Accelerators for Cancer Therapy

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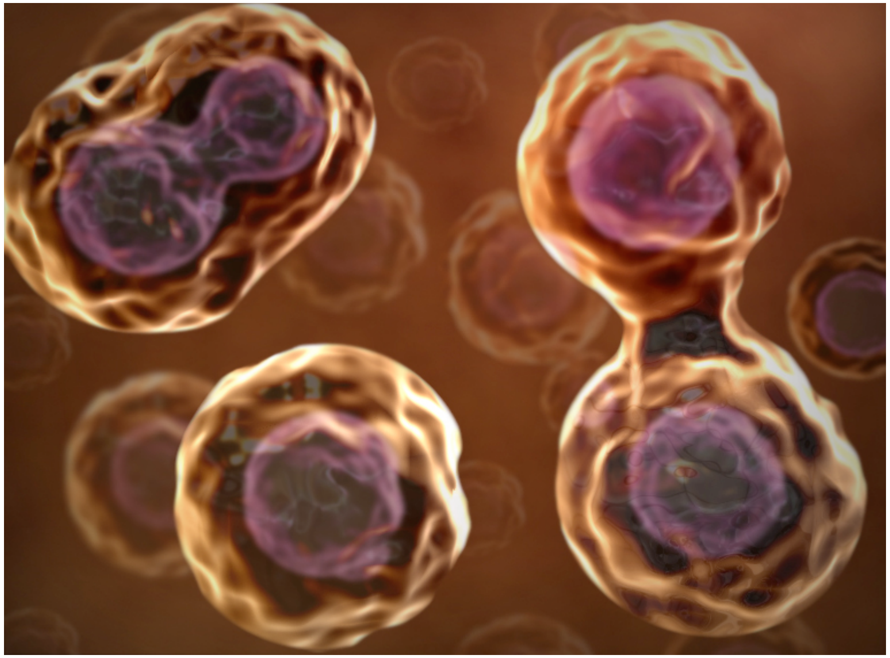
The Body's Cells: Born To Die

All cells in the body have a pre-programmed lifespan:

- White blood cells: <1 day
- Stomach lining: 2 days
- Sperm cells: 3 days
- Platelets: 10 days
- Skin cells: 4 weeks
- Red blood cells: 4 months
- Pancreas cells: 1 year
- Bone cells: 25-30 years
- Neurons: lifetime
- Egg cells: lifetime

Cells reproduce through *mitosis* (cell division).

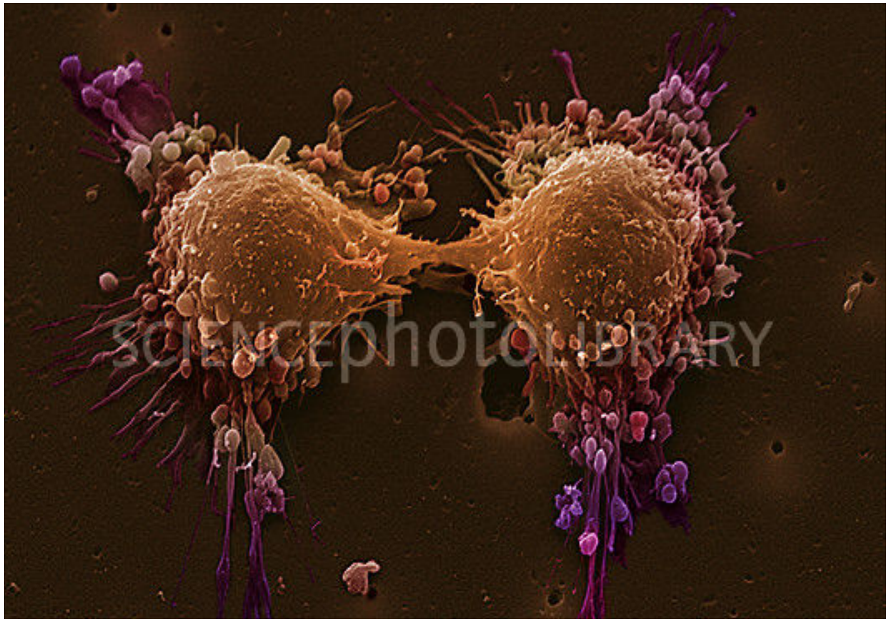
Cells have a built-in self-destruct mechanism: if the cell becomes abnormal it is programmed to die. This is called *apoptosis*.



Cell Division & Control

UCL

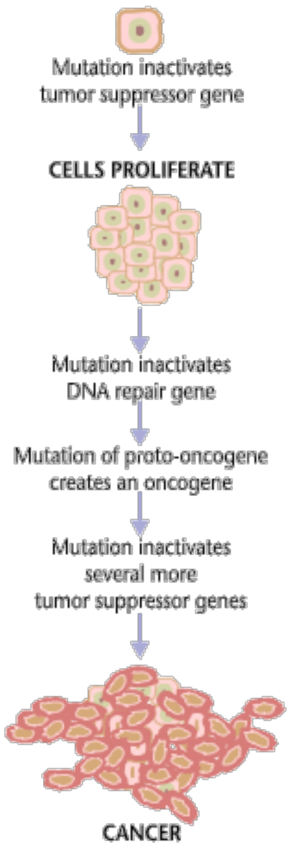
- 2 types of genes regulate cell growth and replication:
  - Oncogenes promote cell growth and reproduction.
  - Tumour suppressor genes inhibit cell division and survival.



- Genetic errors arise from random mutations during mitosis or external carcinogenic agents.
- In a normally functioning cell, apoptosis safeguards the cell against cancer. If significant error occurs, the damaged cell can "self-destruct" through programmed cell death.

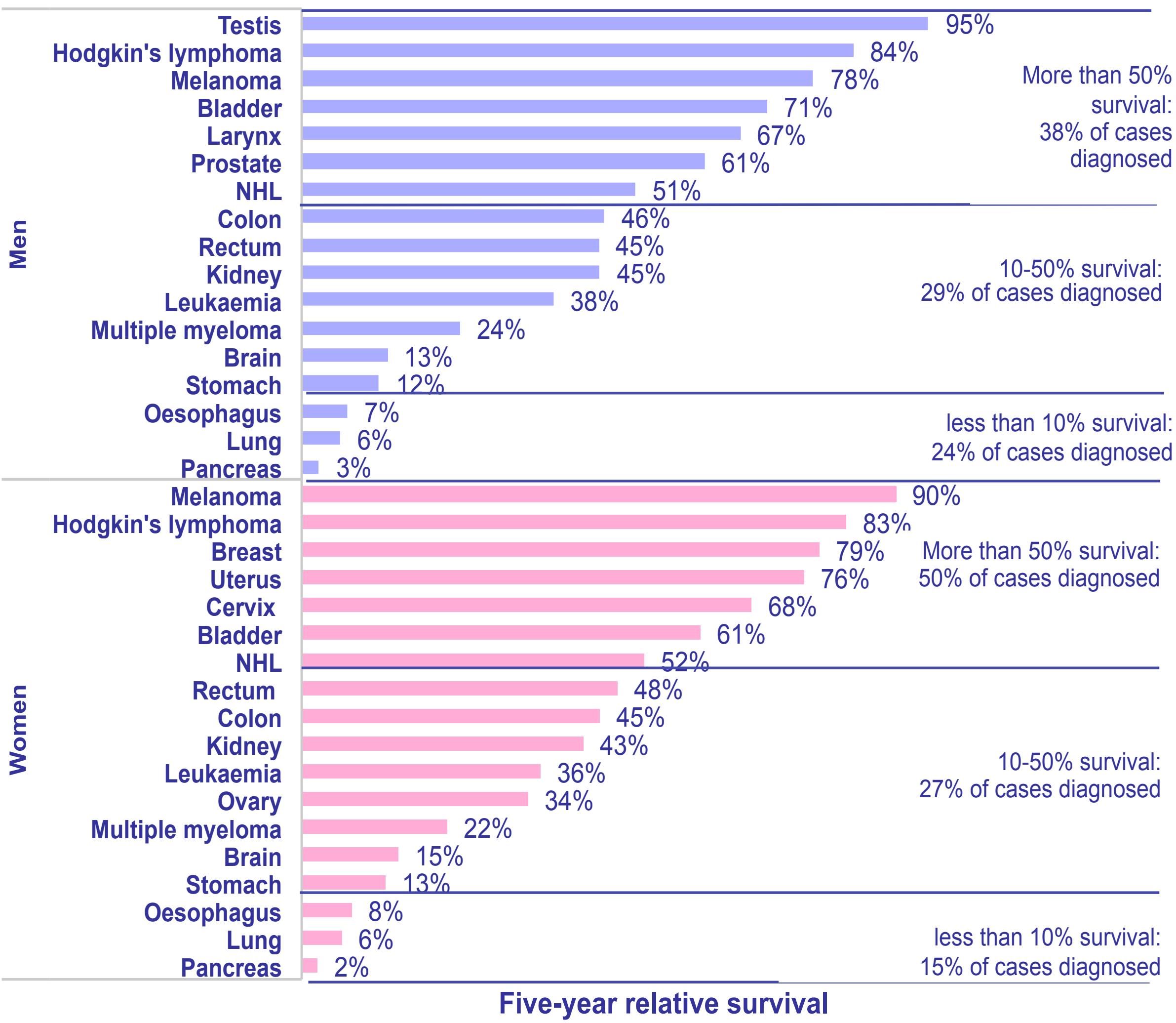
Cancer: Life Uncontrolled

- For cancer to occur, several errors must occur in sequence:
  - A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
  - A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.
  - A further mutation may cause loss of a tumour suppressor gene, disrupting the apoptosis signalling pathway and resulting in the cell becoming immortal.
  - A further mutation in signalling machinery of the cell might send error-causing signals to nearby cells.
- At this stage the cell begins to divide uncontrollably: this is cancer.



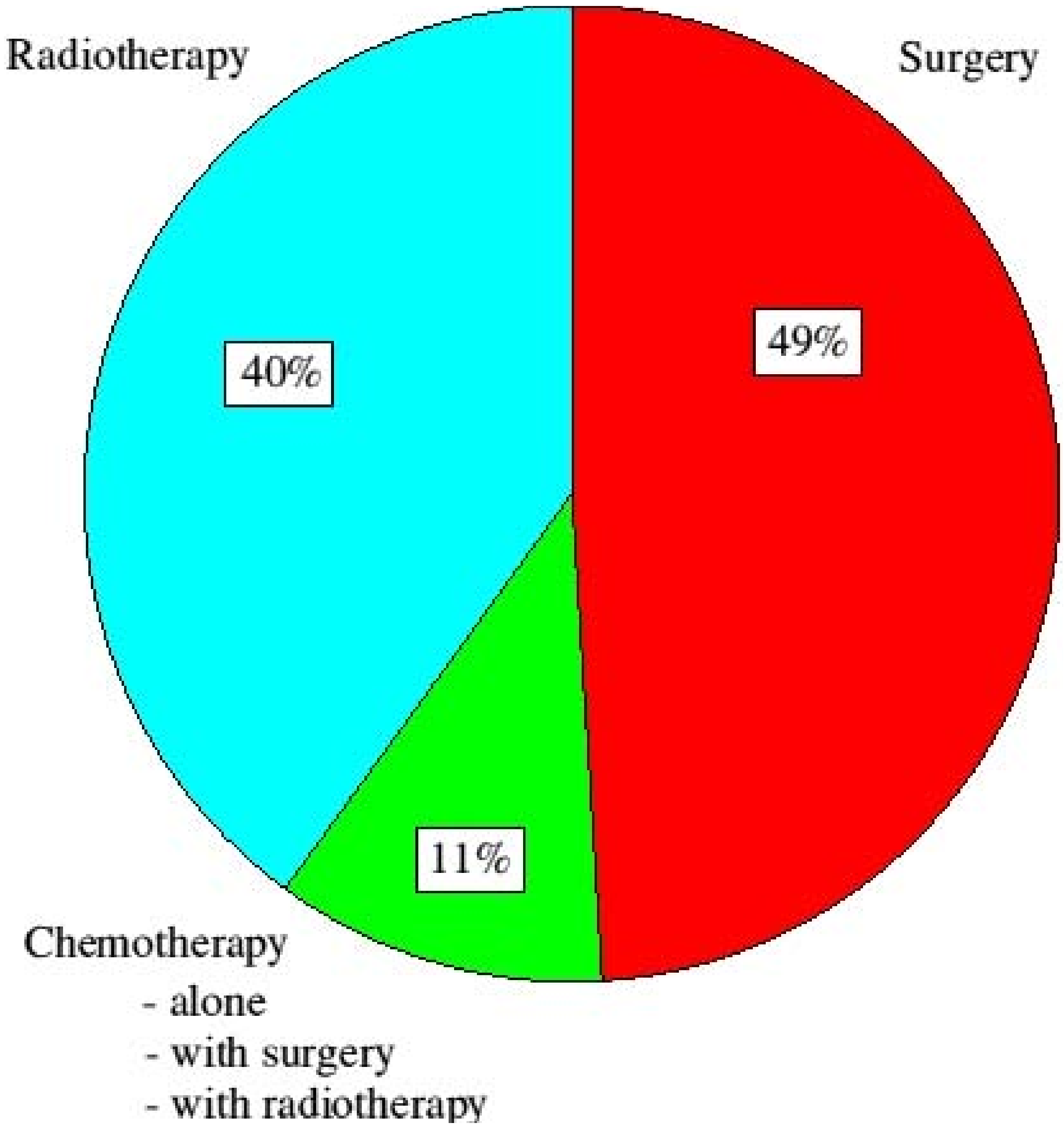
Cancer Types & Survival Rates

UCL



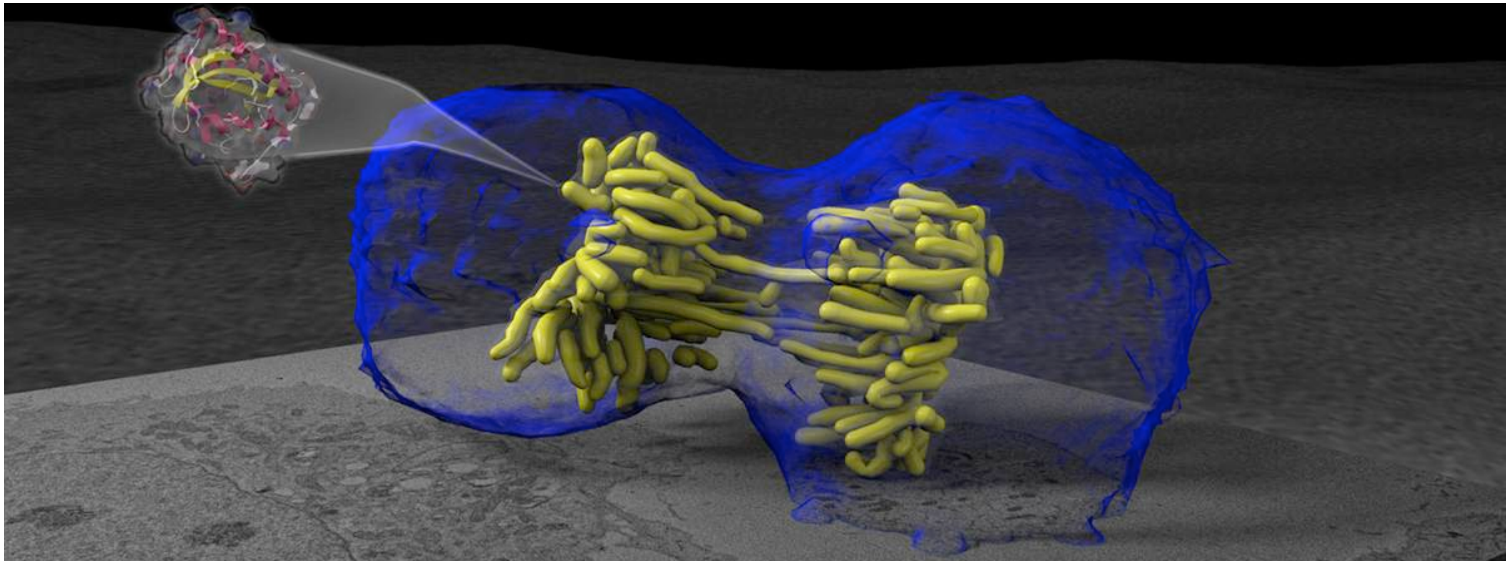
Women	Pancreas	2%
	Lung	6%
	Oesophagus	8%
	Stomach	13%
	Brain	15%
	Multiple myeloma	22%
	Ovary	34%
	Leukaemia	36%
	Kidney	43%
	Colon	45%
	Rectum	48%
	NHL	52%
	Bladder	61%
	Cervix	68%
	Uterus	76%
	Breast	79%
	Hodgkin's lymphoma	83%
	Melanoma	90%
Men	Pancreas	3%
	Lung	6%
	Oesophagus	7%
	Stomach	12%
	Brain	13%
	Multiple myeloma	24%
	Leukaemia	38%
	Kidney	45%
	Rectum	45%
	Colon	46%
	NHL	51%
	Prostate	61%
	Larynx	67%
	Bladder	71%
	Melanoma	78%
	Hodgkin's lymphoma	84%
	Testis	95%

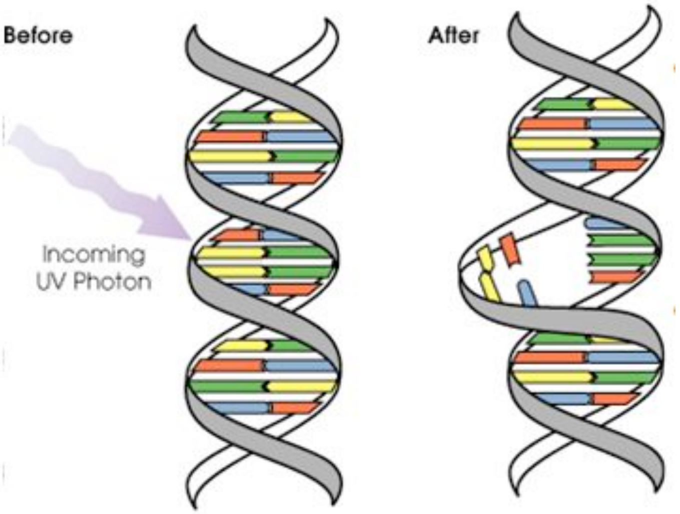
Cancer Treatment: Cures

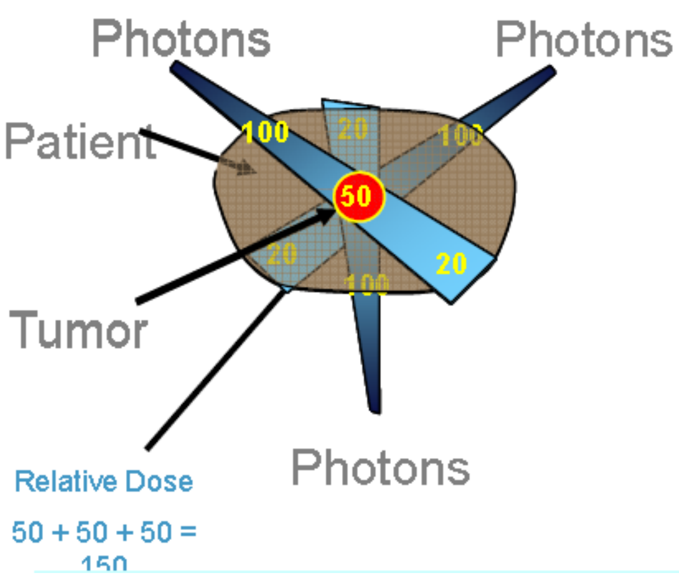


- Cancer treated with 3 different modalities:
  - Surgery
  - Chemotherapy
  - Radiotherapy
- Each has advantages and disadvantages…
- If you want to cure cancer, be a surgeon!
- If you can't remove it with surgery, radiotherapy is the next best option…

How Radiotherapy Kills Cancer



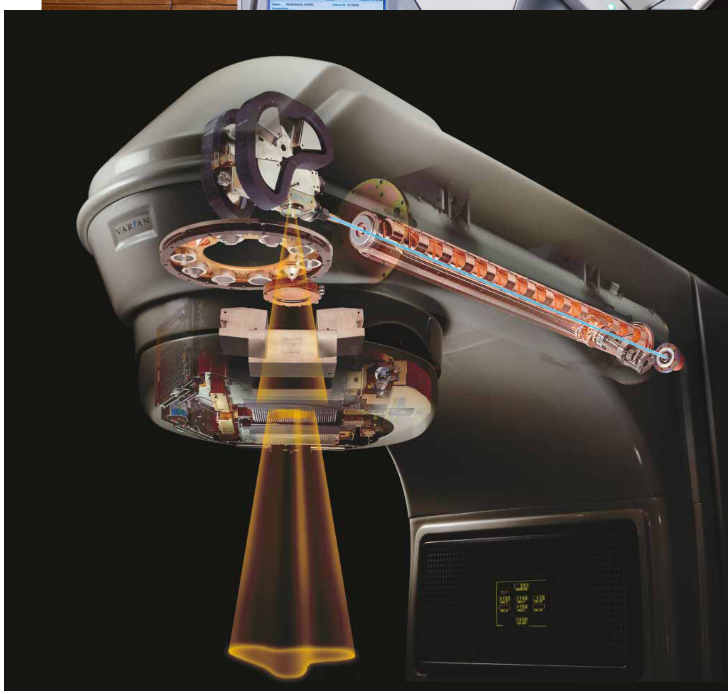


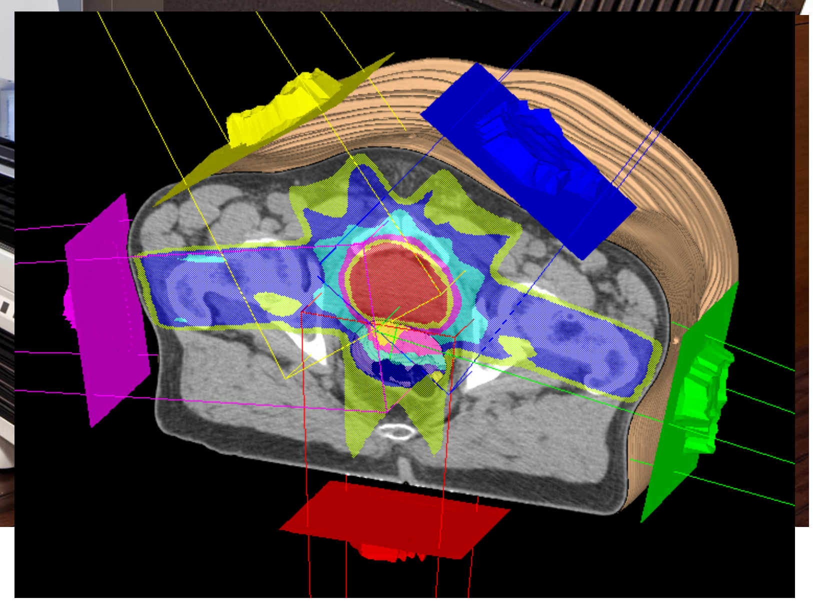


Radiotherapy Treatment Room

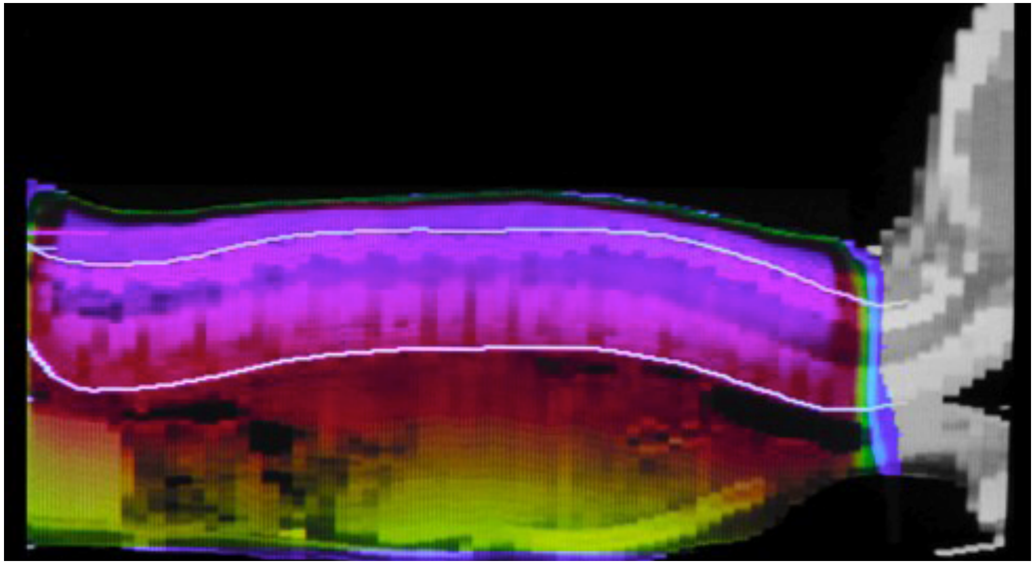
http://thefarbercenter.com/blog/wp-content/uploads/2011/10/linac-room.jpg

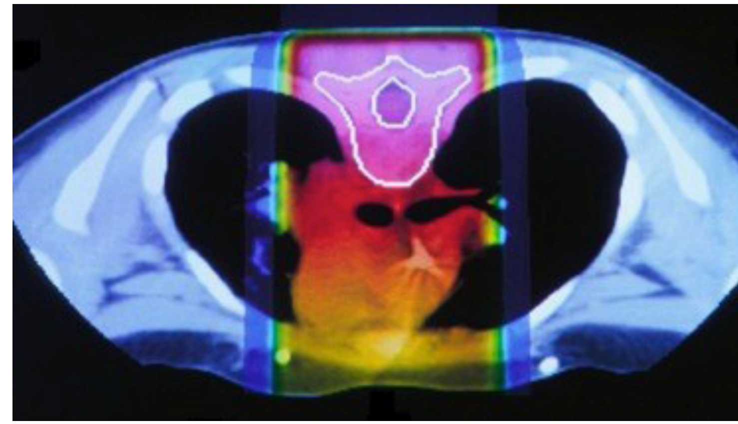
IMRT: Intensity Modulated Radiotherapy

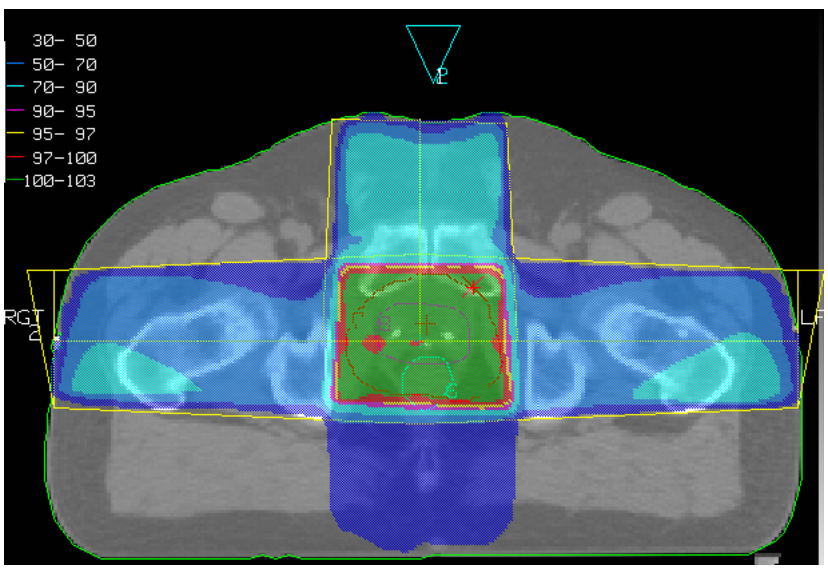


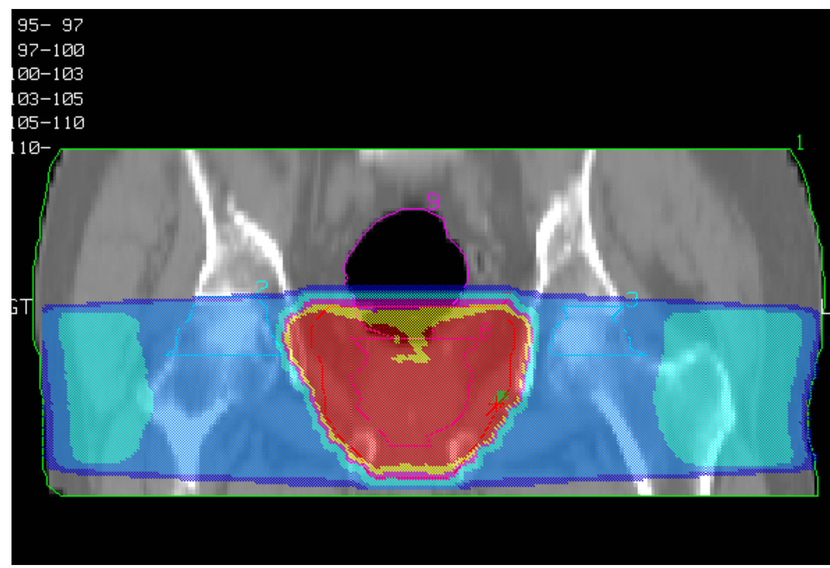


Radiotherapy: Energy Deposition



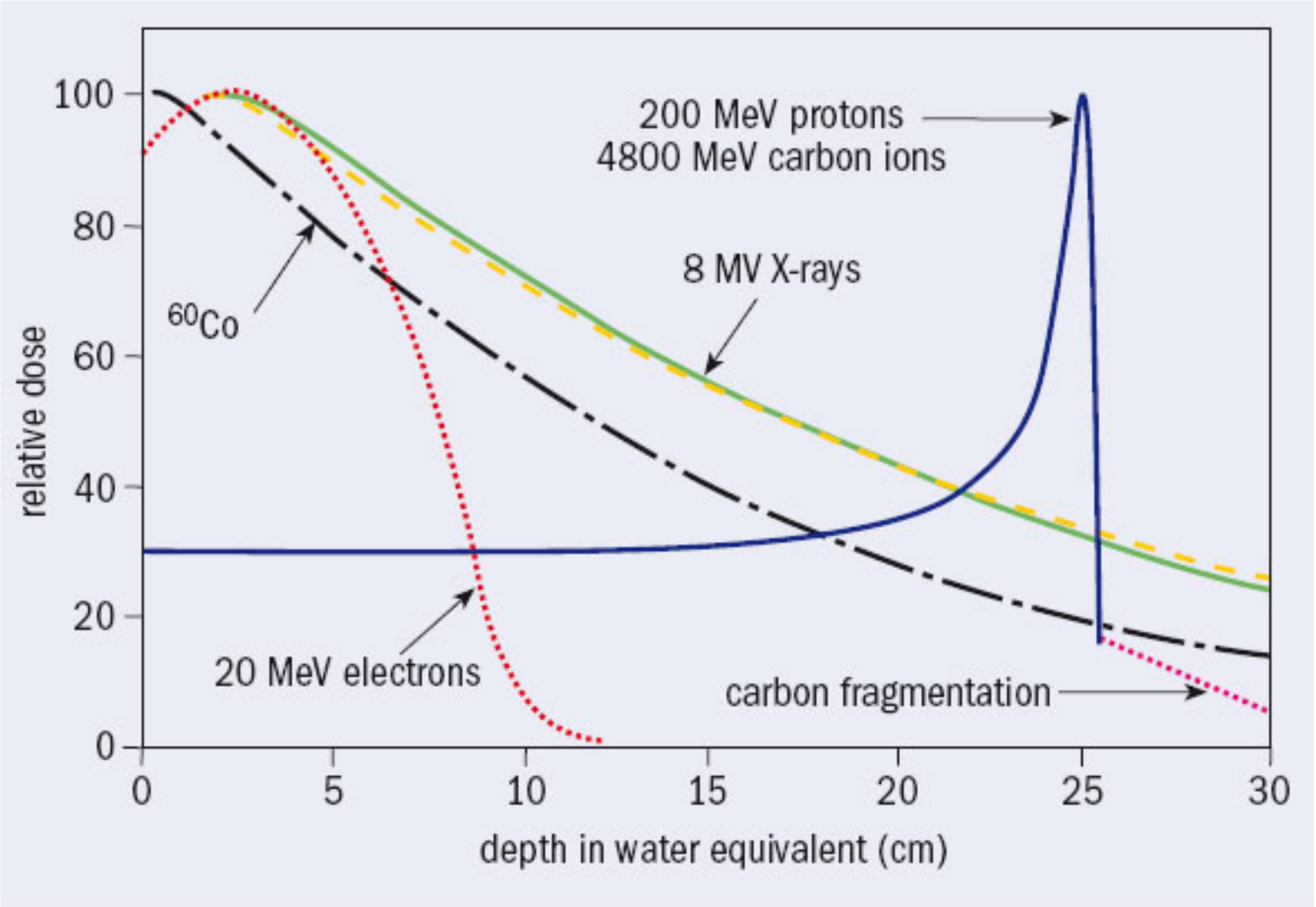






The Bragg Peak

$$-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \frac{n z^2}{\beta^2} \left(\frac{e^2}{4\pi\epsilon_0} \right)^2 \left[\ln \left(\frac{2 m_e c^2 \beta^2}{I\,(1-\beta^2)} \right) - \beta^2 \right]$$



Bethe-Bloch:

E = energy

x = distance

m_e = electron mass

n = electron density

z = particle charge

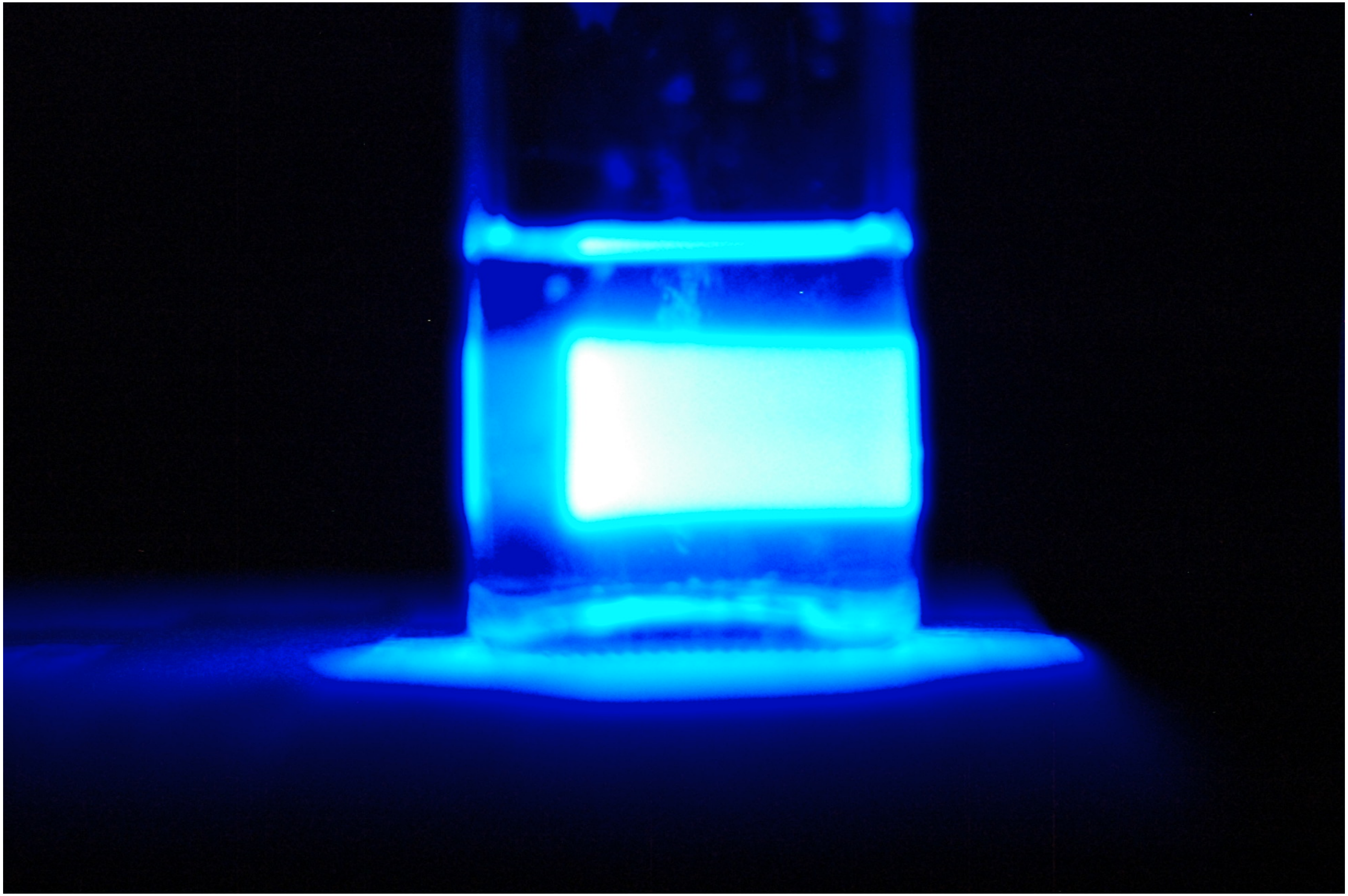
β = particle velocity

e = electron charge

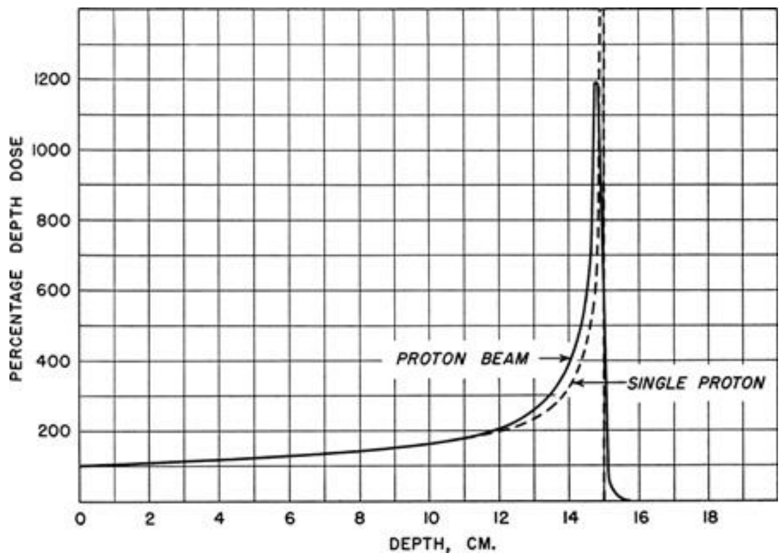
ϵ_0 = vacuum permittivity

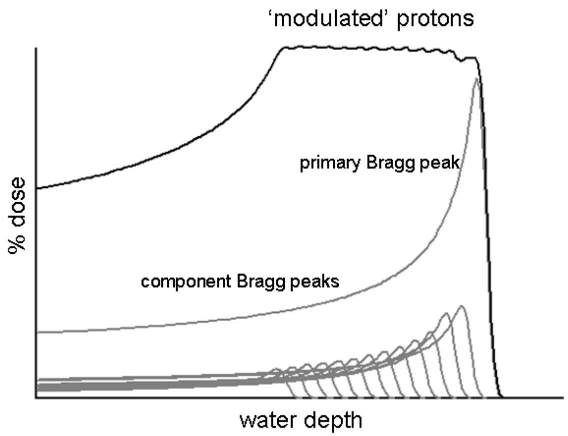
I = mean excitation potential

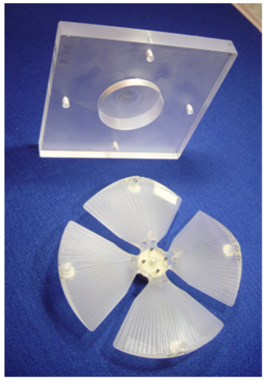
A Real Bragg Peak in Liquid Scintillator



Spread-Out Bragg Peak (SOBP)





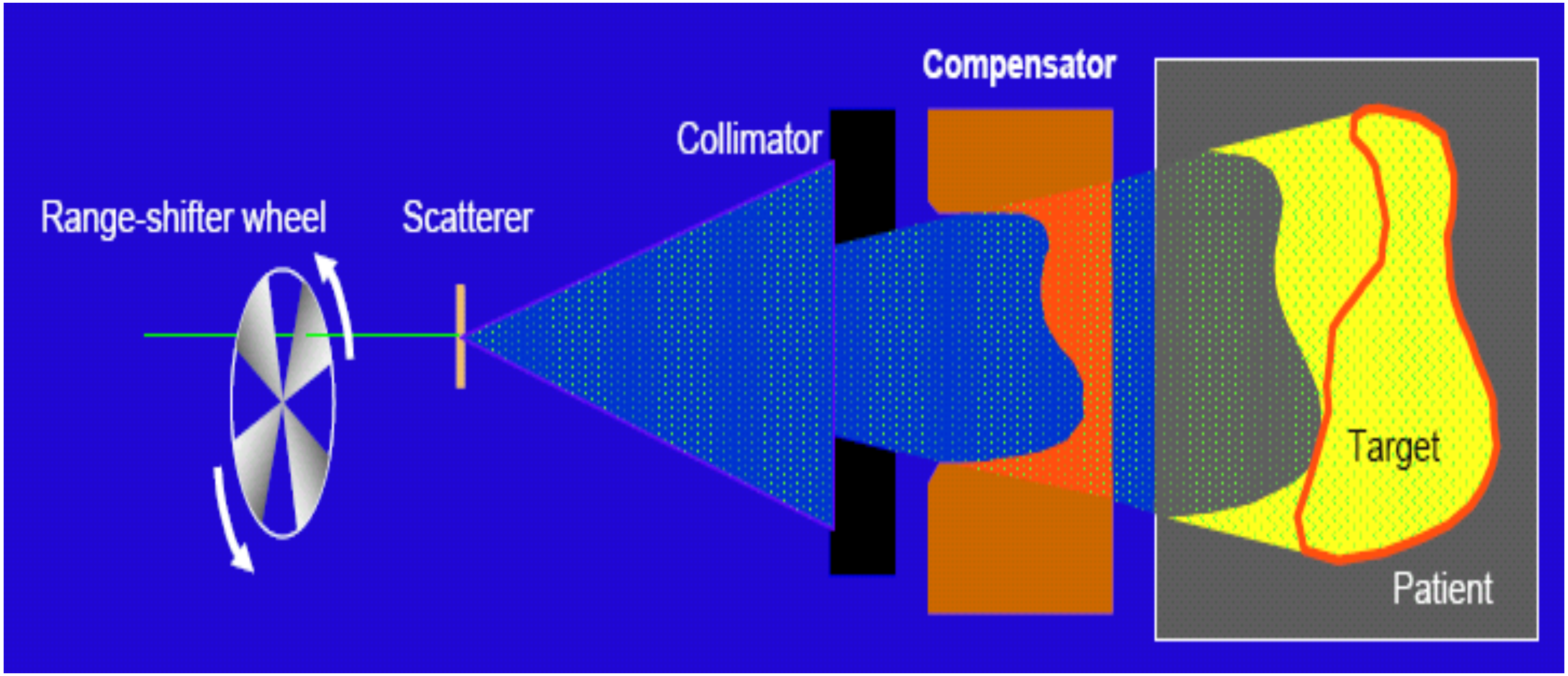


The original picture from R. R. Wilson's paper on proton therapy.
(*Radiology* **47**, 487–491, 1946)

Intrinsic - straggling

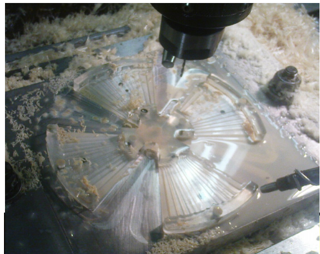
Deliberate – range modulating

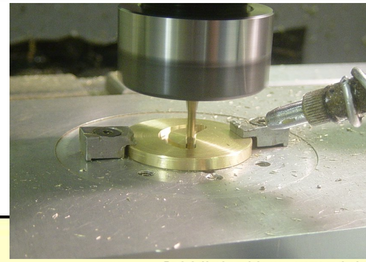
Double Scattering

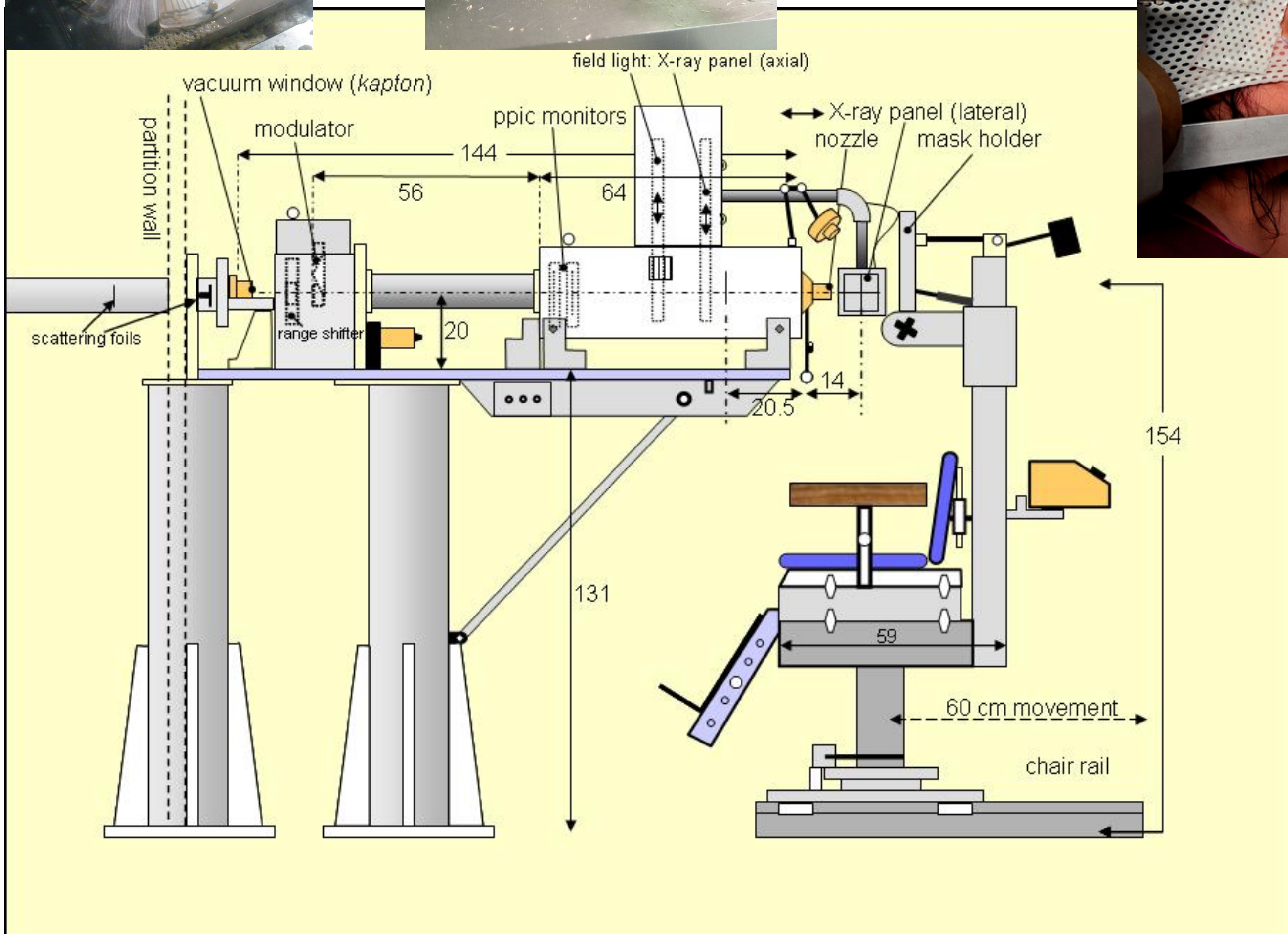


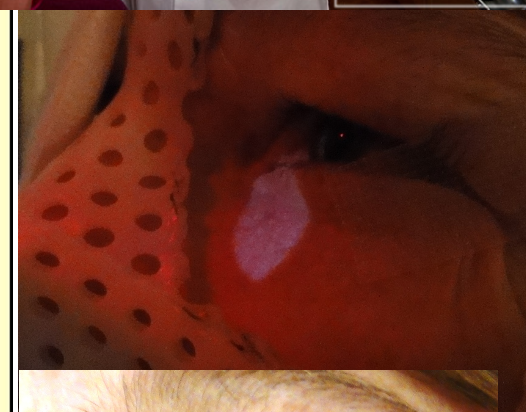
- Beam passes through range-shifter wheel that modulates the proton beam energy to reach front/back of target volume.
- Scatterer enlarges beam to cover whole volume.
- Collimator shapes outer edge of beam to target area.
- Compensator adds further absorption to reduce energy of protons in certain areas and match delivered beam to **distal** edge of tumour (**not** conformal).

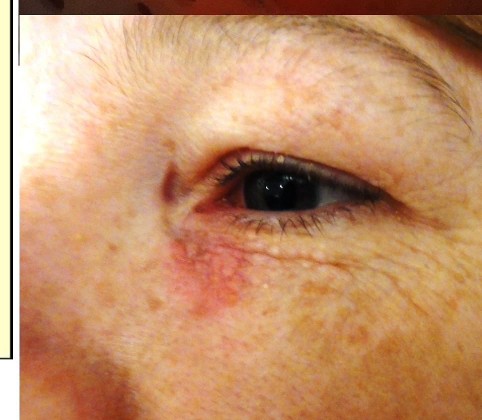
Clatterbridge Cancer Centre



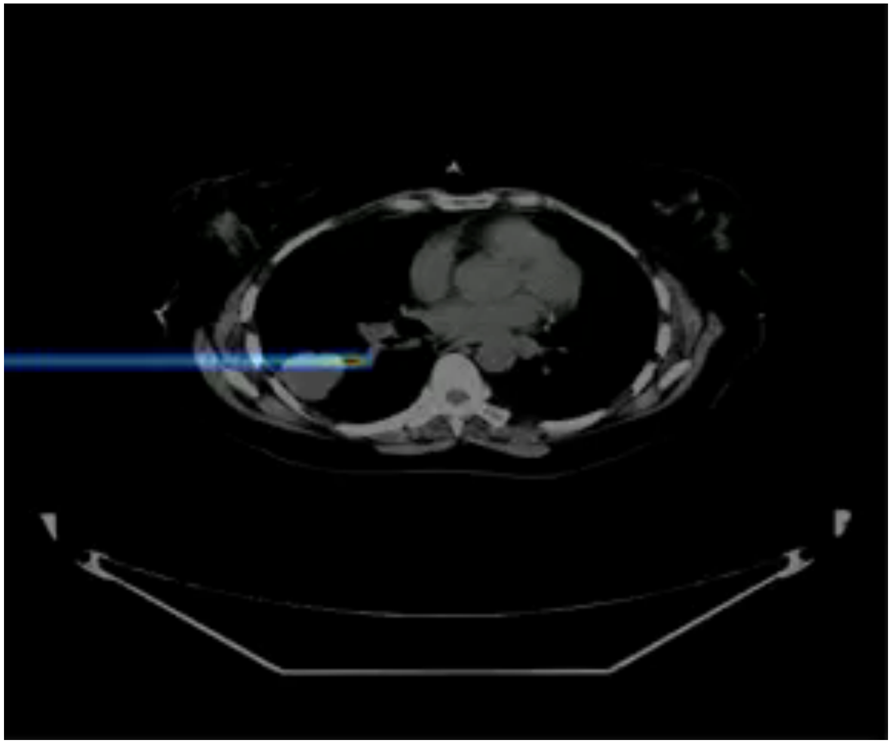


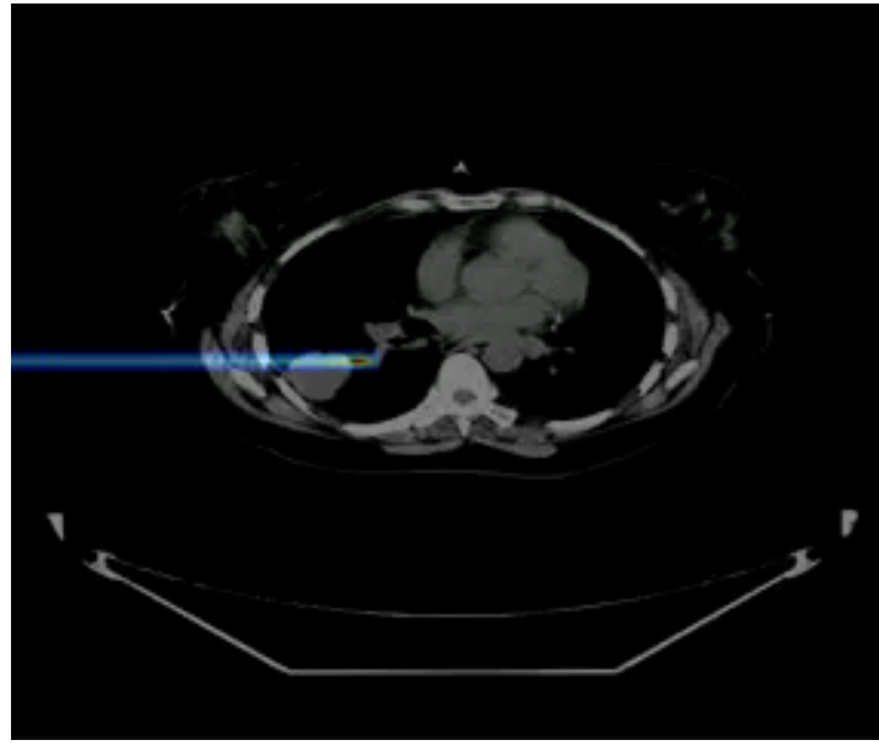






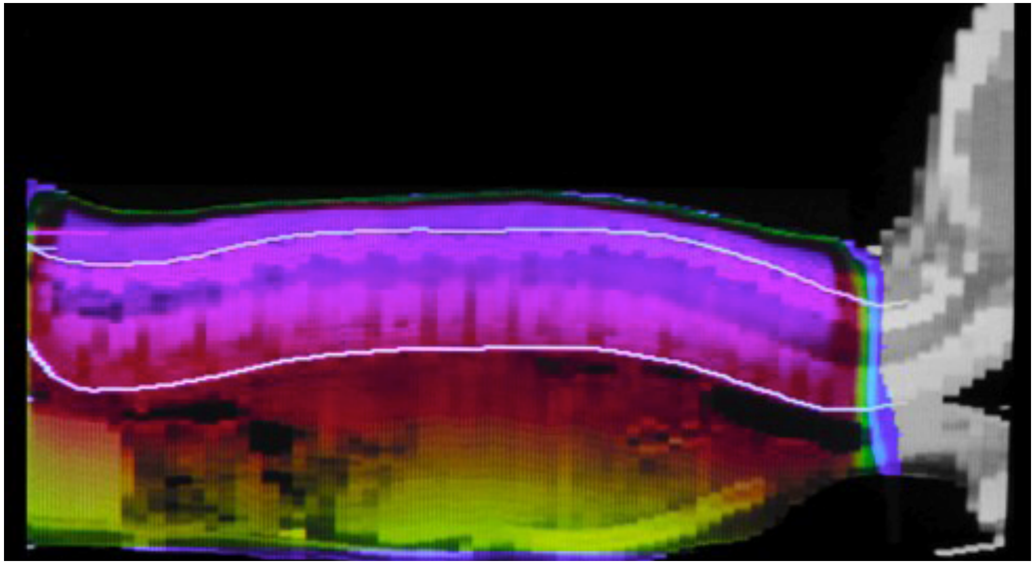
Pencil Beam Scanning

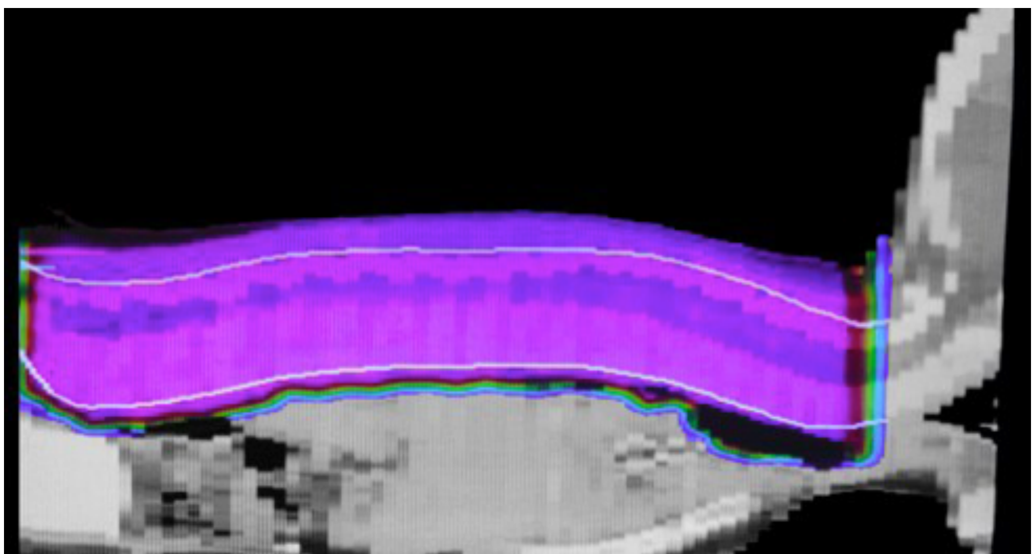


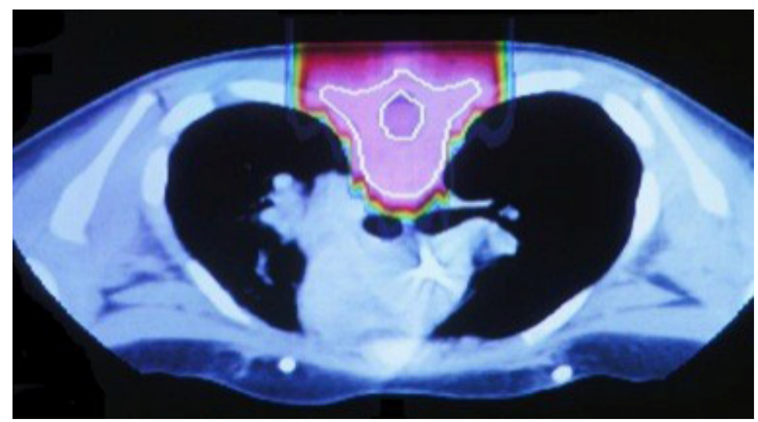


- Pencil beam scanning allows better conformal dose to be delivered to target volume.
- Beam delivered in small "pencil" beams and scanned across target.
- Energy modulated by accelerator: target subdivided into layers and "painted" by using energy variation.

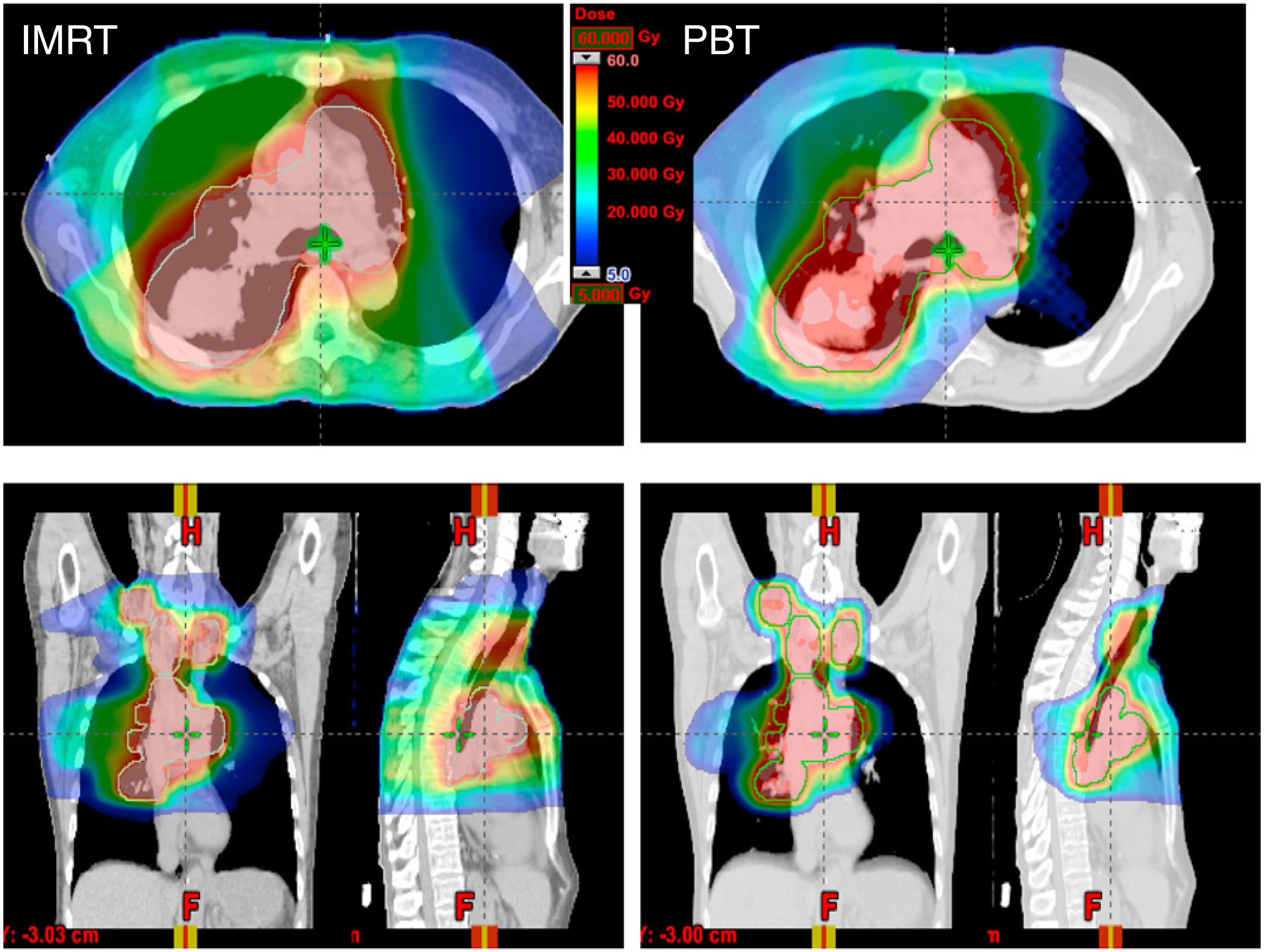
Protons Vs. Photons: Medulloblastoma





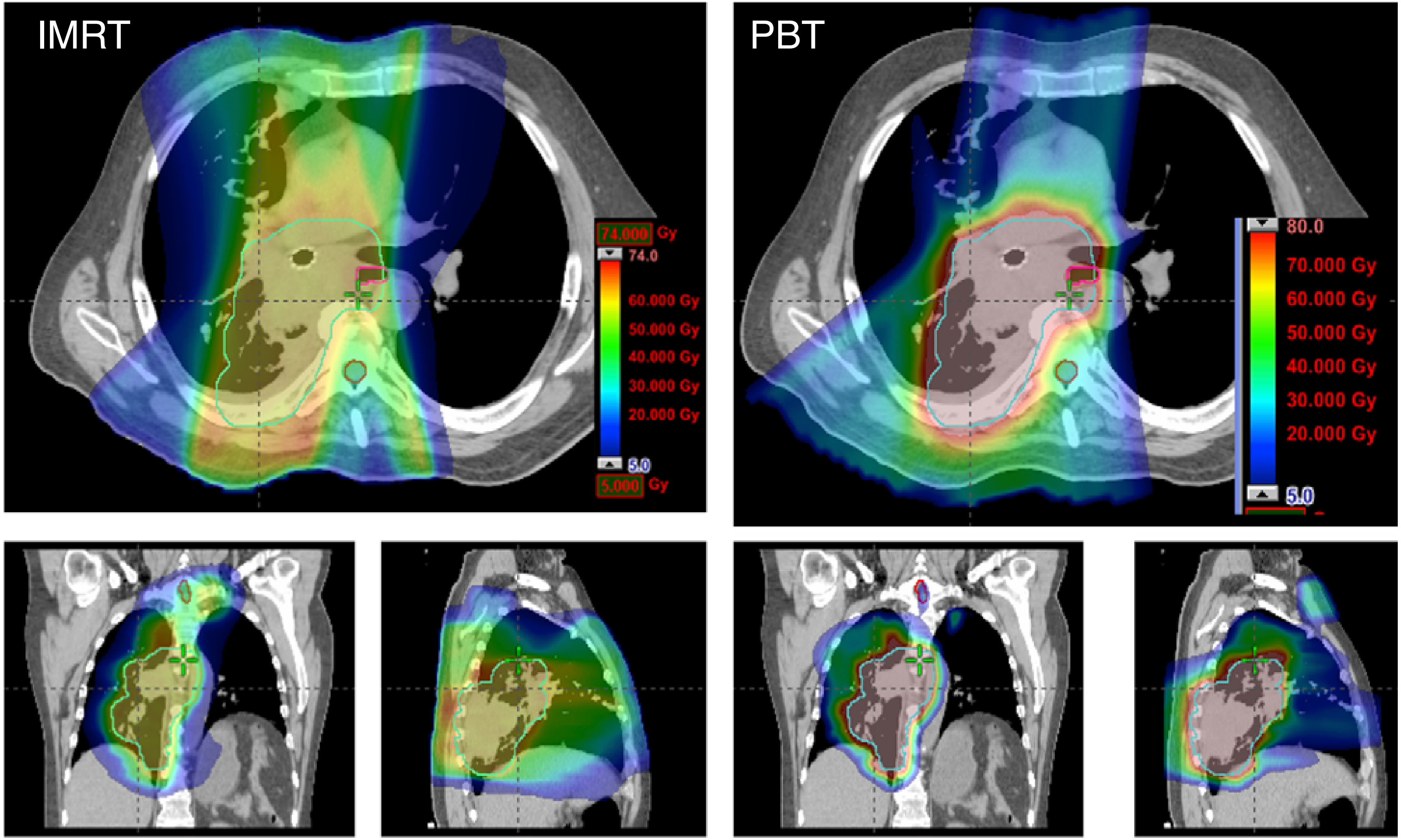


Protons Vs. Photons: NSC Lung Cancer



Zhang X, Li Y, Pan X, et al. *Int J Radiat Oncol Biol Phys.* 2009;77(2):357-366

Protons Vs. Photons: NSC Lung Cancer



Zhang X, Li Y, Pan X, et al. *Int J Radiat Oncol Biol Phys.* 2009;77(2):357-366

Forces

- 2 forces available for accelerating a charged particle:
  - Electric (E)
  - Magnetic (B)

$$F = q\vec{E} + q\left(\vec{v} \times \vec{B}\right)$$

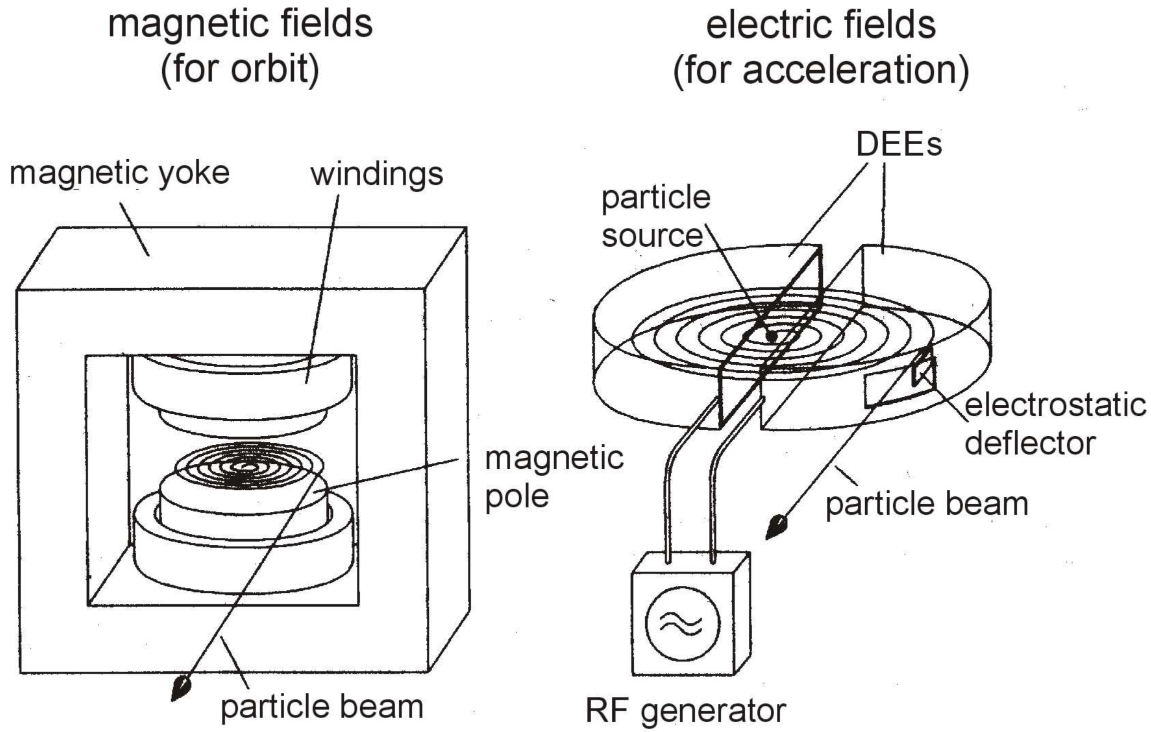
- Electric field only accelerates in one direction: no continuous bending.
- Magnetic field only accelerates perpendicular to particle velocity: no linear acceleration.
- Use Electric fields for acceleration, magnetic fields for bending/steering/focussing.
- Can relate magnetic force to centripetal acceleration:

$$F = q\left(\vec{v} \times \vec{B}\right) = \frac{m_0 \gamma v^2}{\rho} = \frac{pv}{\rho}$$

- The *Magnetic rigidity* relates bending radius ρ to momentum p, magnetic field B and charge q:

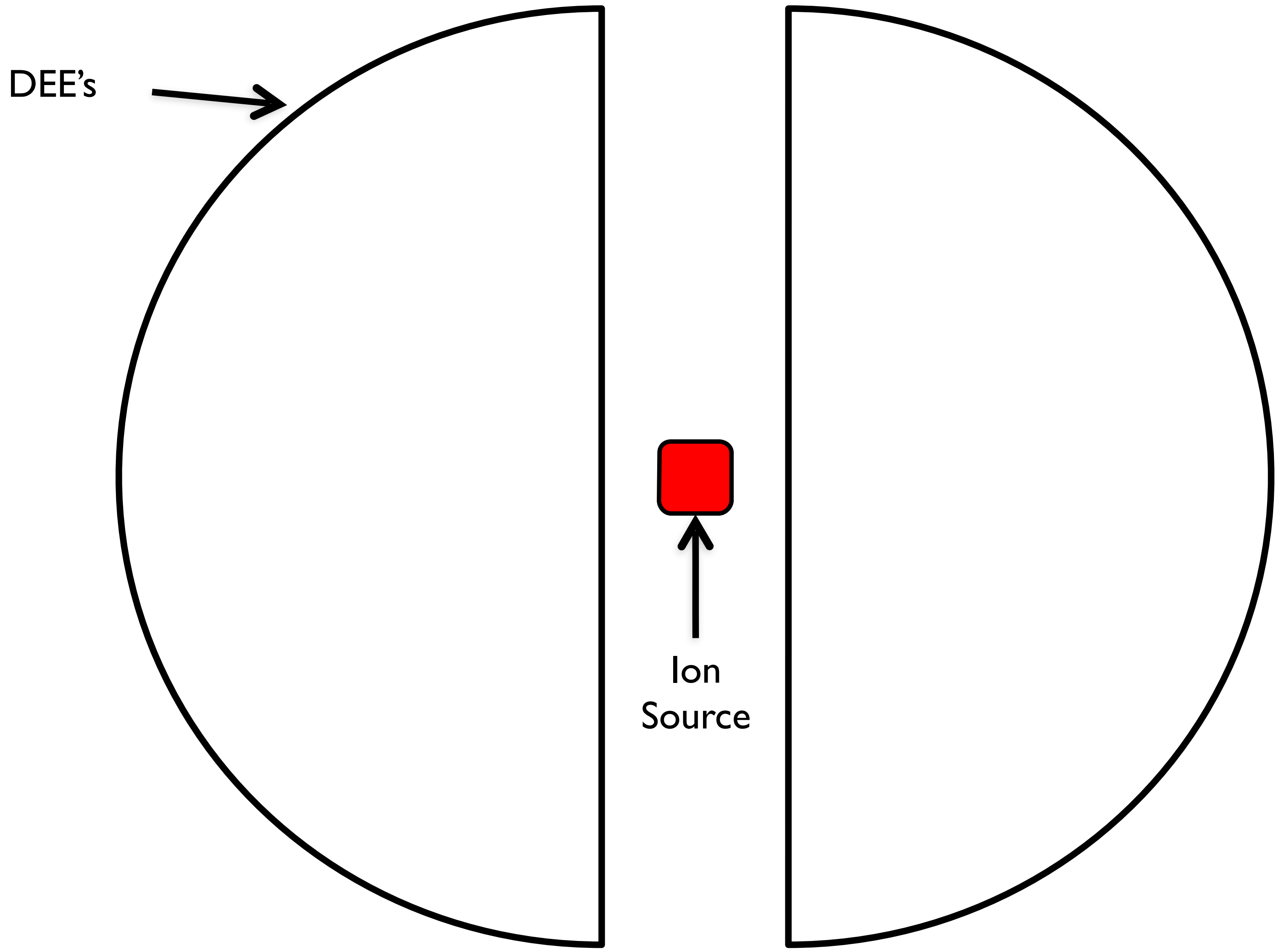
$$\boxed{B\rho = \frac{p}{q}}$$

Cyclotrons

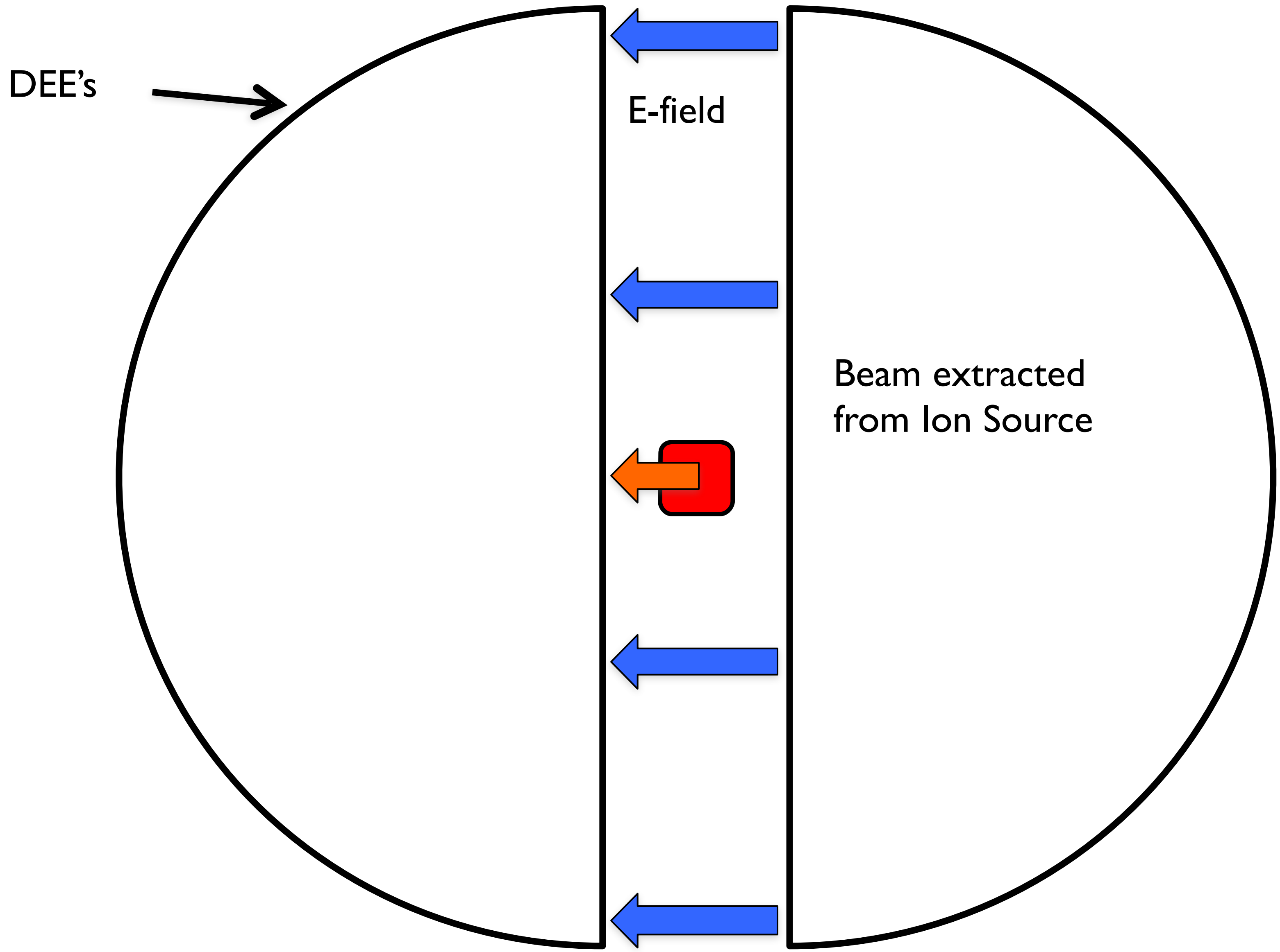


In a classic cyclotron the particles are accelerated by the electric field between the DEE's and permanently deflected by the magnetic field. For $\omega_{HF} = \omega_c$ this process is resonant as long as the mass is constant (typ. $v < 0.15\ c$).

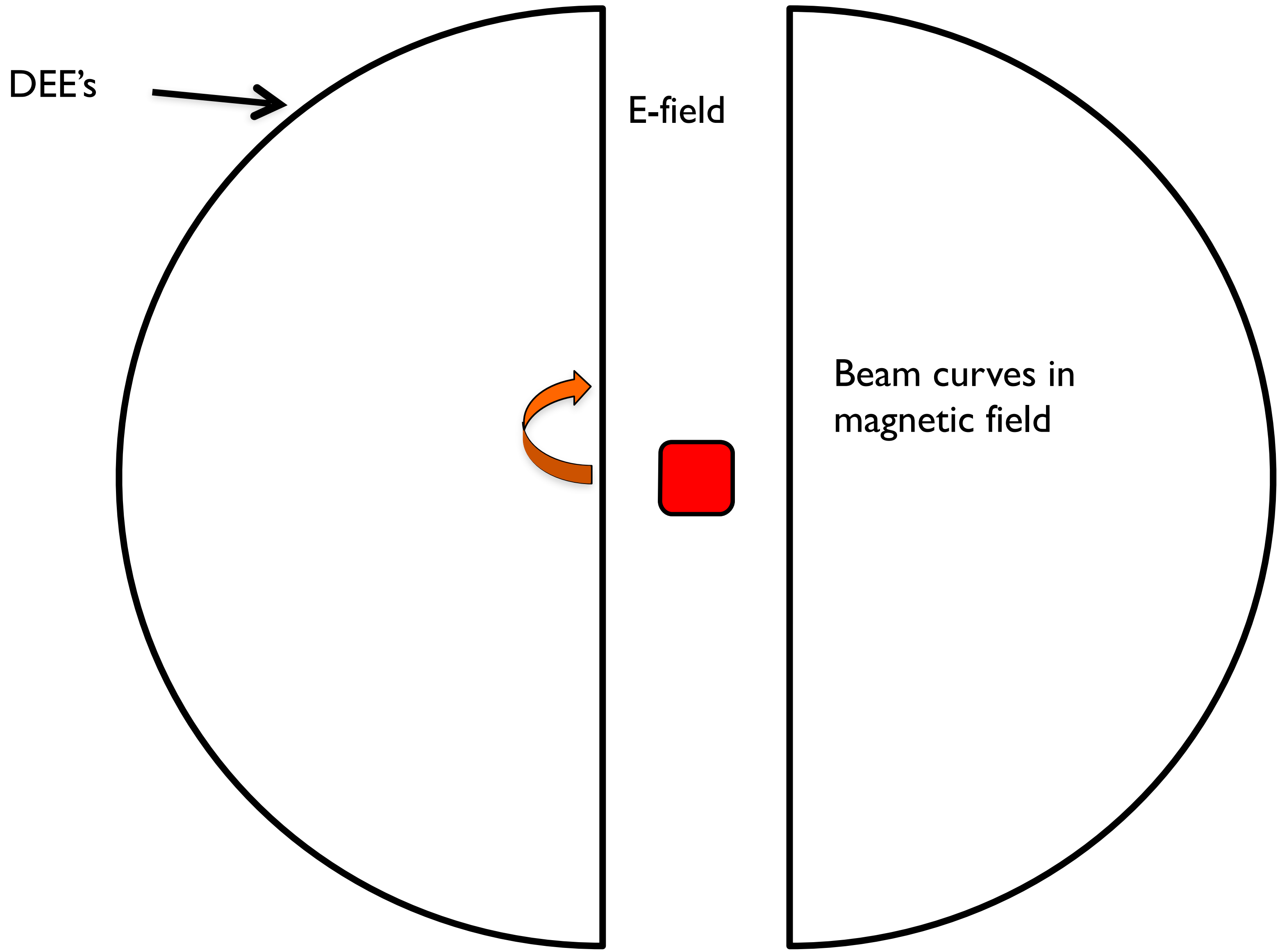
Cyclotron Acceleration (1)



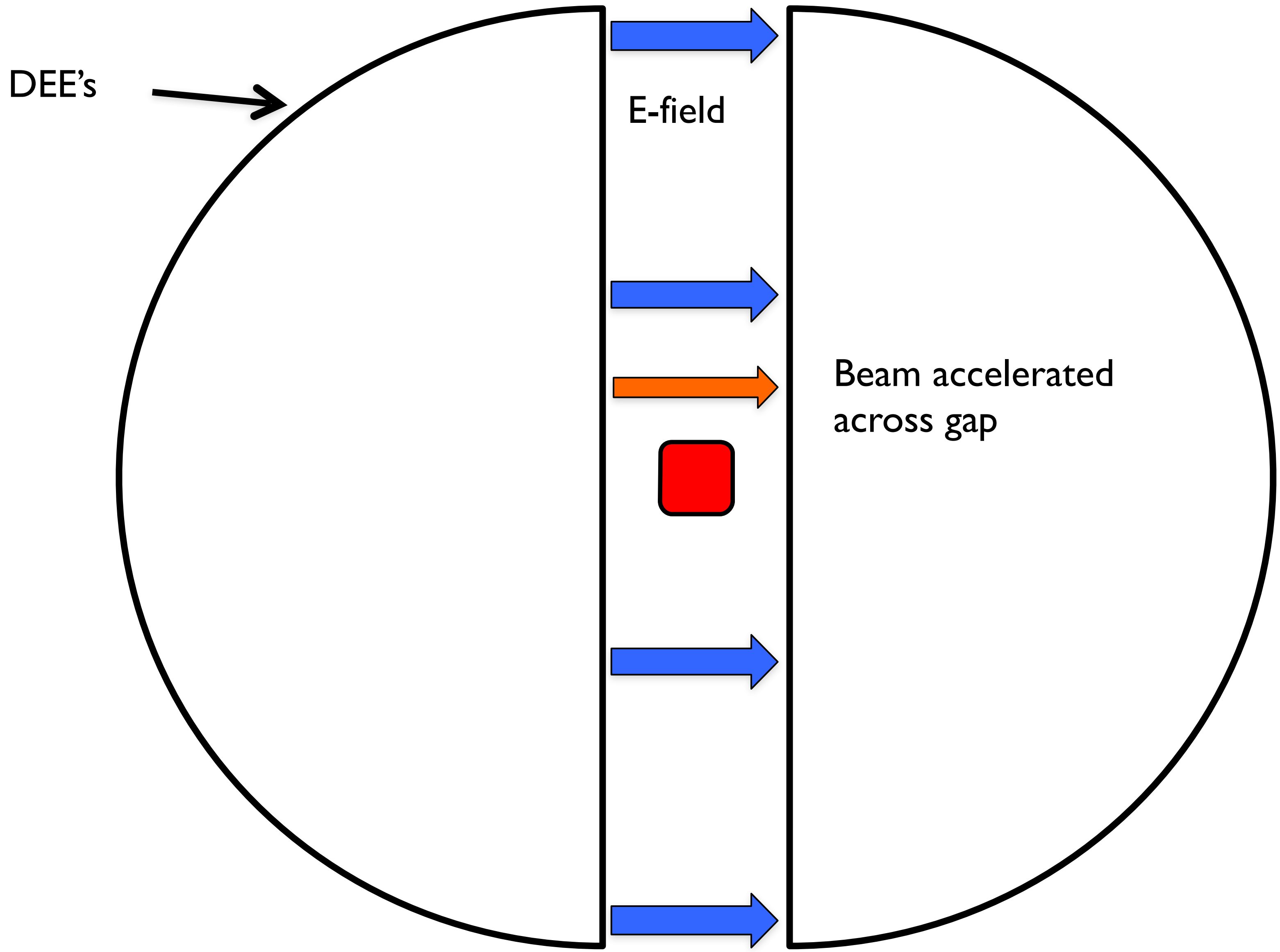
Cyclotron Acceleration (2)



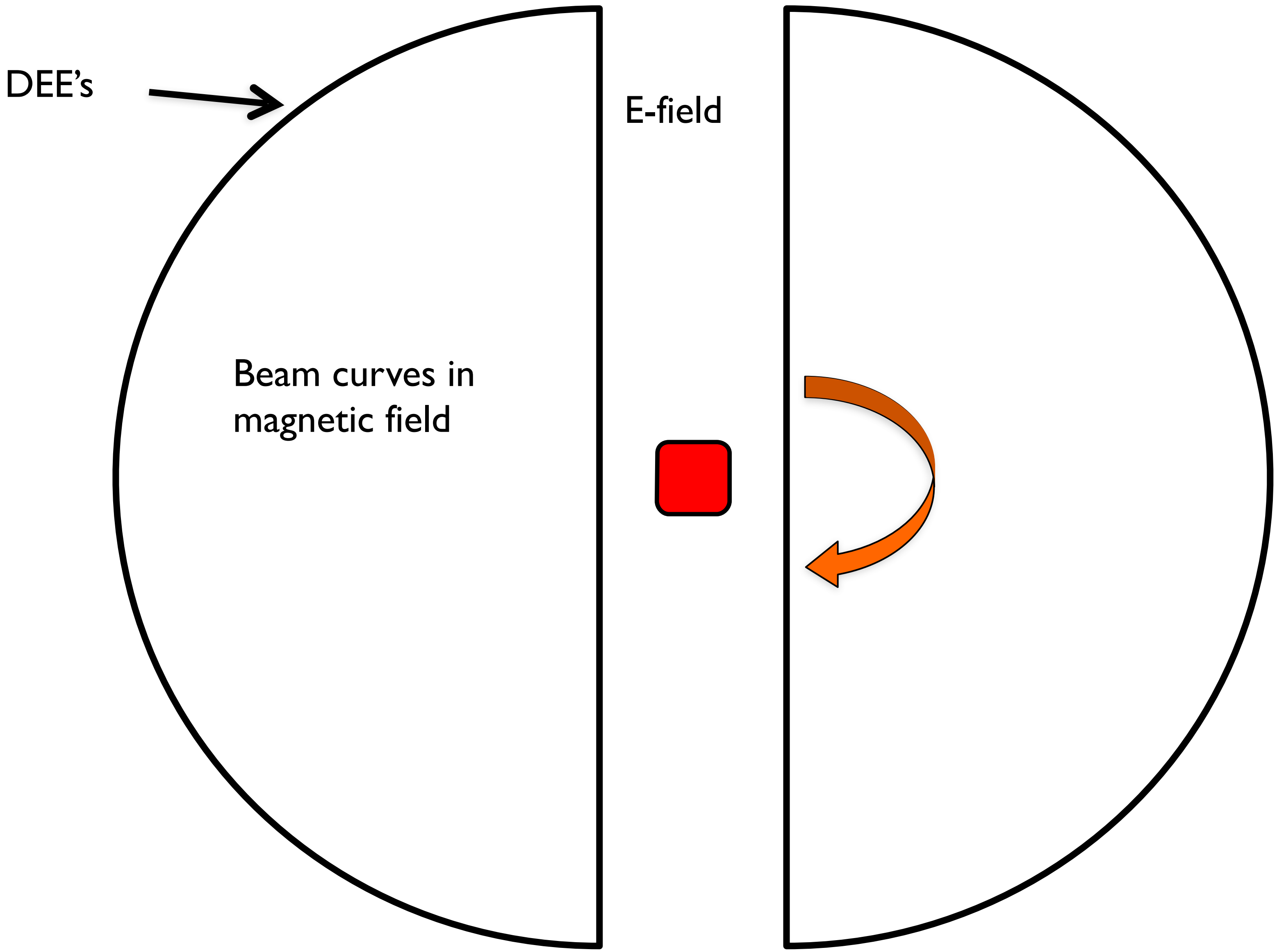
Cyclotron Acceleration (3)



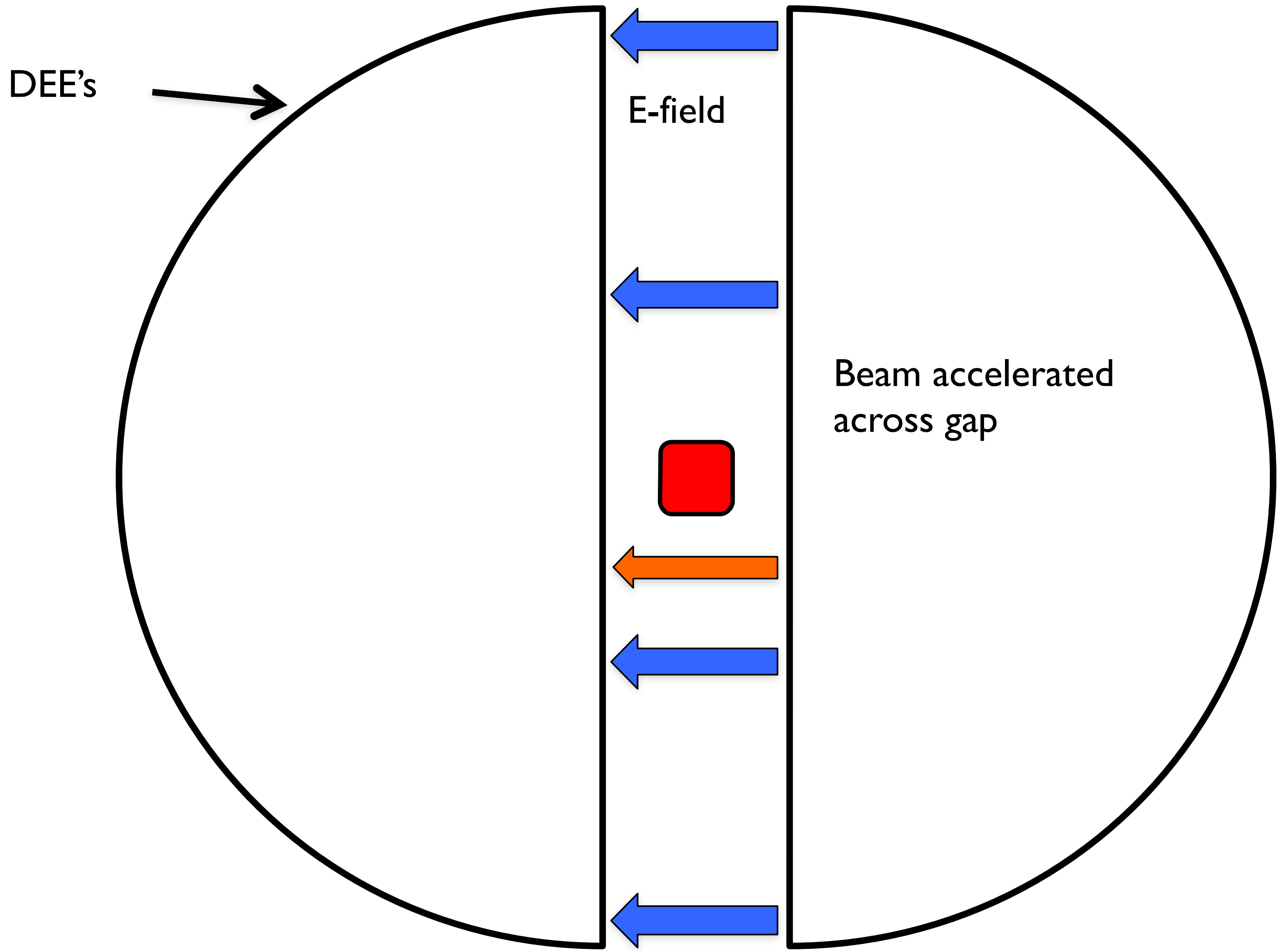
Cyclotron Acceleration (4)



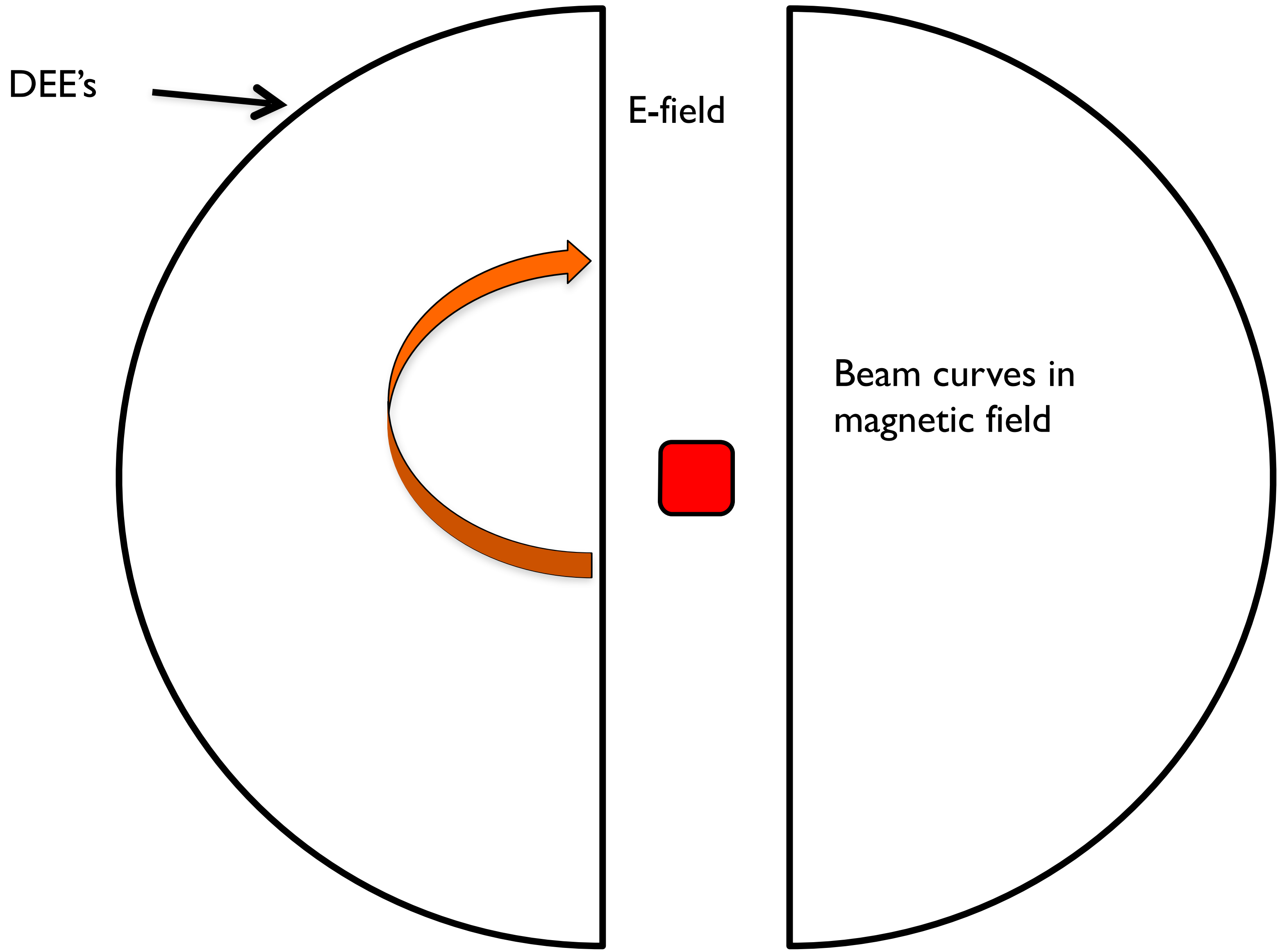
Cyclotron Acceleration (5)



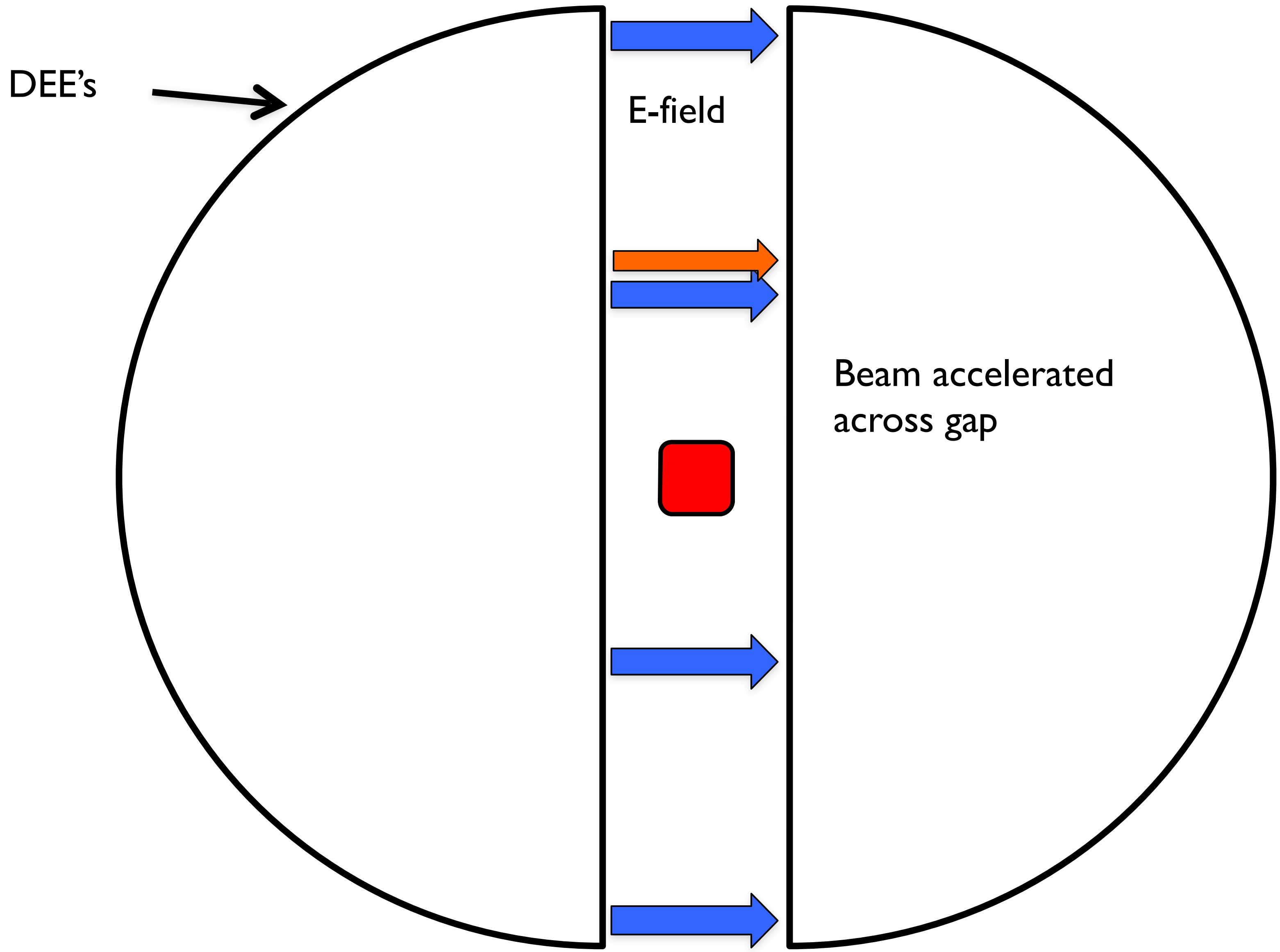
Cyclotron Acceleration (6)



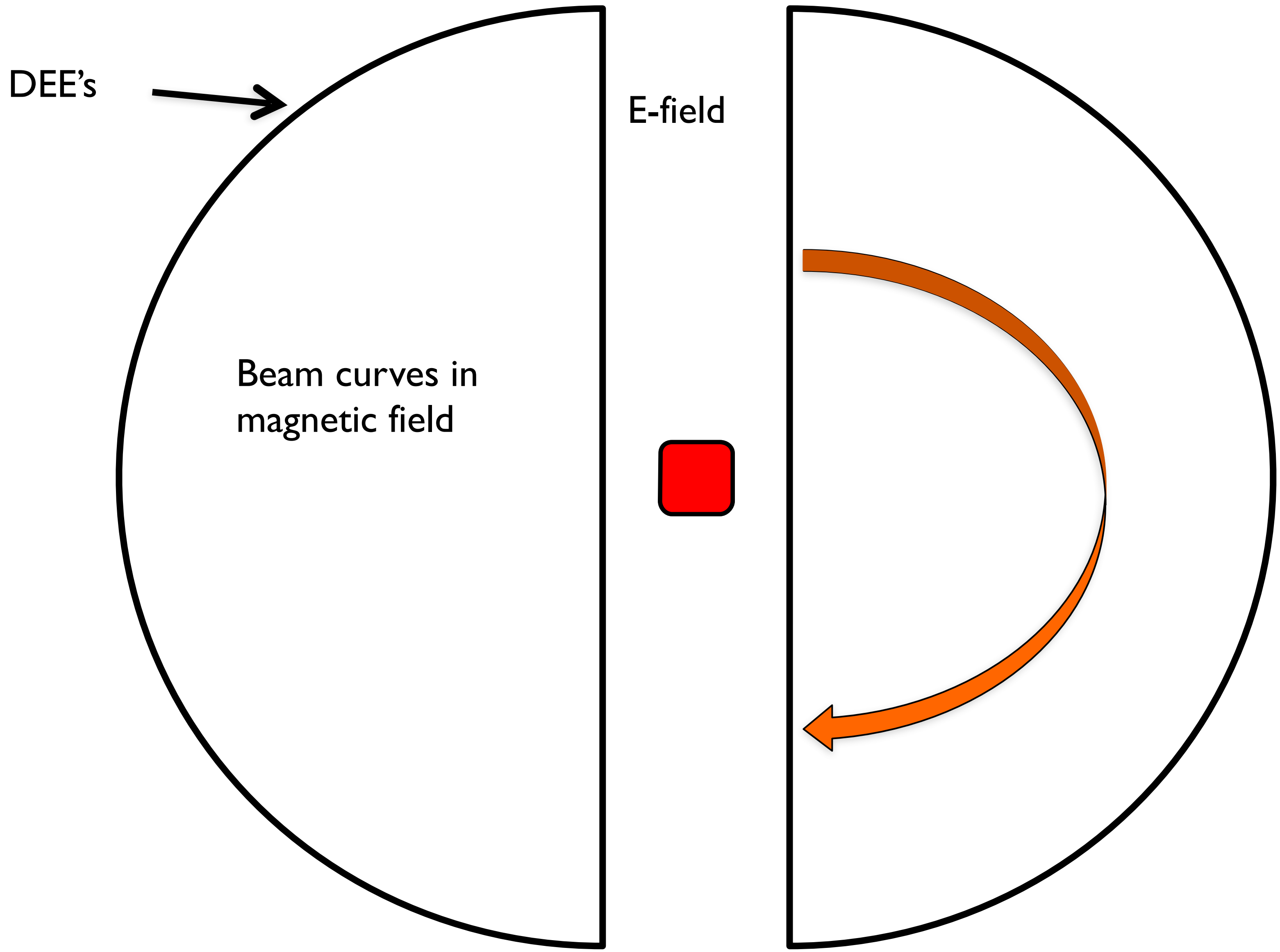
Cyclotron Acceleration (7)



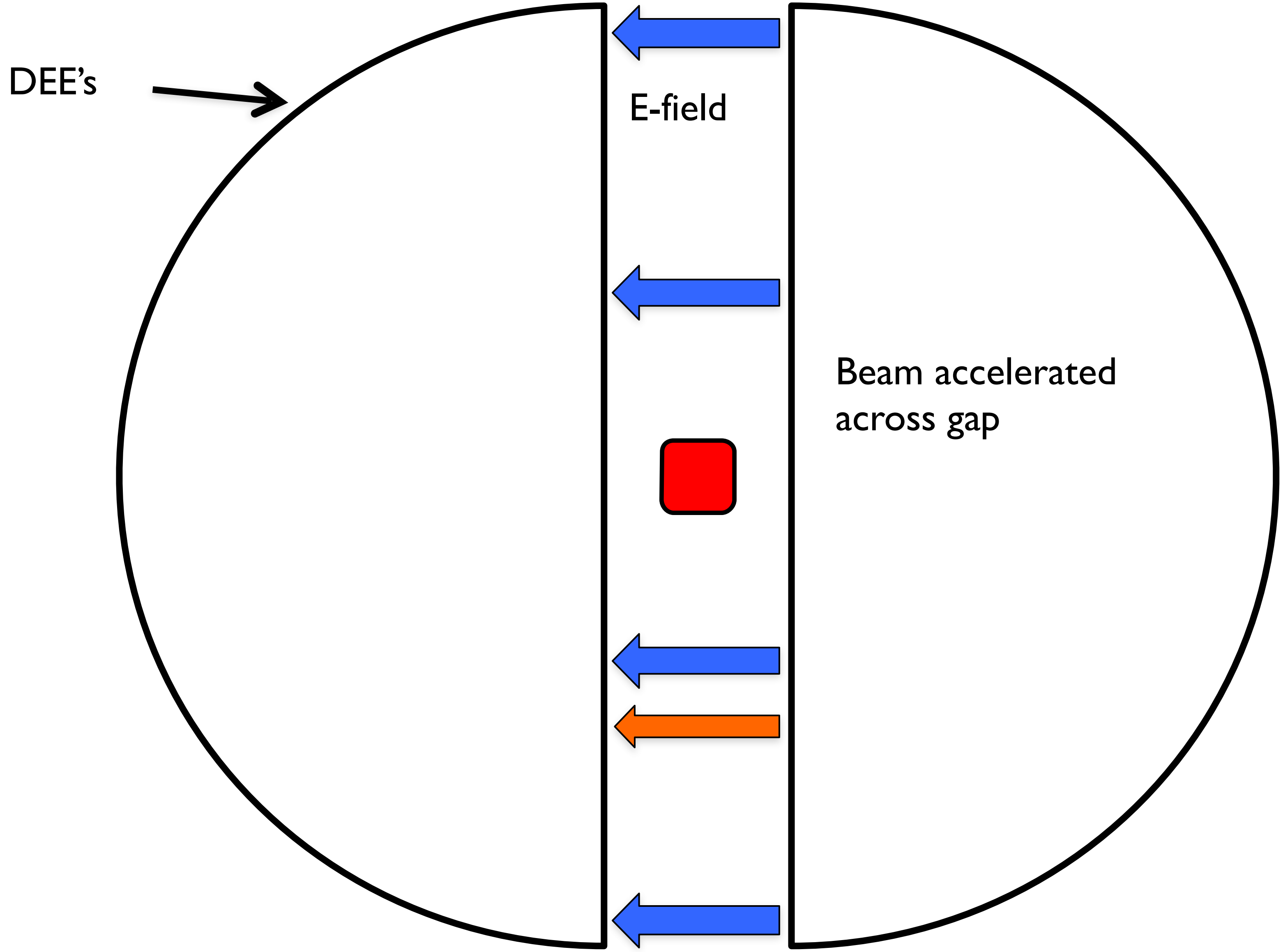
Cyclotron Acceleration (8)



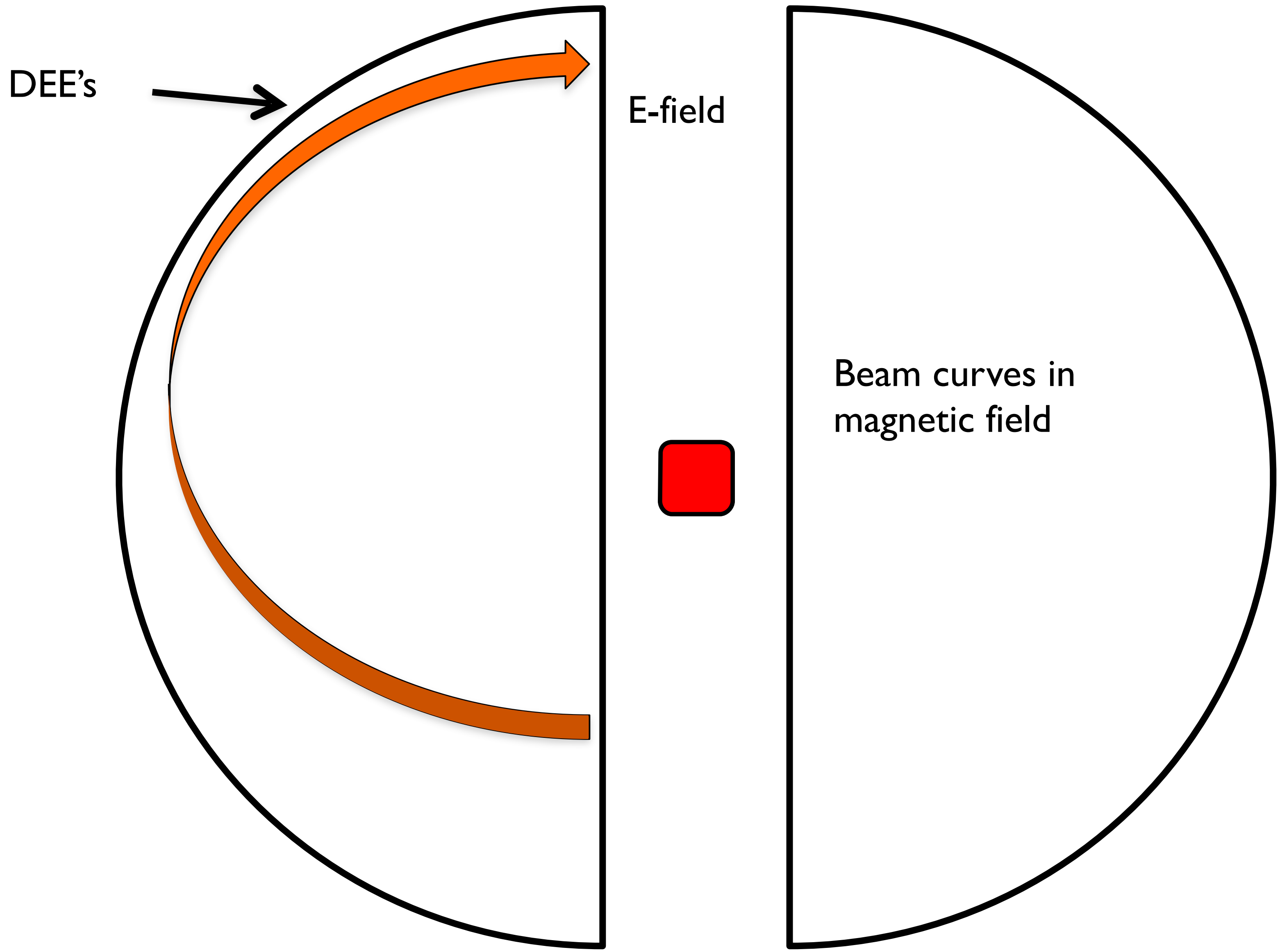
Cyclotron Acceleration (9)



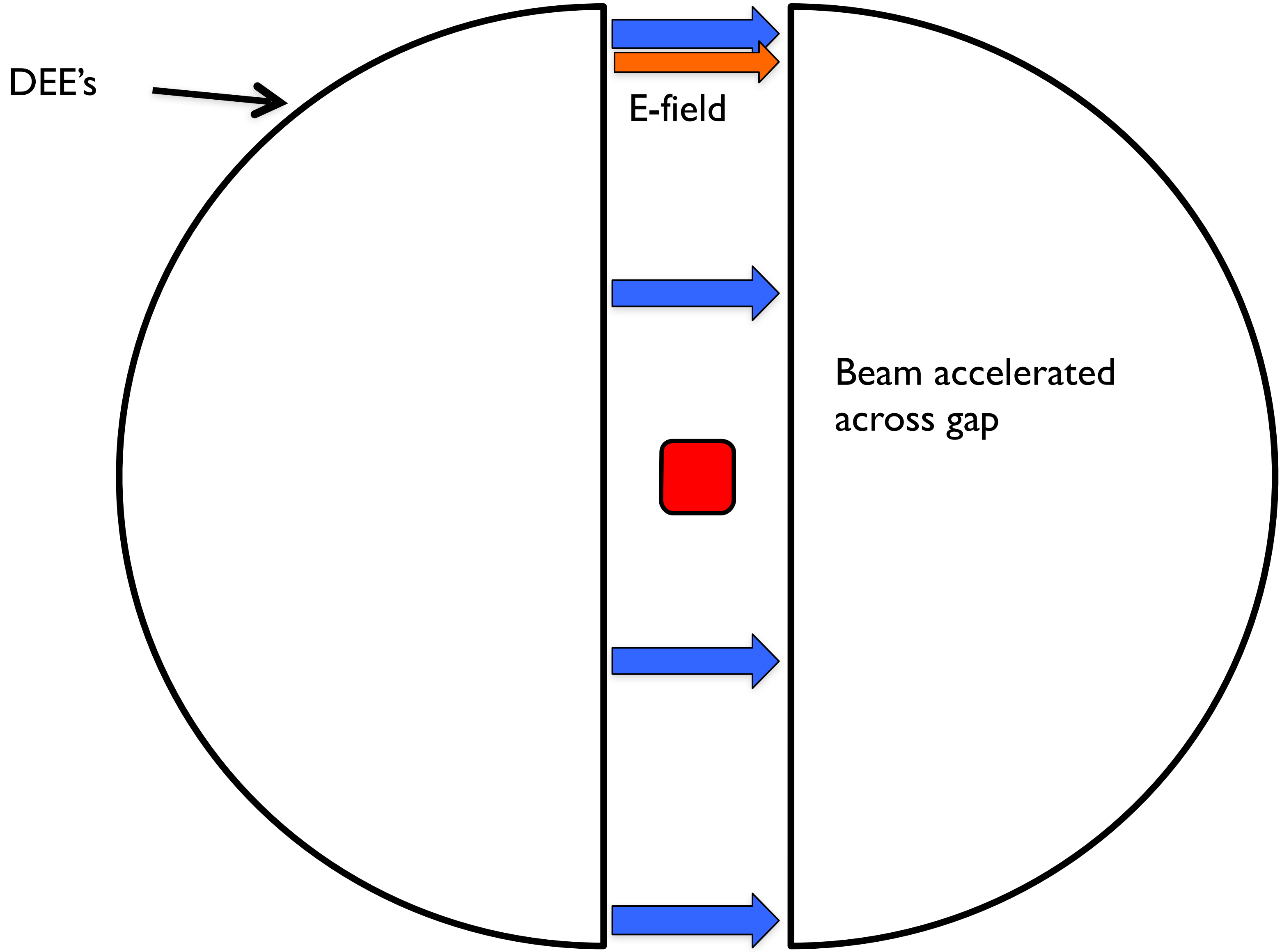
Cyclotron Acceleration (10)



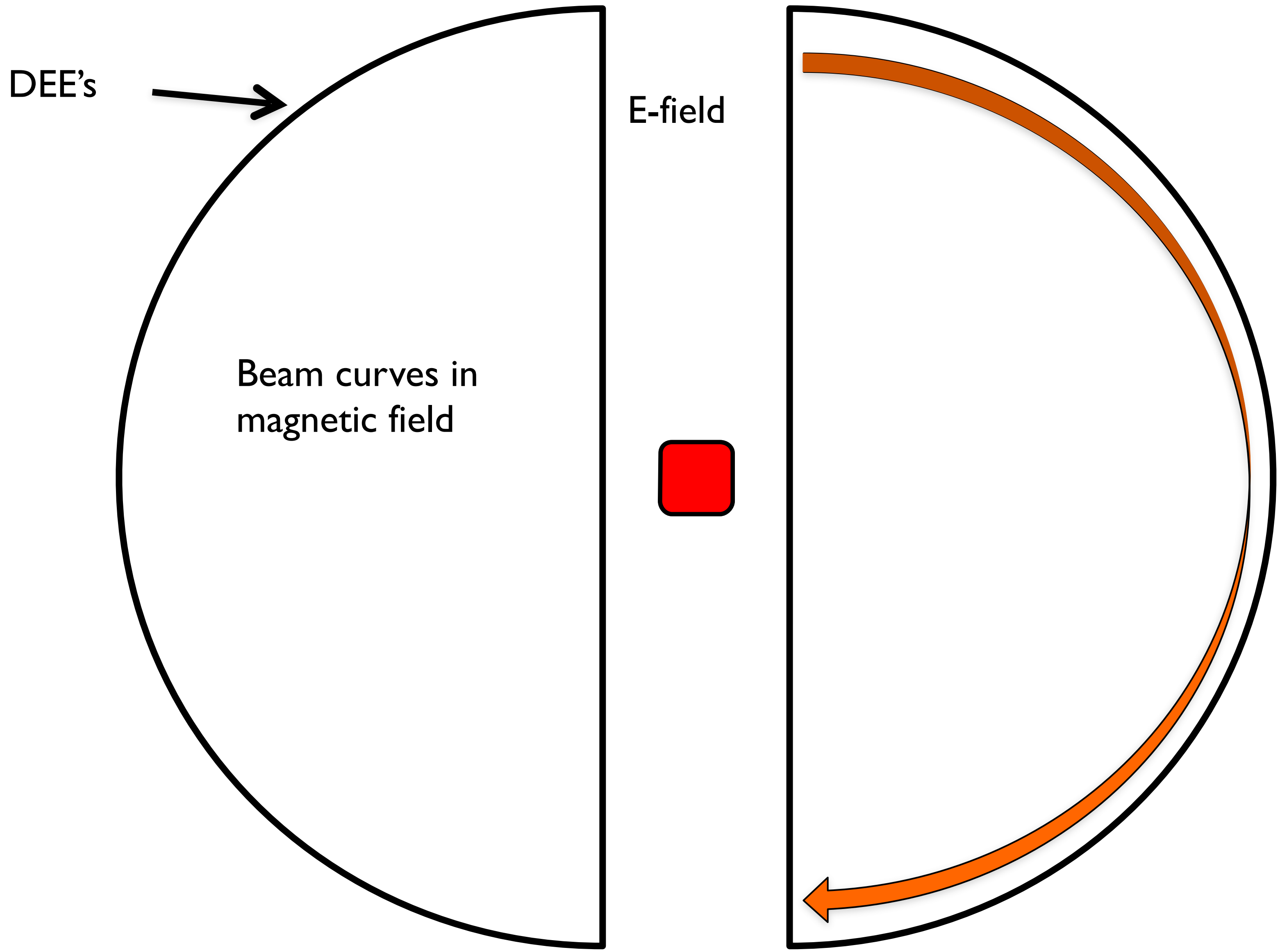
Cyclotron Acceleration (11)



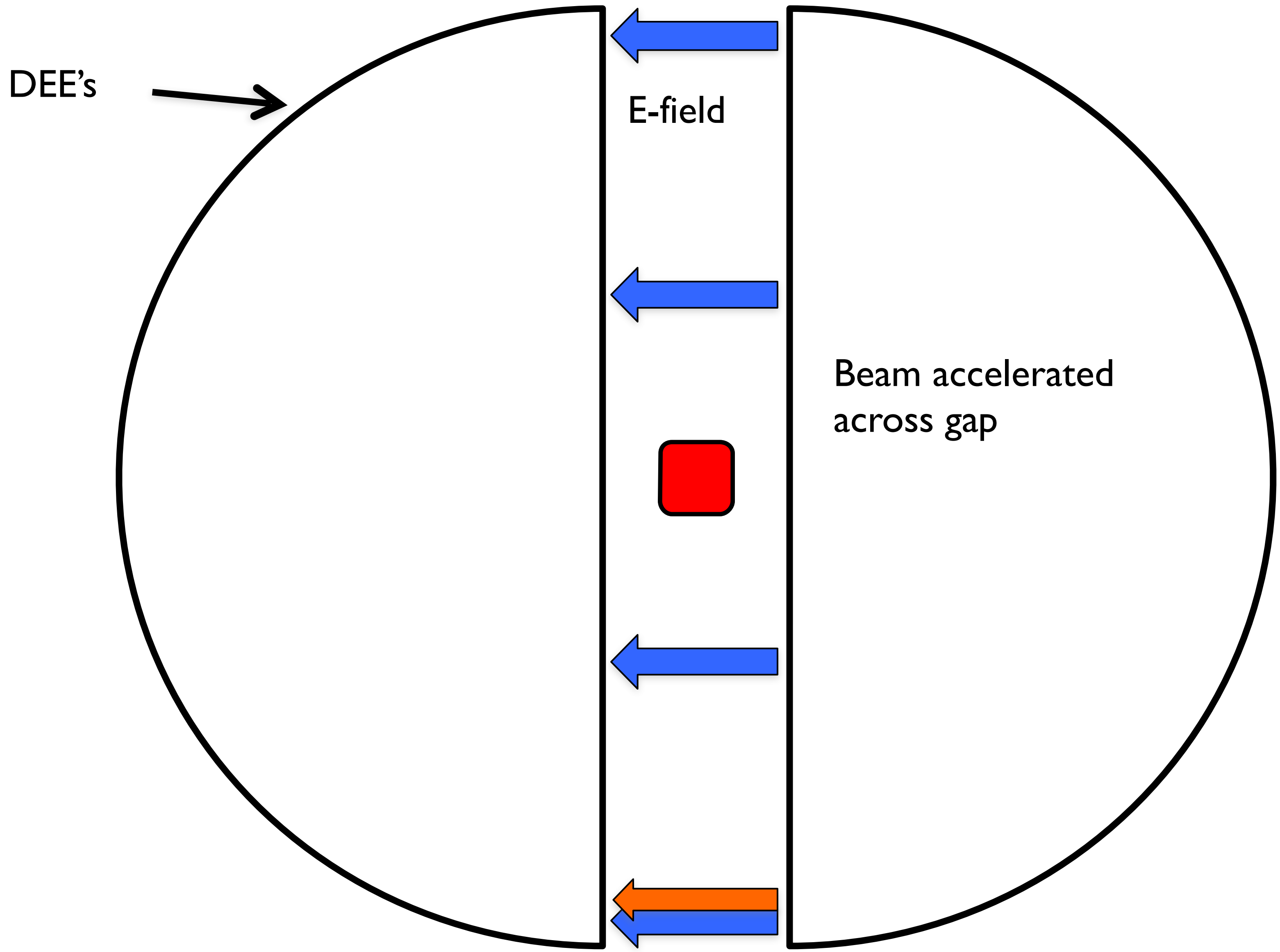
Cyclotron Acceleration (12)



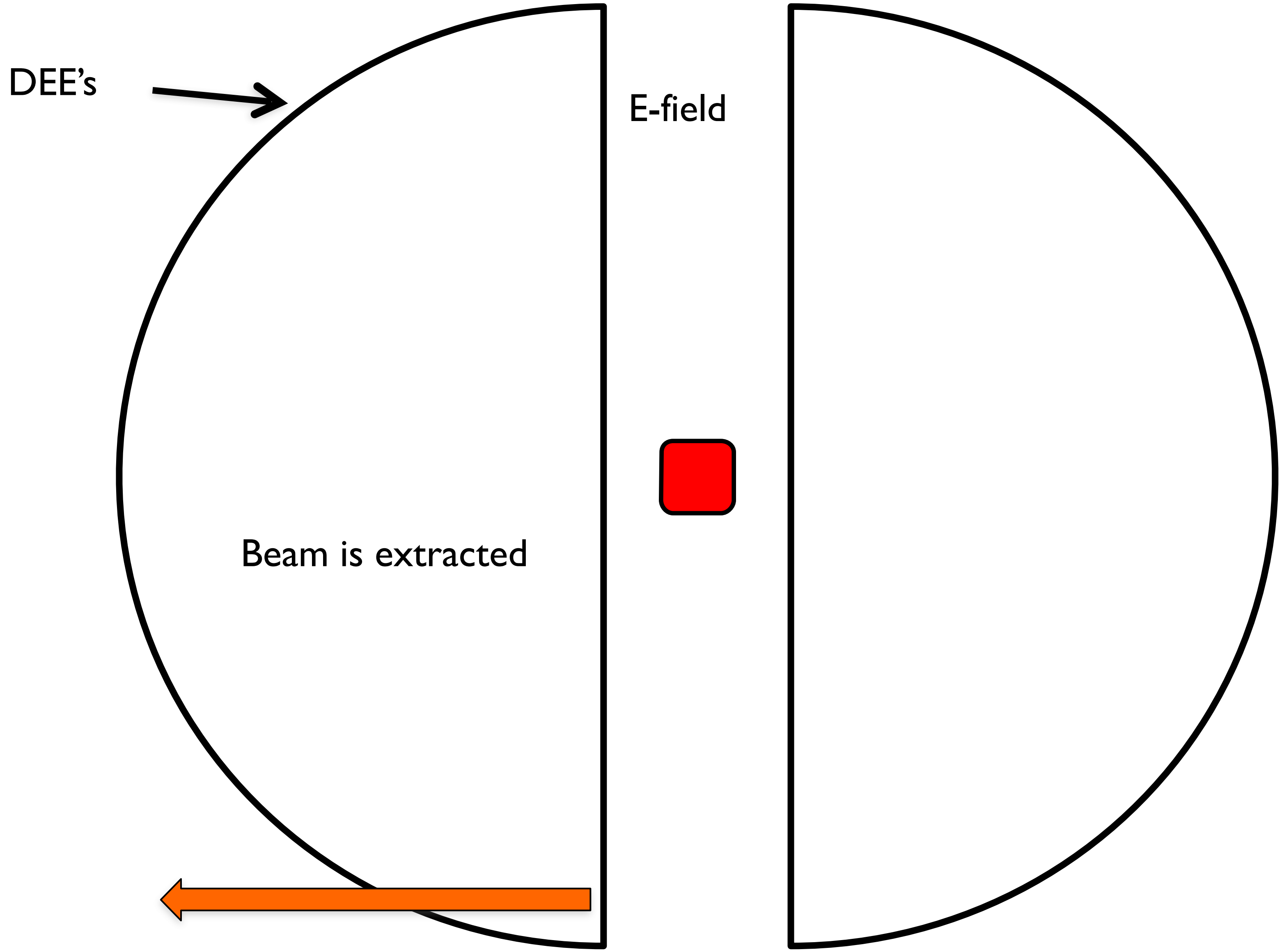
Cyclotron Acceleration (13)



Cyclotron Acceleration (14)

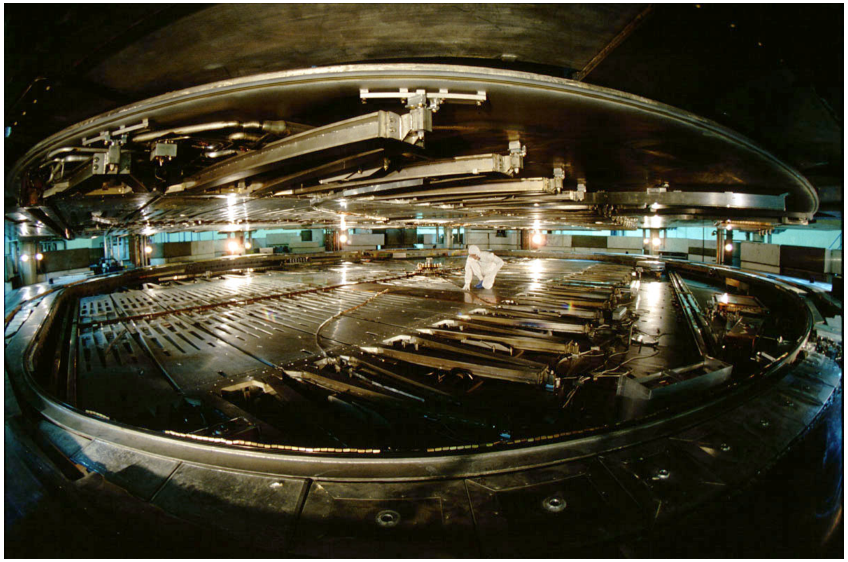


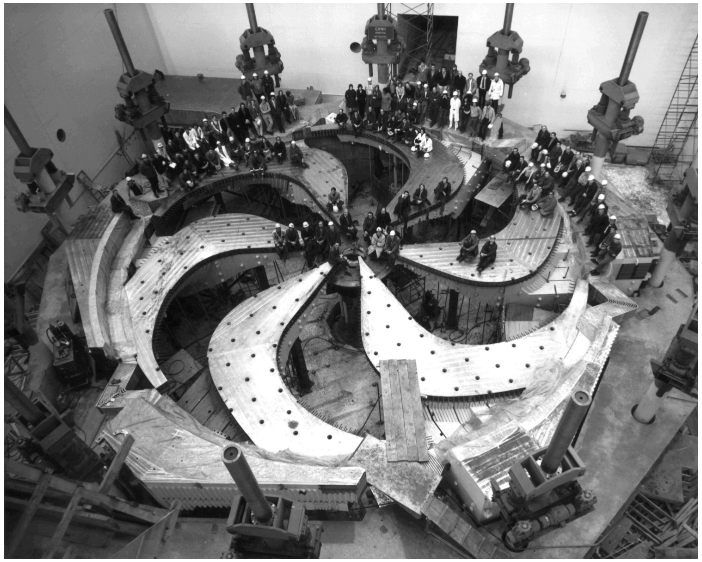
Cyclotron Acceleration (15)



Cyclotron Basics

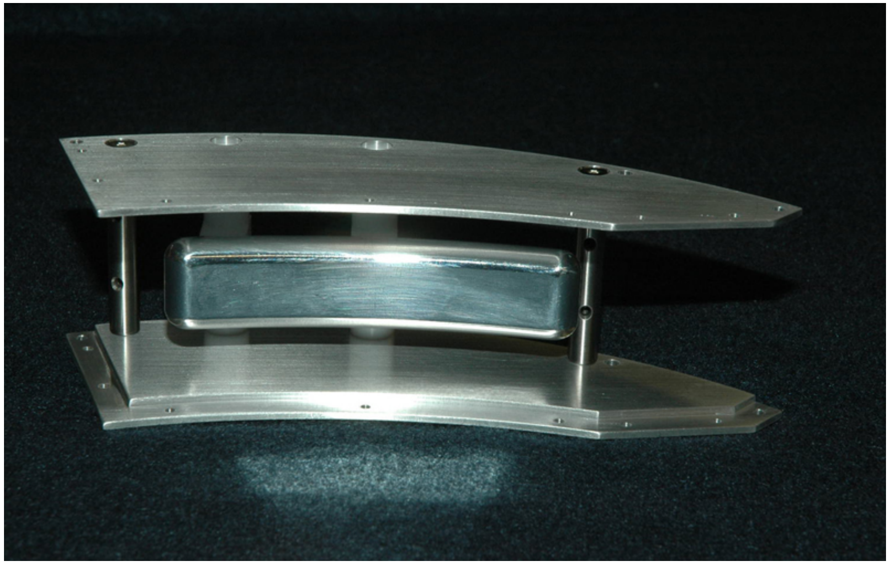
- Cyclotron invented in 1929 by E.O. Lawrence.
- Central ion source generates particles and introduces them into the center of the magnetic field where they begin their path.
- The cyclotron is tuned to accelerate one specific mass of particle to a given energy, governed by $B\rho$.
- Once the particles reach their desired energy at the outer edge of the magnetic field, they can no longer be contained and will be extracted.
- Cyclotrons still used in HEP (TRIUMF 500 MeV cyclotron shown here) but superseded by synchrotrons…

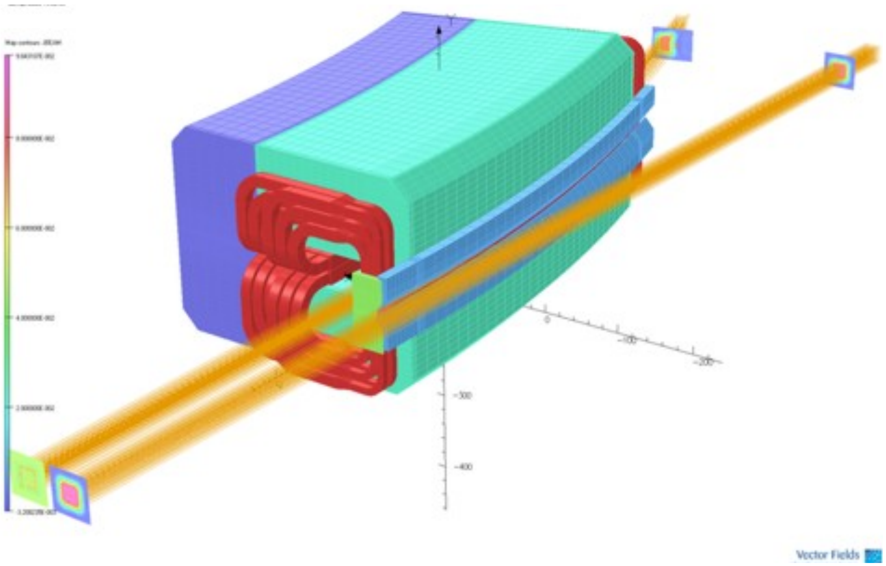


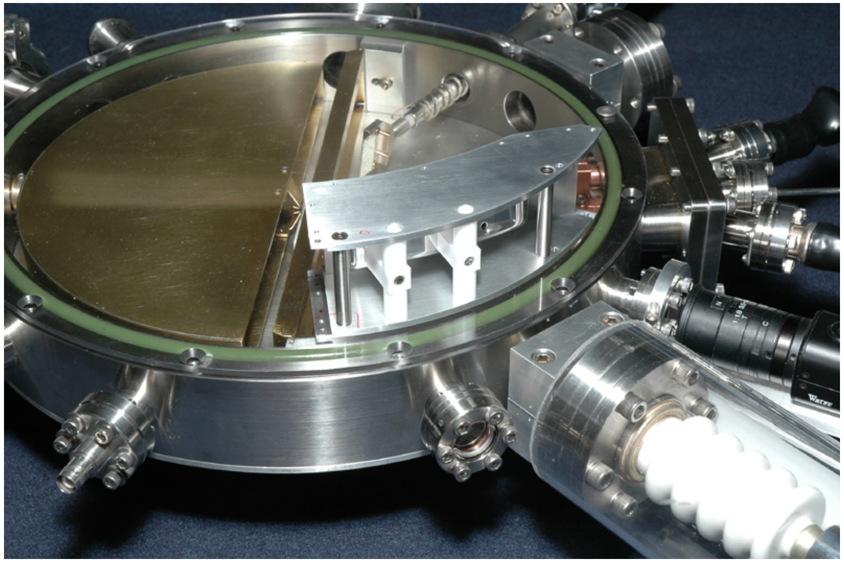


Extraction: Septum Magnets

- Septum turns small spatial separation into large spatial separation.
- Beam split into 2 paths depending on which side of the septum it is.
- Can either be electrostatic or magnetic.





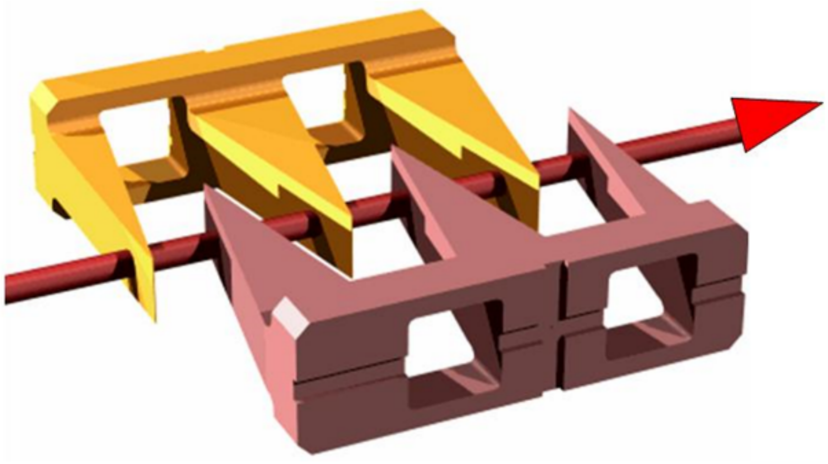


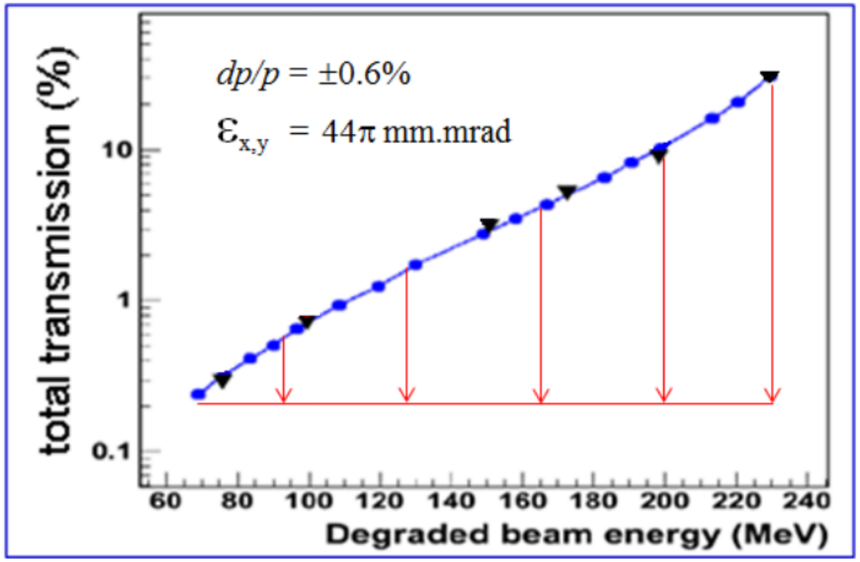
Cyclotrons For Proton Therapy

- Cyclotrons are by far the most common accelerator for proton therapy.
- Accelerates beam to *single energy*, then *reduces* energy as required:
  - Degrader (absorber/wedges)
  - Energy Selection System (ESS): beamline that selects correct energy.
- If *pulsed beam* is required (eg. spot scanning), keep accelerator as-is and pulse high voltage on ion source.

Degraders

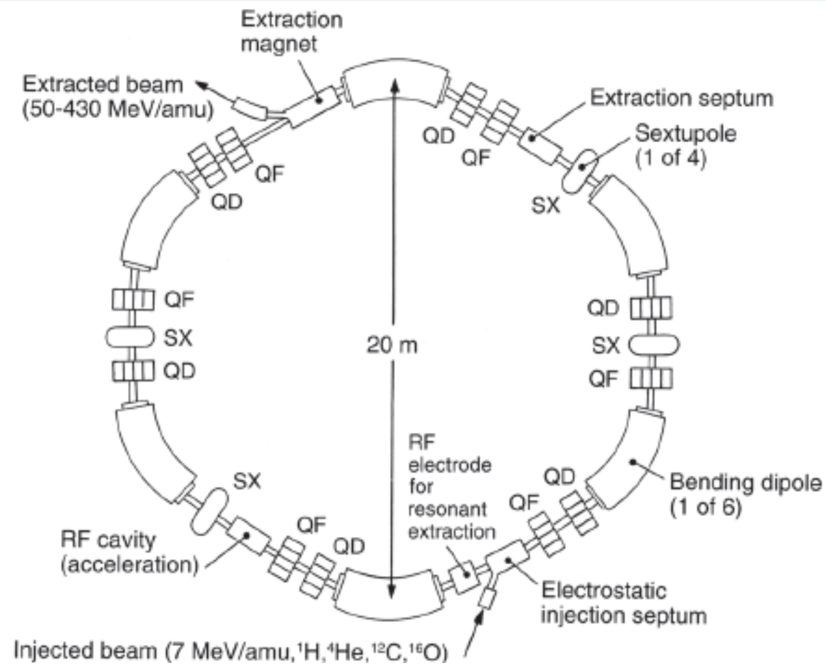
- Degraders are needed in cyclotrons to provide variable energy.
- Series of wedges allow multiple energies to be selected.
- Sounds slow, but mechanical movement still allows rapid energy change (100 ms).
- Degrader increases the emittance of the beam:
  - Beam size increases due to multiple scattering.
  - Energy spread increases.
  - Beam loss due to nuclear reactions in the degrader.
- Beam intensity is strongly reduced.
- Need Energy Selection System to select correct energy and clean up beam.

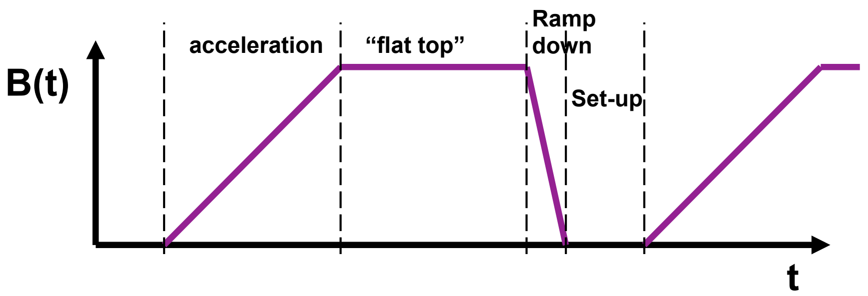




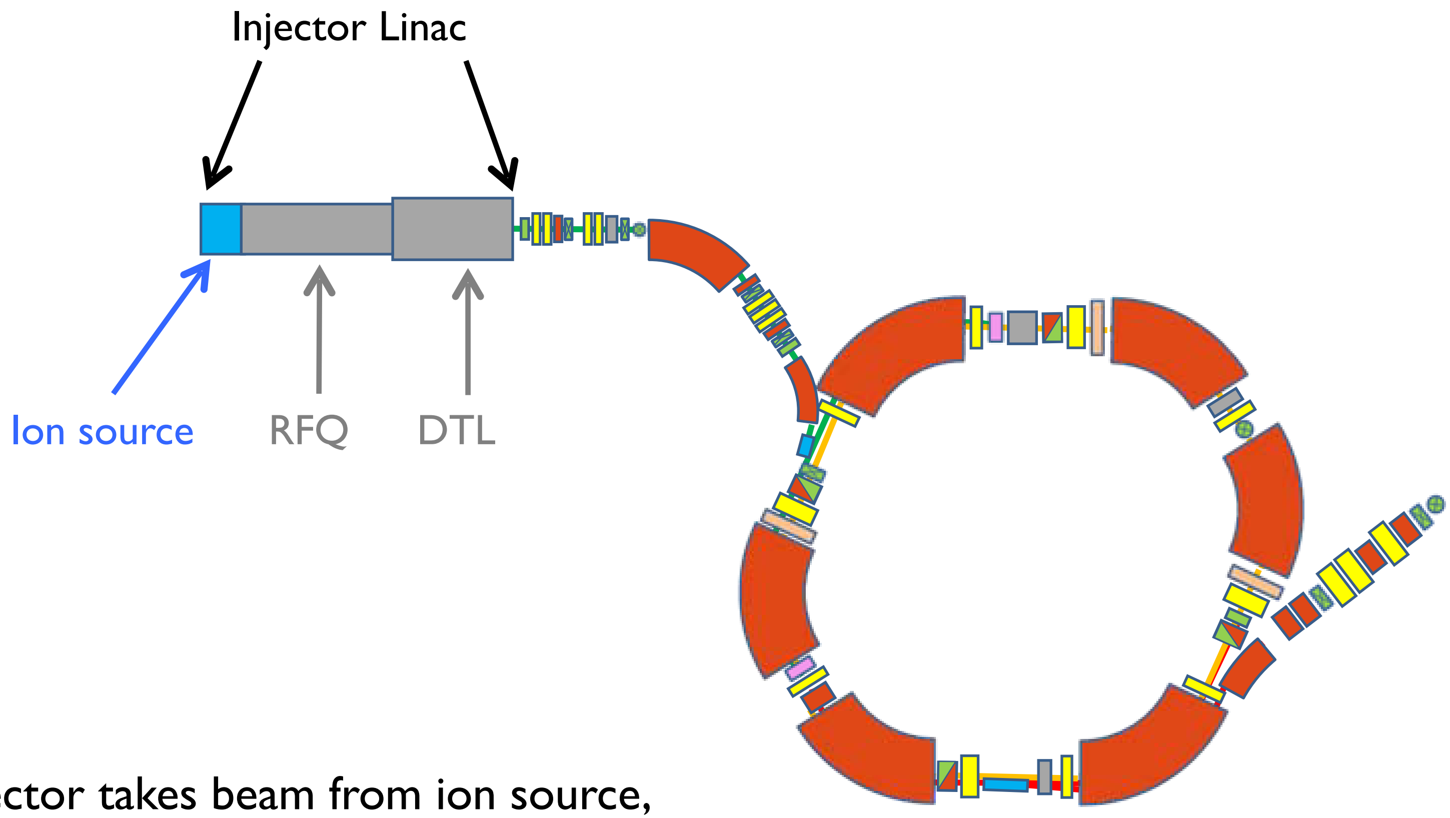
Synchrotrons

- Synchrotrons take opposite approach:
  - Fix particle radius.
  - Increase magnetic field.
  - Adjust RF frequency to match particles as they get faster.
  - *Synchrotron* because strength of magnetic field and frequency, amplitude and phase of RF and focussing strength of the lenses have to be *synchronised*.
- Dipole magnets to bend particles round in circle, and to inject and extract the beam.
- RF electric fields to accelerate particles – particle passes accelerating cavities many times.
- Instead of large single vacuum chamber, evacuated volume much smaller:
  - Narrow beam pipe with discrete components.
  - Focussing magnets contain 99.9% of injected beam (more like 50% for cyclotrons!)
- Normally consist of short straight accelerating/focussing/diagnostic sections, separated by bending sections with dipoles.
- B = 0 not possible and therefore a non-zero initial energy is necessary: chain of accelerators.





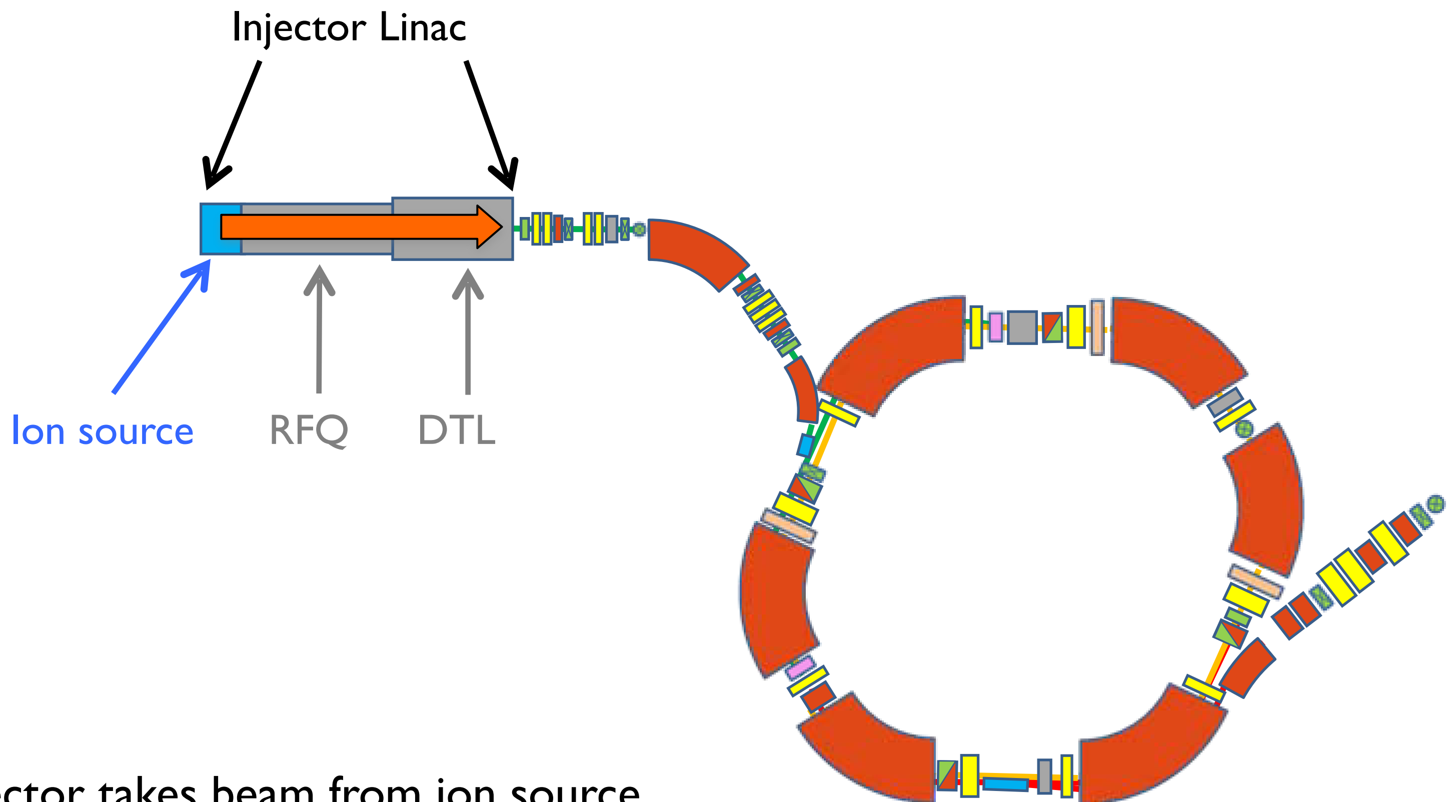
Synchrotrons: Injector



Injector takes beam from ion source, focuses it down to correct size and accelerates it to 7 MeV.

Need to do this with a linac as space charge within beam requires rapid acceleration and continuous focussing.

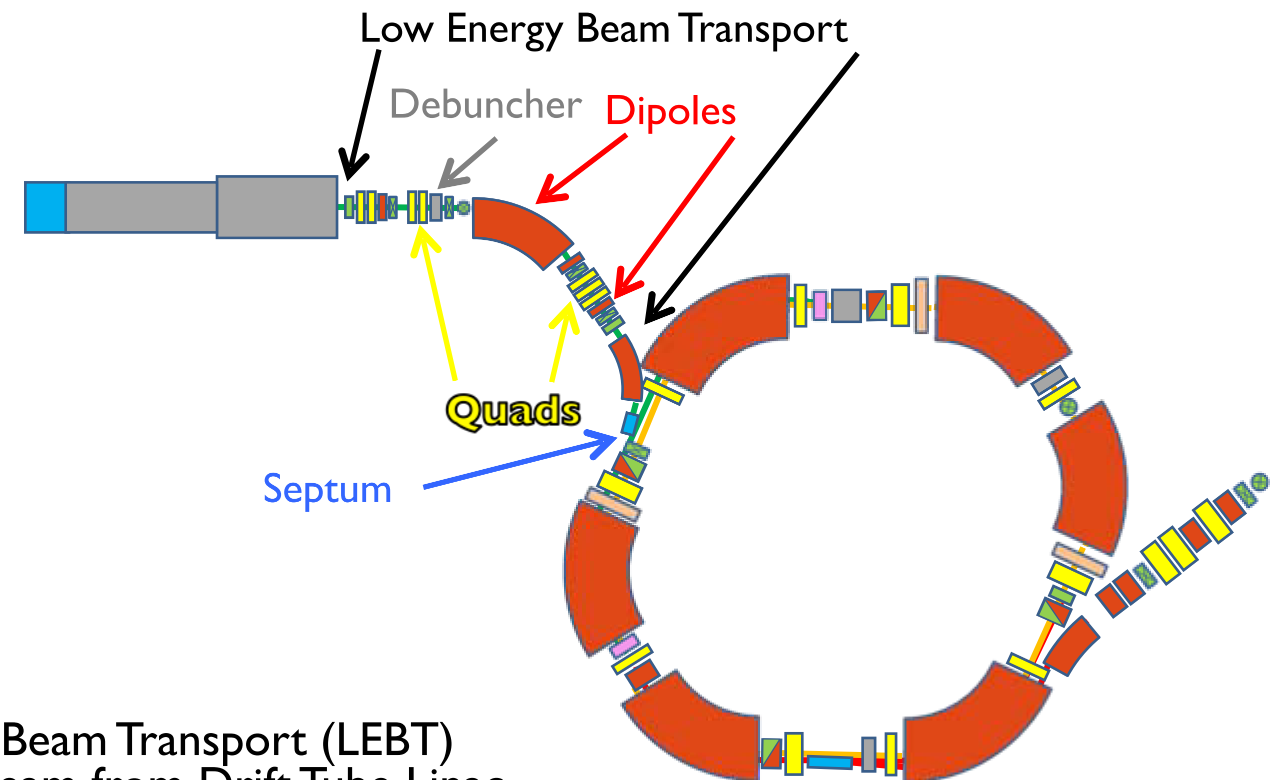
Synchrotrons: Injector



Injector takes beam from ion source, focuses it down to correct size and accelerates it to 7 MeV.

Need to do this with a linac as space charge within beam requires rapid acceleration and continuous focussing.

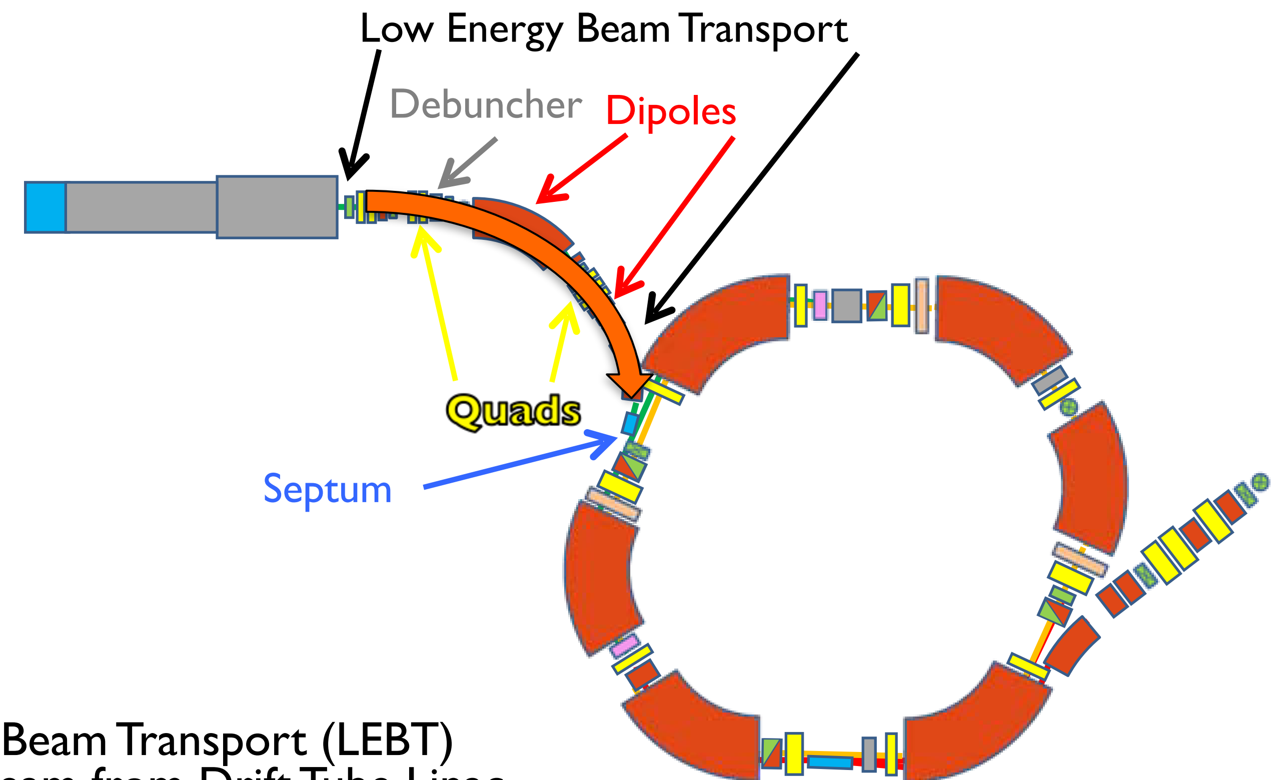
Synchrotrons: LEBT



Low Energy Beam Transport (LEBT) transports beam from Drift Tube Linac (DTL) exit to synchrotron injection.

Consists of several quadrupole doublets for focusing, steering dipoles, beam position monitors and a debuncher to match the beam to synchrotron frequency.

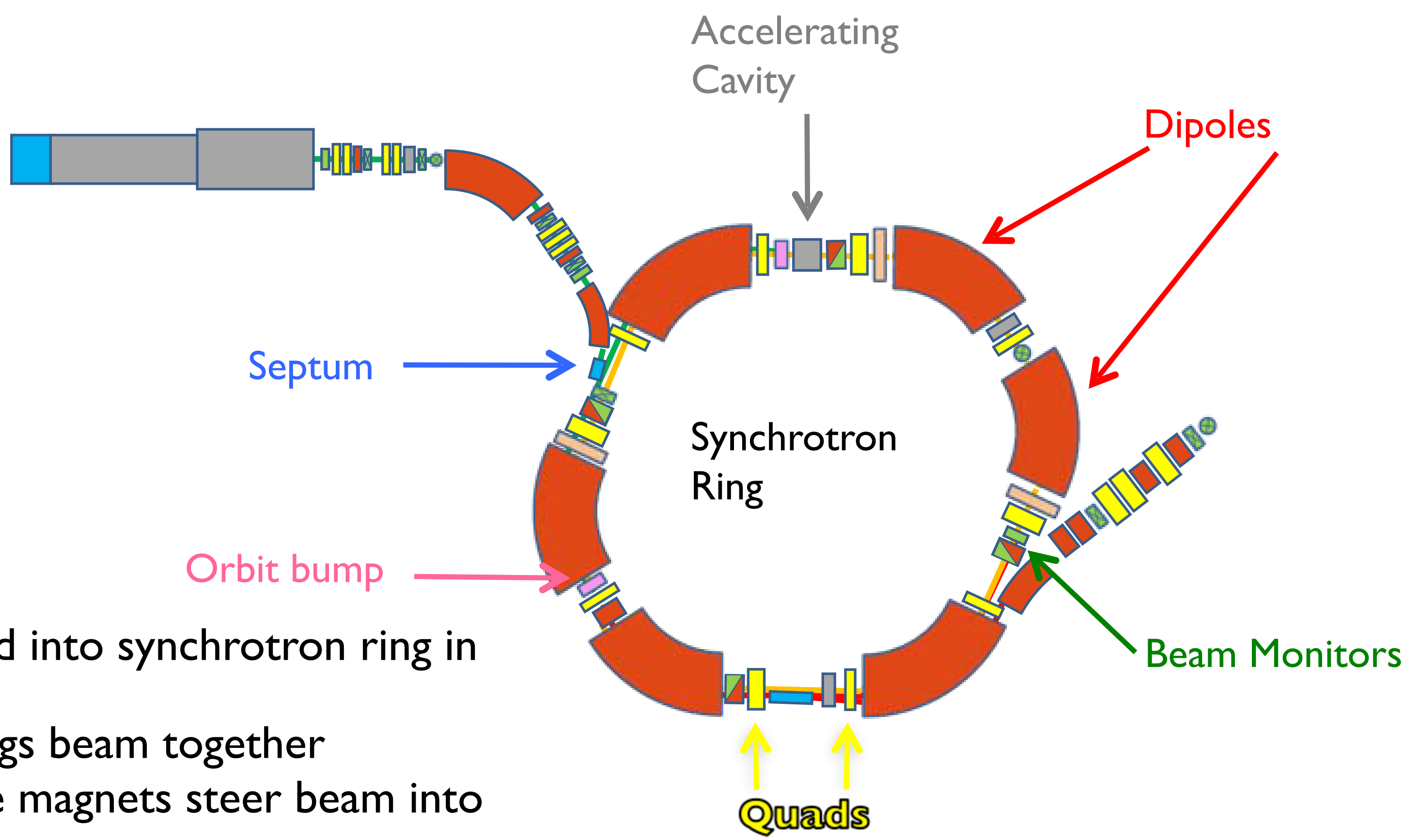
Synchrotrons: LEBT



Low Energy Beam Transport (LEBT) transports beam from Drift Tube Linac (DTL) exit to synchrotron injection.

Consists of several quadrupole doublets for focusing, steering dipoles, beam position monitors and a debuncher to match the beam to synchrotron frequency.

Synchrotrons: Acceleration (1)

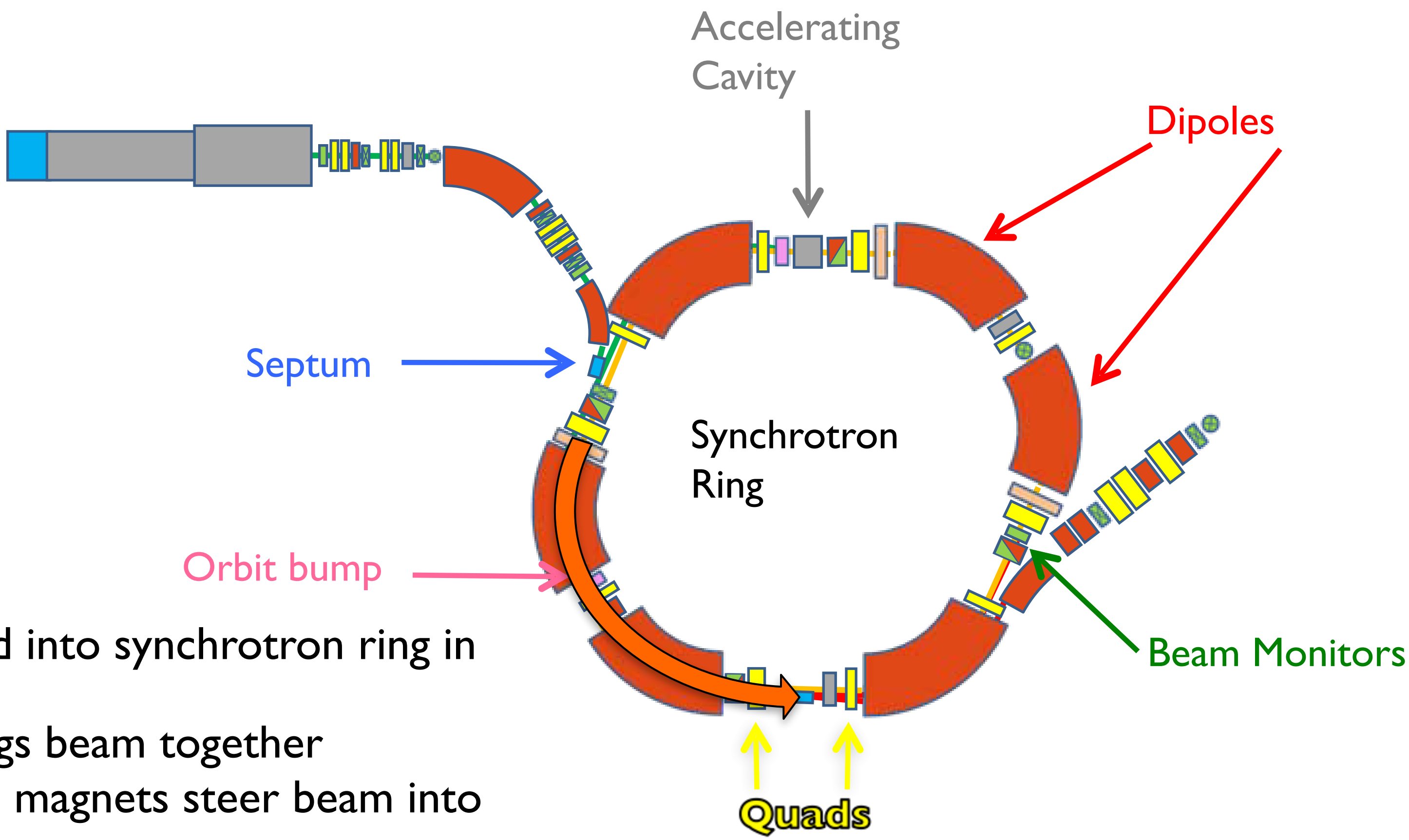


Beam injected into synchrotron ring in stages:

- Septum brings beam together
- Bump dipole magnets steer beam into correct orbit.
- Dipoles steer beam in a circle.
- Quadrupoles keep beam on correct trajectory.

Synchrotrons: Acceleration (I)

UCL

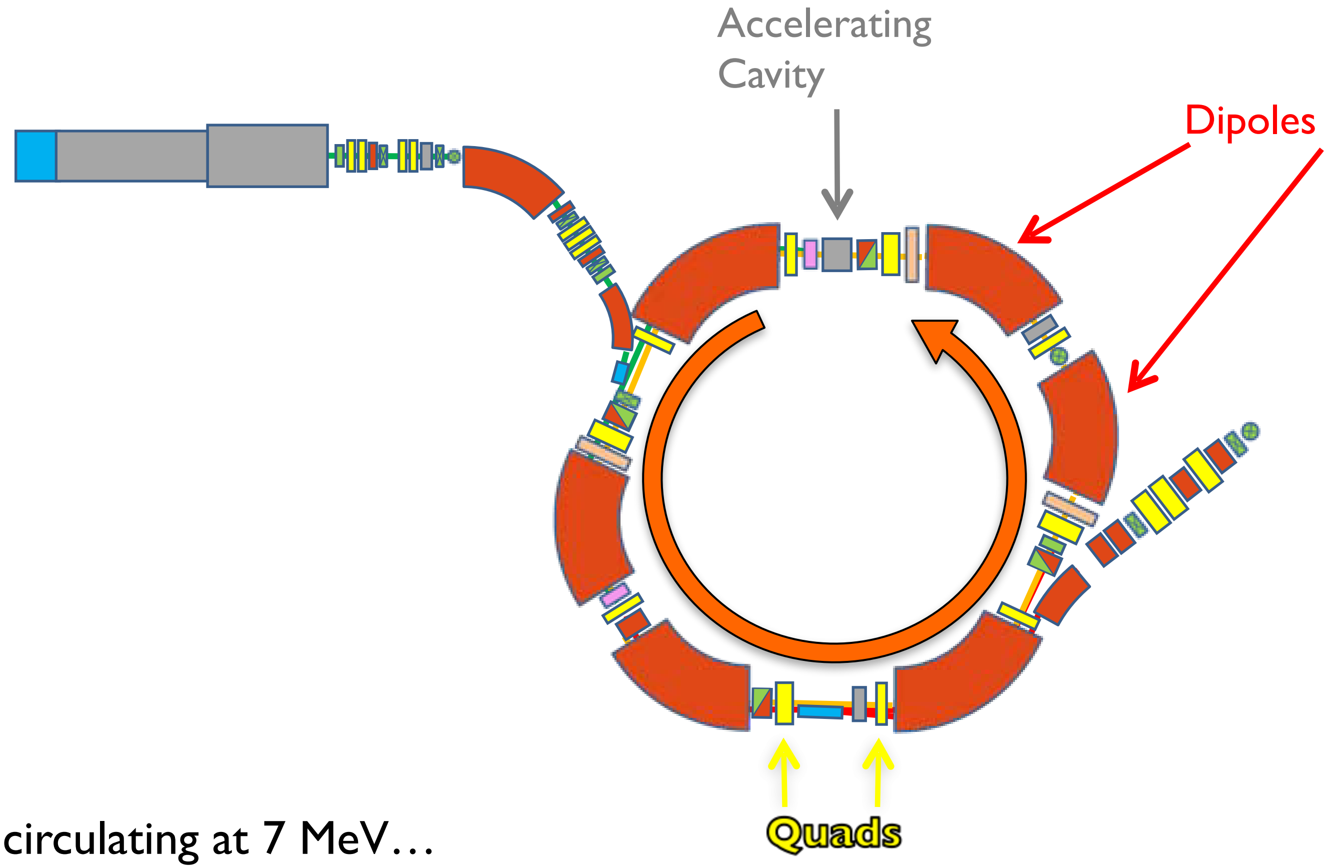


Beam injected into synchrotron ring in stages:

- Septum brings beam together
- Bump dipole magnets steer beam into correct orbit.
- Dipoles steer beam in a circle.
- Quadrupoles keep beam on correct trajectory.

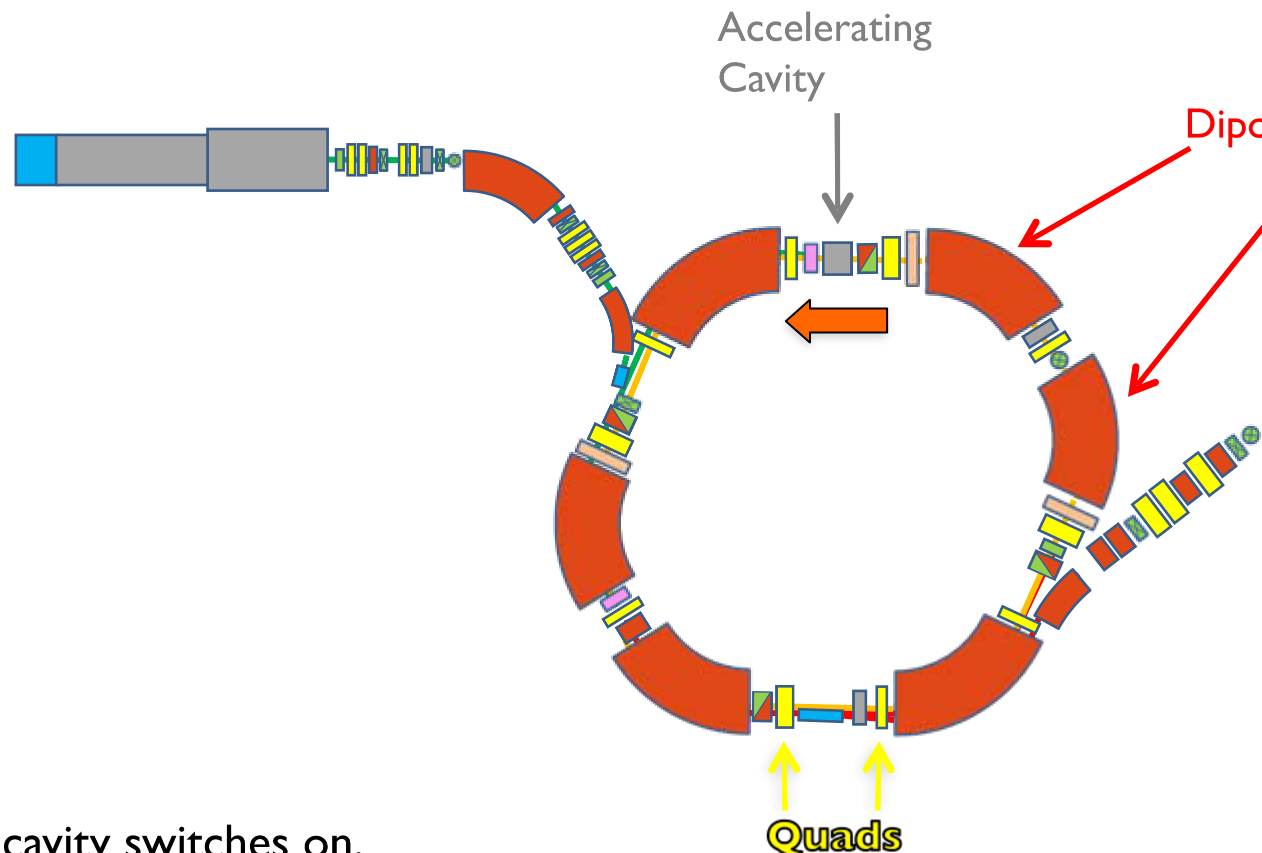
Synchrotrons: Acceleration (2)

UCL



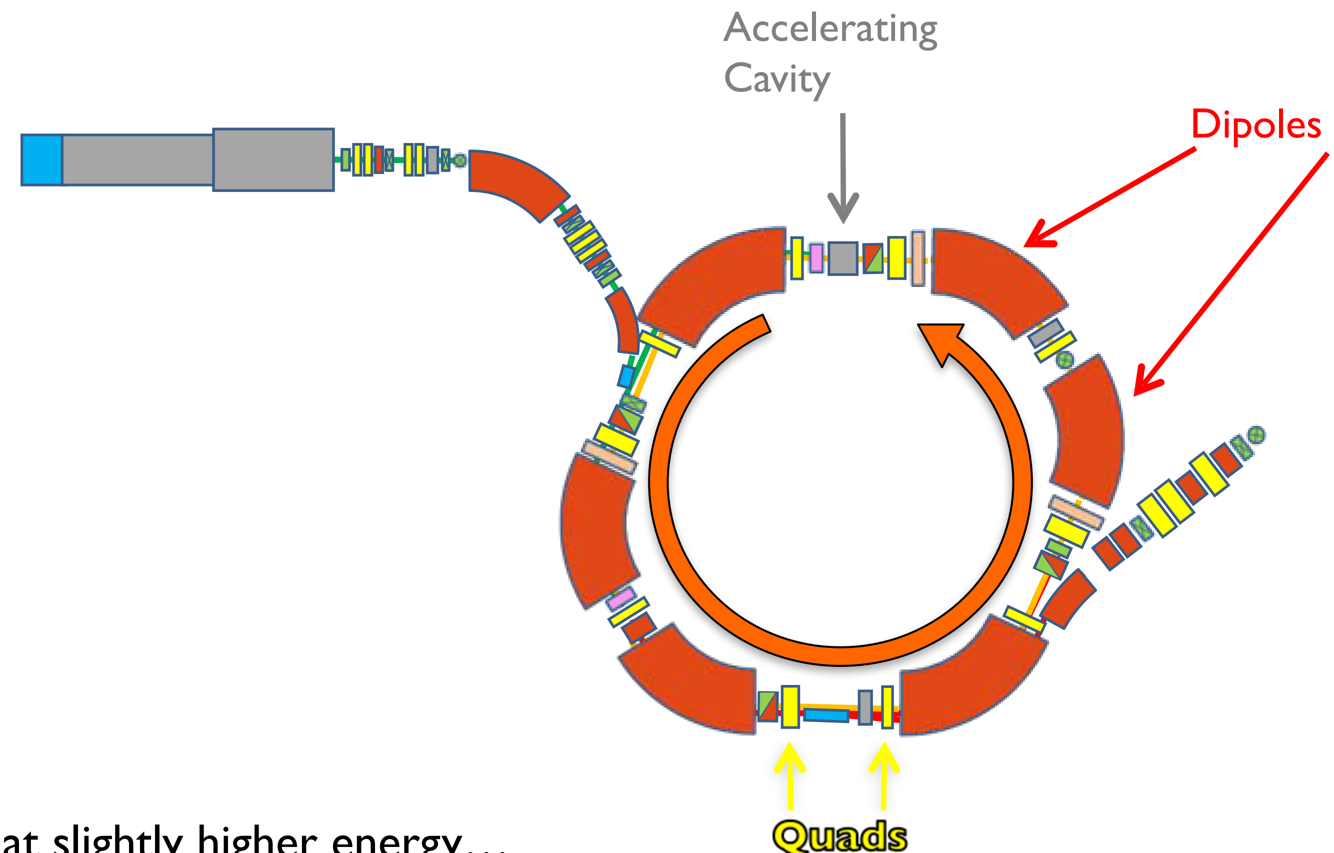
Beam begins circulating at 7 MeV…

Synchrotrons: Acceleration (3)



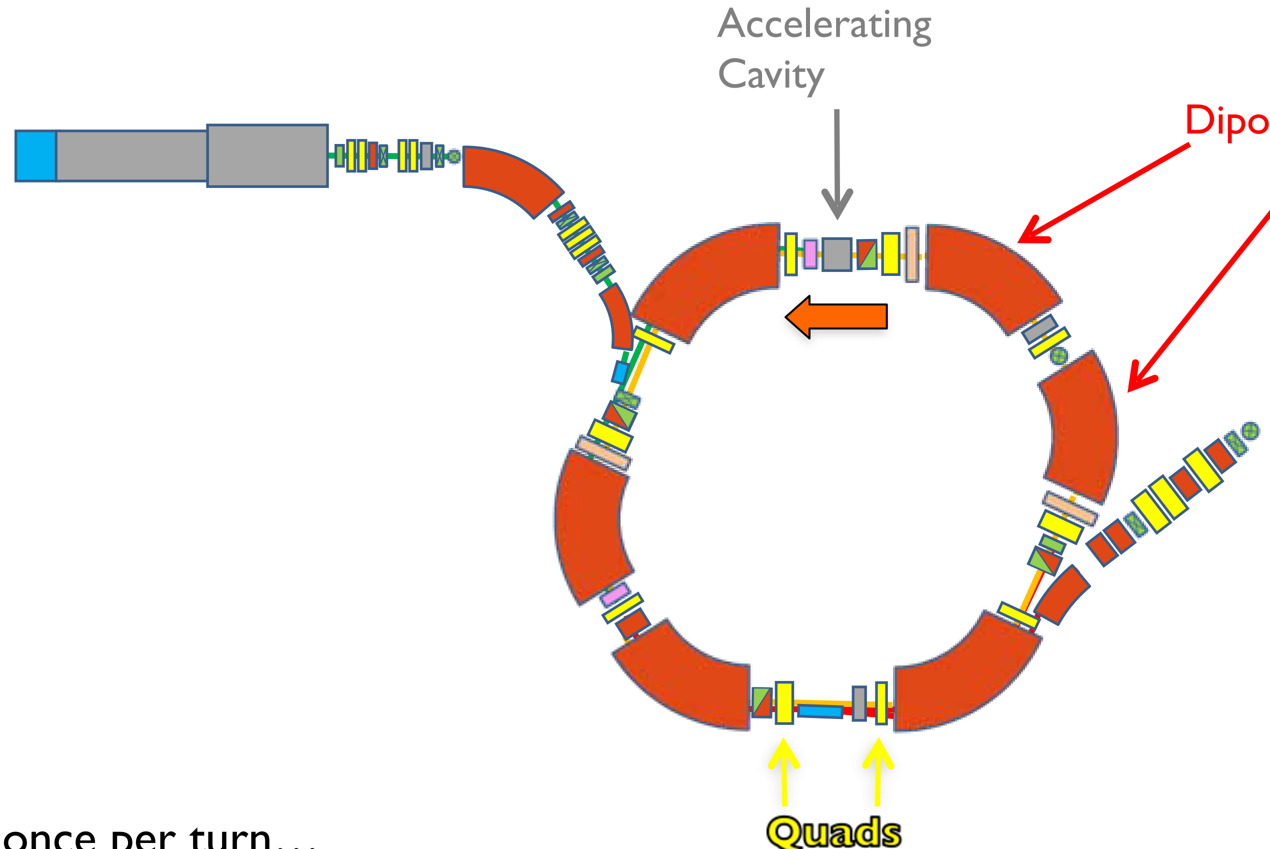
Accelerating cavity switches on.
Beam accelerated once per turn…

Synchrotrons: Acceleration (4)



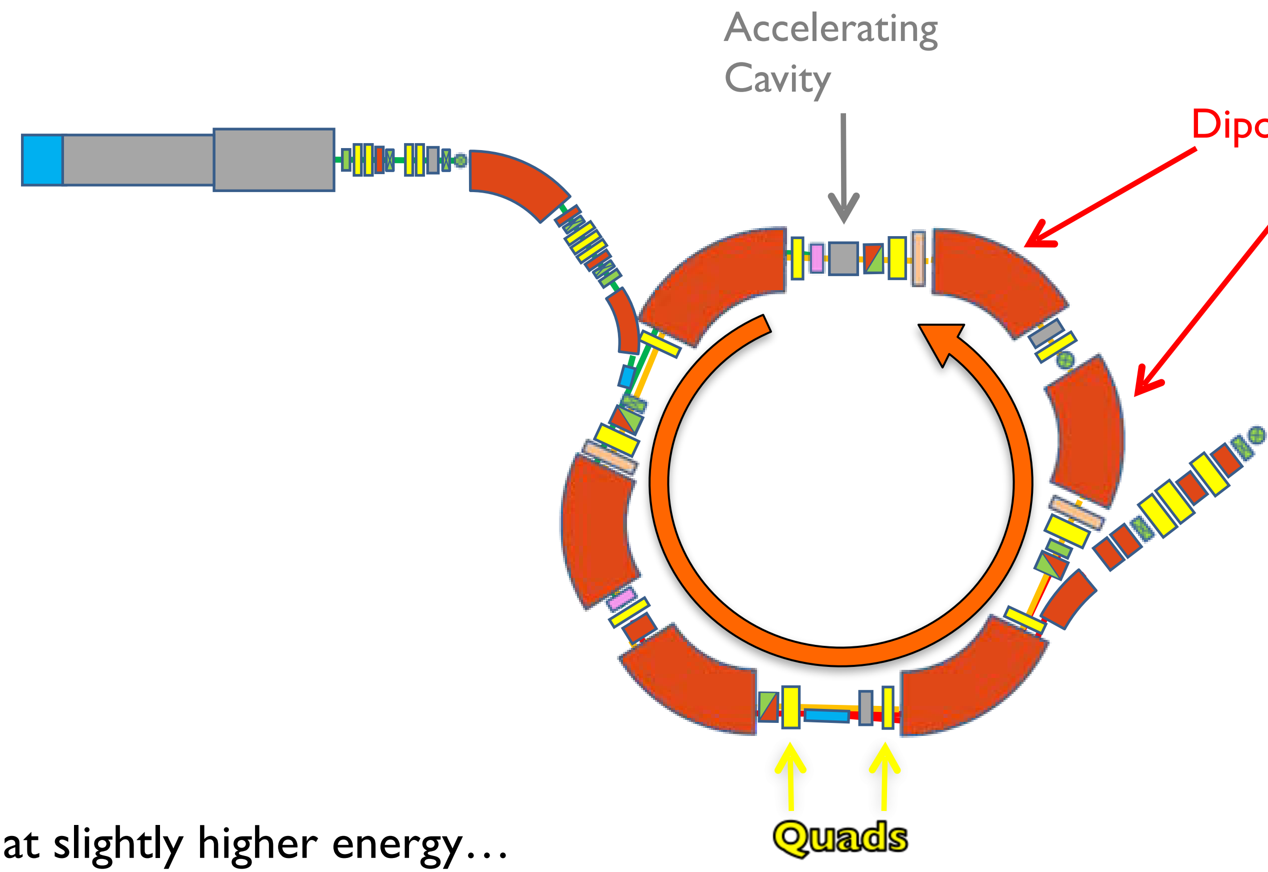
Beam orbits at slightly higher energy…

Synchrotrons: Acceleration (5)

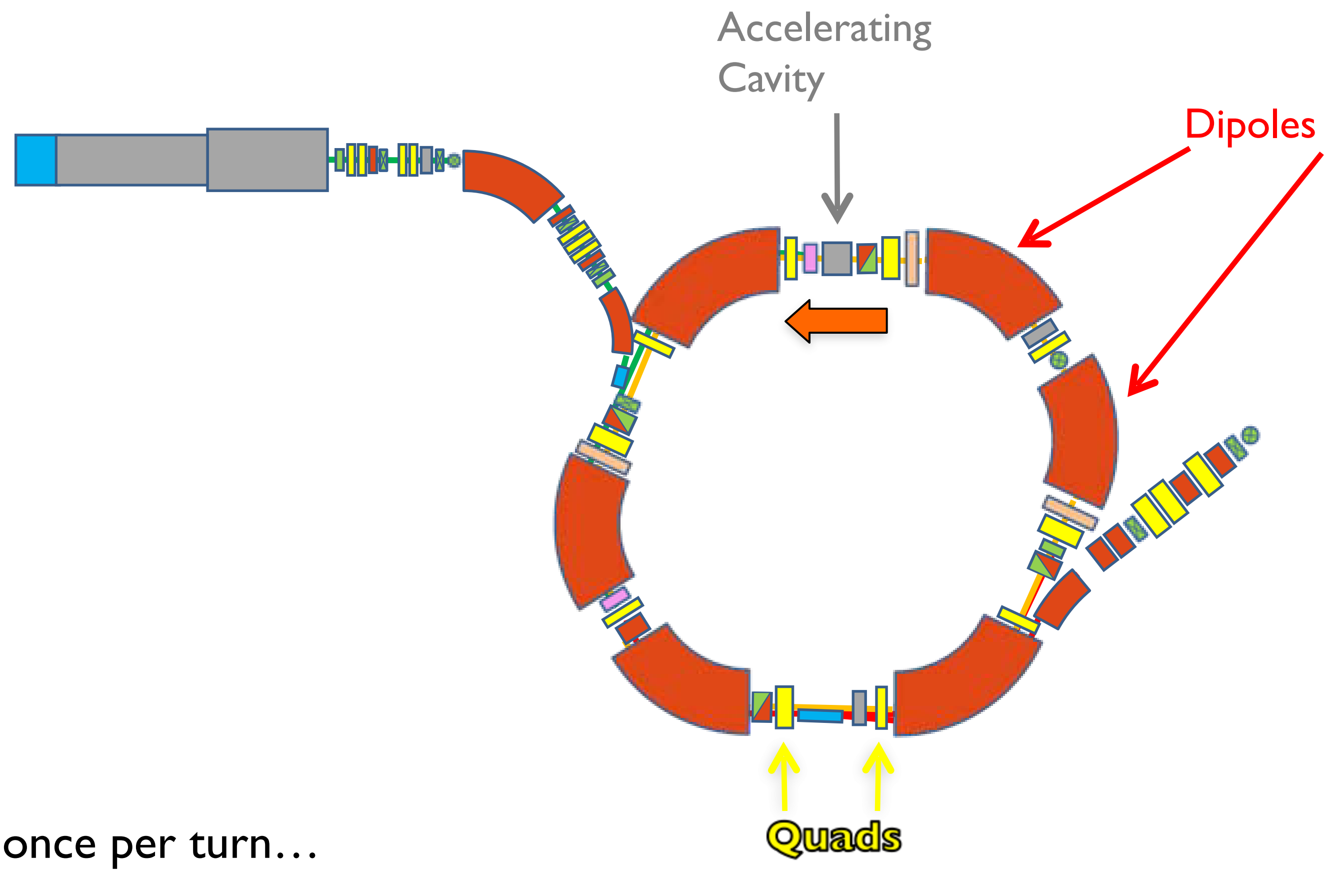


Accelerating once per turn…

Synchrotrons: Acceleration (6)

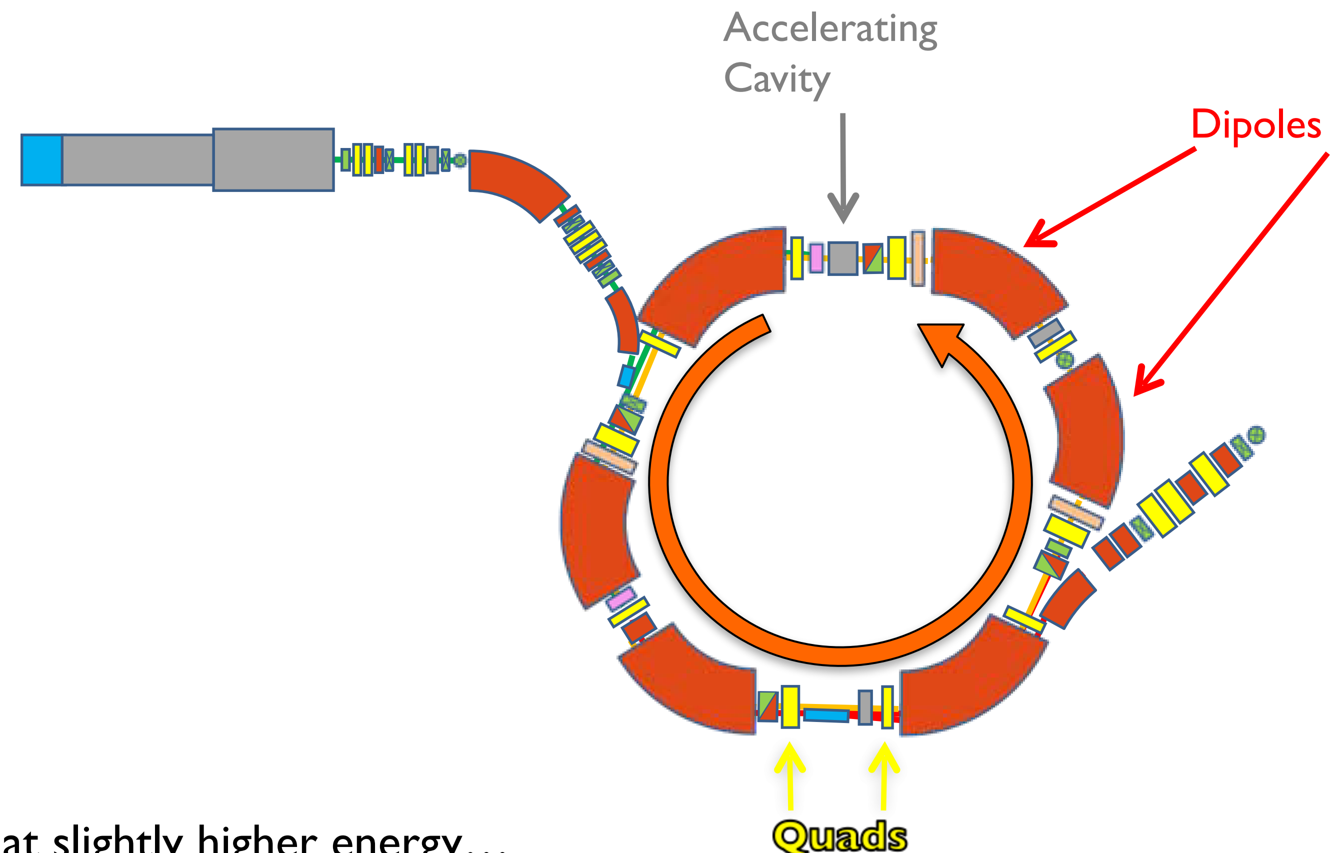


Beam orbits at slightly higher energy…



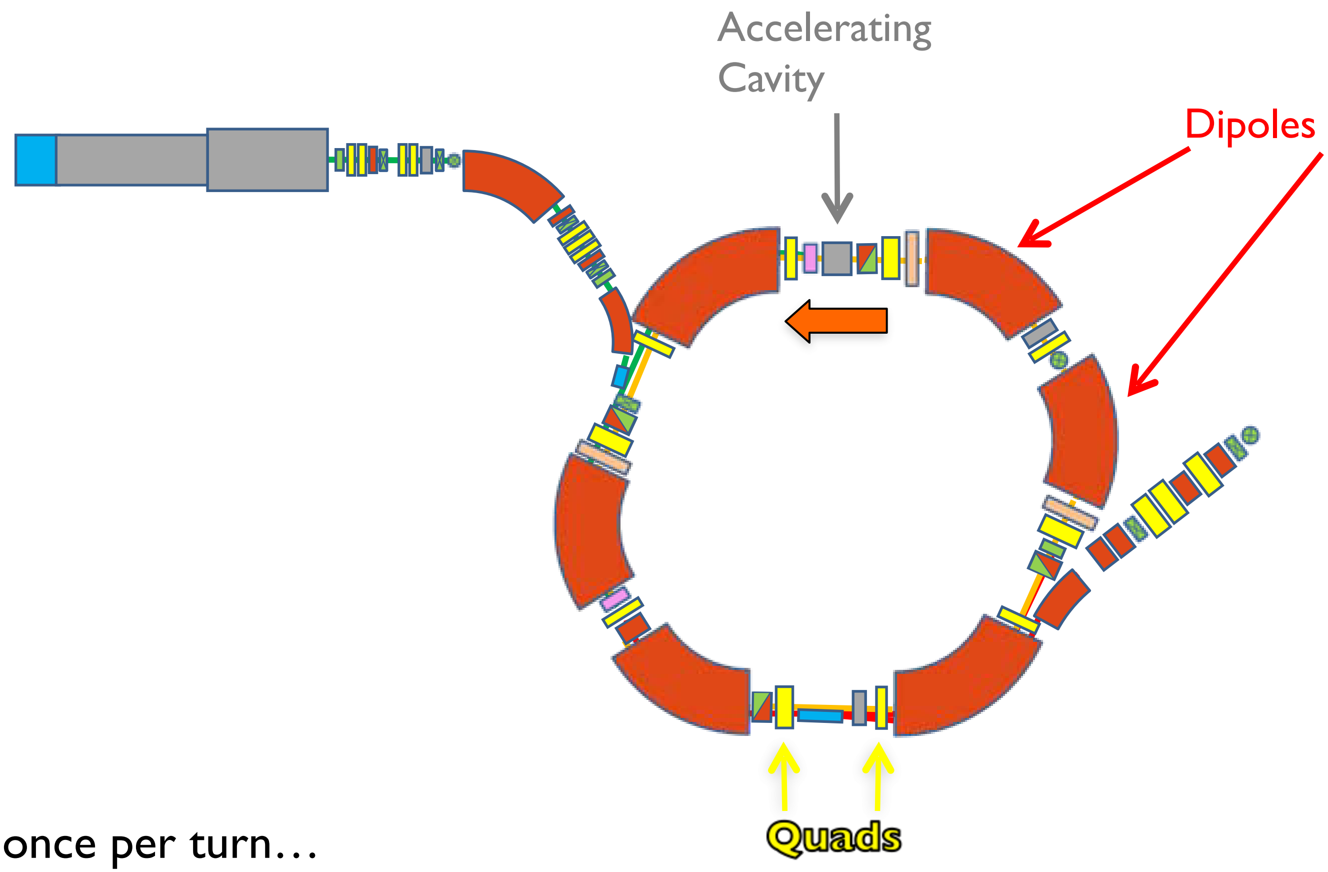
Accelerating once per turn…

Synchrotrons: Acceleration (8)



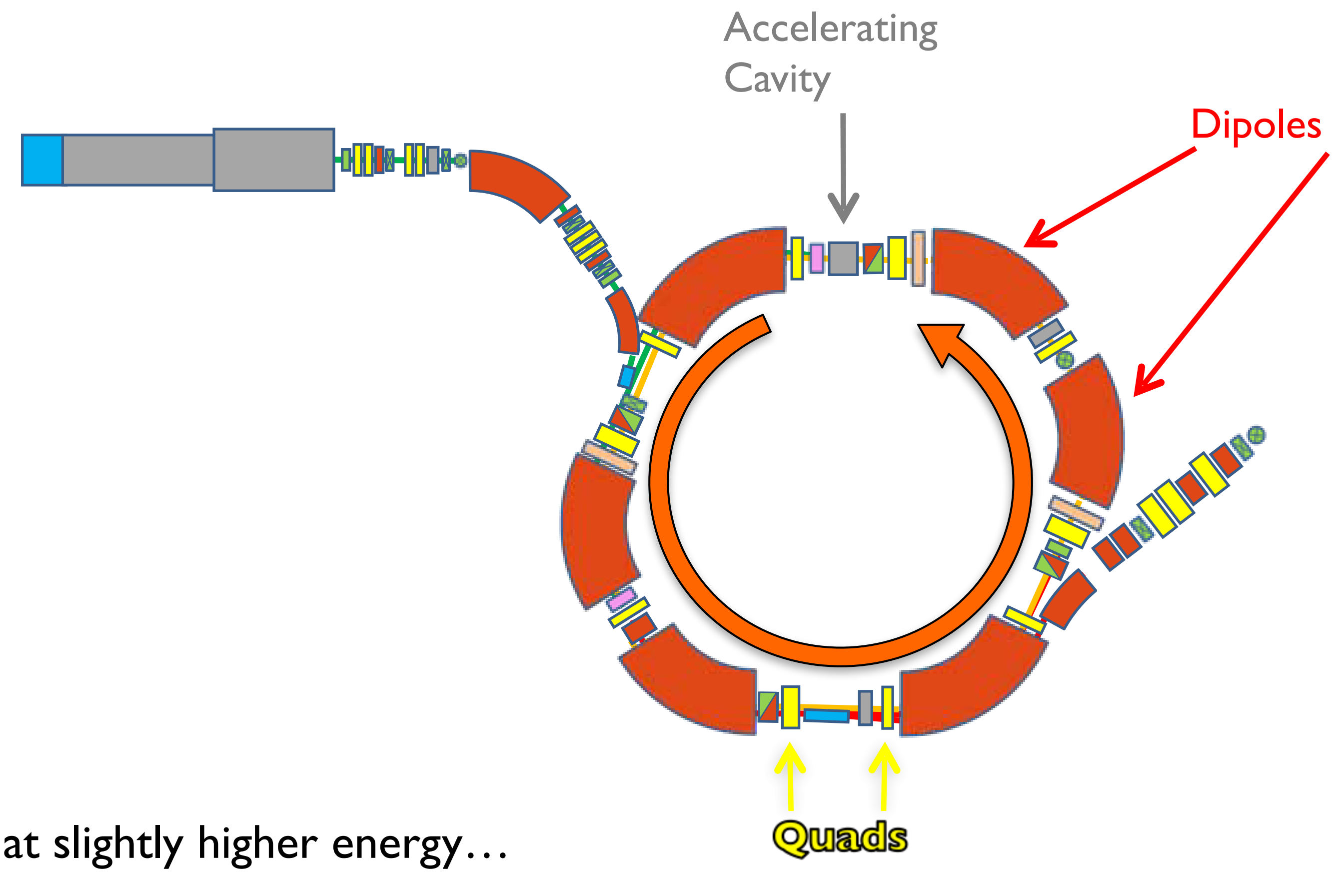
Beam orbits at slightly higher energy…

Synchrotrons: Acceleration (9)



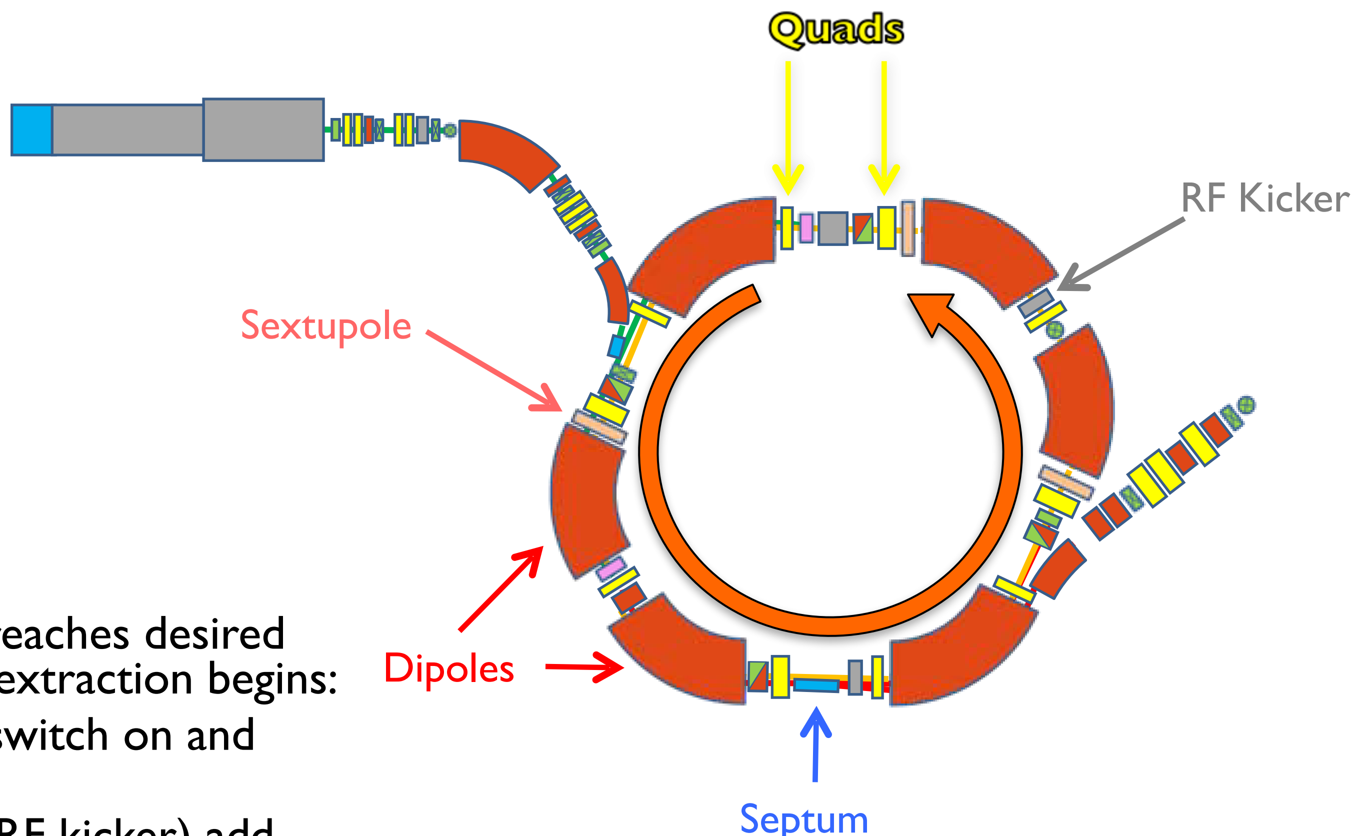
Accelerating once per turn…

Synchrotrons: Acceleration (10)



Beam orbits at slightly higher energy…

Synchrotrons: Extraction (I)



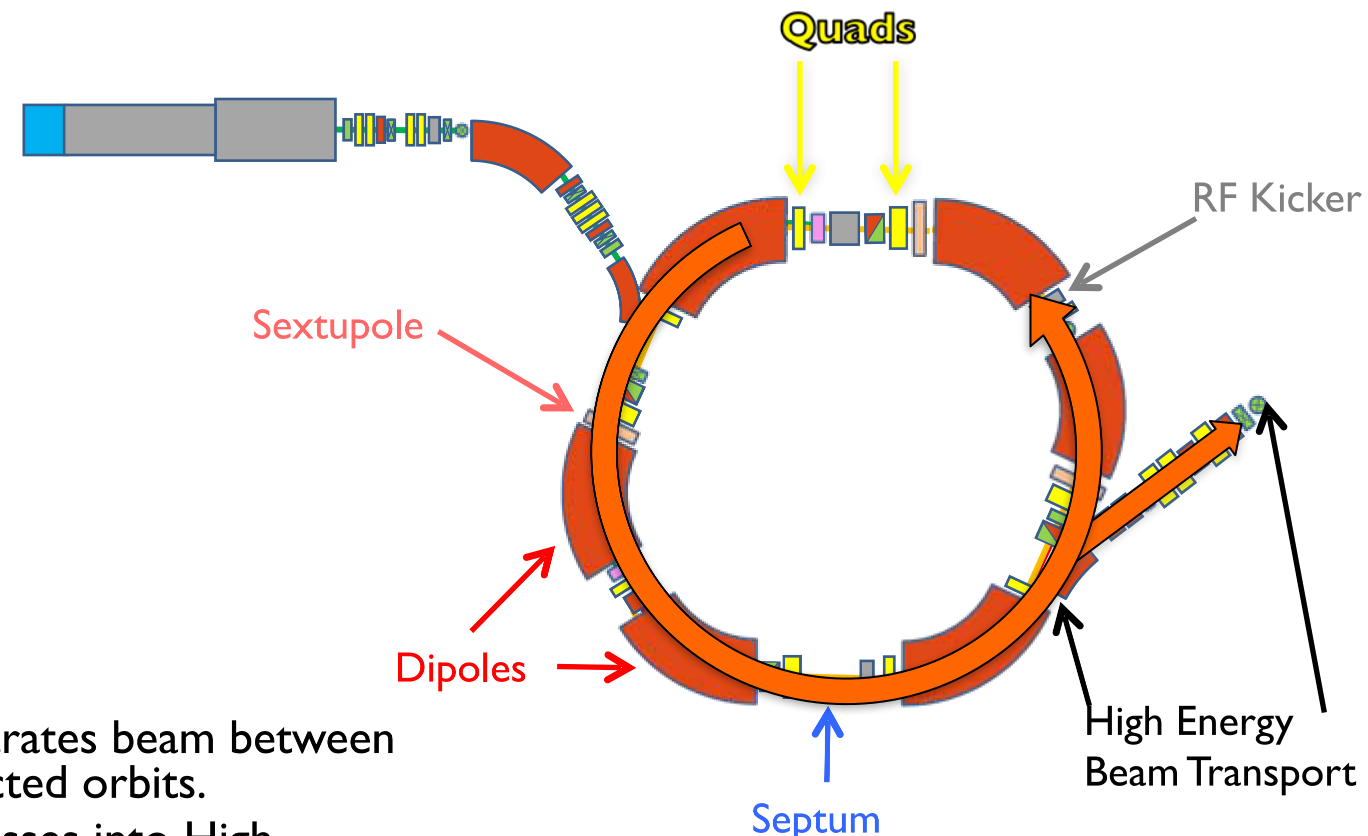
Once beam reaches desired energy, slow extraction begins:

•Sextupoles switch on and change orbit.

•RF cavities (RF kicker) add resonance to orbit.

•Some beam now outside stable orbit.

Synchrotrons: Extraction (2)

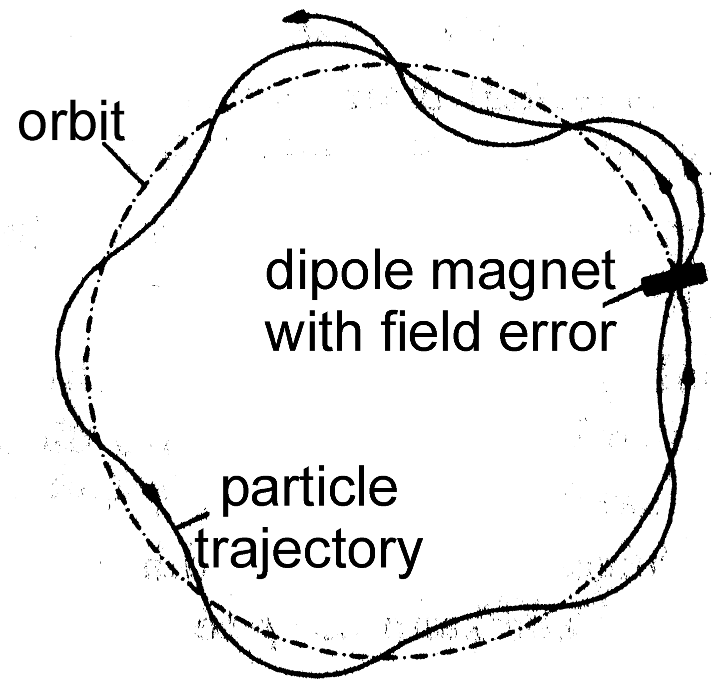


Septum separates beam between stable/extracted orbits.

Extracted passes into High Energy Beam Transport (HEBT) and on to gantries.

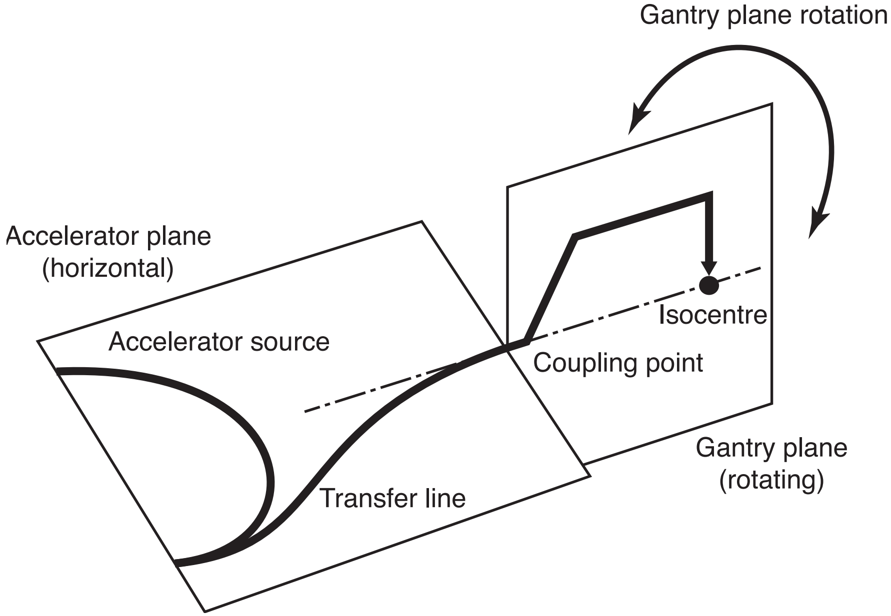
Extraction: Resonances

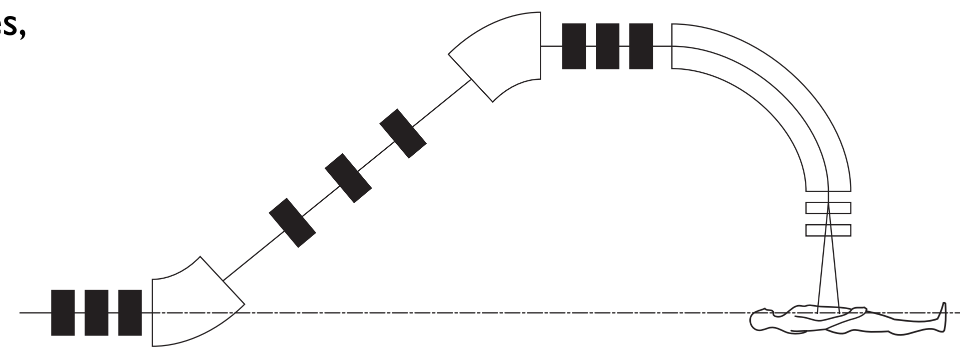
- Resonances play a big part in keeping the beam in a synchrotron.
- Because the beam has to follow the same trajectory, field errors in magnets can add up and the beam can be lost.
- To avoid these resonances, the "tune" – how many revolutions it takes to get the beam back to the same position – is always a non-integer, so field errors do not sum catastrophically.
- Sometimes we *want* to excite a resonant: this can be used for beam extraction.



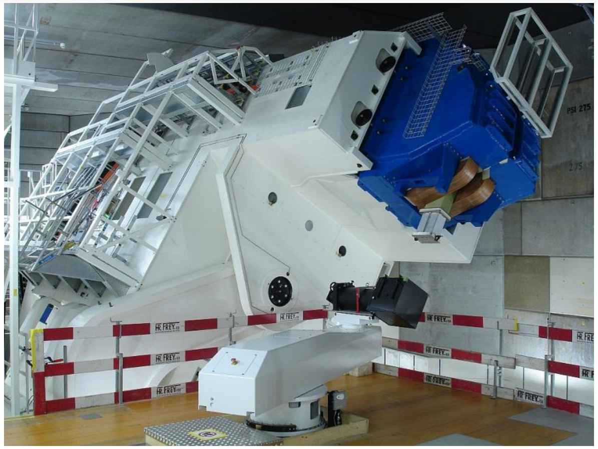
Gantries

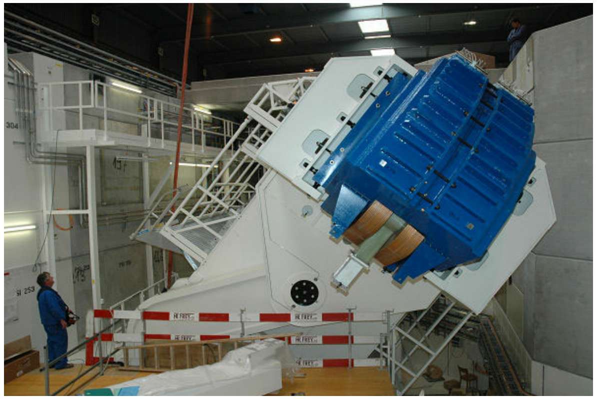
- Gantries deliver beam from accelerator to patient.
- A rotating beam transport line
  - Virtually always a single axis.
  - Focuses and directs particle beam to desired location in target volume, at any angle.
  - Gantry rotation + patient table rotation = full solid angle coverage.
- Patient is supine and stationary: setup before beam delivery on robotic couch.
- Components:
  - Mechanical structure and drive.
  - Beamline components: dipoles, quadrupoles, correctors, vacuum, diagnostics.
  - Nozzle: scattering or scanning.
  - Infrastructure.
- Large structures! Frequently above 200 tonnes, 10 m diameter.

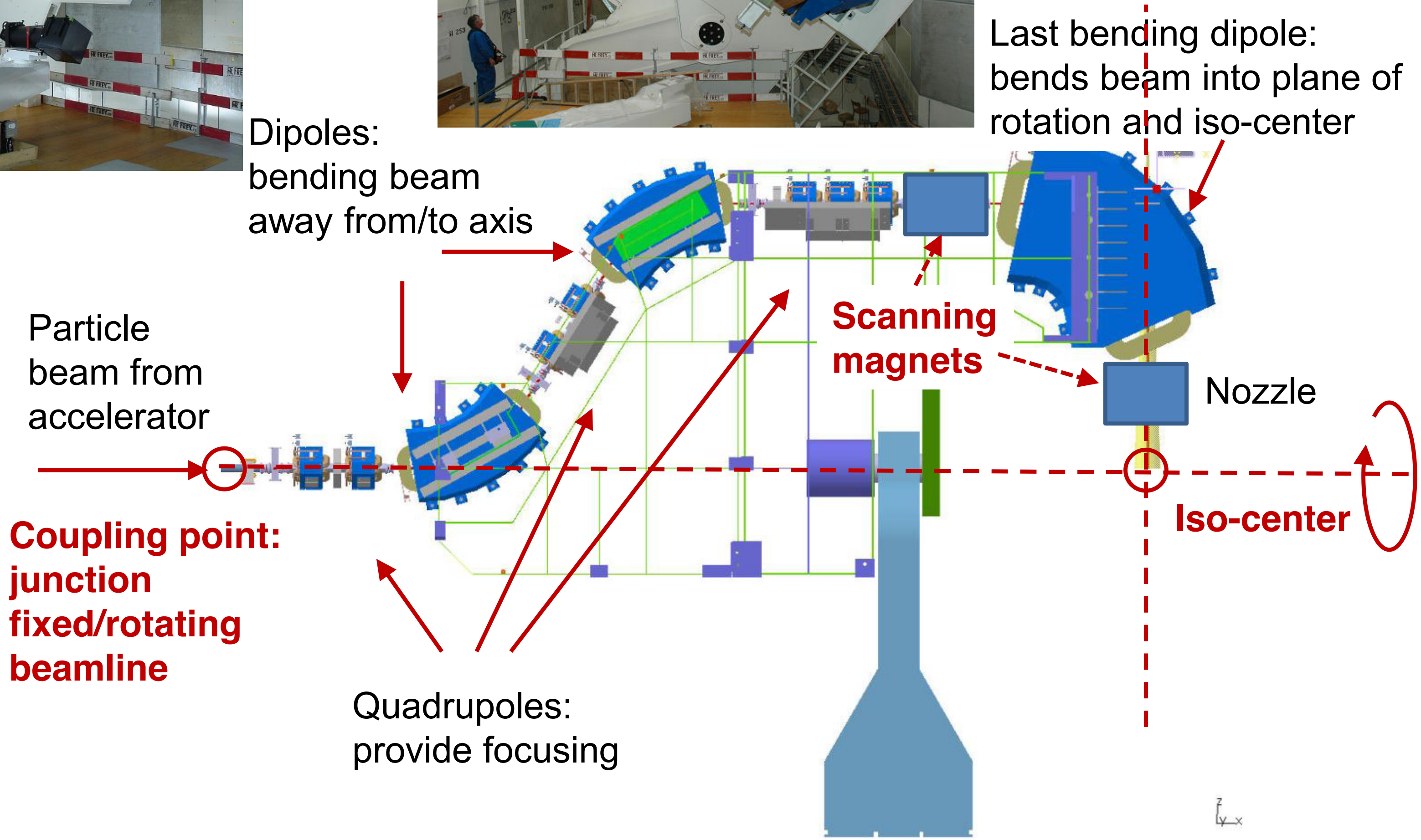




PSI Gantry 2



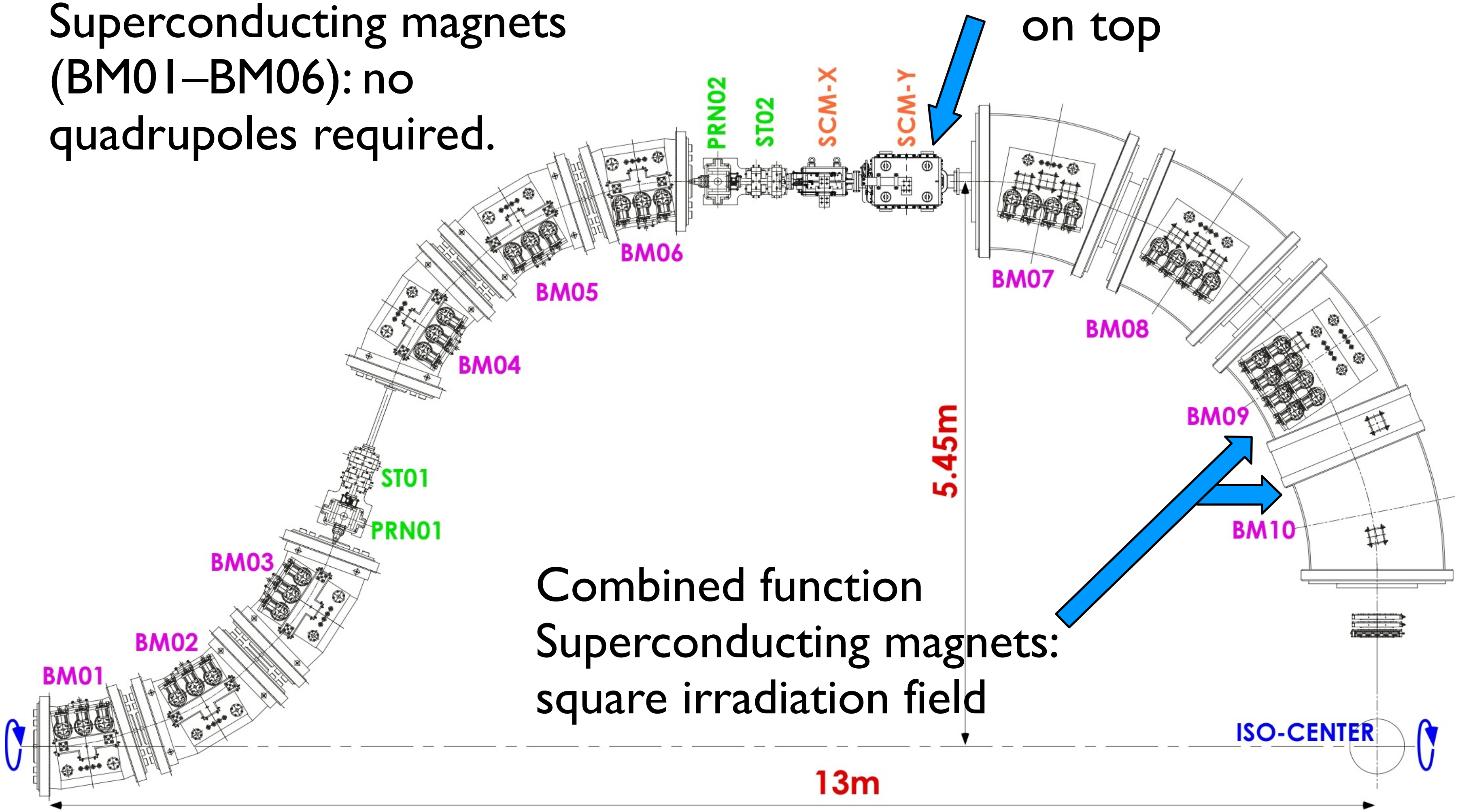



Dipoles:
bending beam
away from/to axis
Last bending dipole:
bends beam into plane of
rotation and iso-center
Particle
beam from
accelerator
Scanning
magnets
Nozzle
Iso-center
Coupling point:
junction
fixed/rotating
beamline
Quadrupoles:
provide focusing

NIRS Superconducting Gantry (2)

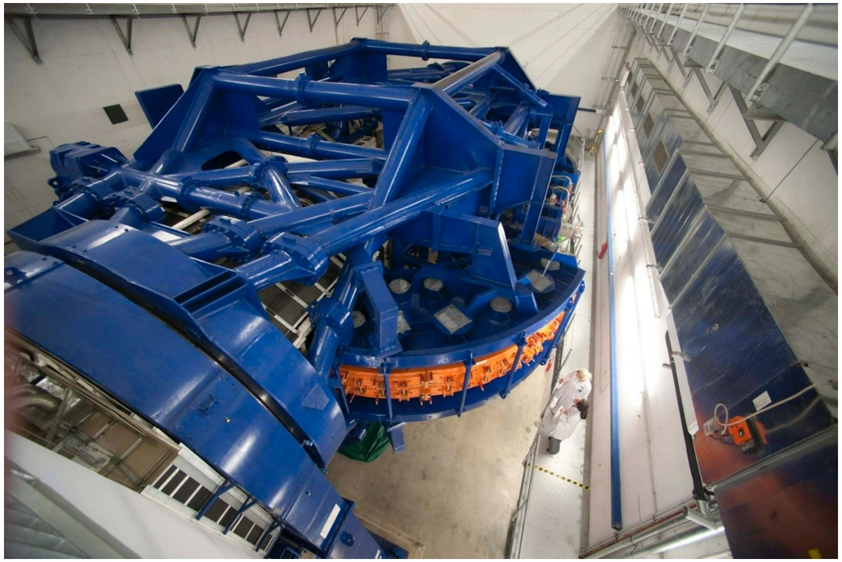
Combined function Superconducting magnets (BM01–BM06): no quadrupoles required.

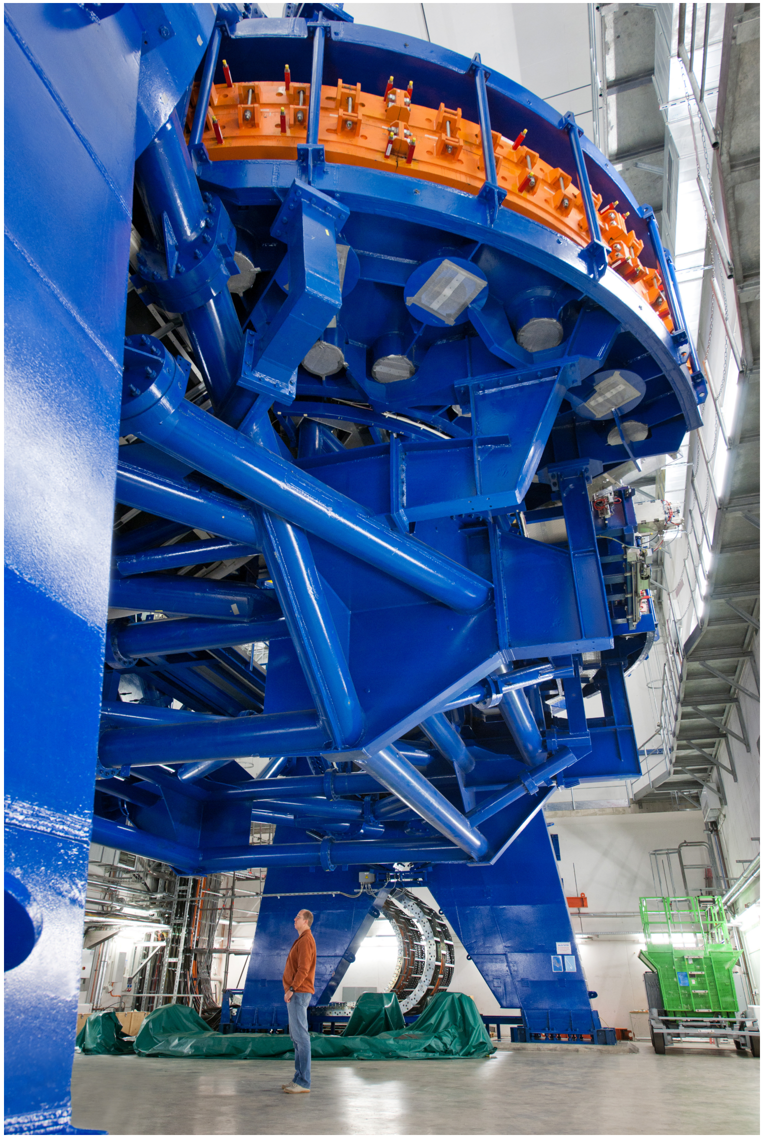
Scanning magnets on top



Combined function Superconducting magnets: square irradiation field

Heidelberg Gantry: 13 m x 22 m

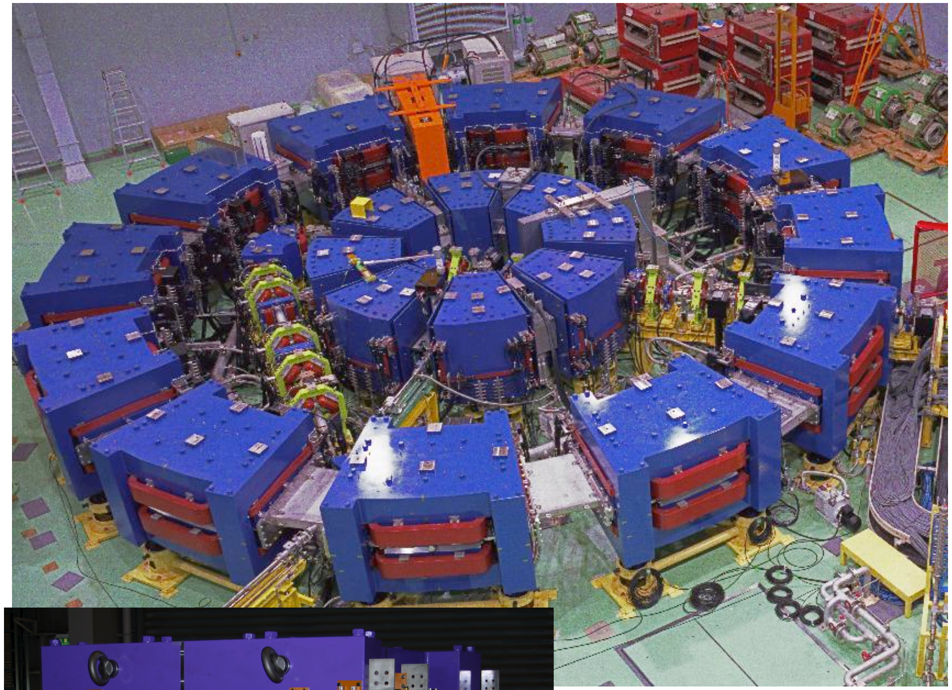
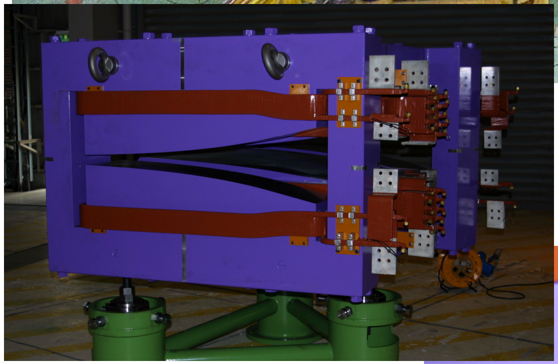
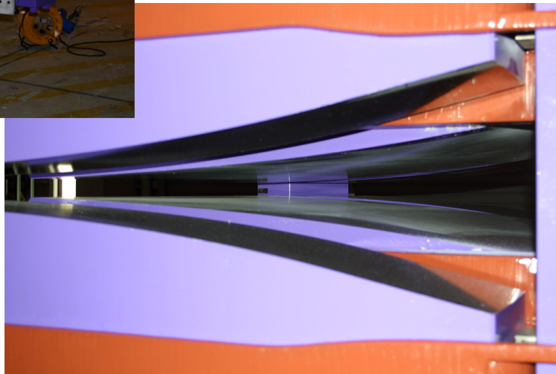
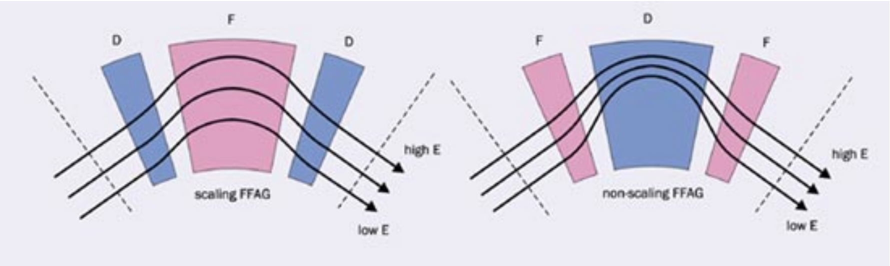




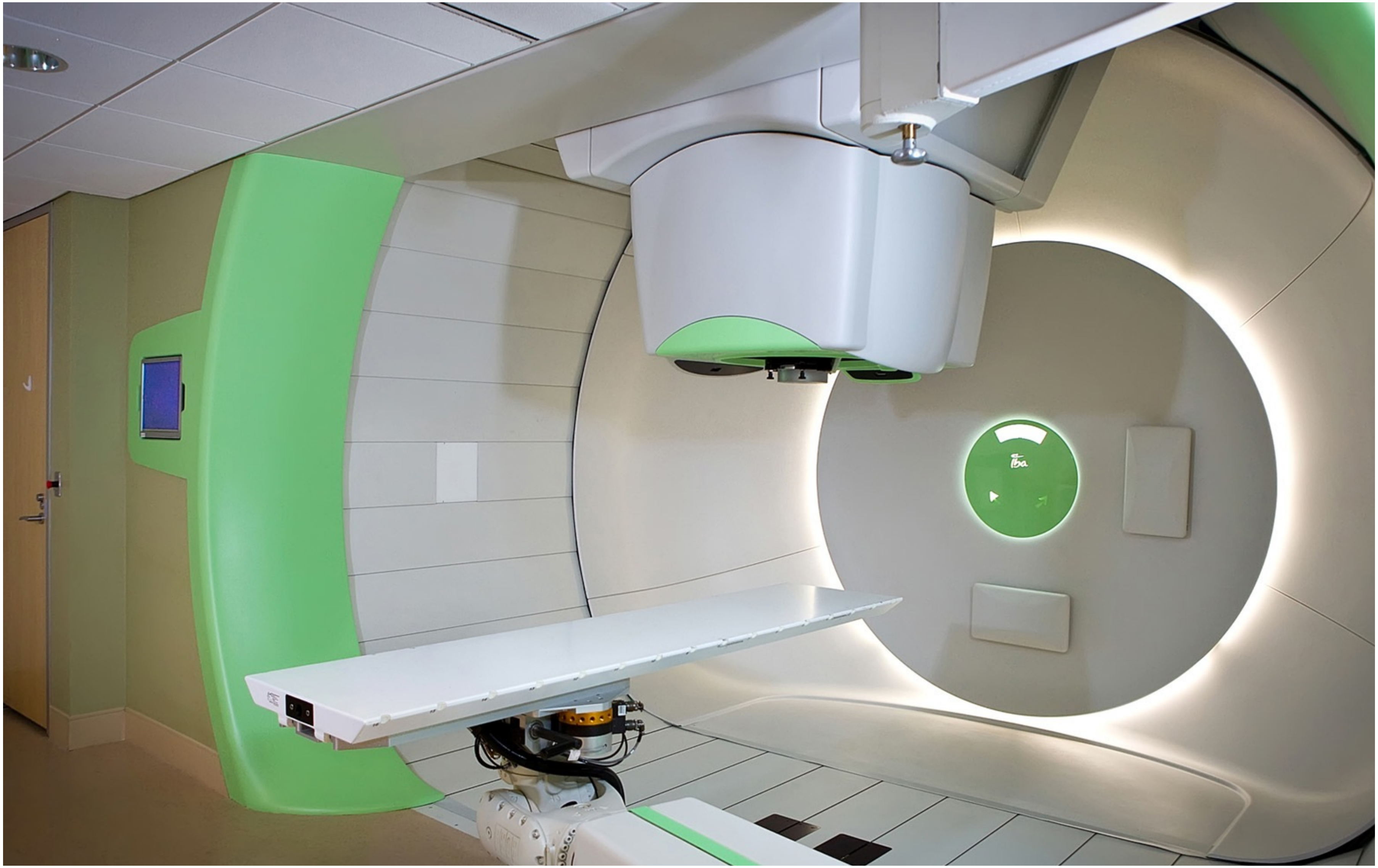
http://www.klinikum.uni-heidelberg.de/HIT-Bildergalerie.114799.0.html

FFAG Accelerators

- Fixed Field Alternating Gradient accelerators (FFAGs) are a combination of synchrotron and cyclotron.
- Field is fixed (like cyclotron) but RF varies (like synchrotron).
- Beam orbit radius increases with energy (like cyclotron), but confined to single (large) beampipe (like synchrotron).
- Taper on dipole pole pieces leads to increasing B-field with radius for simplest scaling version.
- Non-scaling version uses more complex magnet geometries to reduce size of beampipe.
- Allows FAST acceleration cycles (kHz) but with variable energy and fast energy variation since magnets do not need to be ramped.
- Need a matching gantry…

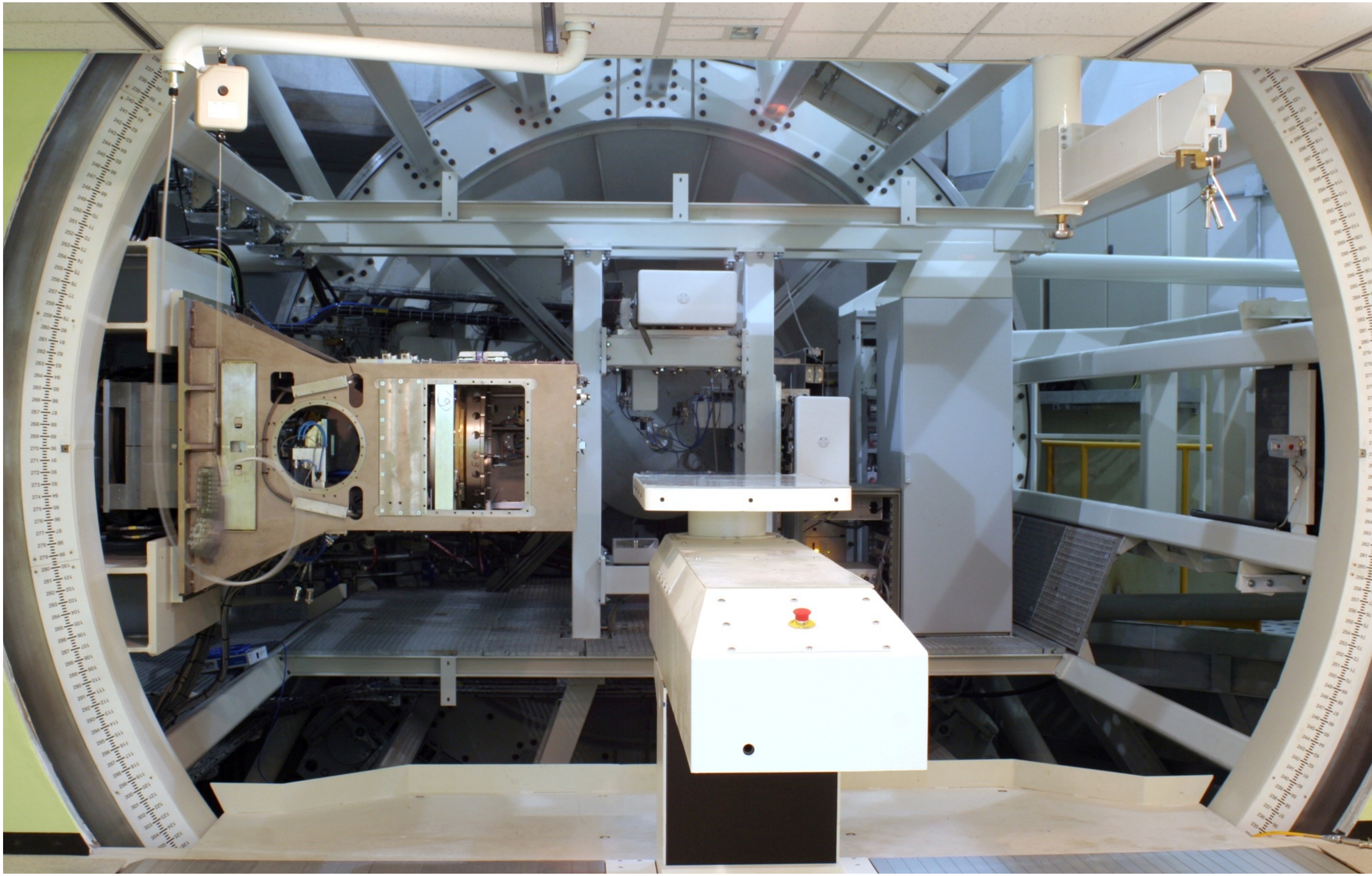





Treatment Room



Treatment Room

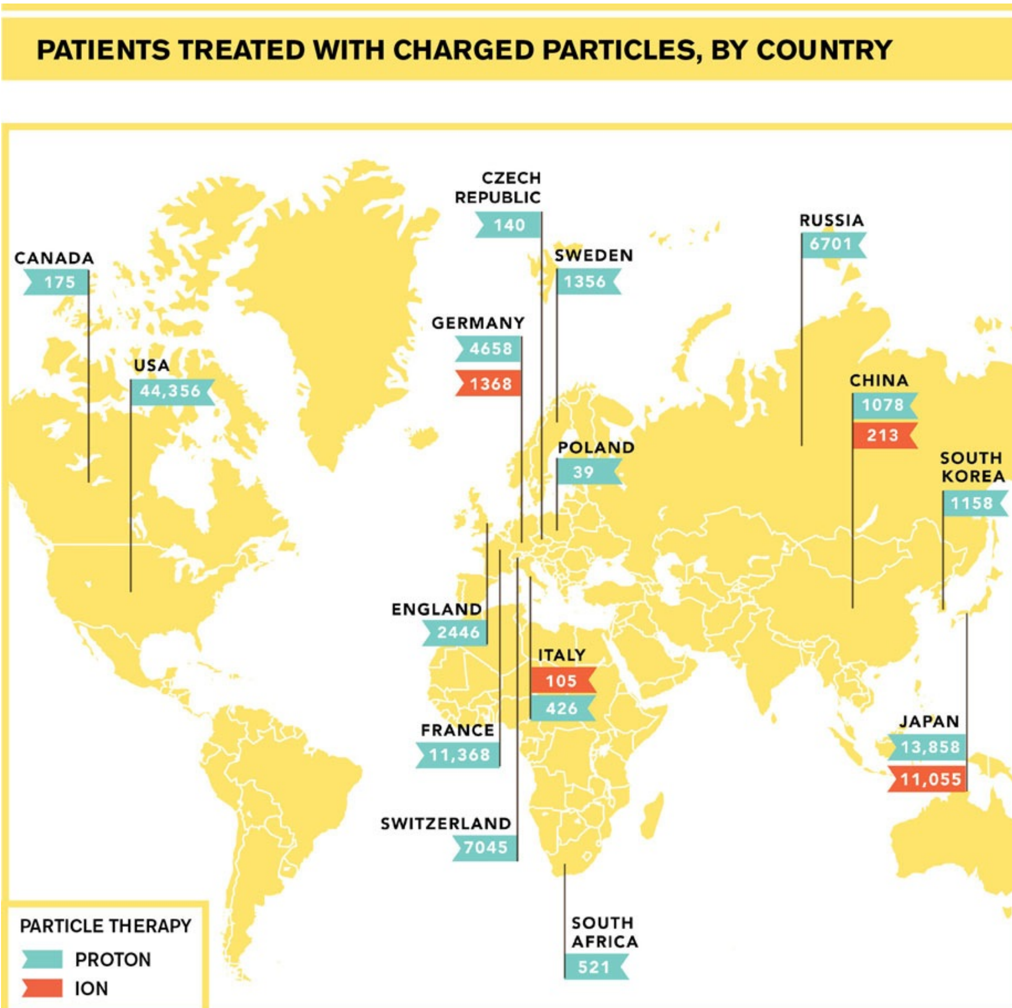
Treatment Room



Spare Slides

UK Proton Therapy

- Currently UK only has 1 proton therapy centre: Clatterbridge (Wirral) treats eyes with 60 MeV protons.
- Around 20 existing proton therapy centres worldwide with around the same number planned.
- Most countries treat private patients with simple tumours (85% prostate…).
- Some British children sent abroad for treatment in Jacksonville, FL.
- Earlier this year, government gave the go ahead for 2 new cancer treatment facilities using protons:
  - UCLH.
  - Manchester/Christie.
- Procurement began 2013, up and running in 5 years.



http://www.symmetrymagazine.org/article/september-2014/accelerating-the-fight-against-cancer

UK Proton Therapy Indications

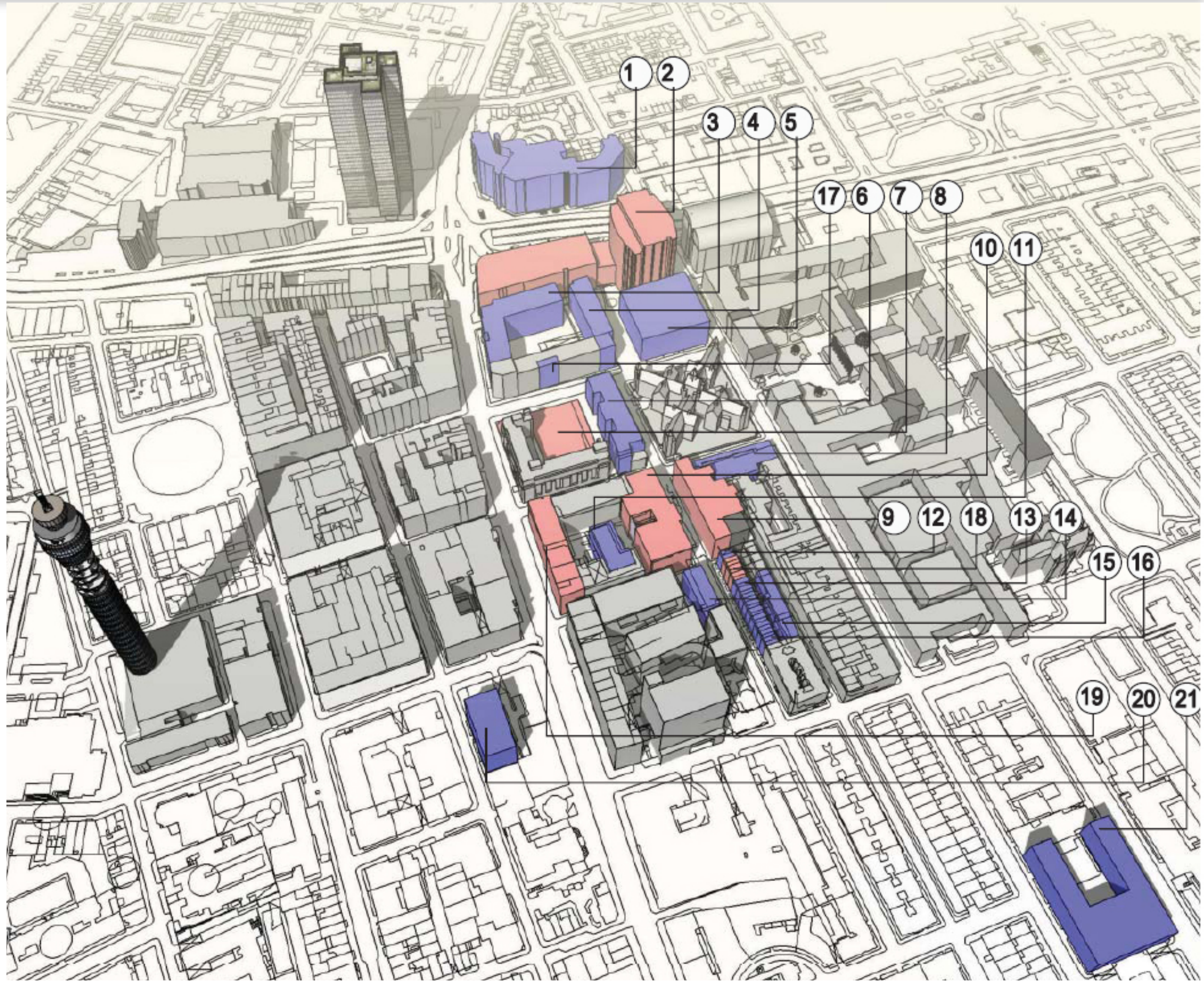
- Indications list is available on the web:
  - Strategic Outline Case: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213045/national-proton-beam-therapy-service-development-programme-value-for-money-addendum.pdf
  - Value-for-money Addendum: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213045/national-proton-beam-therapy-service-development-programme-value-for-money-addendum.pdf
- Will treat most difficult cases:
  - Brain: Chordoma, Glioma, Craniopharyngioma, Meningioma, Intracranial Germinoma
  - Skeletal: Chondrosarcoma, Rhabdomyosarcoma, Osteosarcoma, Ewings sarcoma,
  - Central Nervous System: Ependymoma, Medulloblastoma (PNET), Spinal Sarcoma
  - Head & Neck: Retinoblastoma, Nasopharynx, Acoustic Neuroma
  - Others: Hodgkins

	Indication	Number of patients
Paediatric	Chordoma/ Chondrosacoma	15
	Rhabdomyosarcoma (Orbit)	5
	Rhabdomyosarcoma (Prameningeal and H&N)	15
	Rhabdomysarcoma(Pelvis)	10
	Osteosarcoma	3
	Ewings	9
	PPNET	5
	Ependymoma	25
	Low Grade Glioma	5
	Optic Pathway Glioma	12
	Craniphayngioma	15
	Medulloblastoma (PNET)	70
	Hodgkins	5
	Retinoblastoma	5
	Meninggioma	3
	Intracranial germinoma	10
	Nasopharynx (H&N)	15
	Difficult Cases Esthe/Neuro/Liver)	5
	Very Young Age	20
	Total	**252**
Adult	**Choroidial Melanoma**	100
	Ocular/Orbital	25
	Chordoma	60
	Chondrosarcoma	30
	Para- Spinal / Spinal Sarcoma	120
	Sacral Chordoma	60
	Meningoma	100
	Acoustic Neuroma	100
	Craniospinal NOS (Pineal)	10
	Head & Neck & Paranasal Sinuses	300
	PNET(medulloblastoma Intracranial)	30
	Difficult cases	300
	Total	**1,235**
	GRAND TOTAL	**1,487**

UCLH Cancer Campus

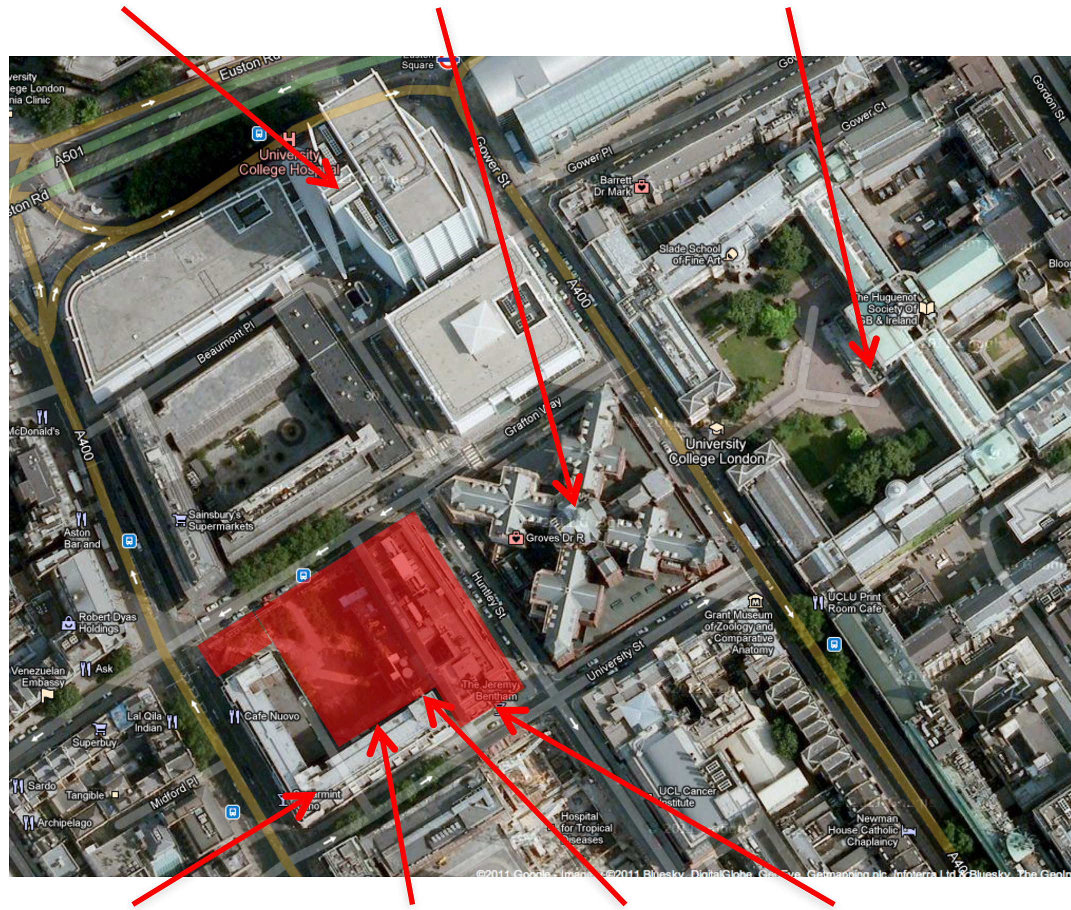
UCH CAMPUS
CANCER RELATED IN 2015

1. 250 EUSTON ROAD
2. UCHL MAIN WING
3. MAPLE HOUSE
4. MAPLE HOUSE LABORATORIES
5. UCHL EGA WING
6. ROSENHEIM BUILDING
7. ODEON SITE
8. ROCKEFELLER BUILDING
9. PAUL O'GORMAN BUILDING
10. CANCER CENTRE
11. HOSPITAL FOR TROPICAL DISEASES
12. 70 HUNTLEY STREET
13. 62 HUNTLEY STREET
14. ROYAL EAR HOSPITAL
15. CHENIES MEWS
16. 46-60 HUNTLEY STREET
17. MAPLE HOUSE FLATS
18. PAUL'S HOUSE (CLIC SARGENT)
19. PROPOSED PATIENTS' HOTEL 170 TOTTENHAM COURT ROAD
20. WHITFIELD STREET LABORATORIES
21. BONHAM CARTER HOUSE / WARWICKSHIRE HOUSE

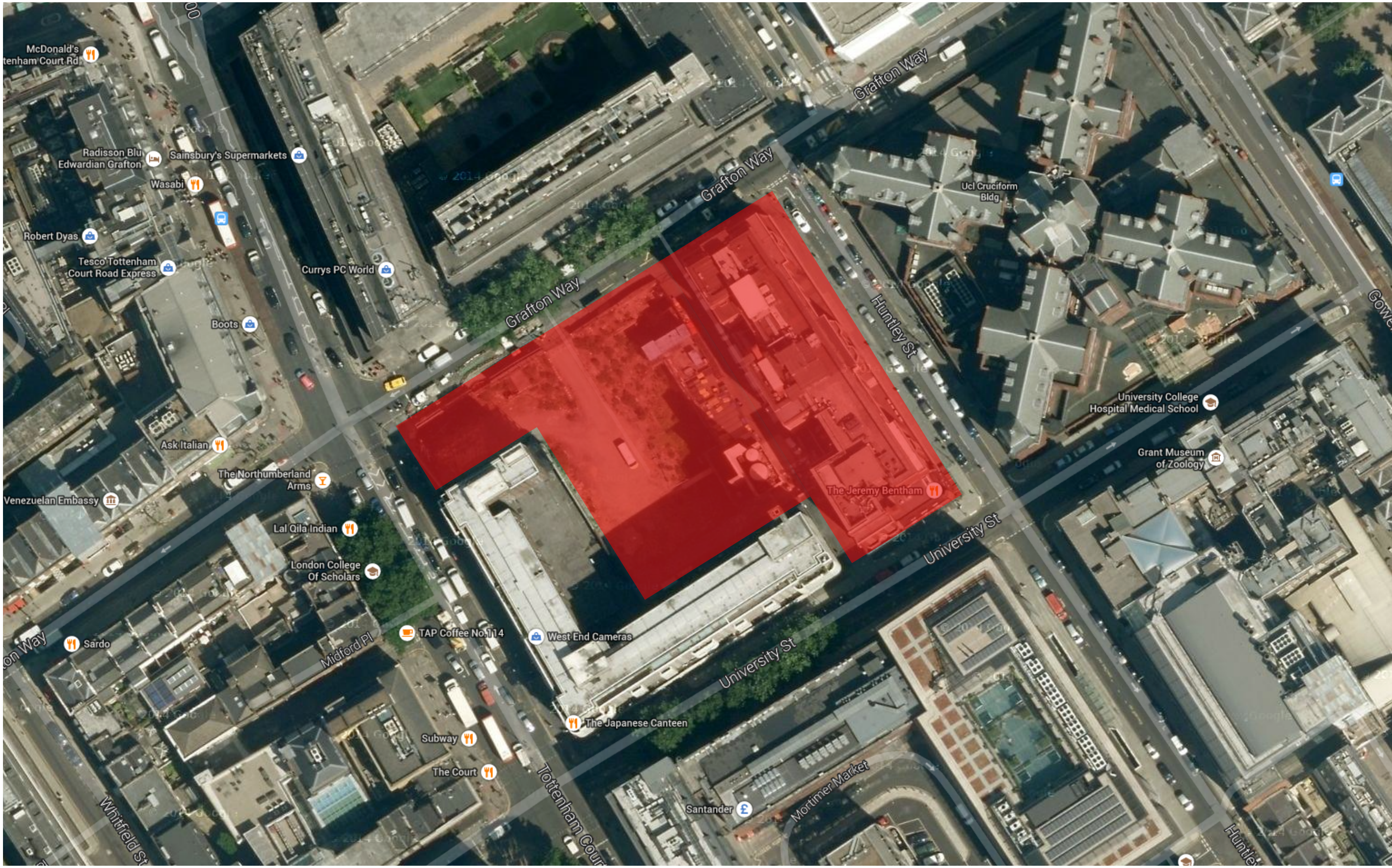


UCLH Proton Therapy Site

- New facility will be on existing UCLH site, next to Tottenham Court Road.
- Linked to UCLH via walkways to allow easy patient transfer.
- Planning to treat ~750 patients a year.
- 1 proton accelerator feeding 4 gantries (plus research room).
- Total cost: £150 million.

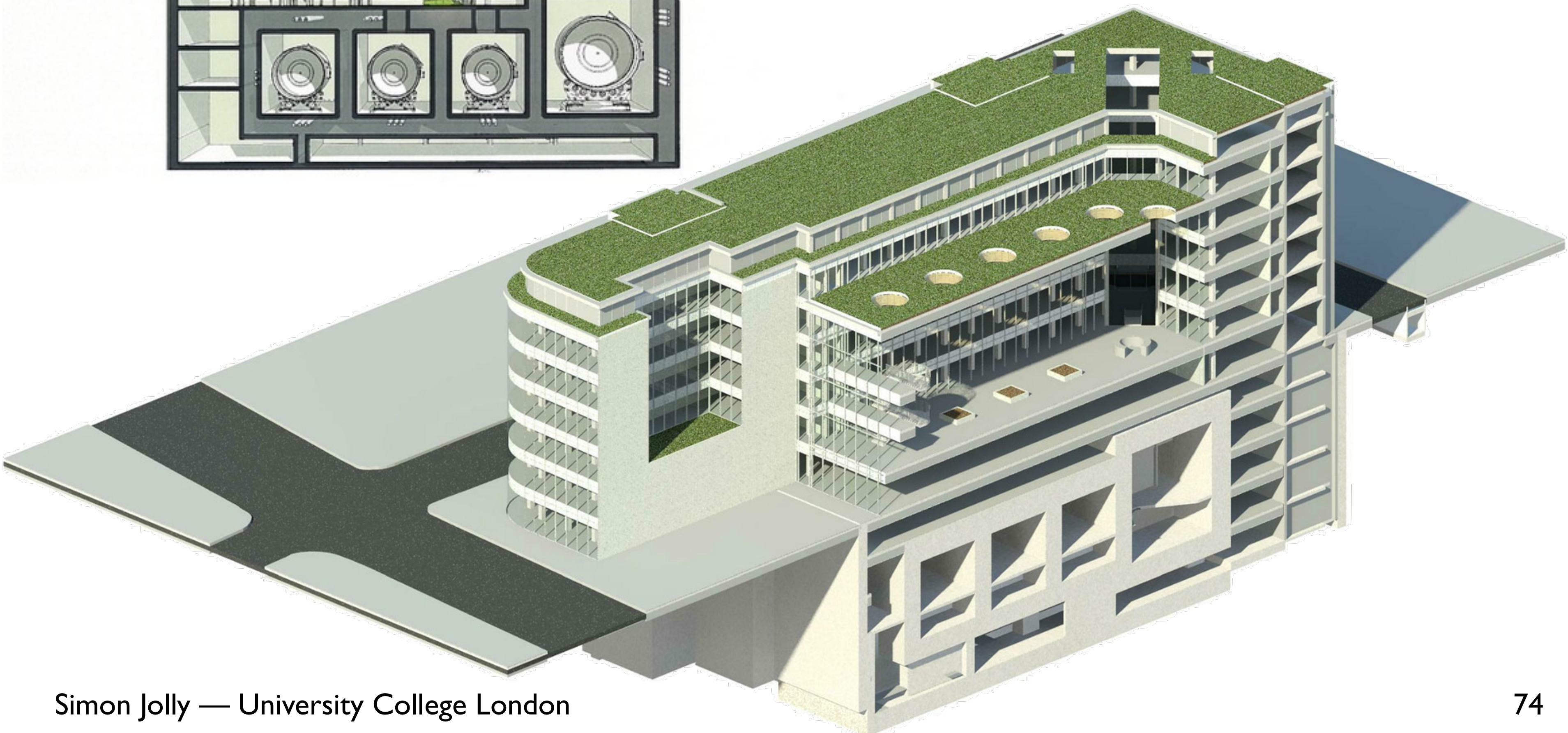


UCLH PBT Site



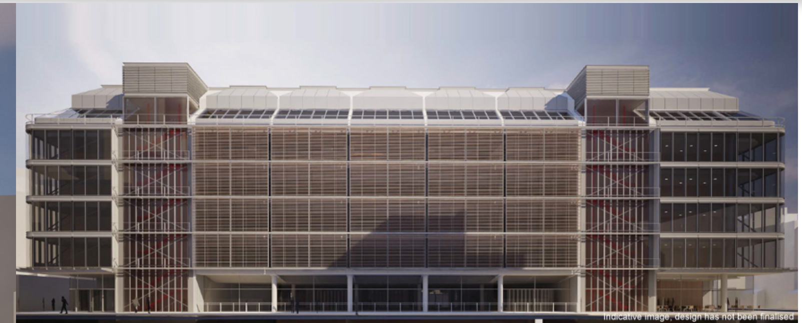
Google Maps

UCLH PBT Cut-through (Old)

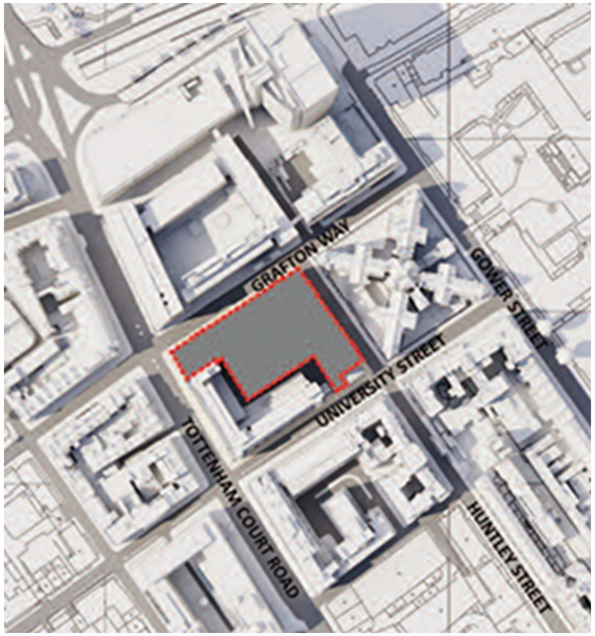


UCLH PBT Building

UCLH PBT External



UCLH PBT (TCR/Grafton Way)



UCLH PBT (Grafton Way)

Down Comes The Rosenheim…