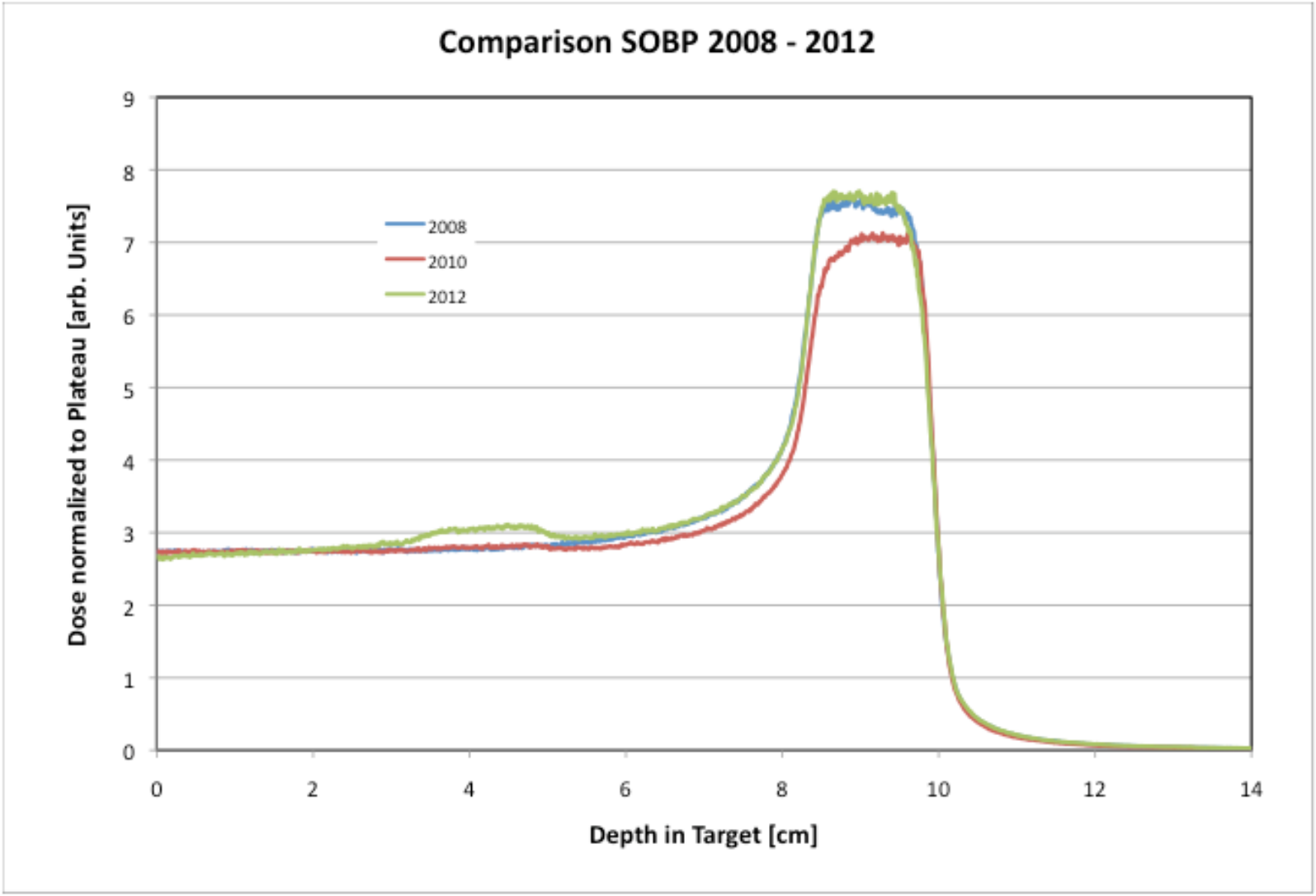


x-Axis for 2008 needed to be shifted by 4 mm

Building the Spread-Out Bragg Peak (SOBP)



SOBP Comparison between Years

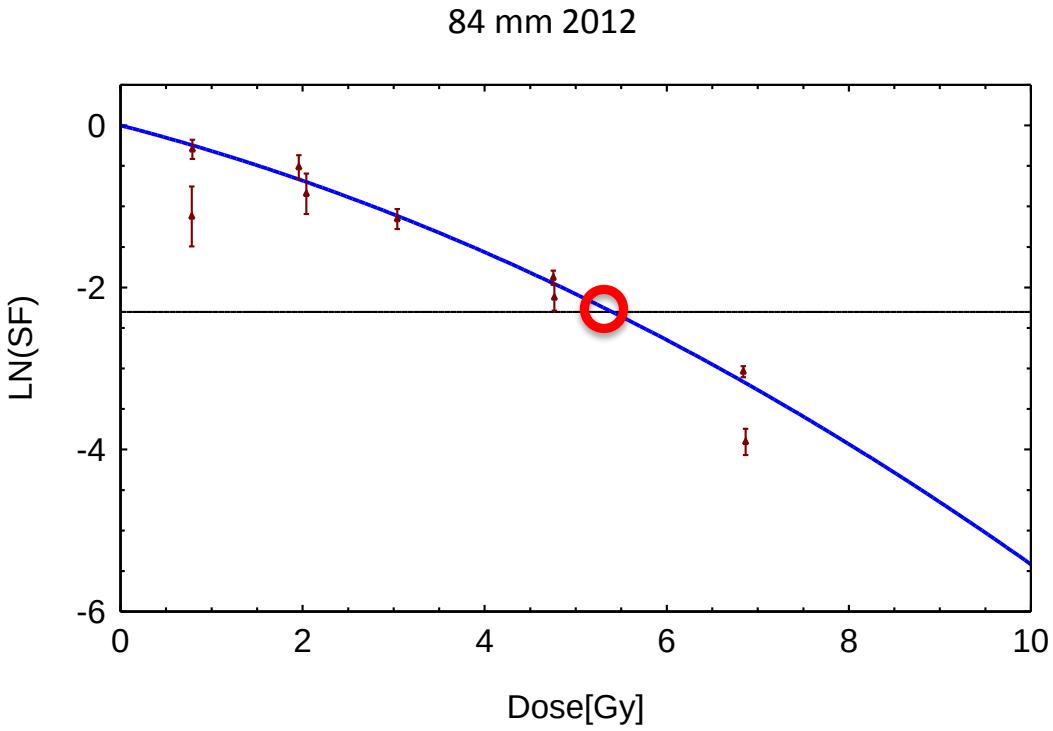


RBE Analysis

Correct survival fraction for Plating Efficiency

(obtained from unirradiated tubes and/or from unrestricted fits)

Fit data to $\ln(SF) = -\alpha x - \beta x^2$, obtain α, β, and sigma(α), sigma(β)



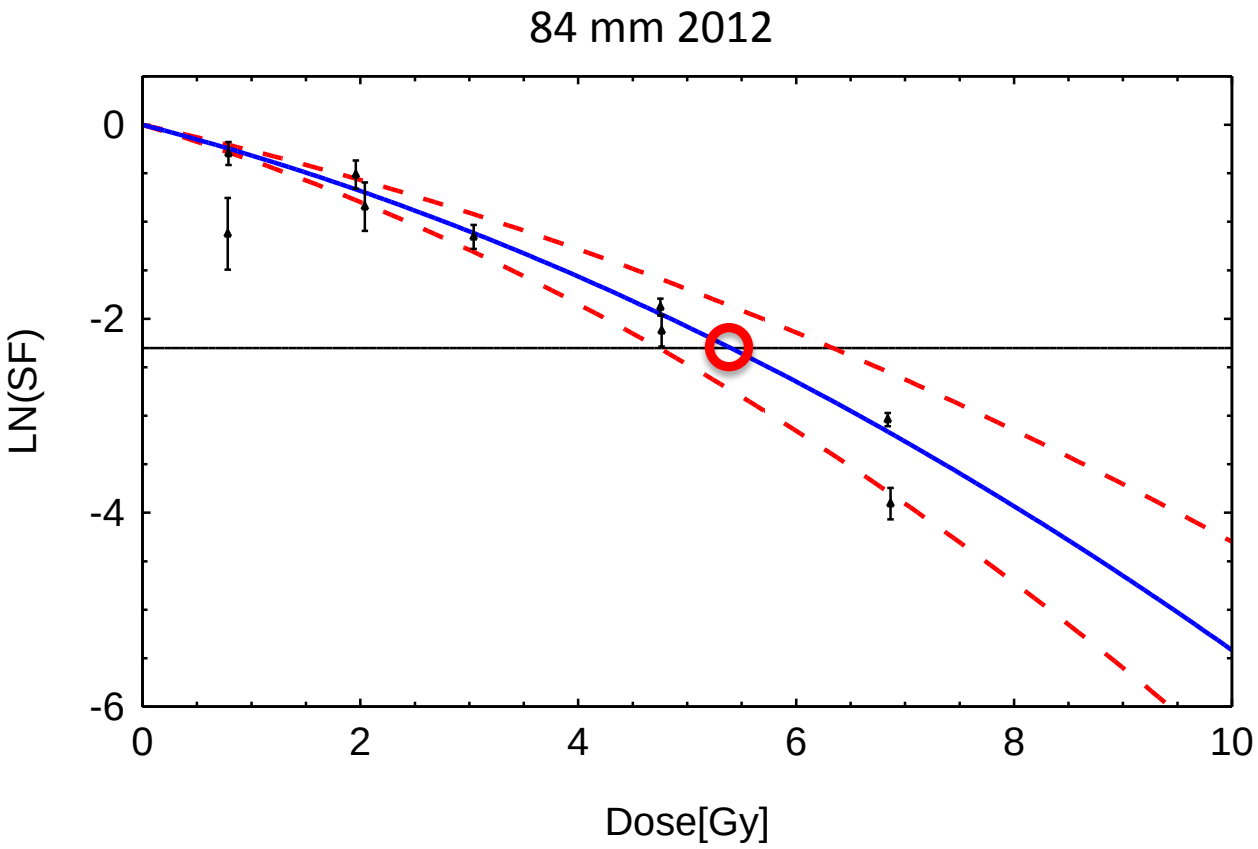
Extract Dose for 10% survival $D_{10\%}$

RBE Analysis - Errors

Use $\sigma(\alpha)$ and $\sigma(\beta)$ from fit to establish error band and σ(D10%)

$$\ln(SF) = -\alpha x - \beta x^2 \rightarrow \ln(SF) = -(\alpha \pm \kappa * \sigma(\alpha))x - (\beta \pm \kappa * \sigma(\beta))x^2$$

κ is chosen so that ≈ 68 % of data points are in between the two curves



RBE Analysis

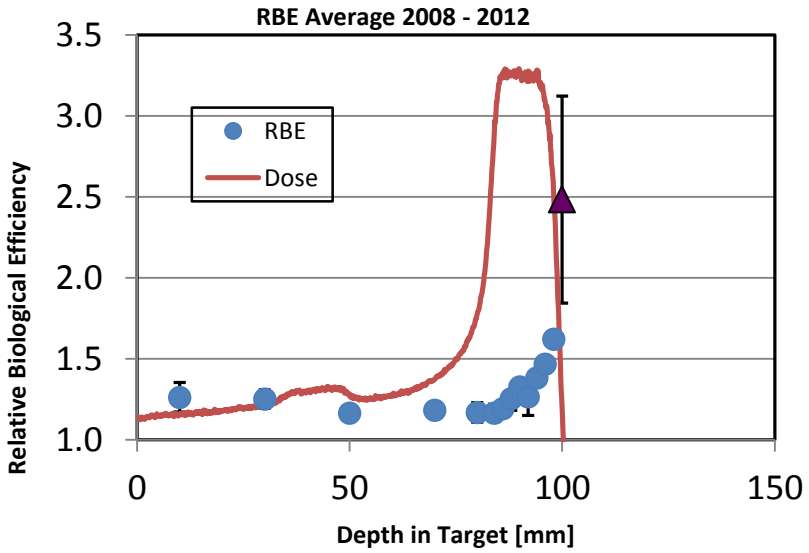
Repeat procedure for all years (2008, 2010, and 2012)

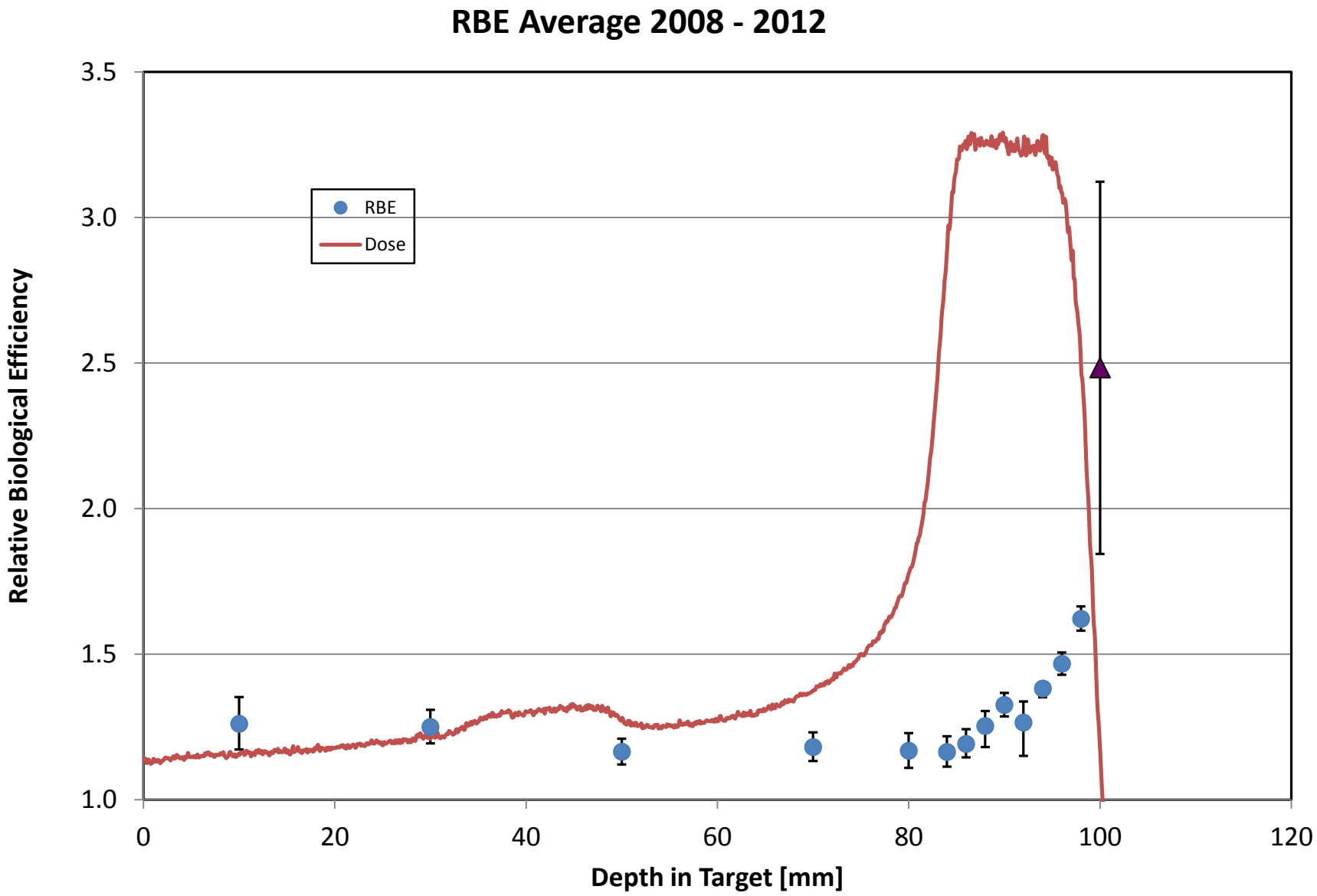
$RBE = D_{10\%,x\text{-}rays}/D_{10\%,\ pbars}$

Plot Average of RBE's for each slice

Combine statistical errors in quadrature

(as long as variance of values is less than 2 sigma)




RBE Average 2008 - 2012
Relative Biological Efficiency
3.5
3.0
2.5
2.0
1.5
1.0
RBE
Dose
0
20
40
60
80
100
120
Depth in Target [mm]

Discussion

Error bars contain only statistical variations (counting of survival)

Systematic errors affecting the result for each set are probably "covered" by averaging all sets. These are:

Error in Plating efficiency (11% - 15%)

Error in Dose calculation (<10%)

Definition of beam spot size and position and beam divergence

(Dose calculations with all parameters changed by respective sigma's and variations added in quadrature)

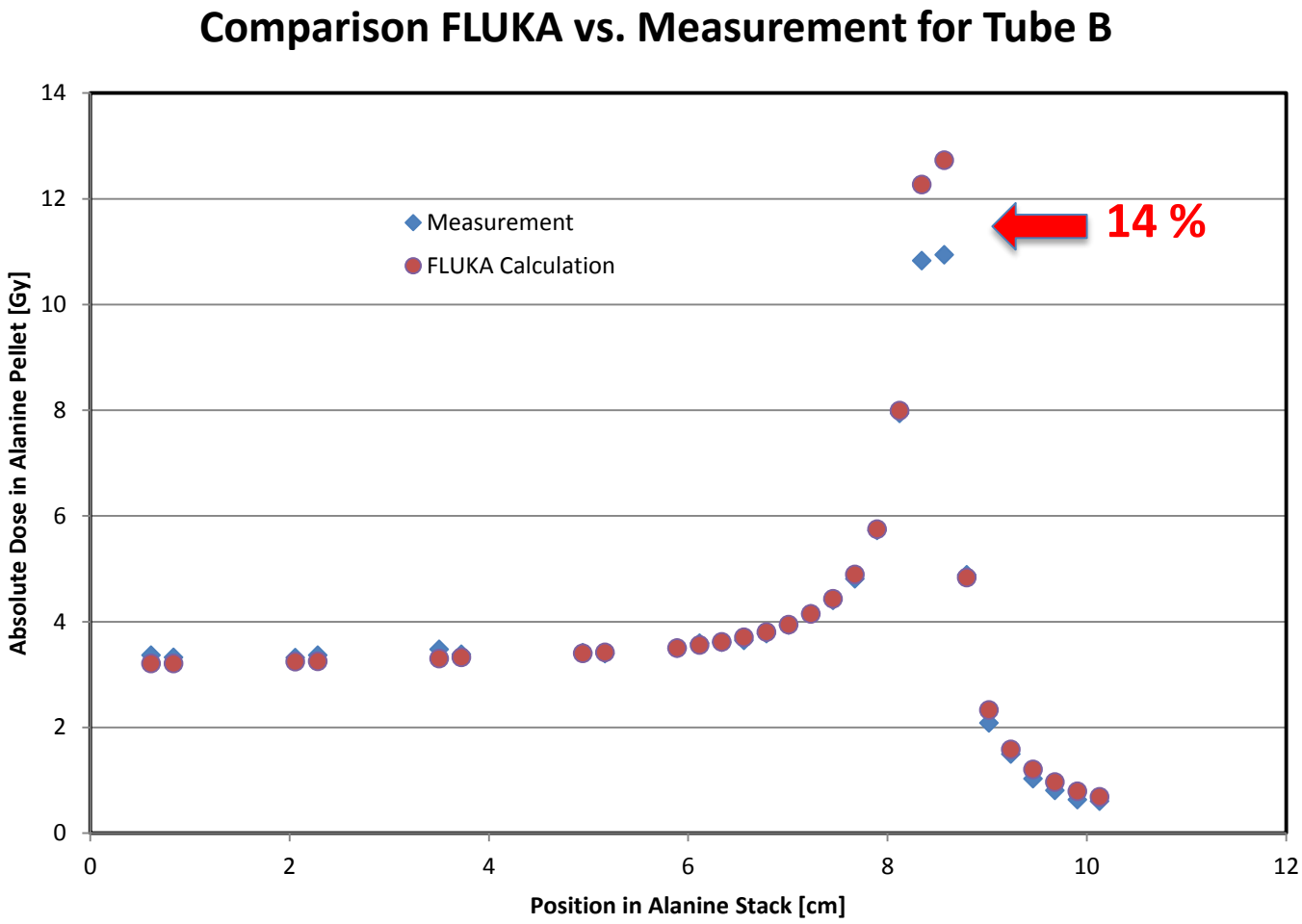
Both would shift the individual RBE vs. Depth curves up and down

Alternative: normalize RBE in plateau? Fit in plateau carries largest errors

Dose error affecting Peak and Plateau region differently:
Final uncertainty of FLUKA dose

2014 Benchmark Experiment

Benchmark Experiment 2014 - Preliminary



Over-estimation of dose in Peak would result in increase of RBE values.
Analysis including correction factors for pressure and temperature in progress

Summary and Discussions

Primary Goal:

✓RBE of antiprotons vs. depth up to the distal edge of the Bragg Peak.

✓Steep increase of RBE confined to the SOBP region.

Lessons learnt?

✧Biology experiments are hard!!

✧Need best possible diagnostic for beam!

Mimotera only installed in 2010, multiple monitors better

✧Clinical beam would have been much better, but unrealistic!

Flat field of 5 x 5 cm to eliminate divergence and scatter

✧Compress experiment to 1 year to avoid changes over time

(Set-up changes, alignment, MC assisted dosimetry -

but that would have inhibited the “learning curve”).

✧ Leave experiment mounted at all times

Survey of experiment impossible after installation of AeGIS

We close the chapter but not the book

No further real progress achievable with beam at CERN.
Original FAIR/FLAIR facility should have been running by now offering higher intensity and continuous extraction.

Theoretical predictions in general confirmed,
replacing theoretical "guesses" with experimental data.

Principle of real-time imaging confirmed.

Thank you AD Team

AD users

and CERN