Status Report on AD-4/ACE Antiproton Cell Experiment

The Biological Effectiveness of Antiproton Annihilation

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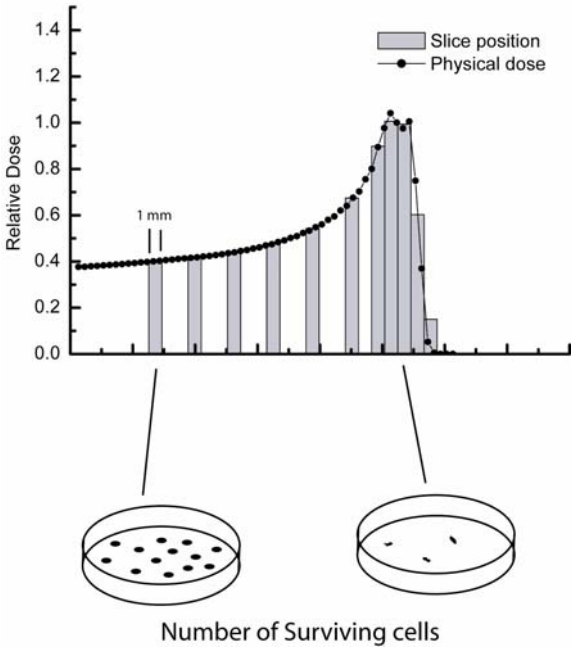
Antiproton Therapy is based on three claims which need proof:

- **Antiprotons deliver a higher biological dose for an equal effect in the entrance channel than protons (and possibly heavy ions).**
- **The damage outside the beam path due to long and medium range annihilation products is small and does not significantly effect treatment planning.**
- **Antiprotons offer the possibility of real time imaging using high energy gammas and pions, even at low (pre-therapeutical) beam intensity.**

Results from the 2003 run period

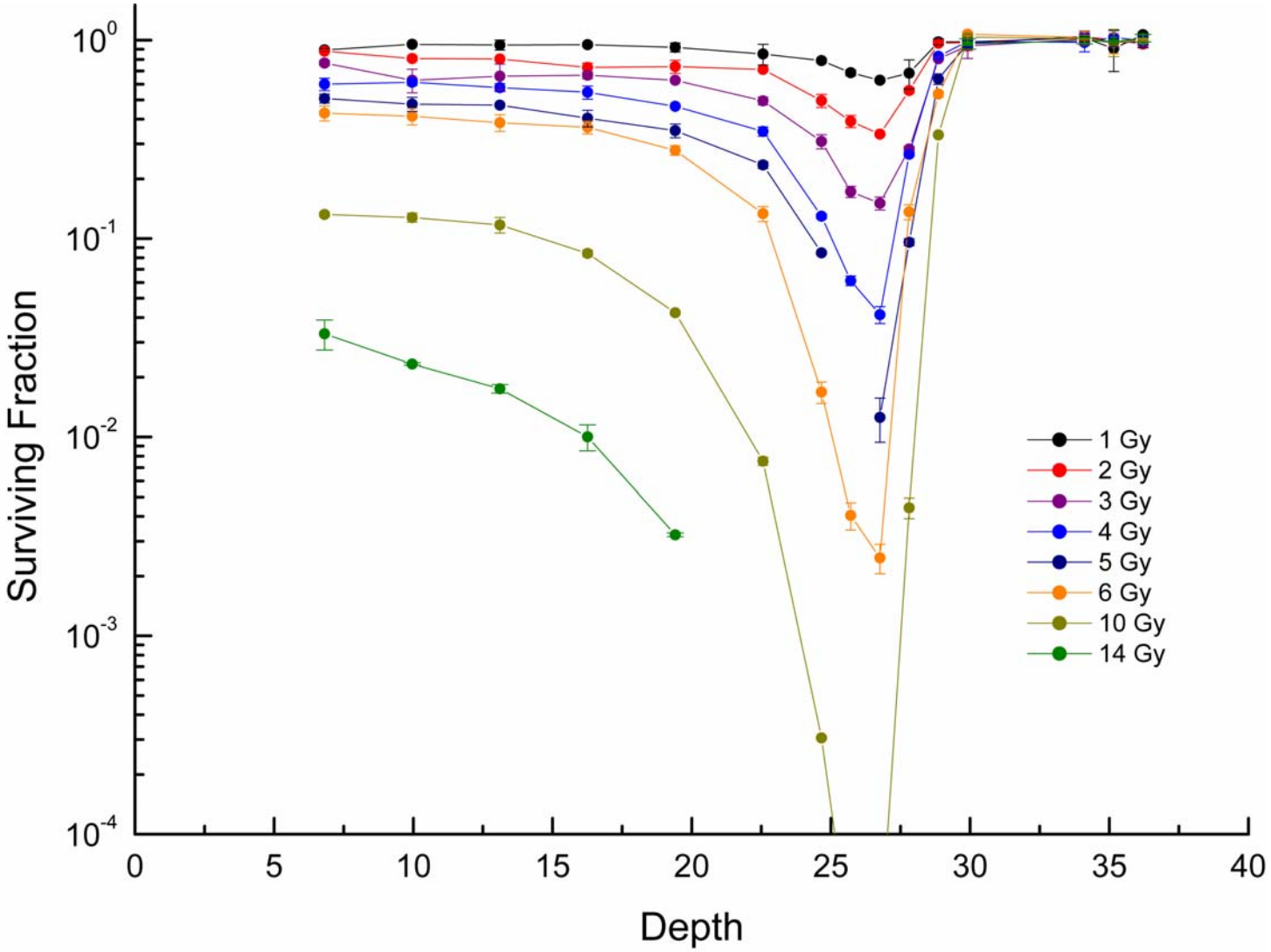
- **We have measured cell survival in the peak and plateau regions of an antiproton beam stopped in a biological medium.**
- **Extracting the relative doses which produce equivalent cell kill in the peak and the plateau region we can define the BEDR (Biological Effective Dose Ratio) as the ratio of these doses. (We only need to know the relative dose).**
- **We can compare these results to the same experiment using a proton beam of comparable energy.**

Biological Analysis Technique



- Irradiate sample tube with living cells suspended in gel.
- Slice sample tube in <1 mm slices and determine survival fraction for each slice.

➢Repeat for varying (peak) doses.



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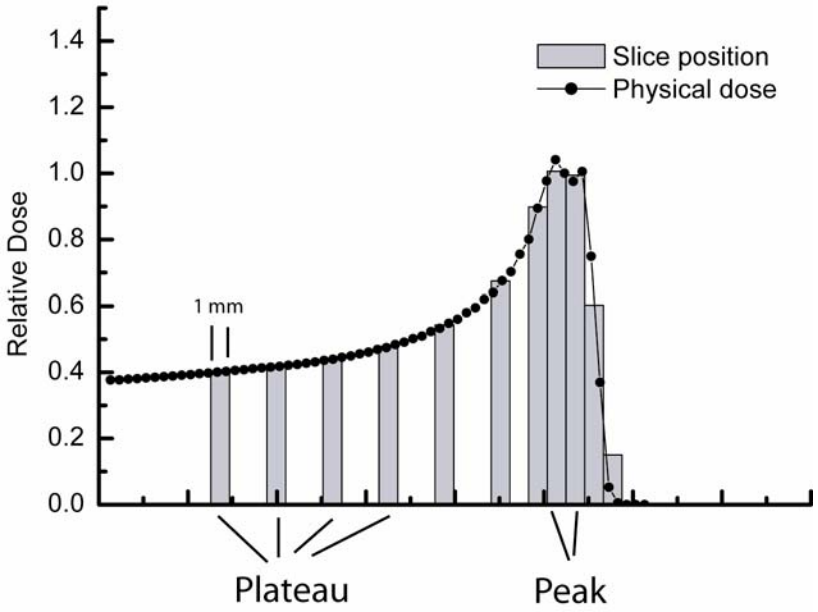
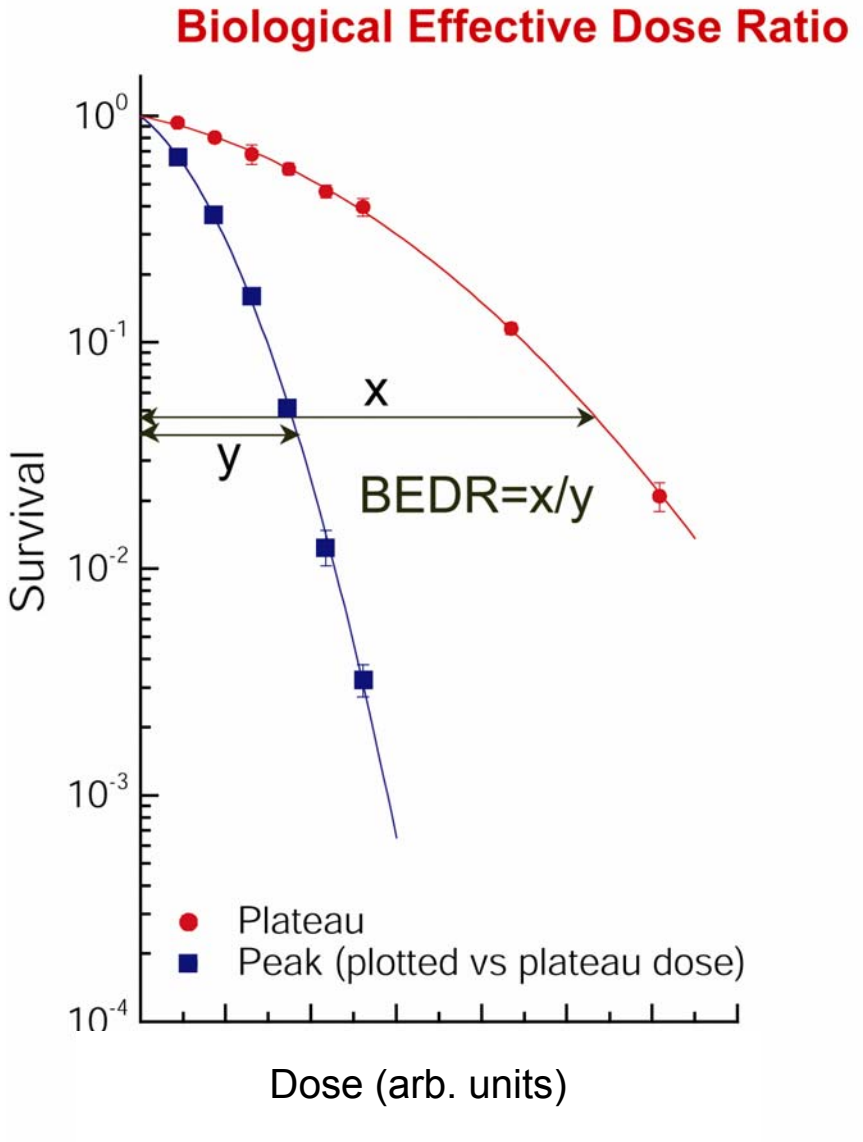
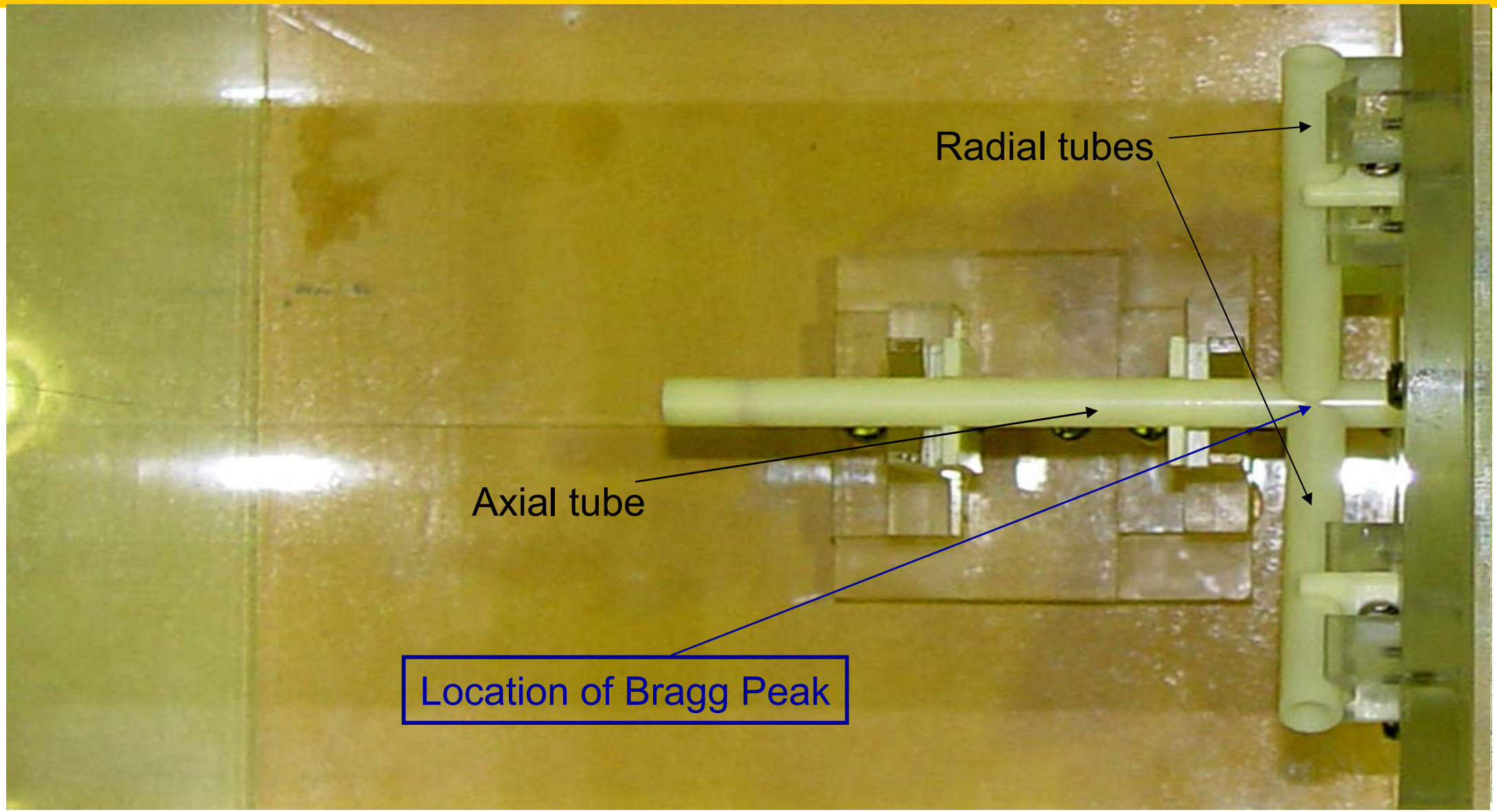


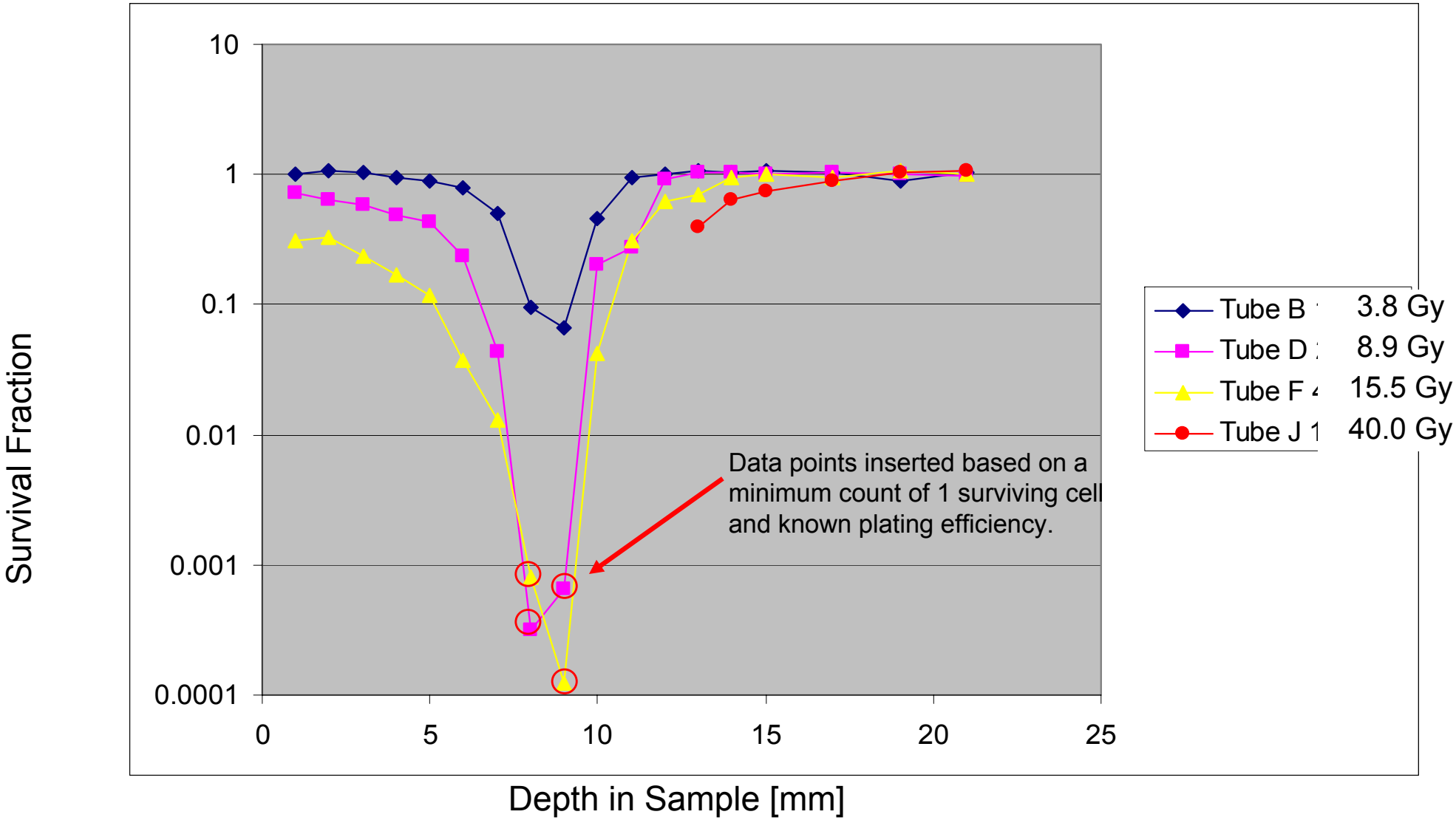
- Calculate “plateau” survival using slices 1 – 4.
- Determine “peak” survival from slice 8 and 9.
- ✓Plot “peak” and “plateau” survival vs. relative dose (Plateau dose, particle fluence, etc.) and extract the Biological Effective Dose Ratio (BEDR).

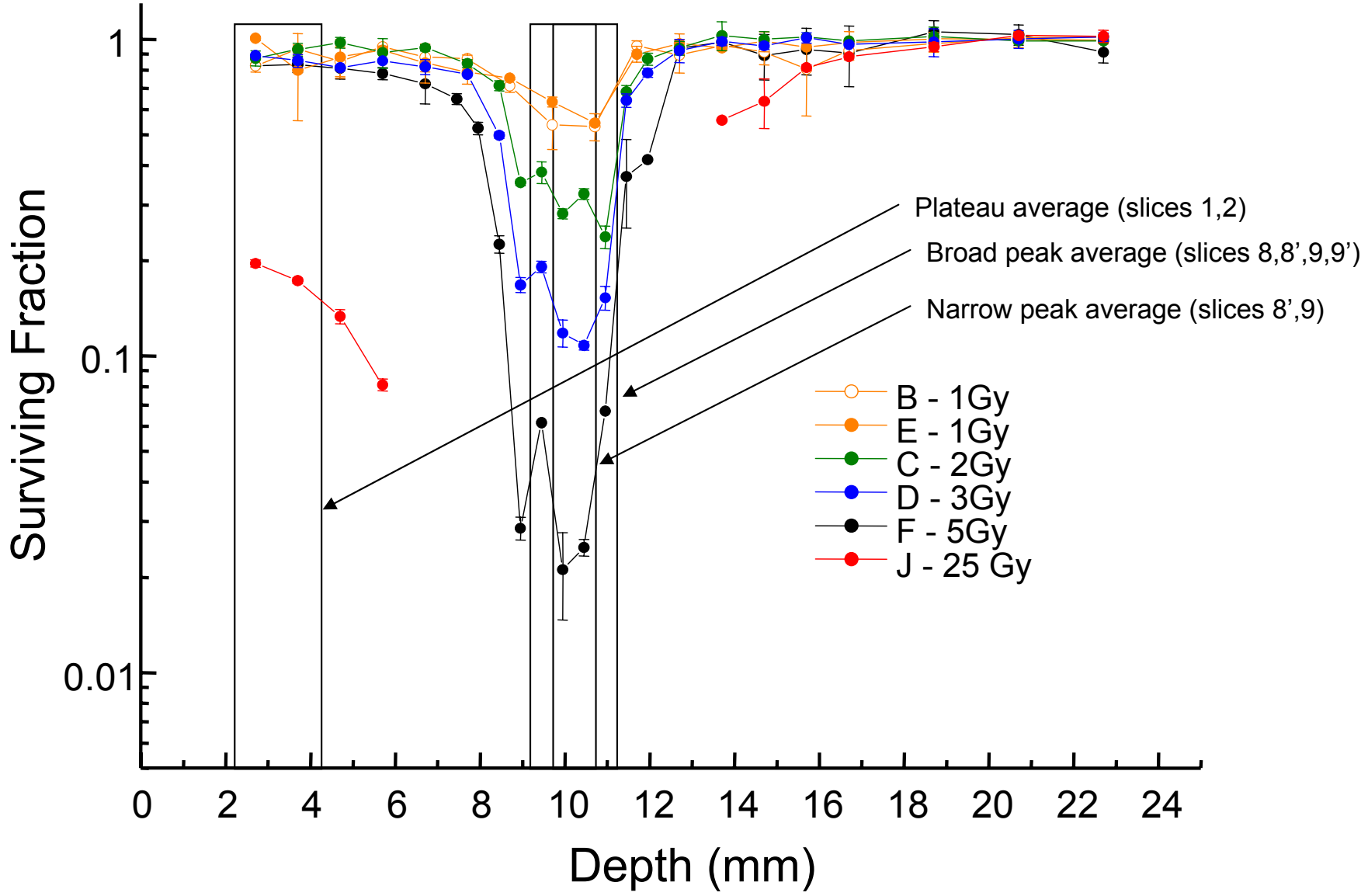


Cell Survival Measurements

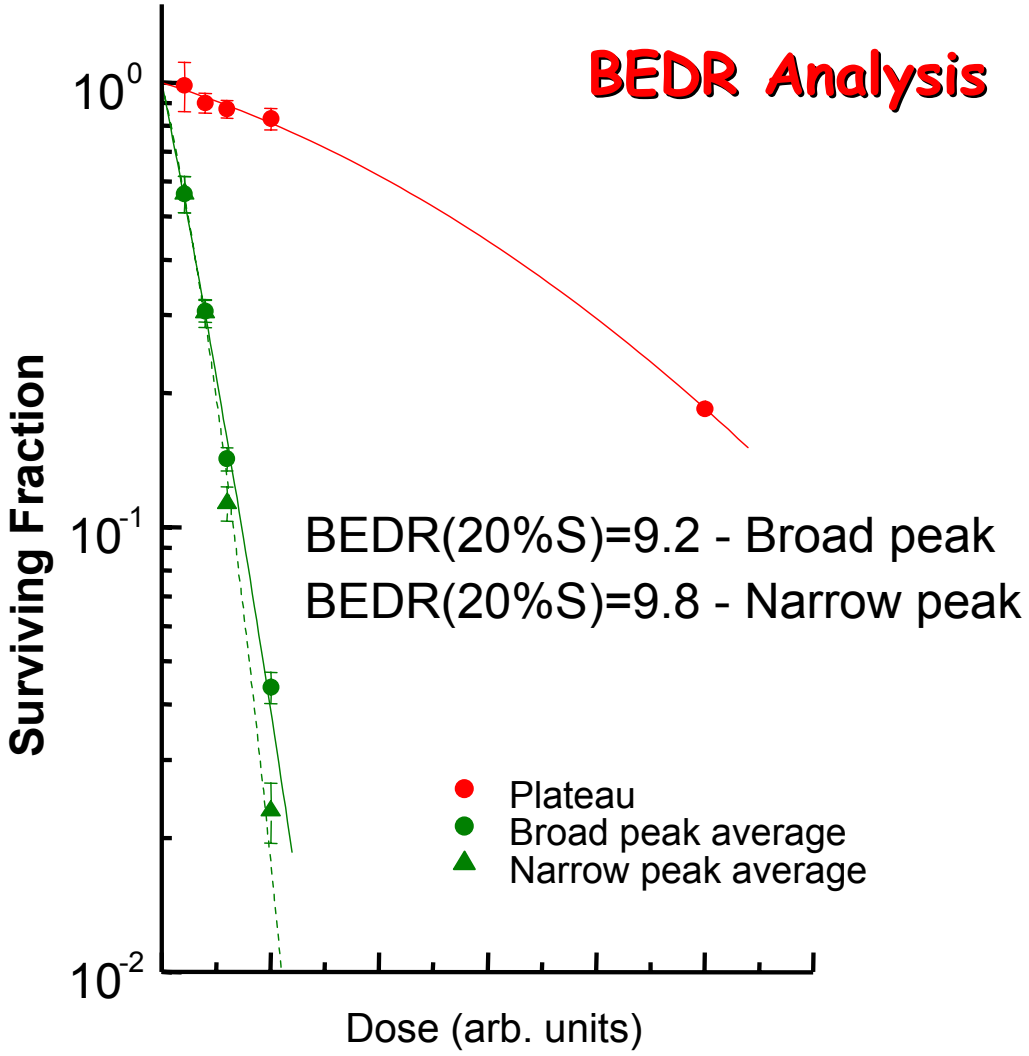


Cell Survival Measurements

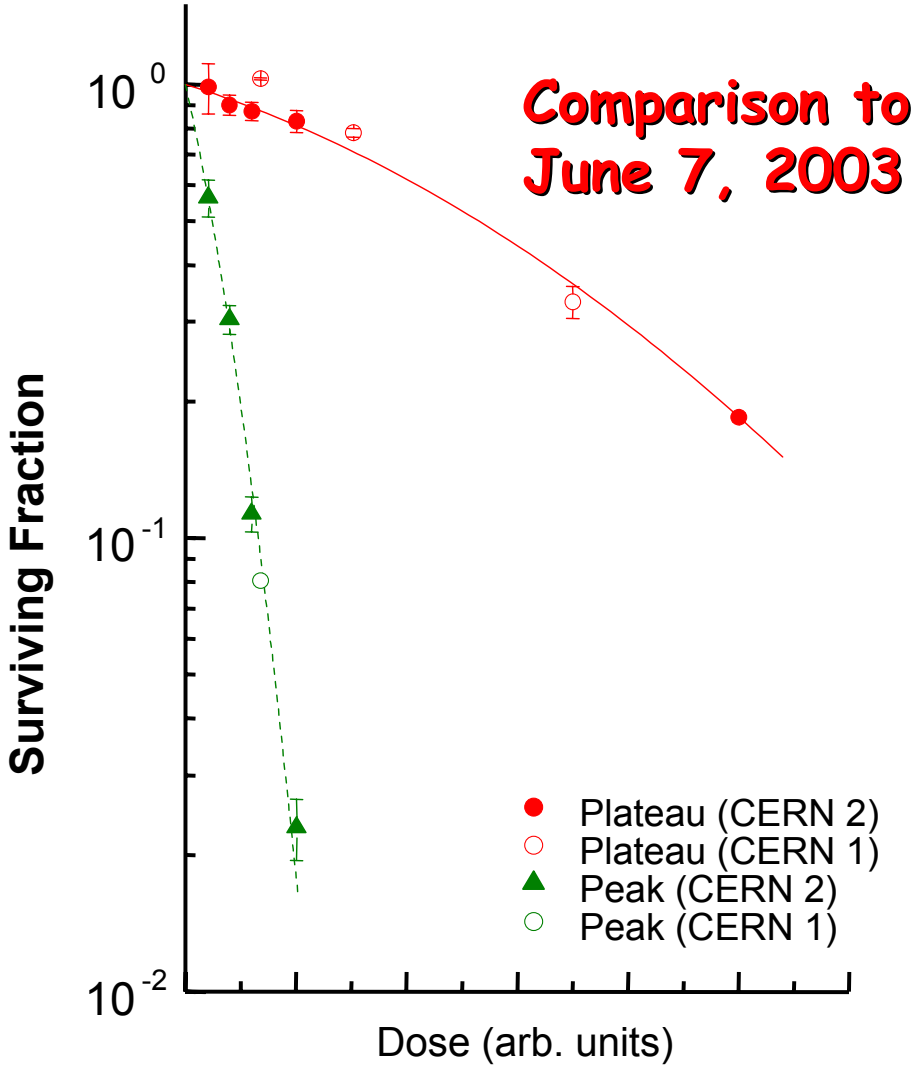



Surviving Fraction
1
0.1
0.01
0
2
4
6
8
10
12
14
16
18
20
22
24
Depth (mm)
Plateau average (slices 1,2)
Broad peak average (slices 8,8',9,9')
Narrow peak average (slices 8',9)
B - 1Gy
E - 1Gy
C - 2Gy
D - 3Gy
F - 5Gy
J - 25 Gy

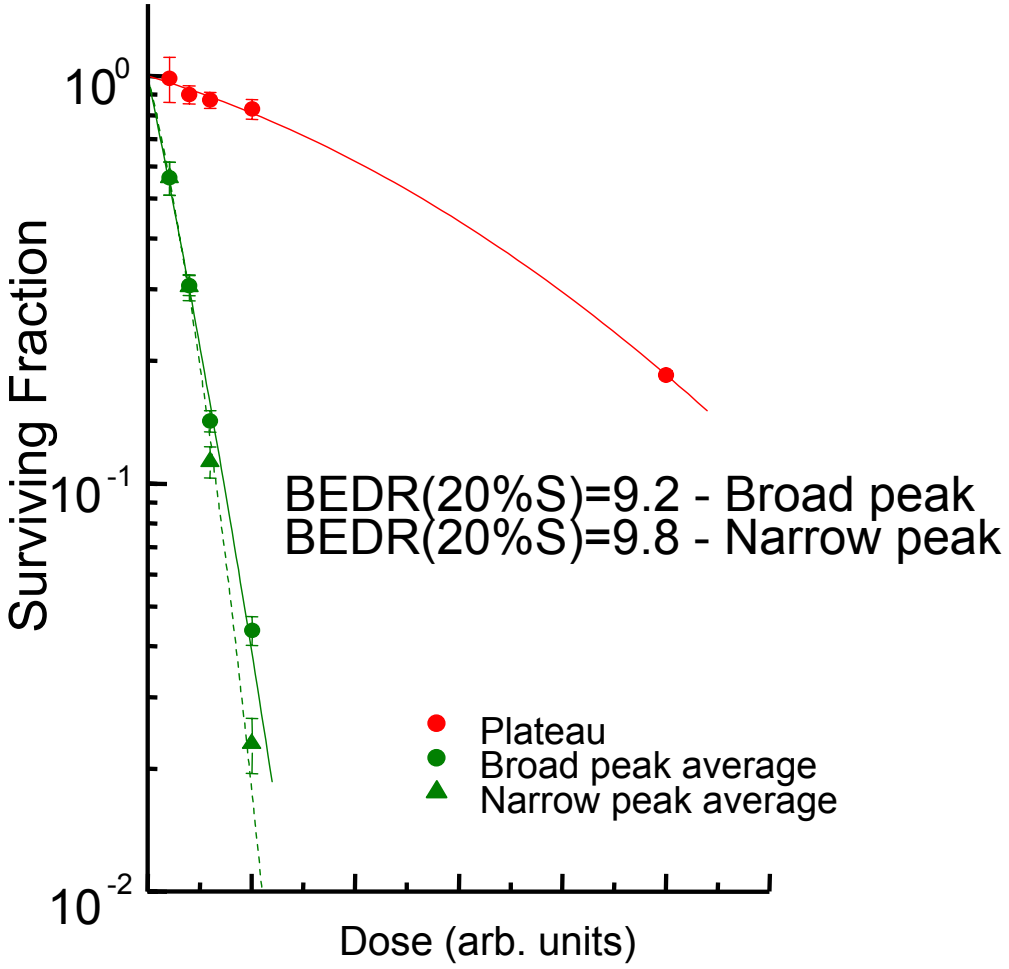
BEDR Analysis



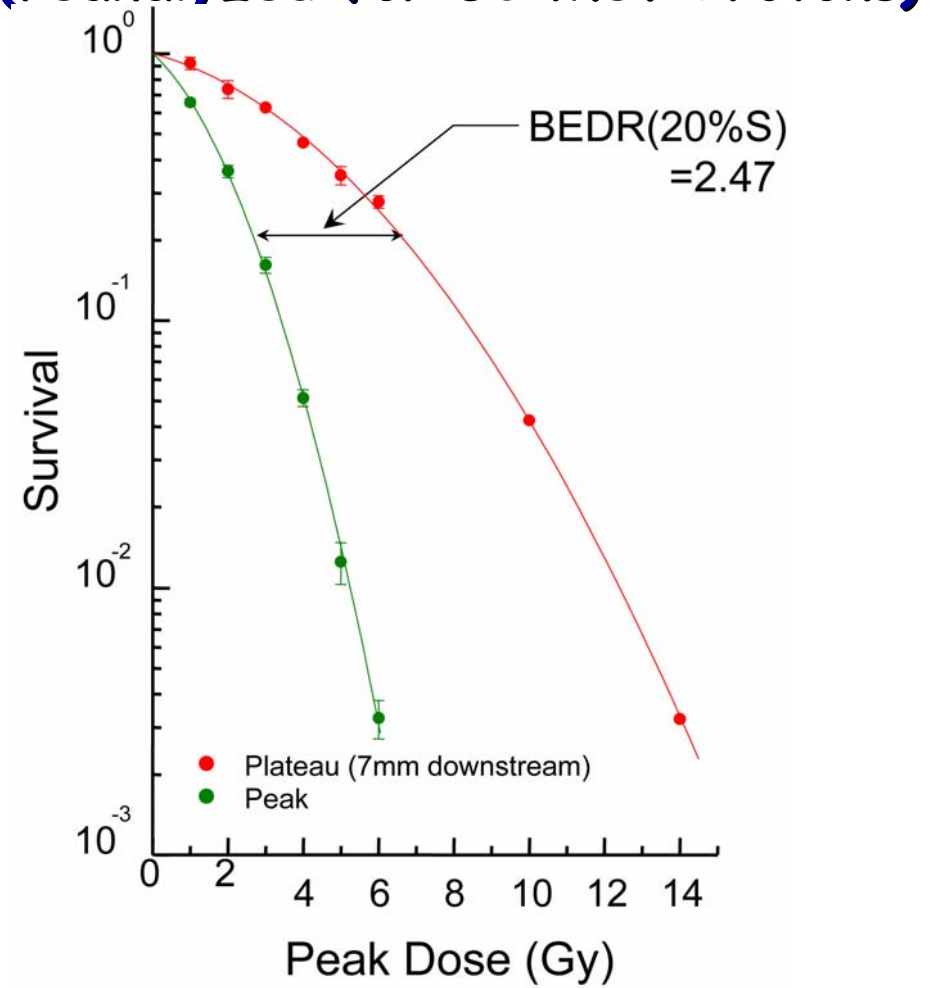
Comparison to June 7, 2003



CERN (50 MeV Antiprotons)



TRIUMF (reanalyzed for 50 MeV Protons)



Summary at end of 2003

- **The method works very well.**
- **We are able to measure the survival response of V79-WNRE cells in the plateau and peak regions of a SOBP antiproton peak.**
- **In the early test experiment we obtained good data at 3 different doses in the plateau, and complete data at one dose in the peak.**
- **In the September run we obtained complete survival curves for 5 different doses (in 6 measurements). The sensitivity in axial direction is high enough to detect the dose modulation due to the degrader used.**
- **An analysis of the data for the BEDR gives a result which is significantly higher than the value for protons (obtained at slightly higher energy and using a different degrader) .**
- **We observe only negligible cell kill outside of the beam in either the radial or axial (beyond the peak) position at even the highest dose. This means not only that there is no significant spread of dose outside the beam due to the annihilation event but also no significant pion contamination in the beam.**

2004 Run Cycle

- **The BEDR enhancement has been proven to be significant.**

NEXT STEPS:

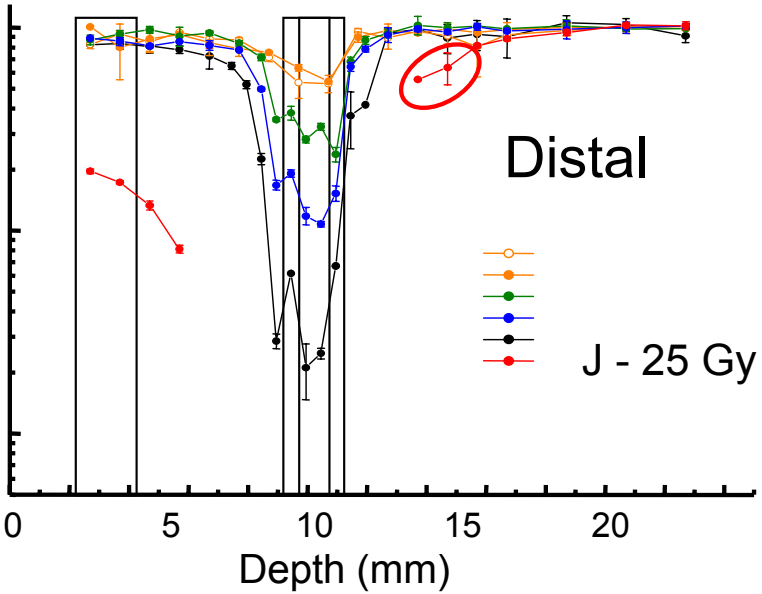
- **Detailed studies of the peripheral damage due to the medium and long range products from the antiproton annihilation.**

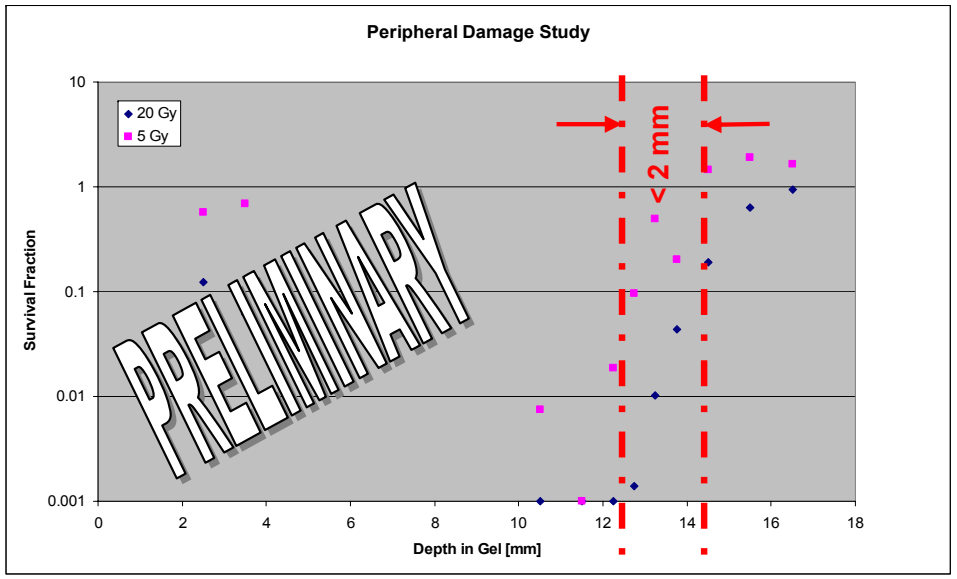
  Clonogenic studies may not be the best approach
  ➔ search for alternative assays.

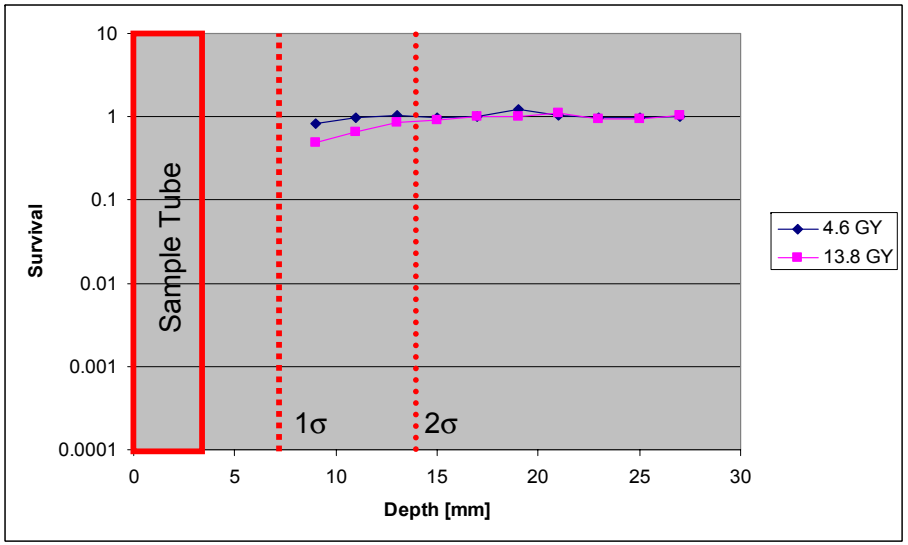
  Increased efforts on dosimetry in the periphery to the beam

- **Systematic studies to find faster (and more automated) methods to extract biological data.**
- **Preparatory studies towards real time imaging.**

Evidence of LOW Peripheral Damage





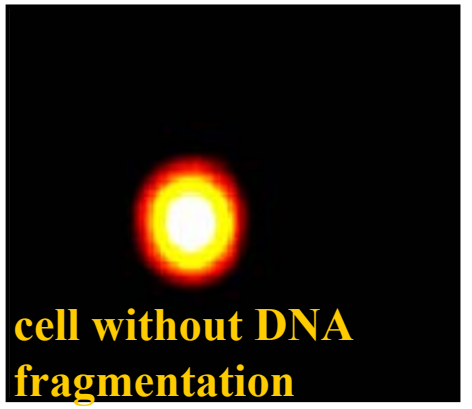


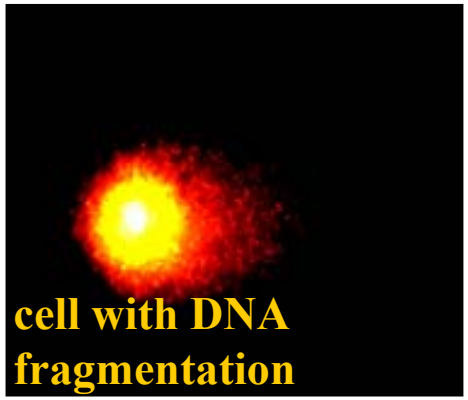
At the highest doses we can see a small effect outside the Bragg peak up to 1 – 2 mm distance

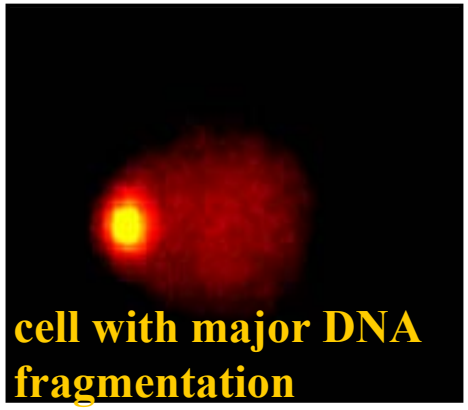
- Need more sensitive assay
- Clonogenic may not be best
- DNA damage is detectable

The COMET Assay

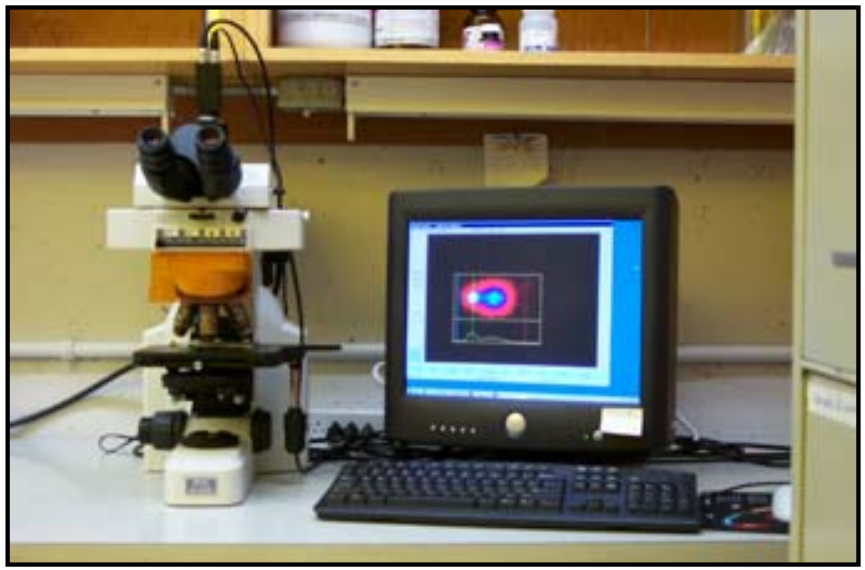
The comet assay is a gel electrophoresis method used to visualize and measure DNA strand breaks in individual cells using microscopy:







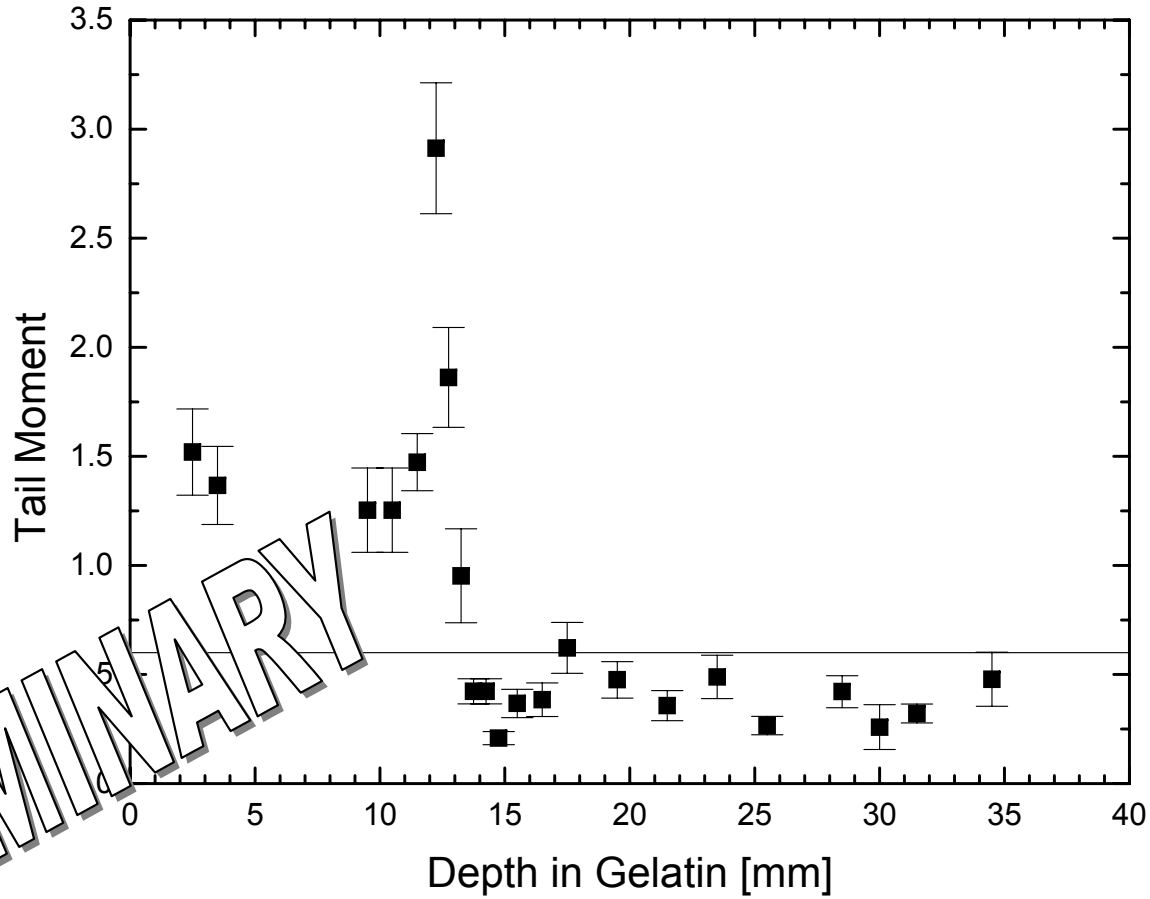
Automated Analysis on individual cells



Statistical accuracy through analysis of > 100 cells per sample

The COMET Assay – Early Results

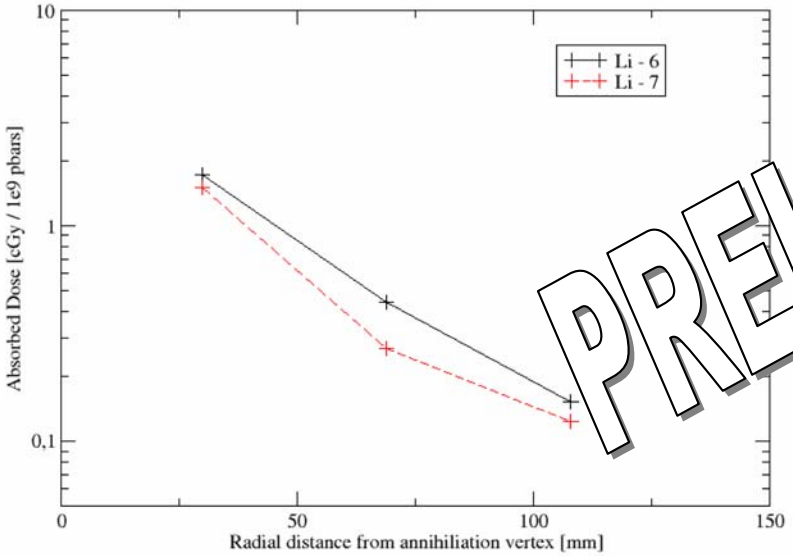
- Cell sample irradiated with 15 Gy
- Slices (0.5 mm and 1 mm) for
  - plateau
  - peak
  - peripheral (distal)
- COMET Assay performed by the Inst. for Occup. Medicine, Zagreb
- No detectable damage above control sample

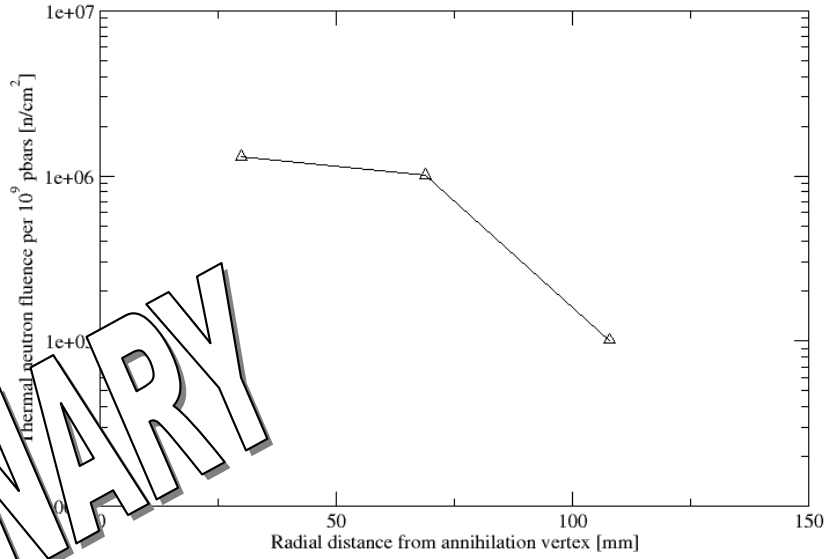


Peripheral Damage – Neutron Dosimetry

Placement of ^{6}Li and ^{7}Li TLD chips
at 30 to 120 mm from annihilation volume

Total dose in Peak ~ 7 Gy
Dose seen at 20 mm < 2 cGy





PRELIMINARY

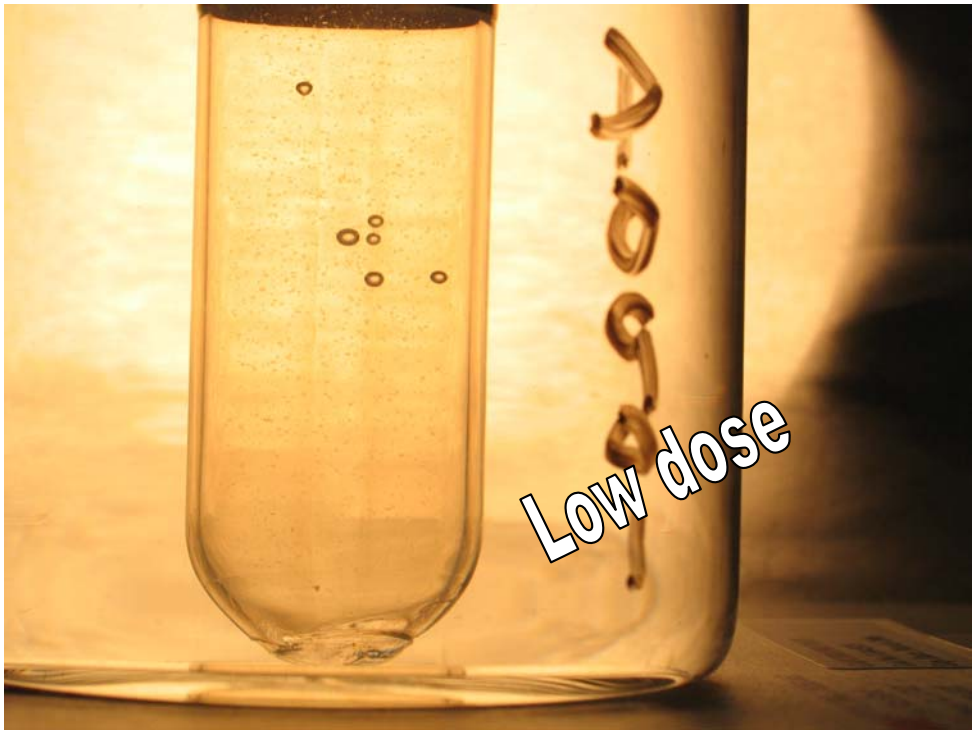
Additional dose in ^{6}Li from thermal neutrons only

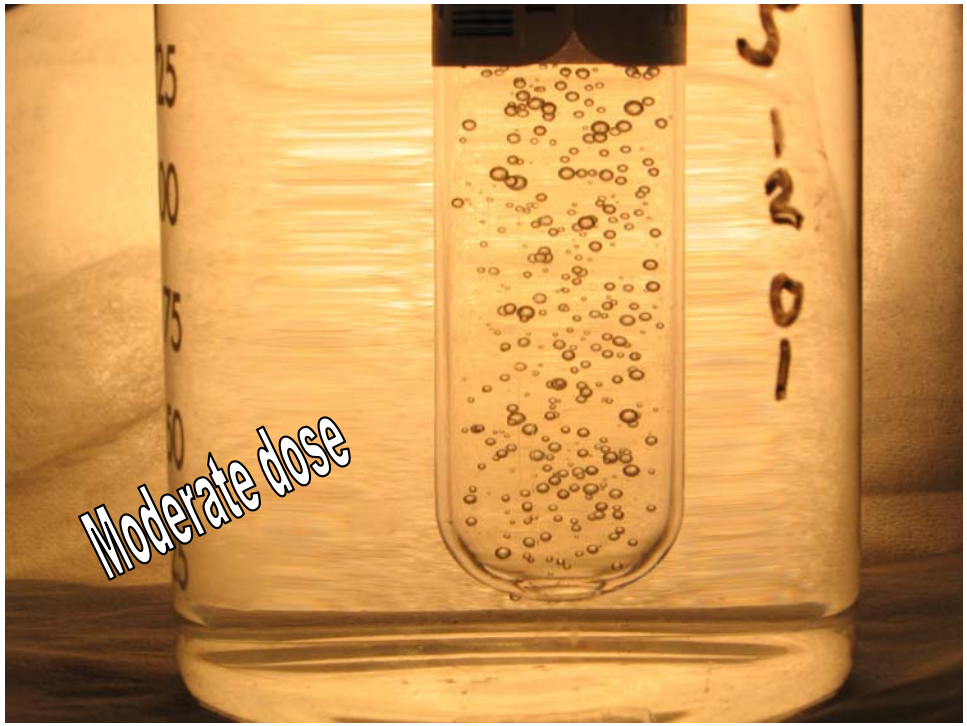
Additional measurements to establish neutron spectrum in preparation

PBAR MEDICAL

Bubble Technology Industries (BTI) Neutron Dosimeters

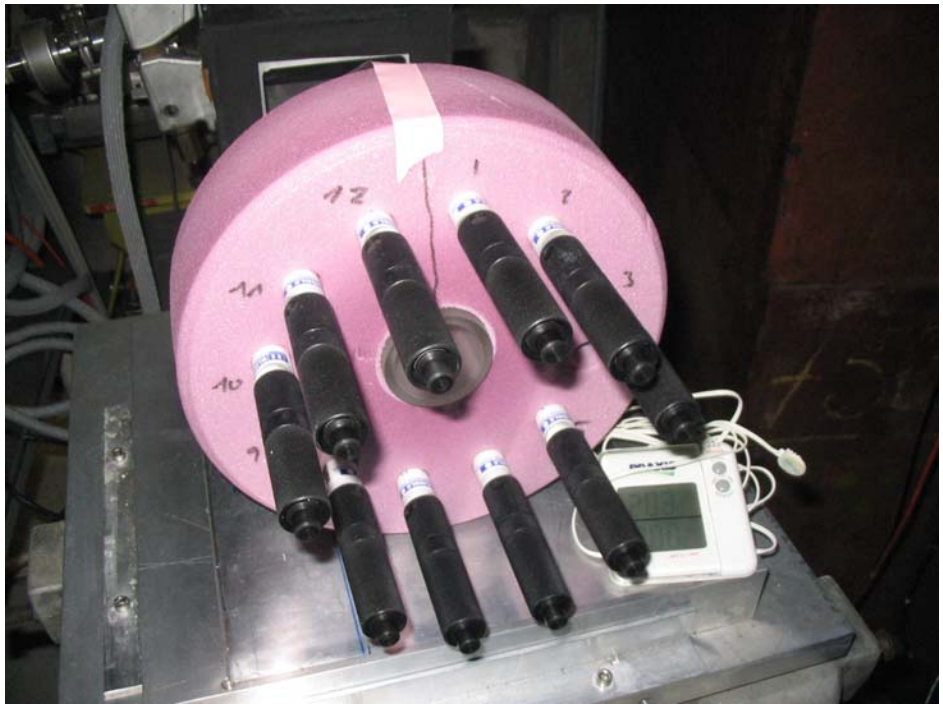
Superheated freon bubblets in gelatin undergo phase transitions when hit by neutrons



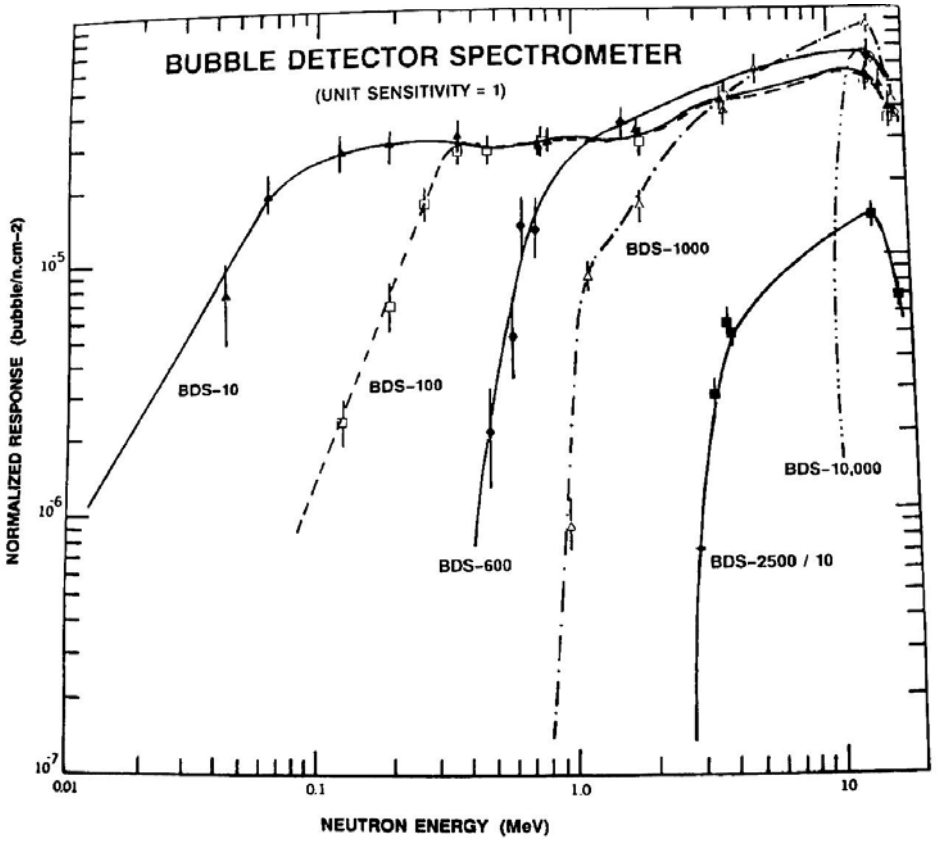


Peripheral Damage – Neutron Dosimetry

Detectors are re-usable



Detectors are energy dependent



Monte Carlo Simulations

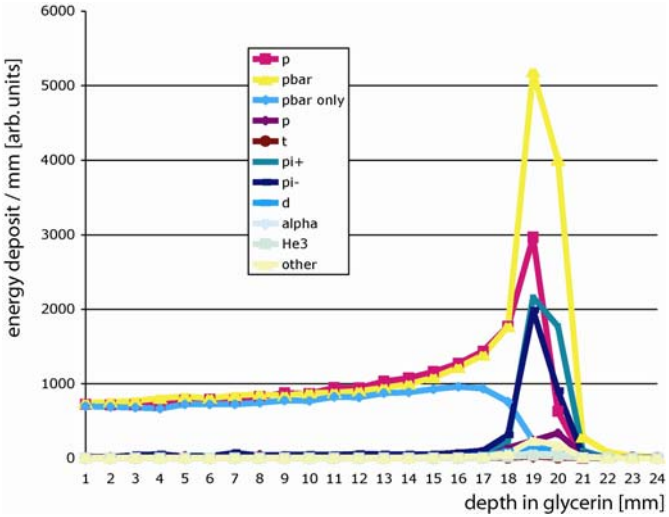
Original GEANT4 did not properly describe antiproton annihilation!

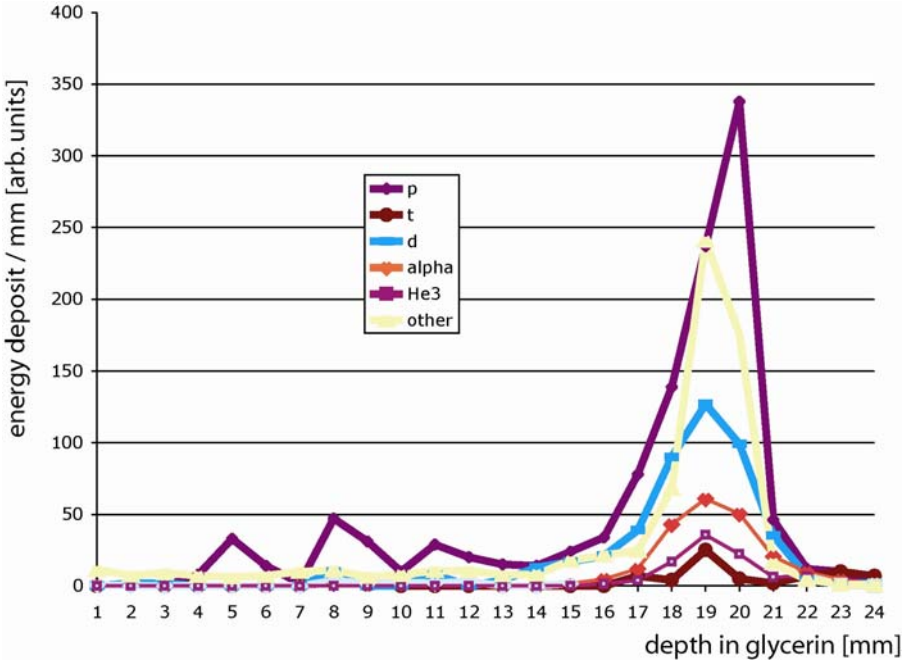
No ions produced above α's

Newest version of GEANT4 with addition of (unofficial) modules now produces ions

But still no annihilation on periphery included

Results are still questionable – need benchmarks to test code





Real Time Imaging Tests

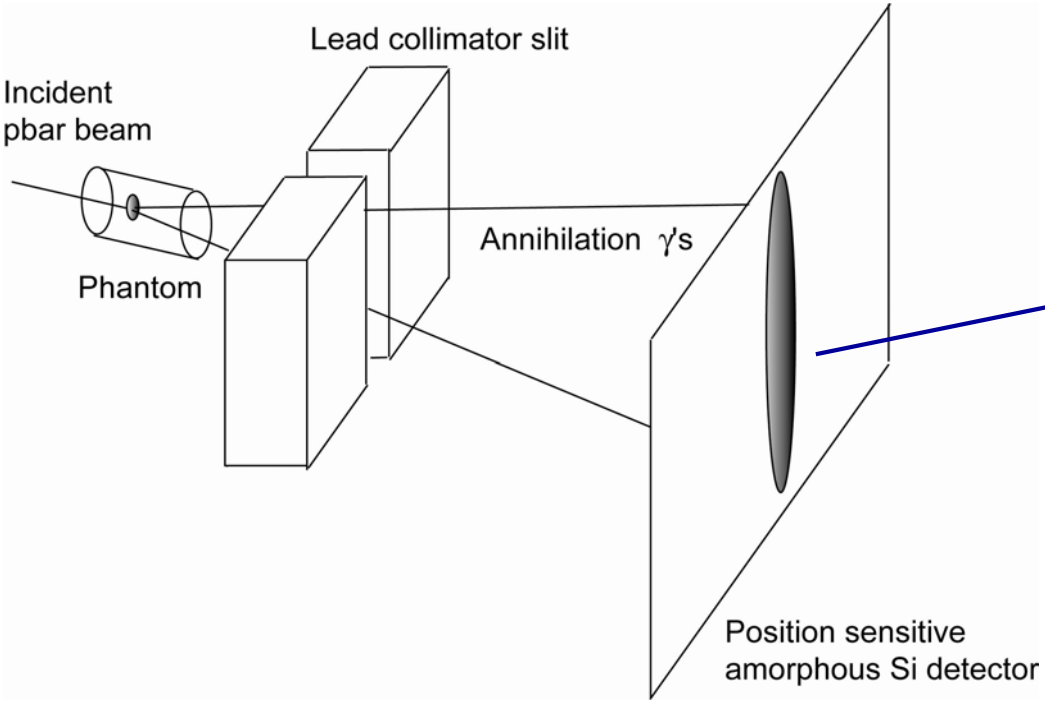
Antiprotons stop in target:

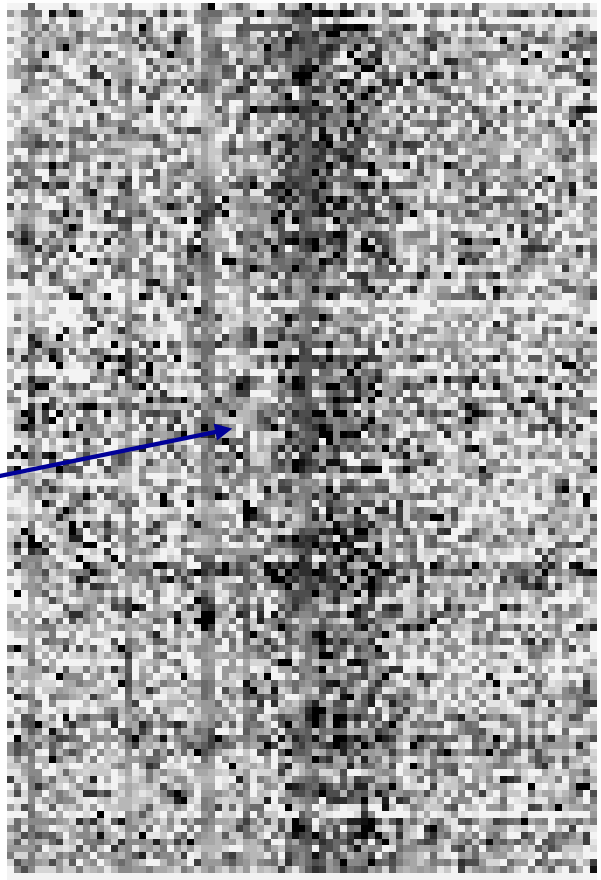
Disc of 1.5 cm diameter and 2 mm thickness

Set-up 1 cm slit using 10 cm thick led blocks

➔Image seen if slit is in line of sight with source

➔Background only if slit points away from source





Future Directions

Finish Laying the Foundations (2004/2006)

- Finalize Clonogenic Assay Studies
- Intensify Peripheral Damage Studies
- First Demonstration of Real Time Imaging of shaped targets

Source of Pbars: AD (3 – 5 x 10^7/85 seconds, ΔT = 100 – 500 ns)

Initial Demonstration only established detector capability

High resolution imaging at low intensity will need small focus and would be much easier with slow extraction (detector pile-up)

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Comparison with protons and heavy ions (2005)

Moving Forward: R&D towards final certification (2006 +)

- ❖ Development of beam delivery and energy modulation
  ~ 1 mm focus, scanning possibility (Complete DEM line)
- ❖ Real time imaging of shaped target
  Implement semi-slow extraction (106 – 107/second)?

(Semi-)Slow Extraction?

Hardware needed:

Excitation sextupoles:

2 XRC available in dispersion free regions (sections 16 and 41)

Electrostatic septum:

not available in AD

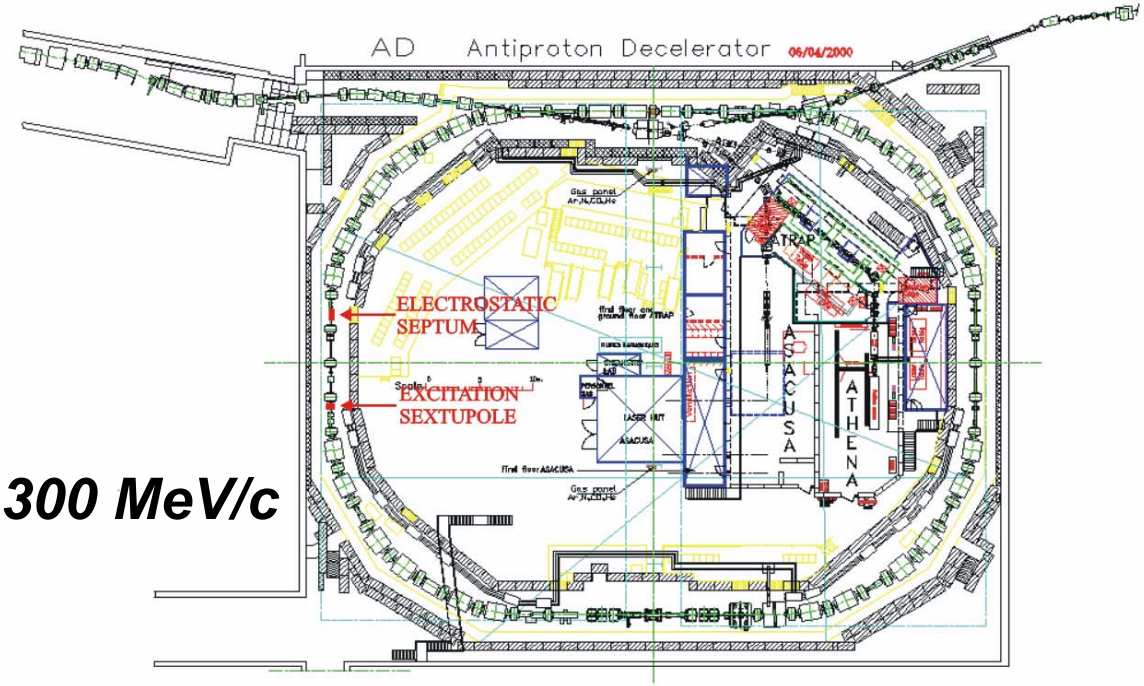
Magnetic septum:

SM5306 is available

More detailed design study

Beam lifetime measurements at 300 MeV/c

Commissioning of this option



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Comparison with protons and heavy ions (2005)

Moving Forward: R&D towards certification of method (2006 +)

- ❖ Development of beam delivery and energy modulation
  ~ 1 mm focus, scanning possibility (Complete DEM line)
- ❖ Real time imaging of shaped target
  Implement semi-slow extraction (10^6 – 10^7/second)?
- ❖ Initial in vivo testing?
  4 x 10^8 pbars deliver 1 Gy to 1 cc tumor (10 shots or 15 minutes)
  Possibilities to increase intensity per shot exist
  Need studies on life-time and radiation protection issues

Mode of Operation

Biological Measurements require long beam times

Irradiation of 4-5 cell samples at biological relevant dose levels requires 24 hours of beam time.

Time window between sample preparation and analysis is maximum 72 hours.

Logistics is difficult as several teams need to be working in concert

….and have low repetition rate

Cell preparation + analysis typically takes 4+ weeks

Continue with few long run periods (4 x 24 hours)

Mode of Operation

'Physics' studies (dosimetry, imaging, beam delivery)

are possible with shorter shifts (8 hours)

can be done by separate small sub-teams

and can be performed back-to-back

This would be best if 8 hour shifts could be taken one week (5 shifts) at a time

Mode of Operation

Date	Time Scheduled	Topics	Comments
May 21	*8 hours*	*Beam Development*	*Cancelled due to PS delay*
June 11	*8 hours*	*Focussing tests/Dosimetry*	*Cancelled due to AD/PS Problems*
June 28	**16 hours**	**Dosimetry using TLD's**	**Significant time lost to AD problem**
July 2	**8 hours**	**Alanin tests**	**Found misalignment of beam line**
July 19	*24 hours*	*Peripheral damage studies*	*Cancelled to PS problem (septum)*
August 6	**8 hours**	**^{6}Li, ^{7}Li dosimetry**	**First smooth run of the year**
August 23	**24 hours**	**Alternative assay studies**	**Initial studies of COMET**
August 27	**8 hours**	**Dosimetry**	**Peripheral neutron dose**
September 10	**8 hours**	**Dosimetry**	**2nd run on neutron dose**
September 20	*24 hours*	*Biological studies*	*Cancelled due to collaboration timing*
September 24	**8 hours**	**Neutron Bubble Spectrometer**	**Fast neutron spectrum**
October 15	**8 hours**	**Imaging tests**	**First high energy gamma detection**
October 25	**24 hours**	**Peripheral damage studies**	**COMET and clonogenic assays**