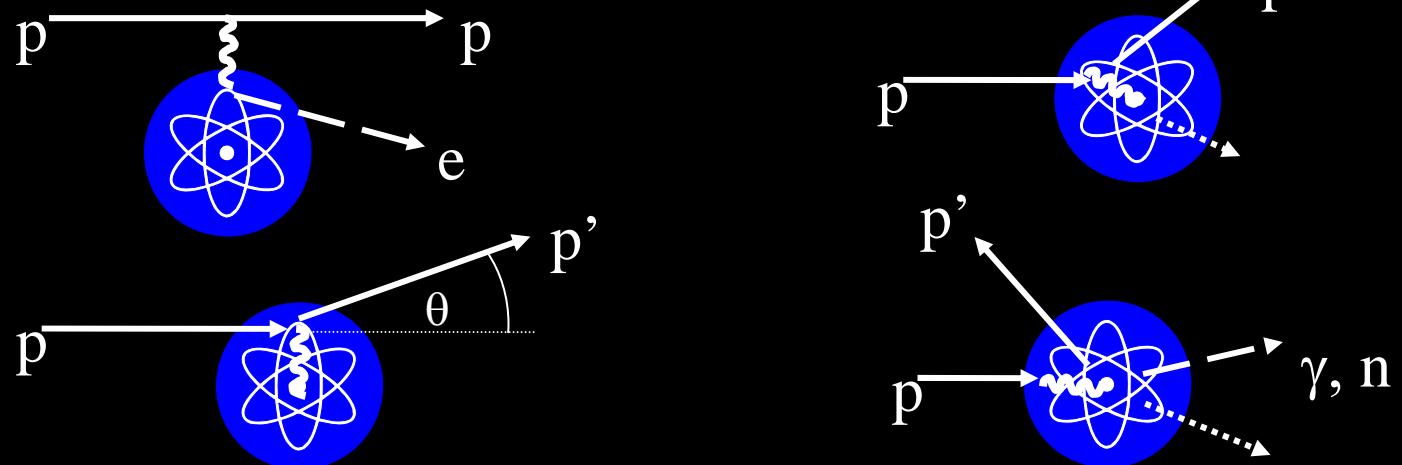
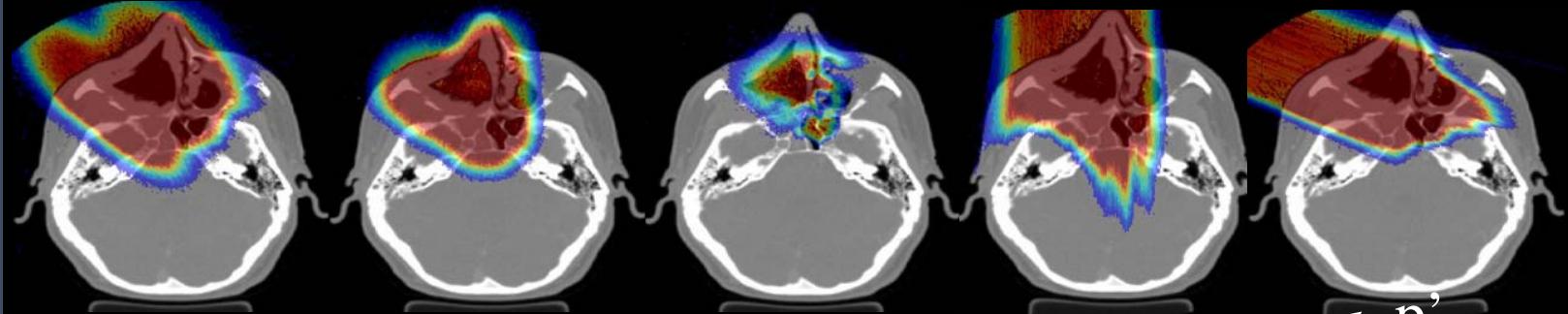


Nuclear data impact on proton radiation therapy calculations



Harald Paganetti



MASSACHUSETTS
GENERAL HOSPITAL

HARVARD
MEDICAL SCHOOL



Nuclear data impact on proton radiation therapy calculations

- Impact of nuclear interactions on dose
- Neutron dose in proton beam therapy
- PET imaging for quality assurance
- Monte Carlo benchmarking



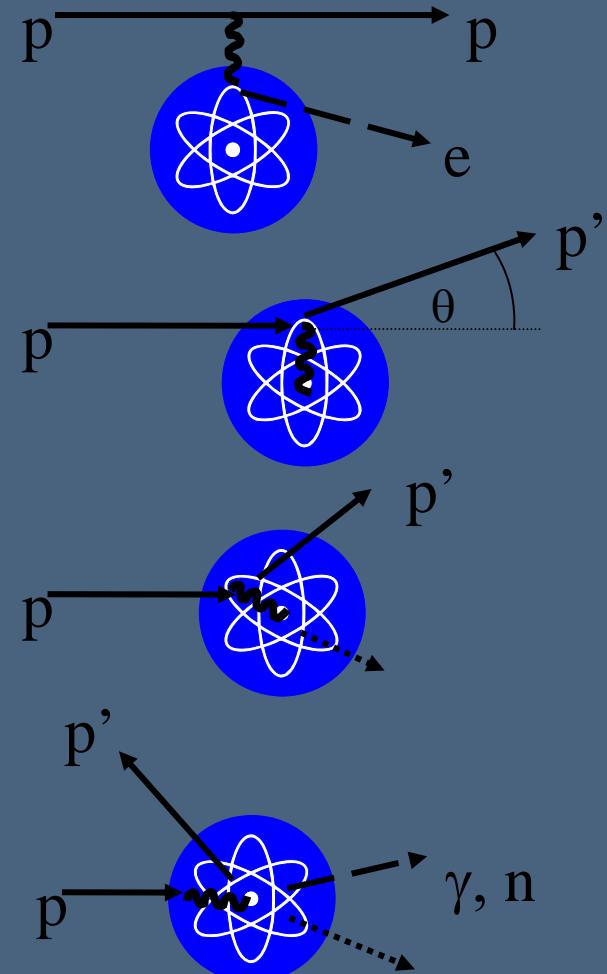
Nuclear data impact on proton radiation therapy calculations

- Impact of nuclear interactions on dose



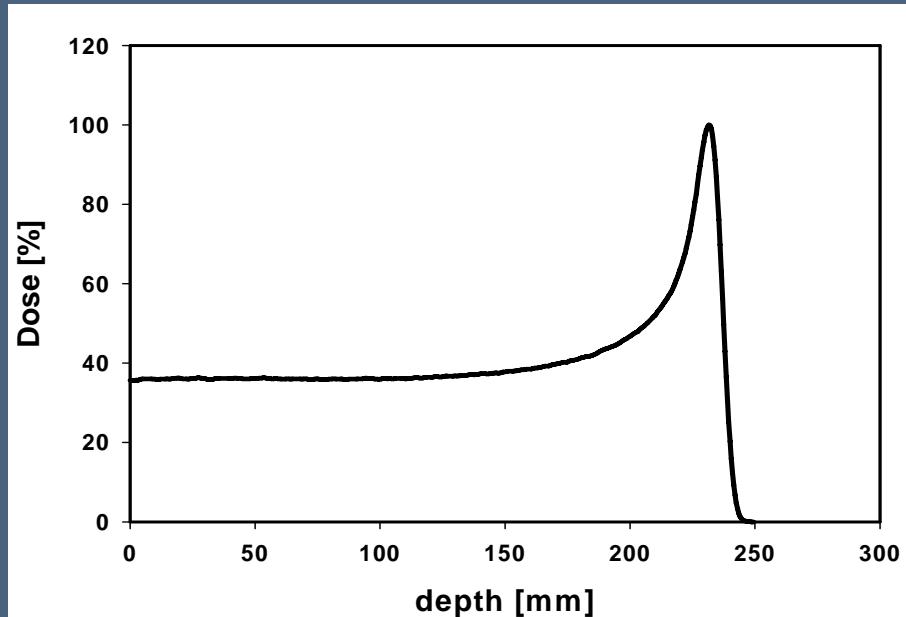
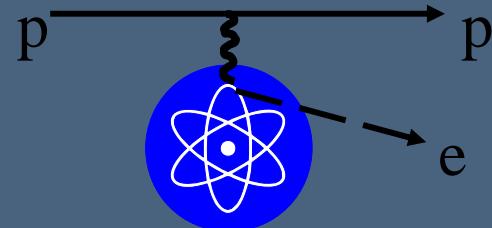
Energy deposition of protons

- Electronic (energy loss)
 - Ionization
 - Excitation
- Nuclear (energy loss, fluence reduction)
 - Multiple Coulomb scattering , small θ
 - Elastic nuclear collision, large θ
 - Nuclear interaction



Electromagnetic energy loss of protons

- Distal distribution

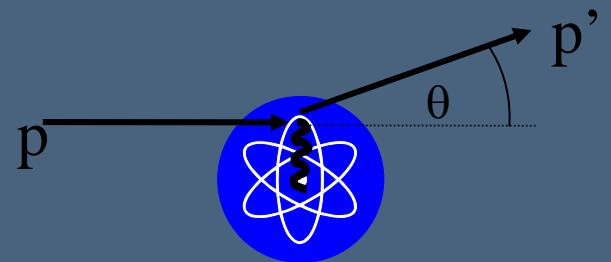


Peak broadening due to range straggling

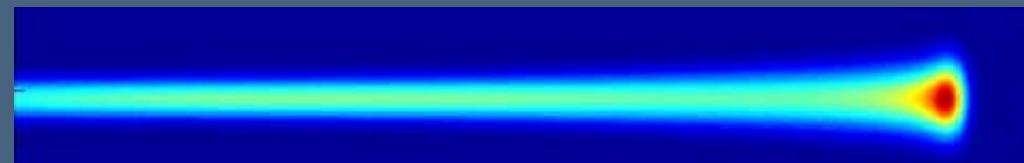
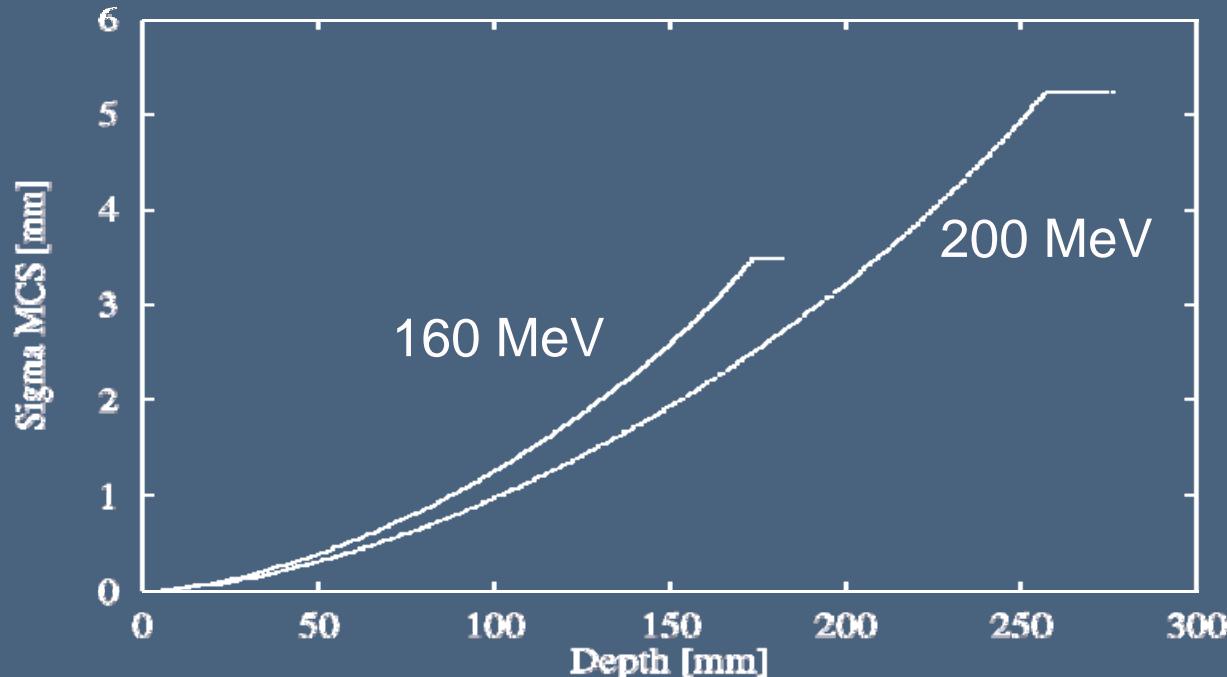


Electromagnetic energy loss of protons

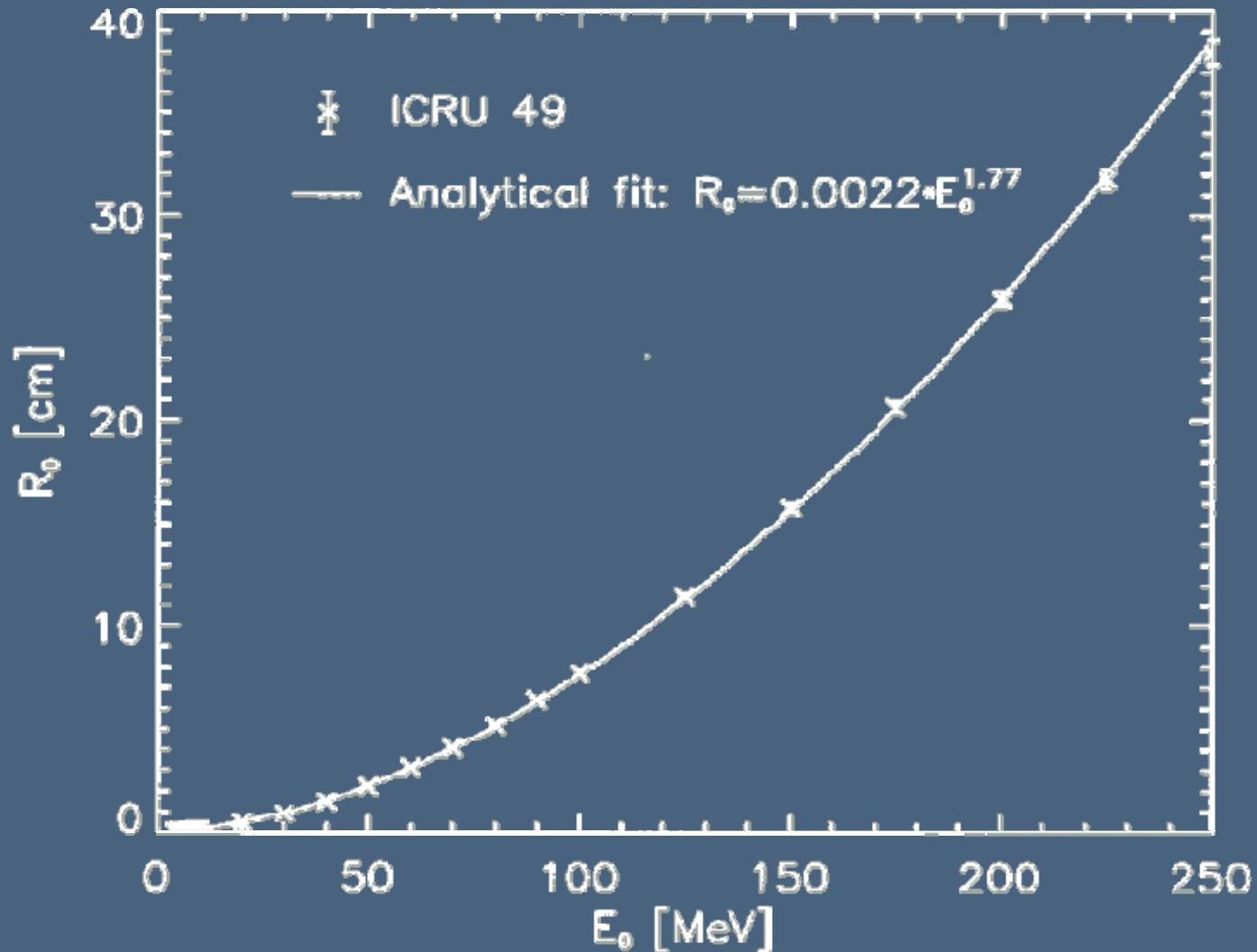
- Lateral distribution



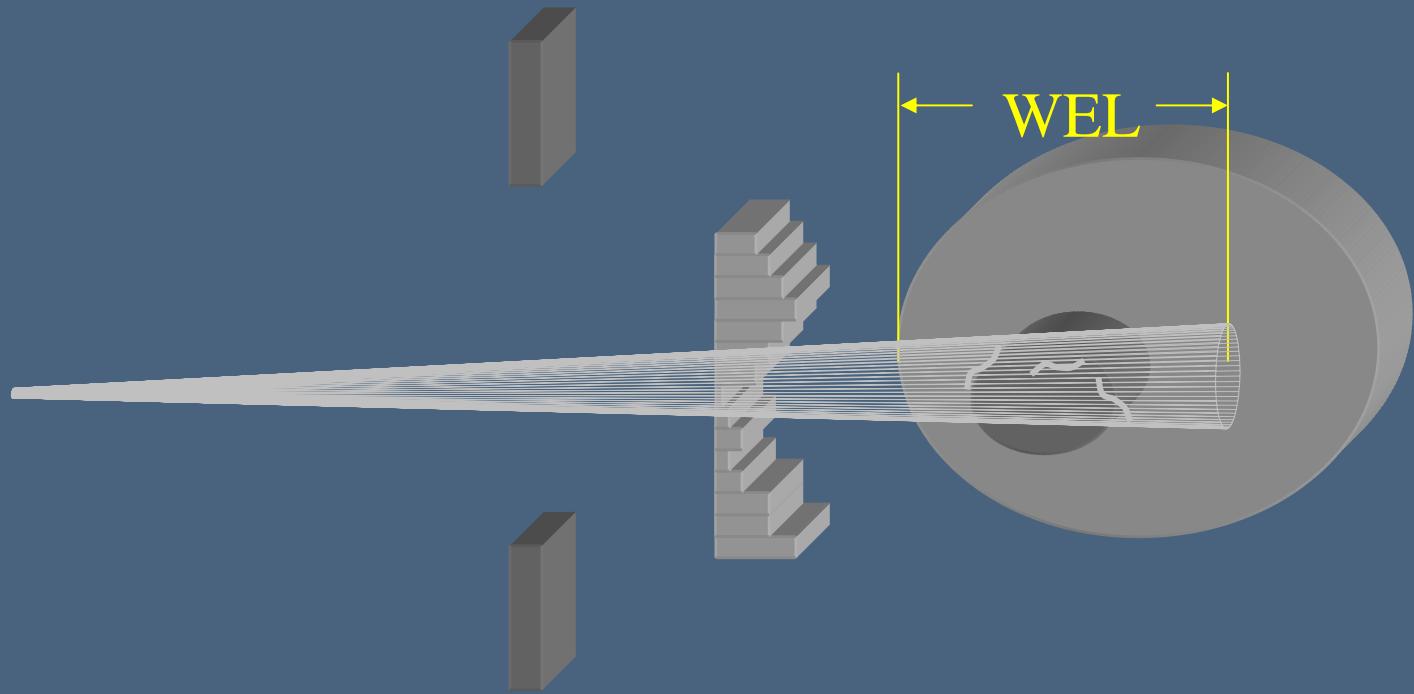
Multiple Coulomb scattering



Energy-range relationship of protons (driven by electronic energy loss)



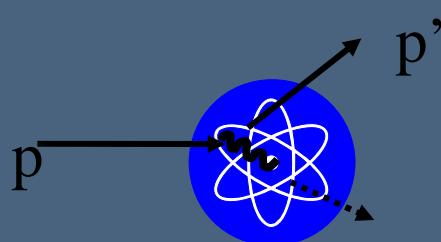
Pencil Beam Algorithms



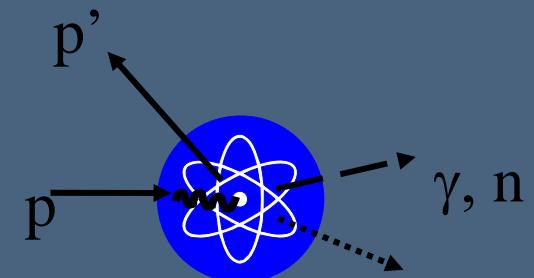
- Measured or calculated pencil kernel
- Water-equivalent pathlength



Nuclear interactions of protons



Elastic nuclear collision (large θ)

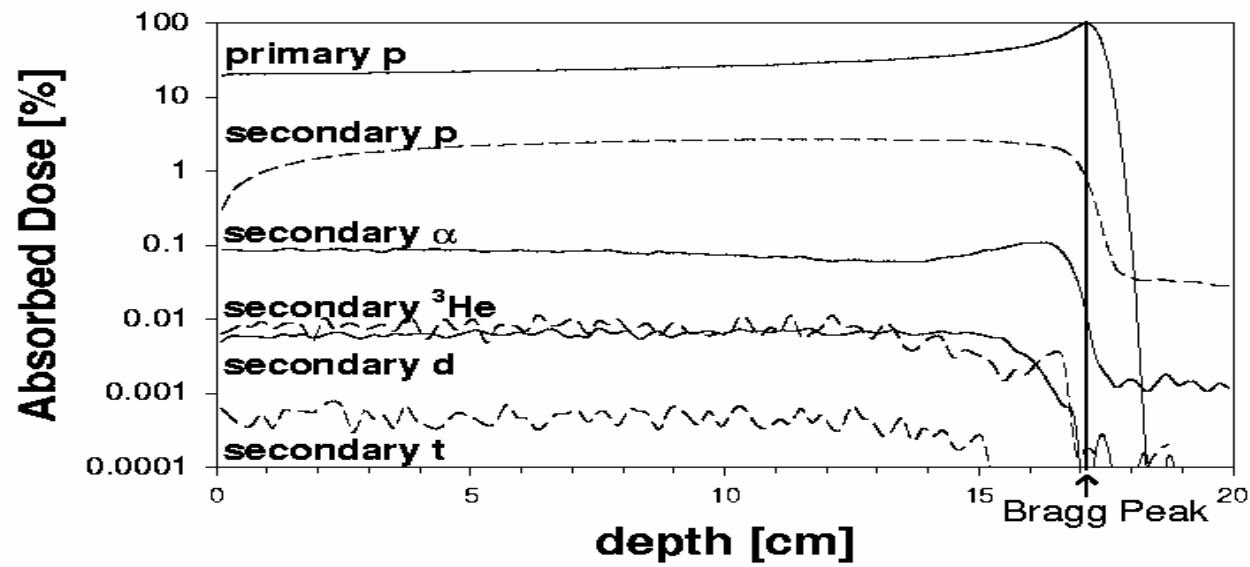
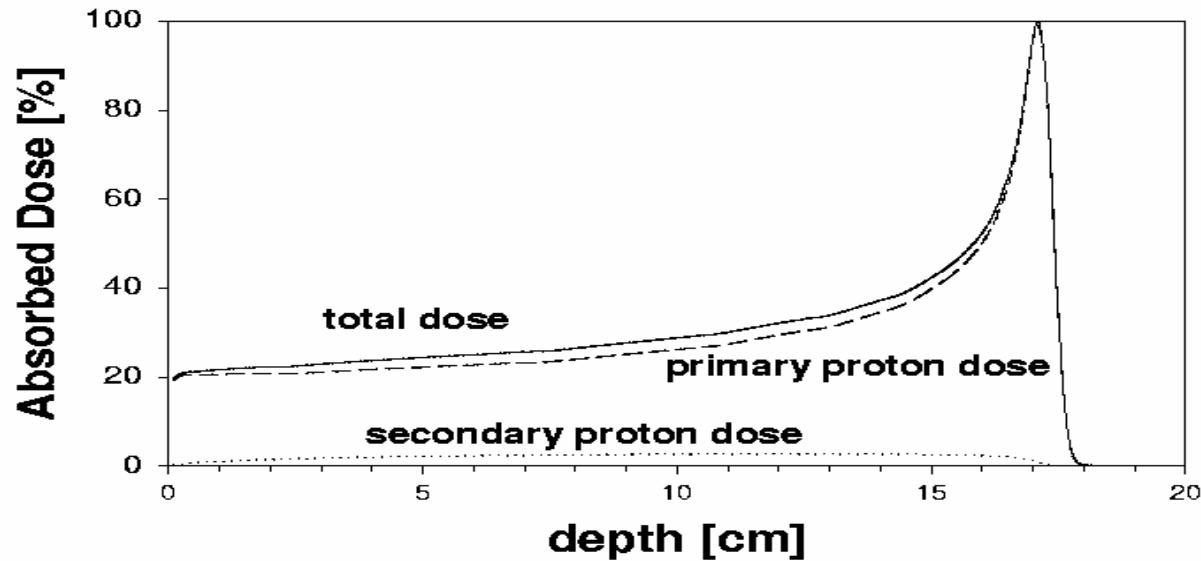


Nuclear interaction

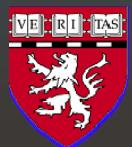
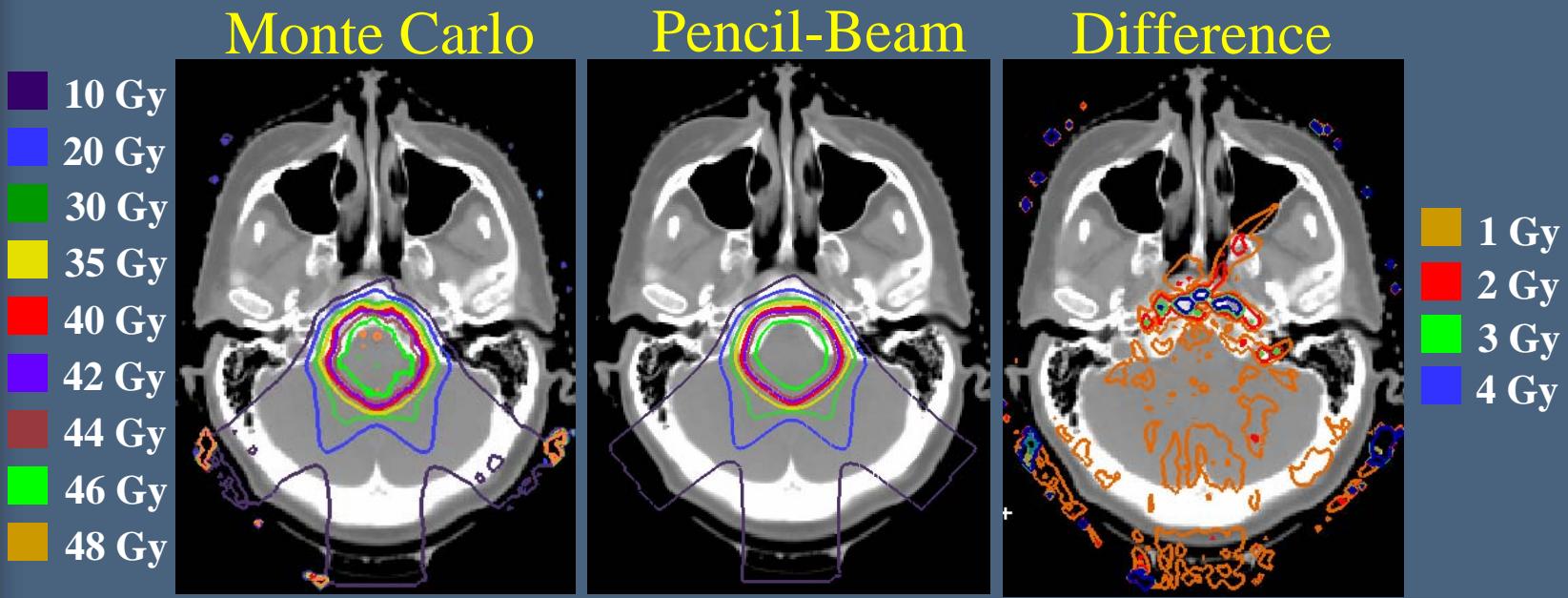
Nuclear interactions lead to secondary particles and thus to

- local dose deposition (secondary protons)
- non-local dose deposition (secondary neutrons)





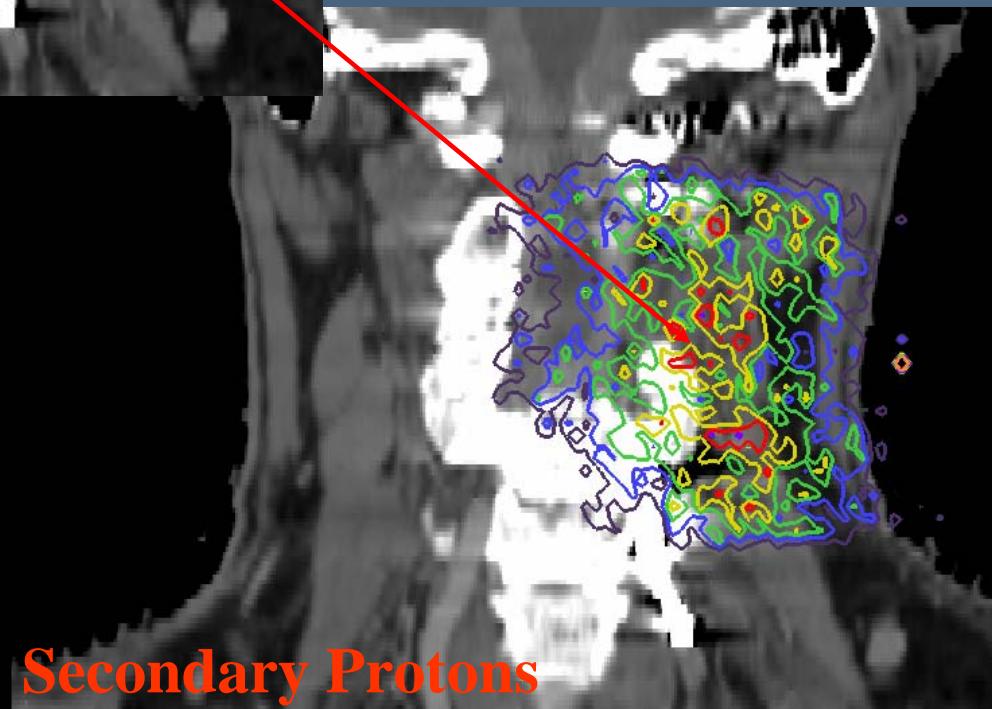
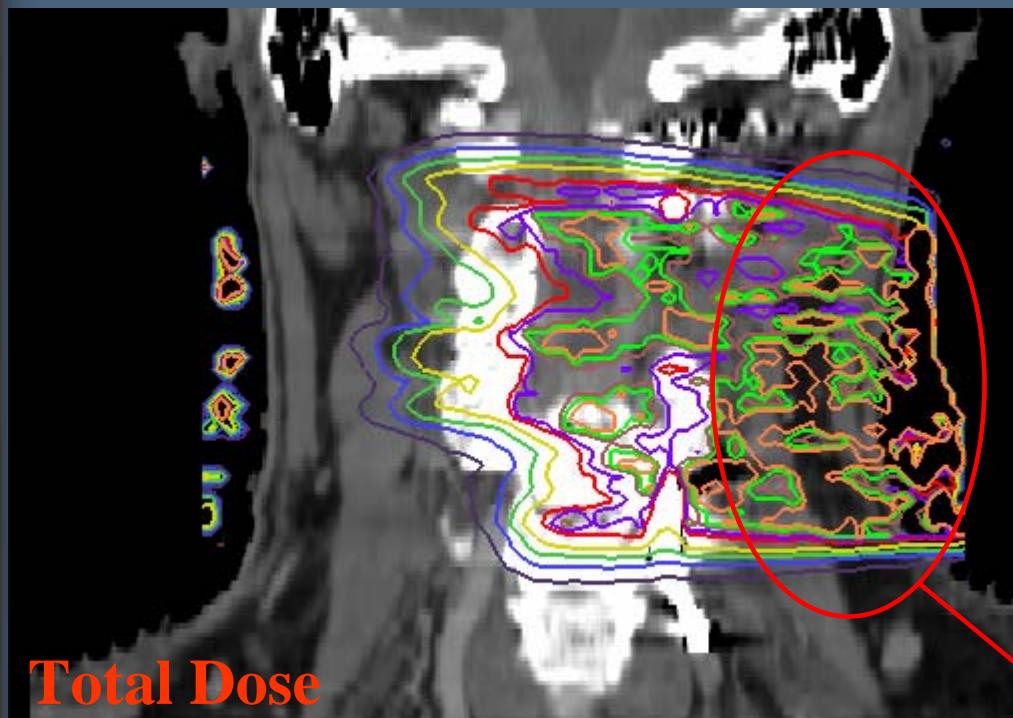
Monte Carlo dose calculation



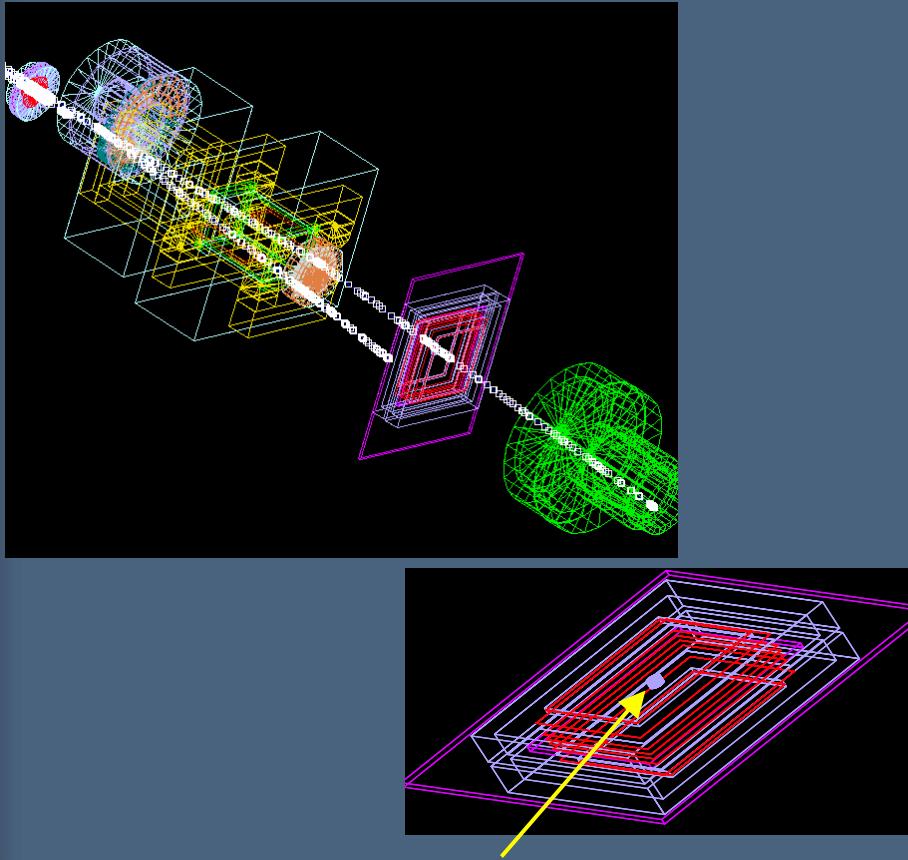
Para-spinal tumor
176 x 147 x 126 slices
voxels: 0.932 x 0.932 x 2.5-3.75 mm³
3 fields: ~15.0 Gy each

Para-Spinal

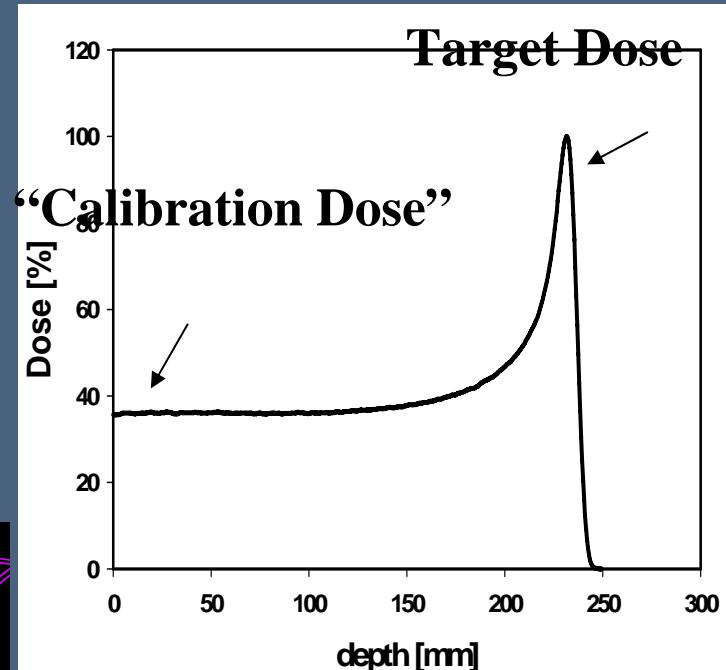
Coronal



Nuclear interactions in absolute dosimetry



Volume for absolute dosimetry



$$\text{Output-Factor} \quad \approx \quad \frac{D_{\text{cal}}}{i_{ic}} \left[\frac{cGy}{MU} \right]$$

$$i_{ic} = \frac{e \cdot \varepsilon_{ic}}{W_{air}} \times \iiint \left(\frac{dE}{dx} \right)_{air} p \cdot d\xi dF$$



Contributions to Output Factor

	R=7.5 M=7	R=10 M=4	R=15.5 M=15	R=22 M=4
Beam energy [MeV]	153.02	169.23	180.99	215.45
Primary P	70.5 %	71.7%	69.8 %	71.3 %
Secondary P	1.1 %	1.3 %	1.3 %	1.6 %
Electrons	27.5 %	27.0 %	27.2 %	26.8 %
Helium	0.9 %	0.1 %	1.6 %	0.6 %
Others	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %



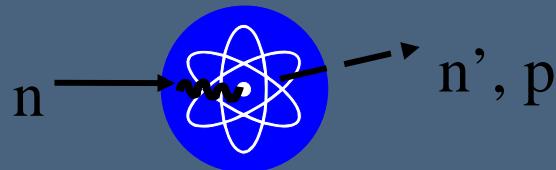
Nuclear data impact on proton radiation therapy calculations

- Neutron dose in proton beam therapy



Neutron interactions in matter (tissue)

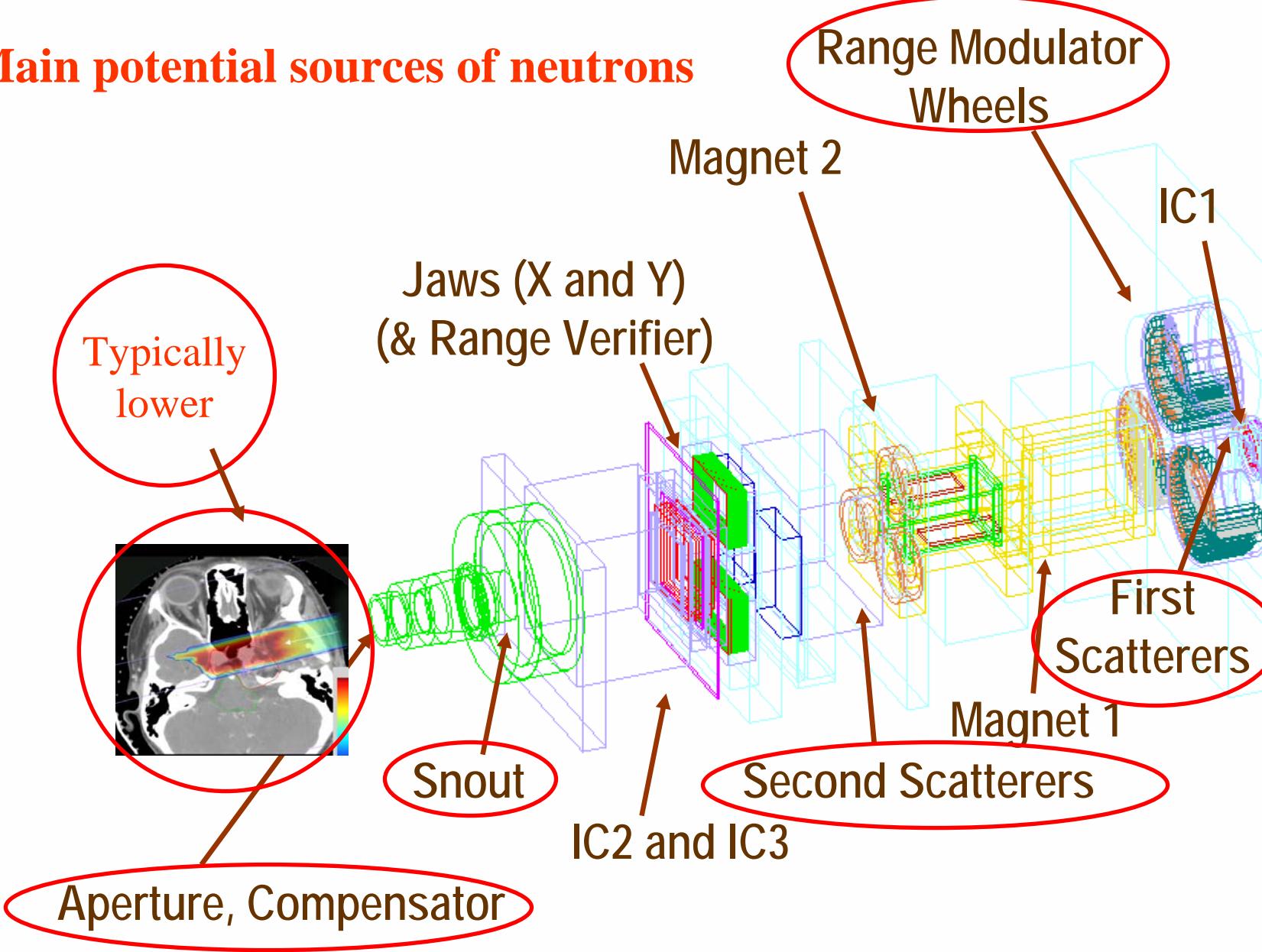
Neutrons are not directly ionizing



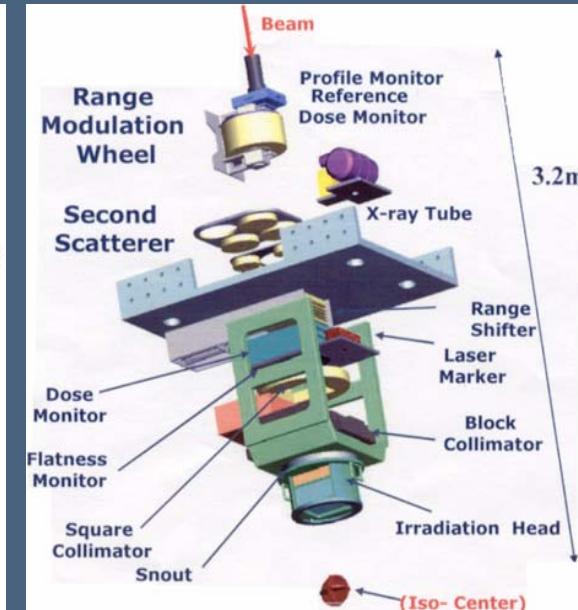
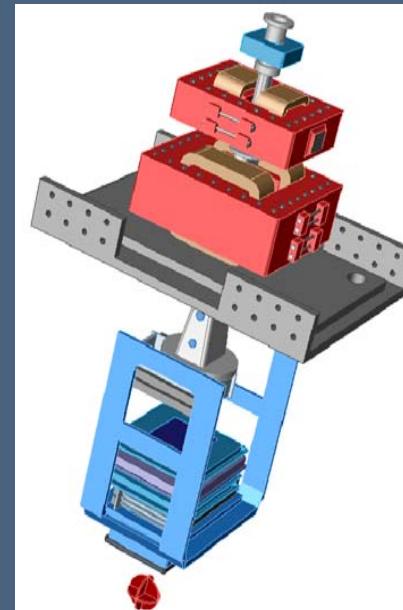
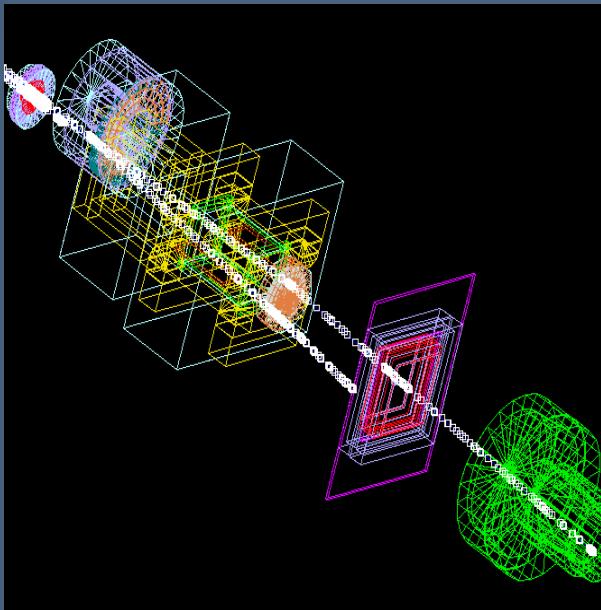
- Neutrons (uncharged) do not interact electromagnetically
 - Nuclear interactions occur only if the neutron comes close to the nucleus
- Attenuation coefficient is small; neutrons can penetrate large amounts of matter
- Low non-local (!) dose deposition



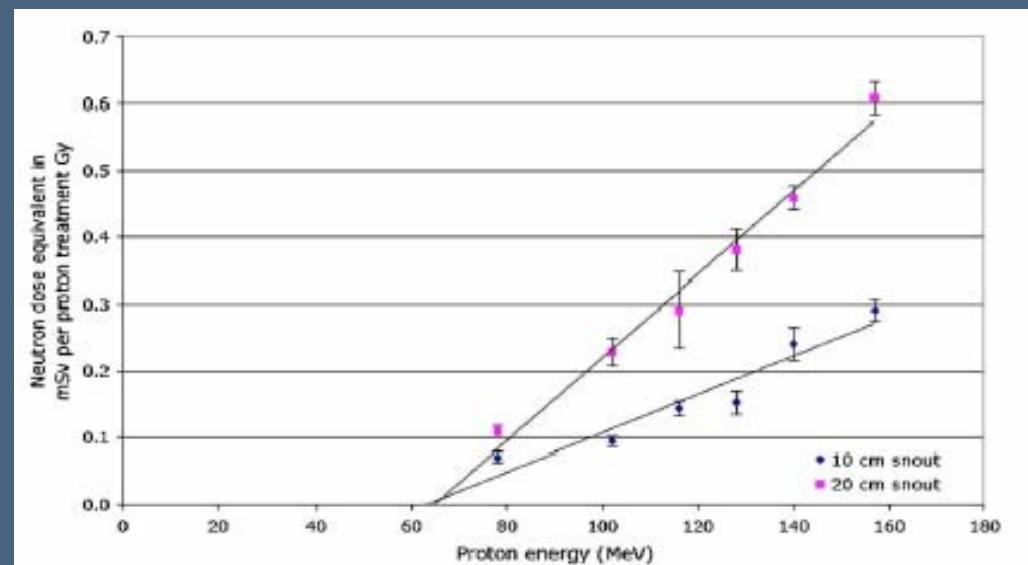
Main potential sources of neutrons



Neutron yield depends on the facility



Neutron yield depends on beam energy

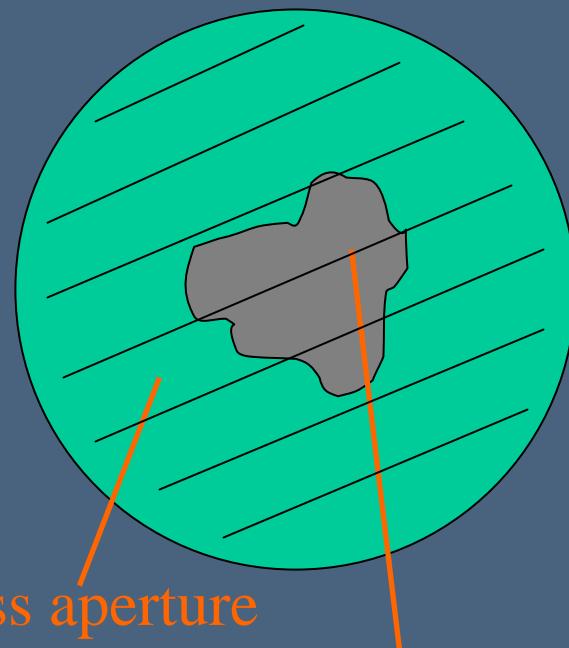
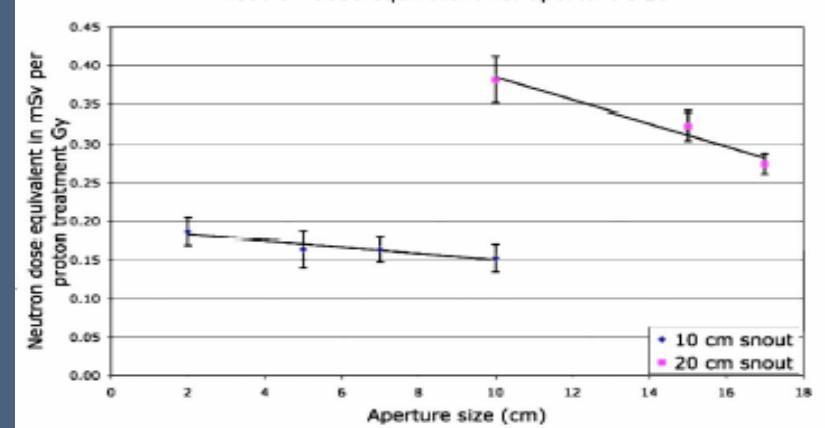


Mesoloras et al: Med Phys
33, 2479-2490 (2006)

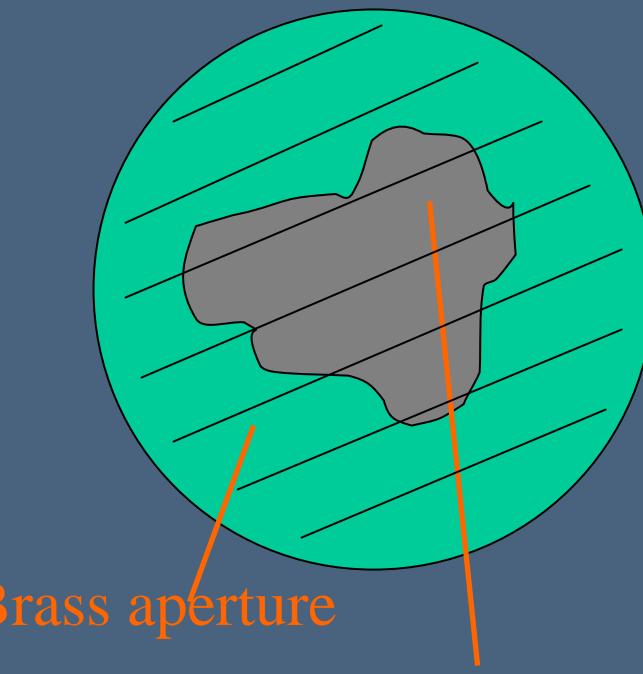


Neutron yield depends on aperture size

*Mesoloras et al: Med Phys
33, 2479-2490 (2006)*



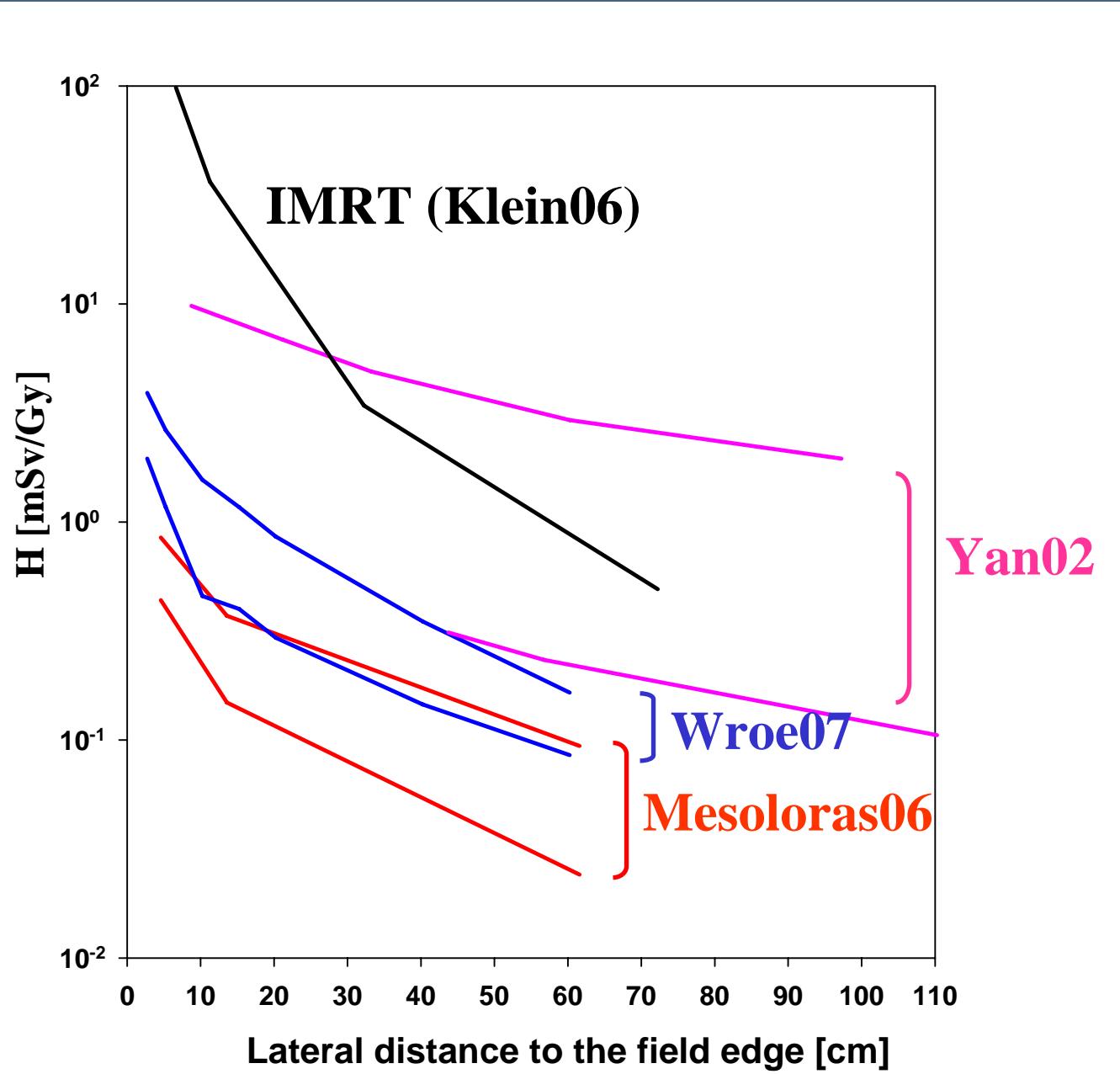
~20% of the beam treats
~80% of the beam produces neutr.



~60% of the beam treats
~40% of the beam produces neutr.



Scattered dose as a function of lateral distance



Is the dose as a function of distance really what we need to know ?

BEIR, Health risks from exposure to low levels of ionizing radiation, BEIR VII, Phase 2. National Research Council, National Academy of Science, 2006:

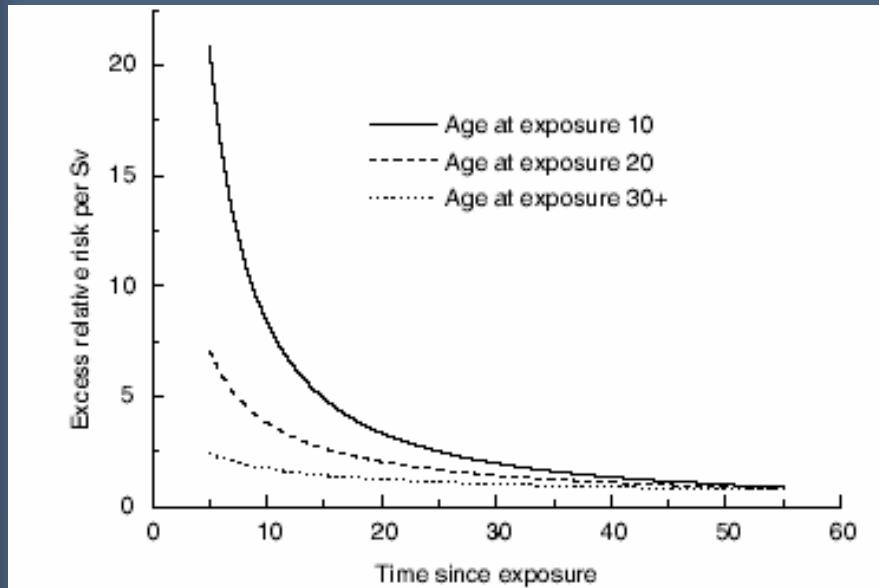
“Epidemiologic studies ... should be based on accurate, individual dose estimates, preferably to the organ of interest ...”
[BEIR VII]



Do we have to worry when treating pediatric patients ?

Pediatric patients

- have a long life expectancy
- show different dosimetric characteristics
- have a higher risk for second malignancies



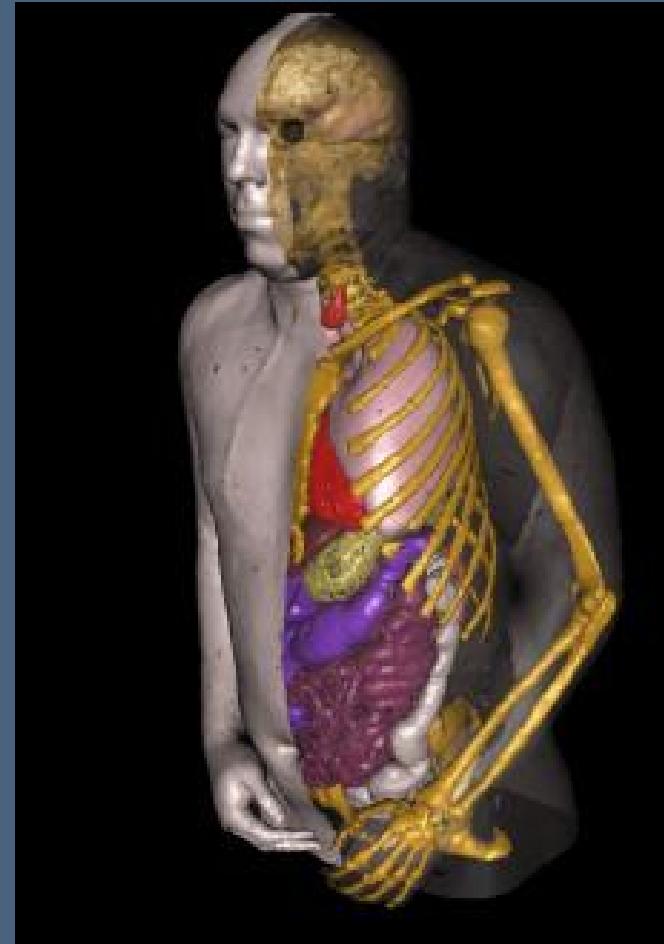
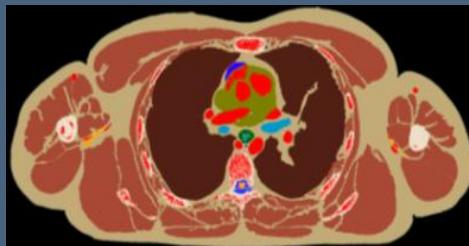
BEIR, Health risks from exposure to low levels of ionizing radiation, BEIR VII, Phase 2. National Research Council, National Academy of Science, 2006



Previous Study [Phys.Med.Biol. 50 (2005) 4337-4353]

Adult phantom (VIP-Man)

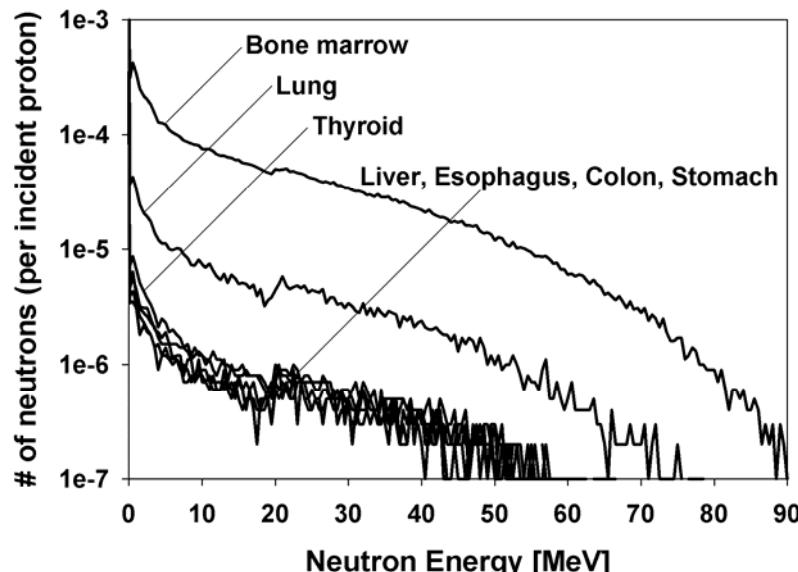
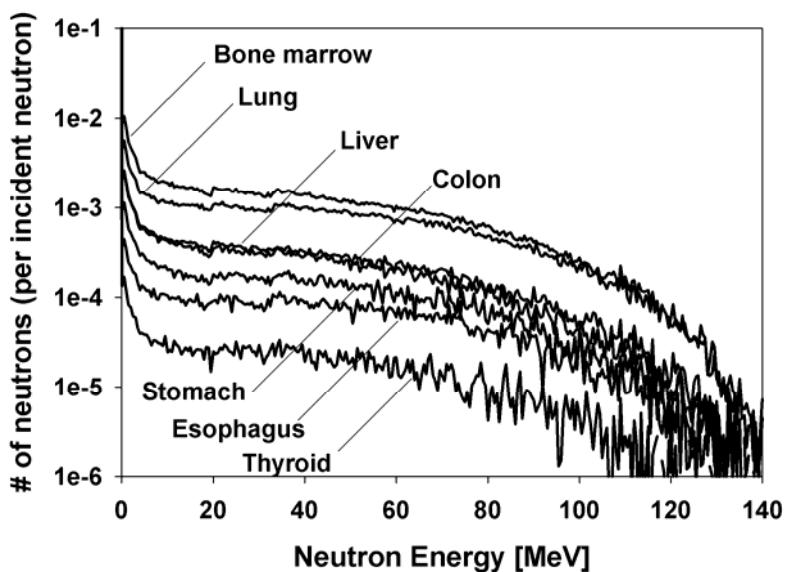
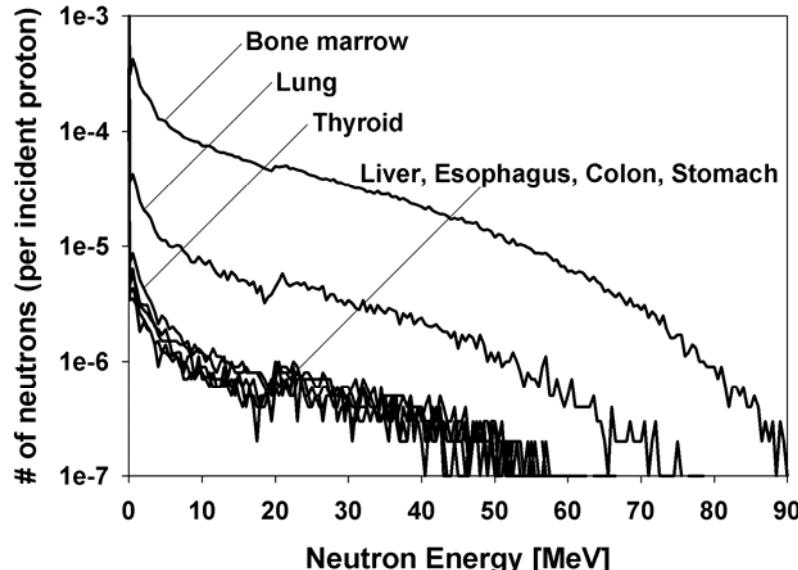
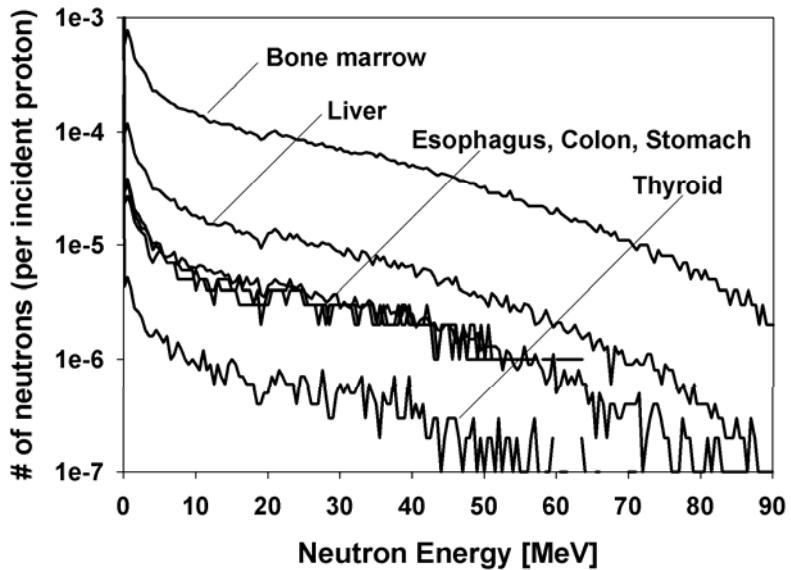
Visible Human Project by the
National Library of Medicine



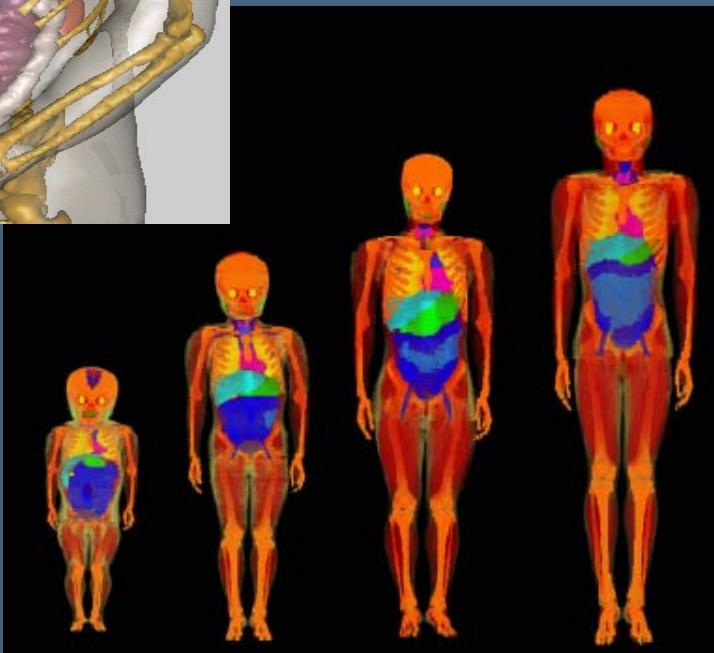
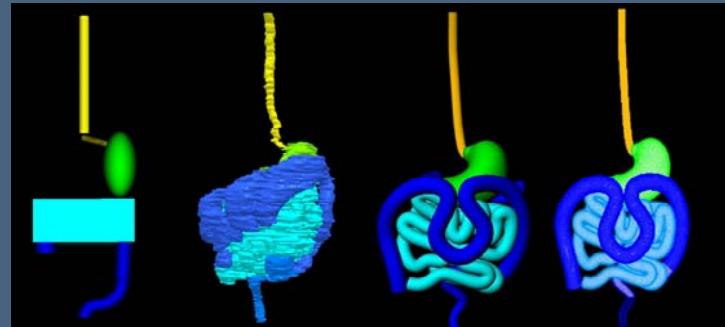
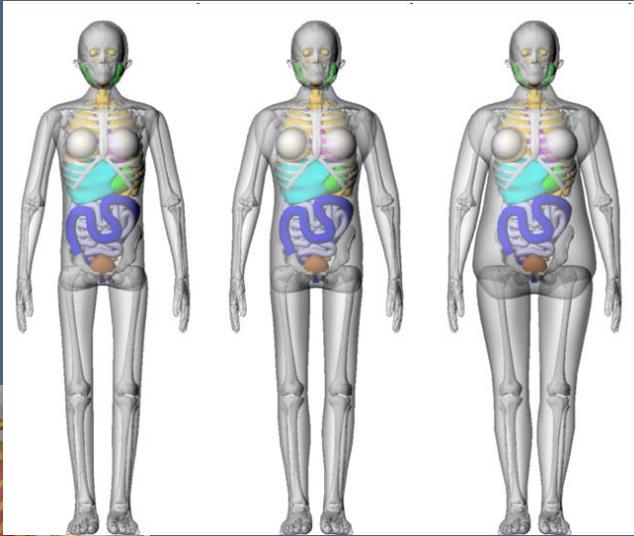
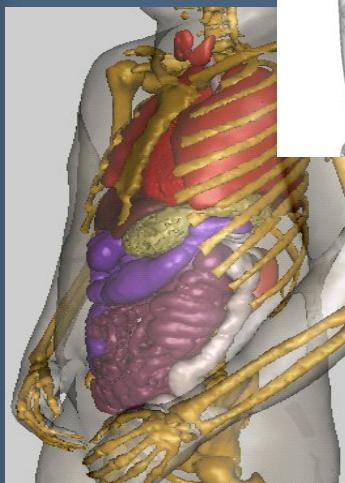
- 63 segmented organs/tissues
- Number of voxels:
 $147 \times 86 \times 470$
- Resolution: $4 \times 4 \times 4 \text{ mm}^3$



G. Xu et al., *Health Phys.* 78 (2000) 476



Whole-body computational phantoms



Pediatric phantoms

Lee, Lee, Williams, et al. Whole-body voxel phantoms of paediatric patients - UF Series B. *Phys Med Biol.* 51, 4649-4661 (2006)



phantom	number of voxels			Density	phantom age (years)				
	X	Y	Z		Newborn	1	5	10	15 (male)
9 month old	289	180	24						
4 year old	351	207	21						
8 year old	322	171	22						
11 year old	398	242	25						
14 year old	349	193	25						
Adult	147	86	47	Density	1.157	1.184	1.219	1.232	1.230

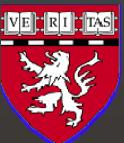
Table 2. Elemental compositions (% by mass) and tissue densities (g cm^{-3}) of individuals at the ICRP reference ages.

Element	phantom age (years)				
	Newborn	1	5	10	15 (male)
Group 1 (cranium/mandible)					
H	5.551	5.272	5.173	5.340	5.434
C	19.150	19.154	20.180	21.953	23.442
N	4.259	4.280	4.230	4.019	3.831
O	51.209	49.850	46.759	44.757	43.526
Ca	12.892	13.852	15.619	15.801	15.773
Na	0.031	0.025	0.104	0.103	0.177
Mg	0.260	0.268	0.187	0.181	0.176
P	6.303	6.969	7.435	7.544	7.346
S	0.287	0.287	0.283	0.276	0.271
Cl	0.018	0.012	0.007	0.006	0.006
K	0.027	0.019	0.011	0.009	0.006
Fe	0.013	0.012	0.011	0.012	0.011
Group 2 (vertebrae—cervical, thoracic, lumbar)					
H	8.760	8.390	7.997	7.901	7.993
C	16.209	17.885	21.884	27.069	29.956
N	2.844	3.020	3.230	3.319	3.247
O	64.925	61.789	55.514	49.237	46.486
Ca	3.948	4.345	6.469	7.575	7.637
Na	0.337	0.289	0.246	0.180	0.193
Mg	0.088	0.114	0.116	0.141	0.146
P	2.908	3.383	3.918	4.110	3.933
S	0.663	0.598	0.485	0.369	0.325
Cl	0.194	0.163	0.112	0.062	0.045
K	0.035	0.006	0.004	0.004	0.003
Fe	0.016	0.019	0.024	0.033	0.036
Density	1.157	1.184	1.219	1.232	1.230

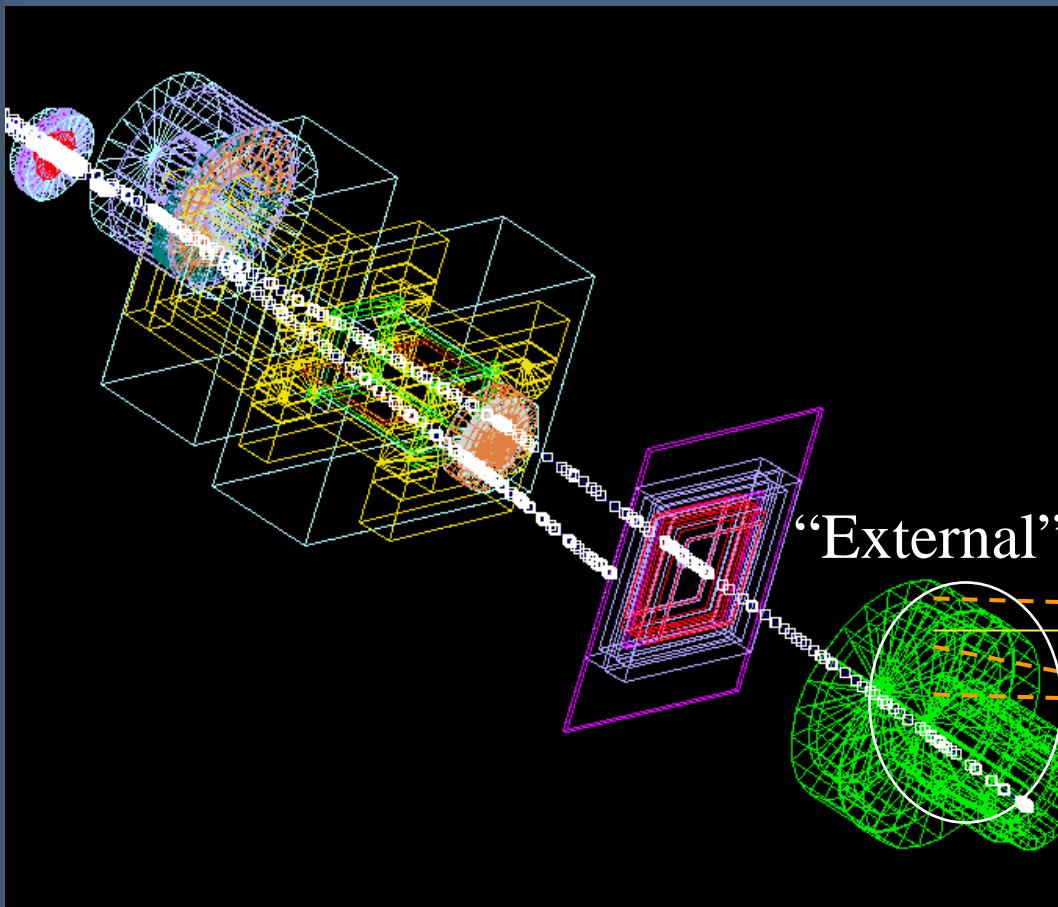


Example: female organ index

organ index	organ/tissue	organ index	organ/tissue	organ index	organ/tissue
1	eyes	17	spleen	33	scapulae
2	tonsil	18	gall bladder wall	34	sternum
3	salivary glands	19	spinal cord	35	upper humerus
4	tongue	20	aorta	36	ribs
5	pharynx	21	adrenals	37	T-vertebrae
6	larynx	22	pancreas	38	lower humerus
7	trachea	23	kidneys	39	L-vertebrae
8	thyroid	24	small intestine wall	40	radii, ulnae
9	thymus	25	colon wall	41	os coxae
10	bronchi	26	ovaries	42	sacrum
11	breast	27	uterus	43	hand
12	lungs	28	bladder wall	44	upper femur
13	esophagus	29	rectosigmoid wall	45	lower femur
14	heart	30	mandible	46	tibiae, patellae
15	liver	31	C-vertebrae	47	fibula
16	stomach wall	32	clavicles	48	ankle, feet



Simulation of the radiation field entering the patient

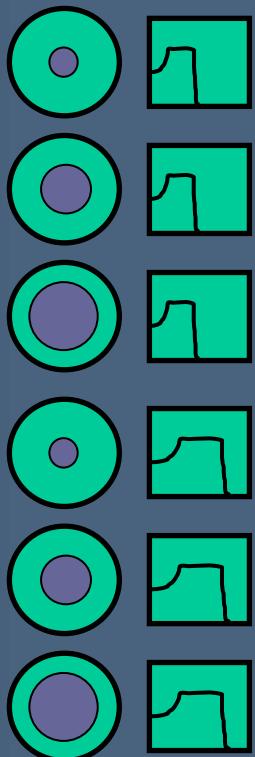


Output:

Neutron phase space (\rightarrow external)
Proton phase space (\rightarrow internal)



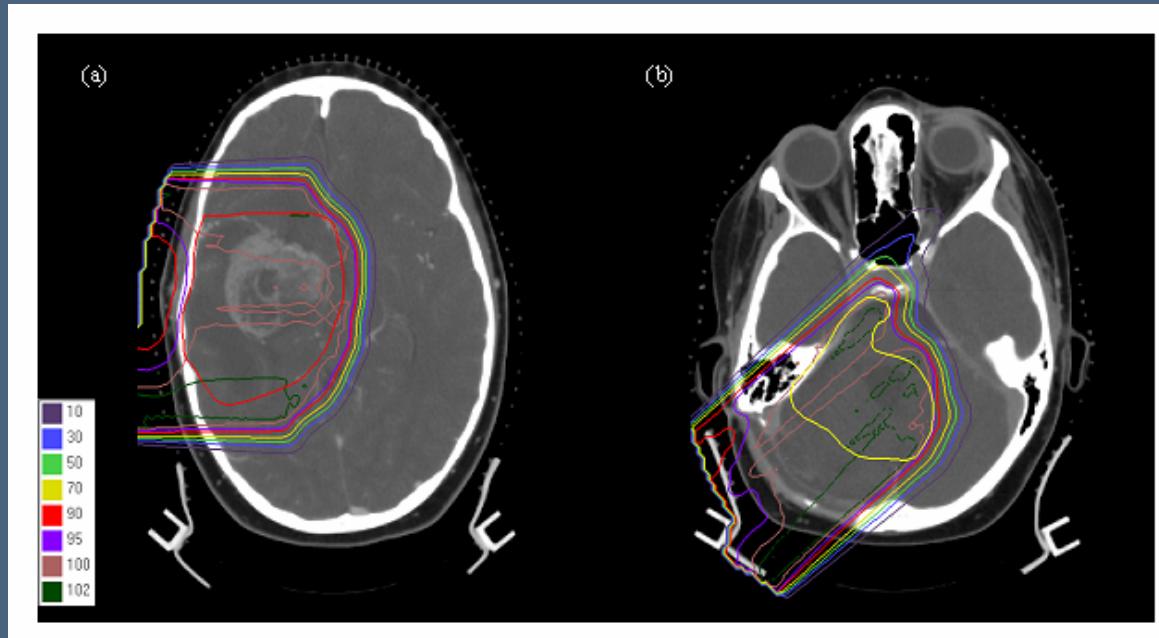
Study Outline / Treatment Fields



Patient	Field	Aperture \varnothing [cm]	Field \varnothing [cm]	Beam E [MeV]	Range [cm]	Modulation [cm]
	1	3	12	169.2	10	5
	2	6	—	—	—	—
	3	9	—	—	—	—
	4	3	—	178.3	15	10
	5	6	—	—	—	—
	6	9	—	—	—	—
1	7	~9.1	—	164.0	9.2	7.9
2	8	~6.4	—	180.1	11.8	9.5

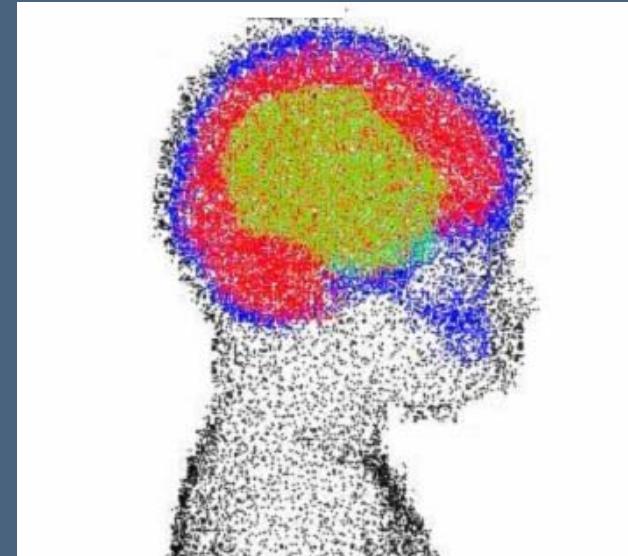


Simulation the patient/phantom as ‘virtual patients’



Patient fields

Field placement:



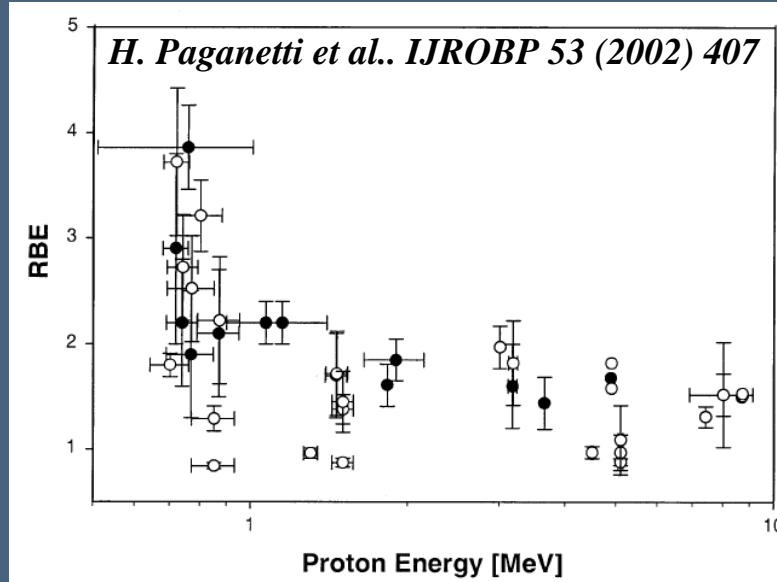
Equivalent dose: $H = w_R D$ - PROTONS -

Protons:
Kinetic energy dependence
for proton w_R :

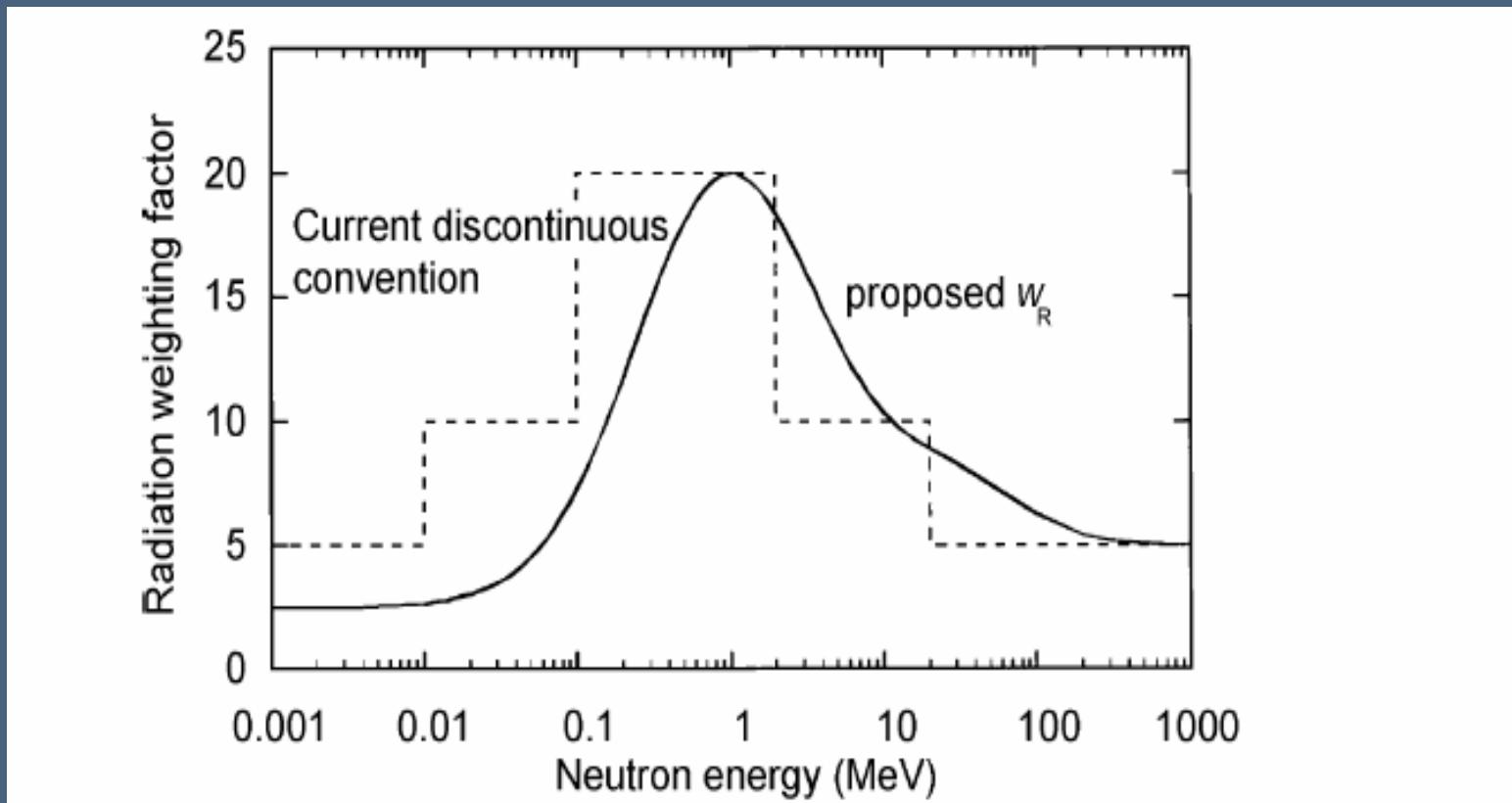
$w_R = 1.1, E_p/\text{MeV} > 1$

$w_R = 2.5, 0.5 E_p/\text{MeV} < 1$

$w_R = 5, \quad E_p/\text{MeV} < 0.5$



Equivalent dose: $H = w_R D$ - NEUTRONS -



From: *Annals of the ICRP; ICRP Publication 92; Relative Biological Effectiveness (RBE), QualityFactor (Q), and Radiation Weighting Factor (w_R)*



Neutron RBE as a function of dose

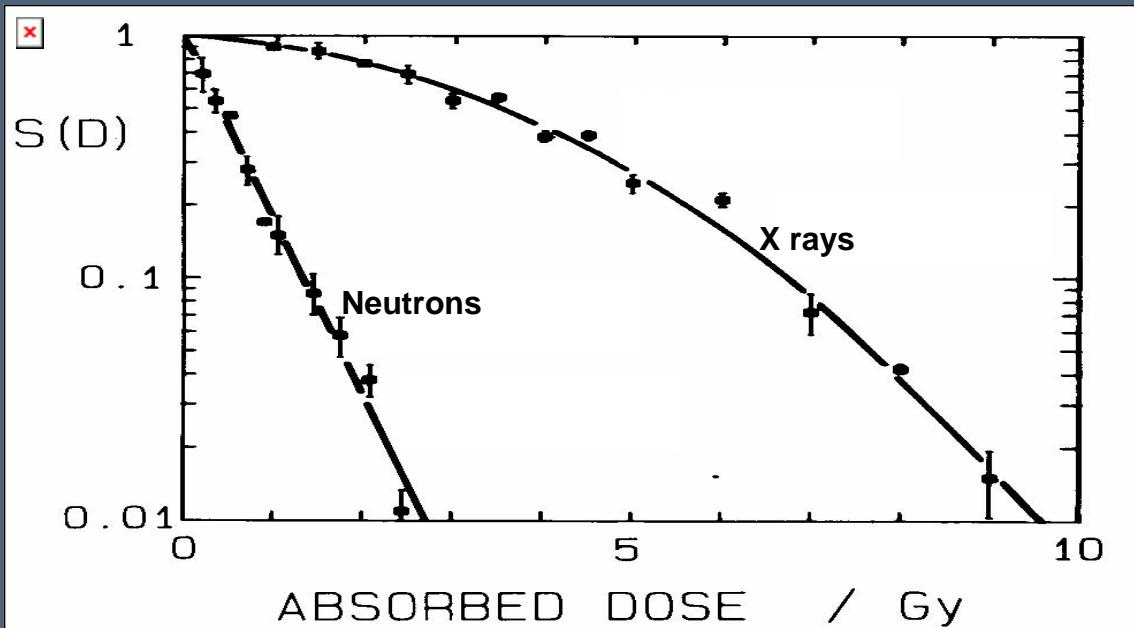


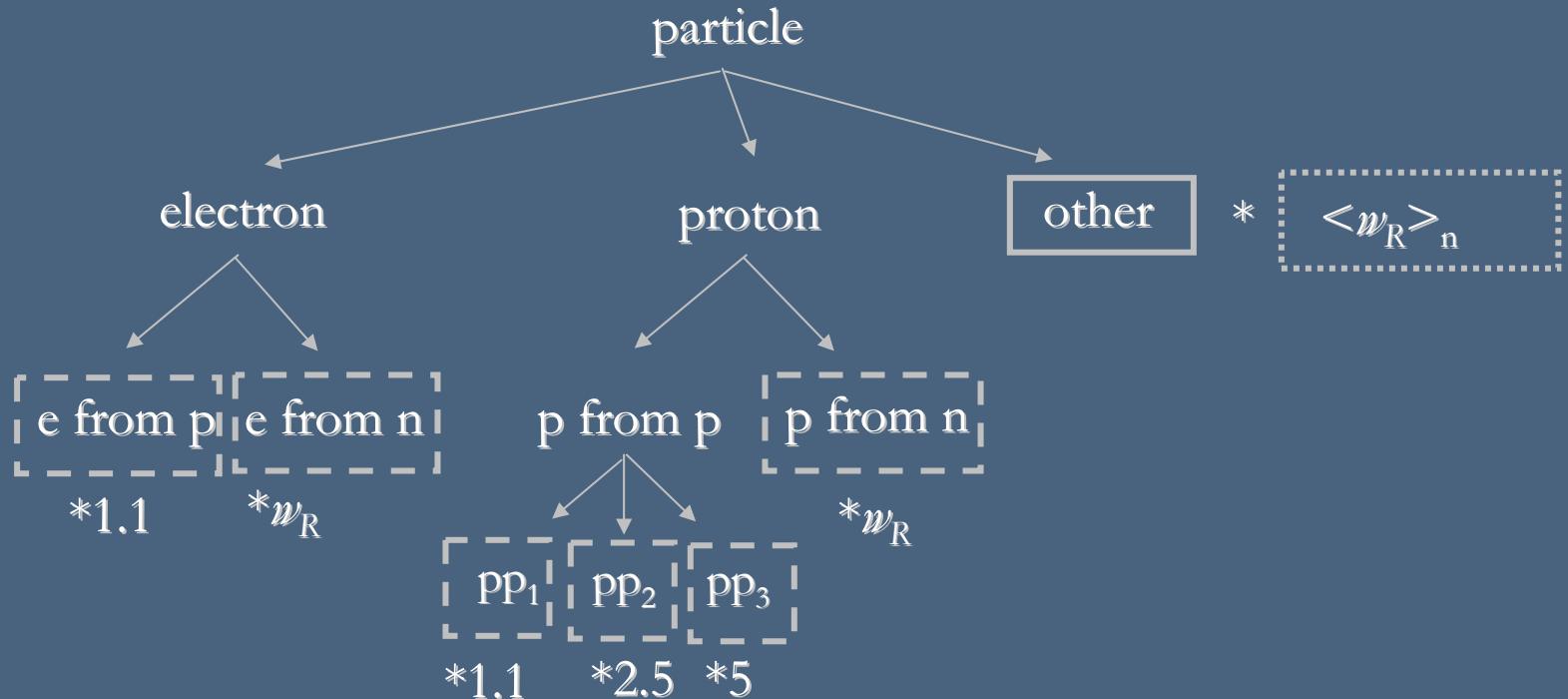
TABLE 9.1—Summary of estimated RBE_M values for fission neutrons versus gamma rays

End point	Range of values ^a
Cytogenetic studies, human lymphocytes in culture	34– 53
Transformation	3– 80 ^b
Genetic endpoints in mammalian systems	5– 70 ^c
Genetic endpoints in plant systems	2–100
Life shortening, mouse	10– 46
Tumor induction	16– 59

NCRP Report No. 104, The Relative Biological Effectiveness of Radiations of Different Quality



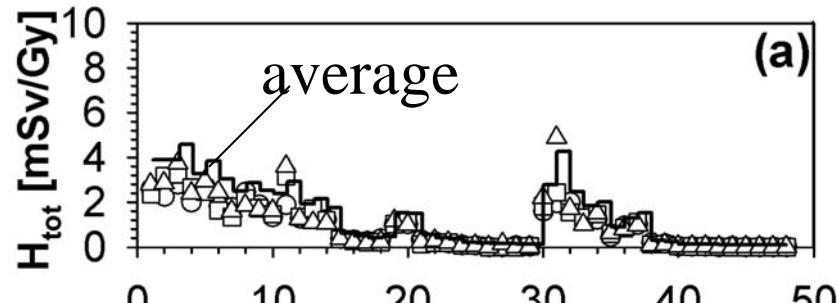
Computation of organ equivalent doses



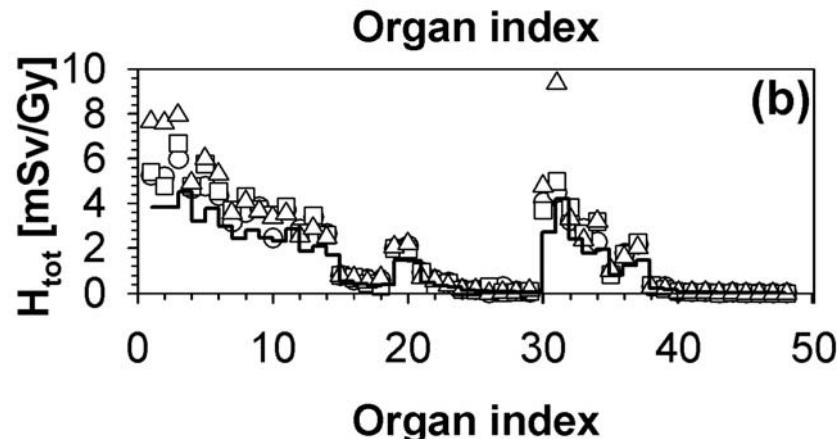
$$H = D_{pp1} * 1.1 + D_{pp2} * 2.5 + D_{pp3} * 5 + D_{ep} * 1.1 + (D_{pnw} + D_{enw} + D_{other}) * w_R$$



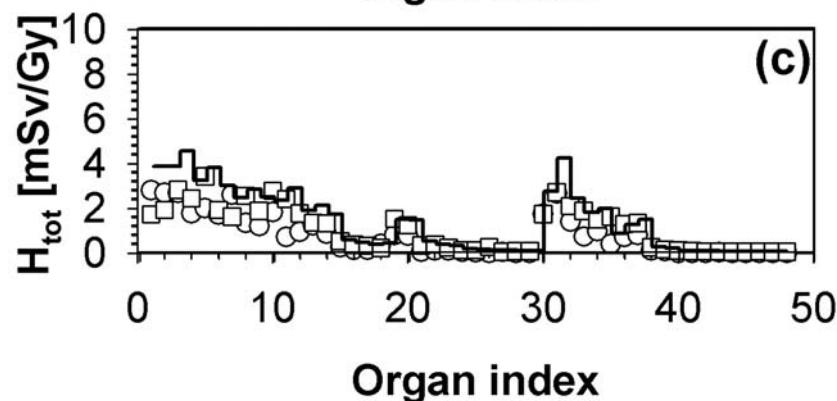
Organ equivalent dose as a function of organ index (4-year-old phantom)



(a) Small Range and Mod



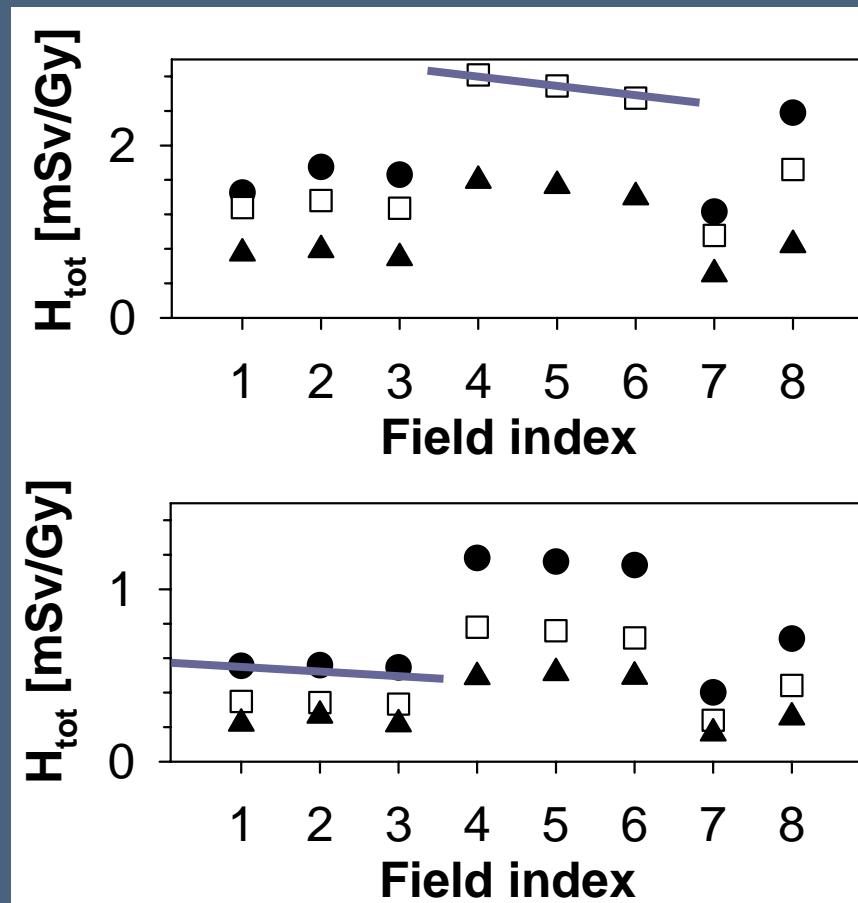
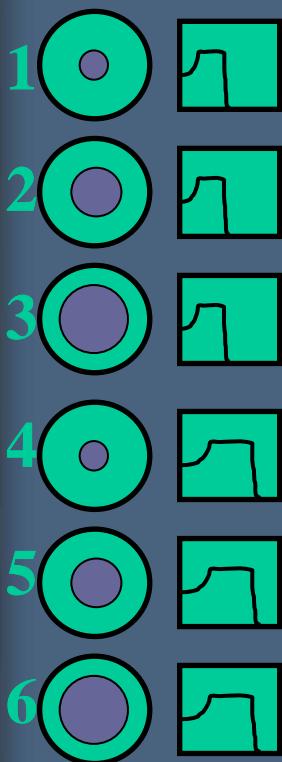
(b) Large Range and Mod



(c) Patient Fields



Total equivalent dose for the lungs

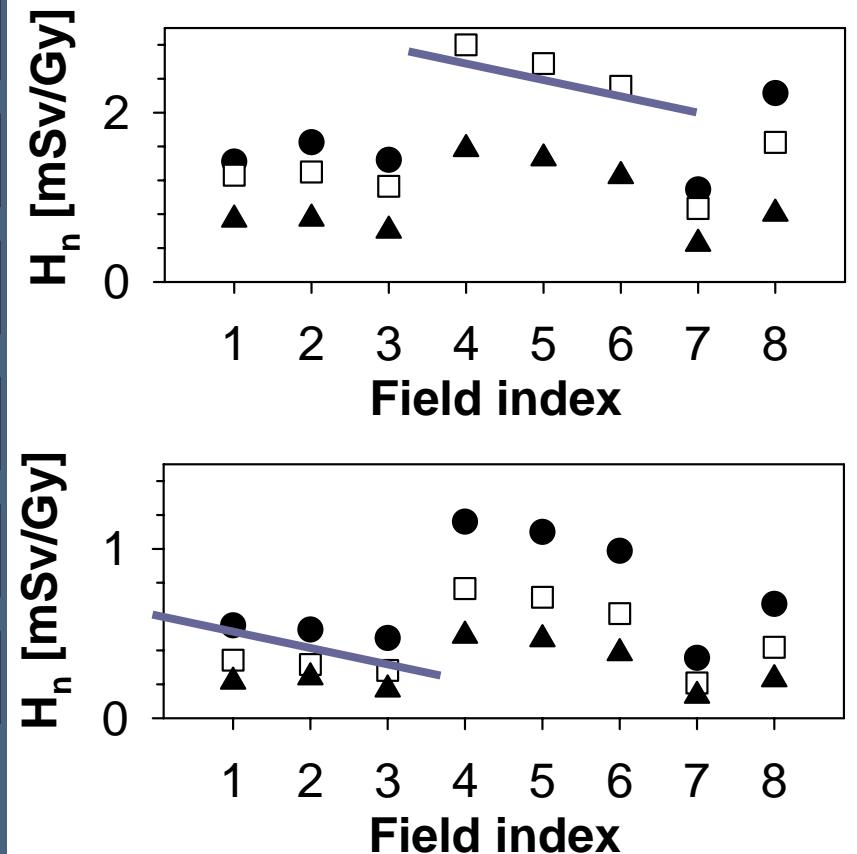
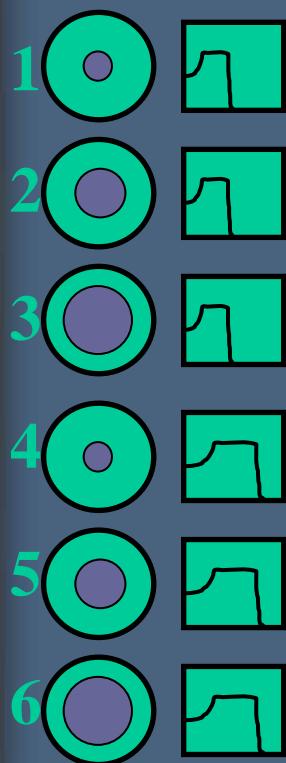


9-mo old (circles)
4-yr old (squares)
8-yr old (triangles)

11-yr old (circles)
14-yr old (squares)
adult (triangles)



External equivalent dose for the lungs

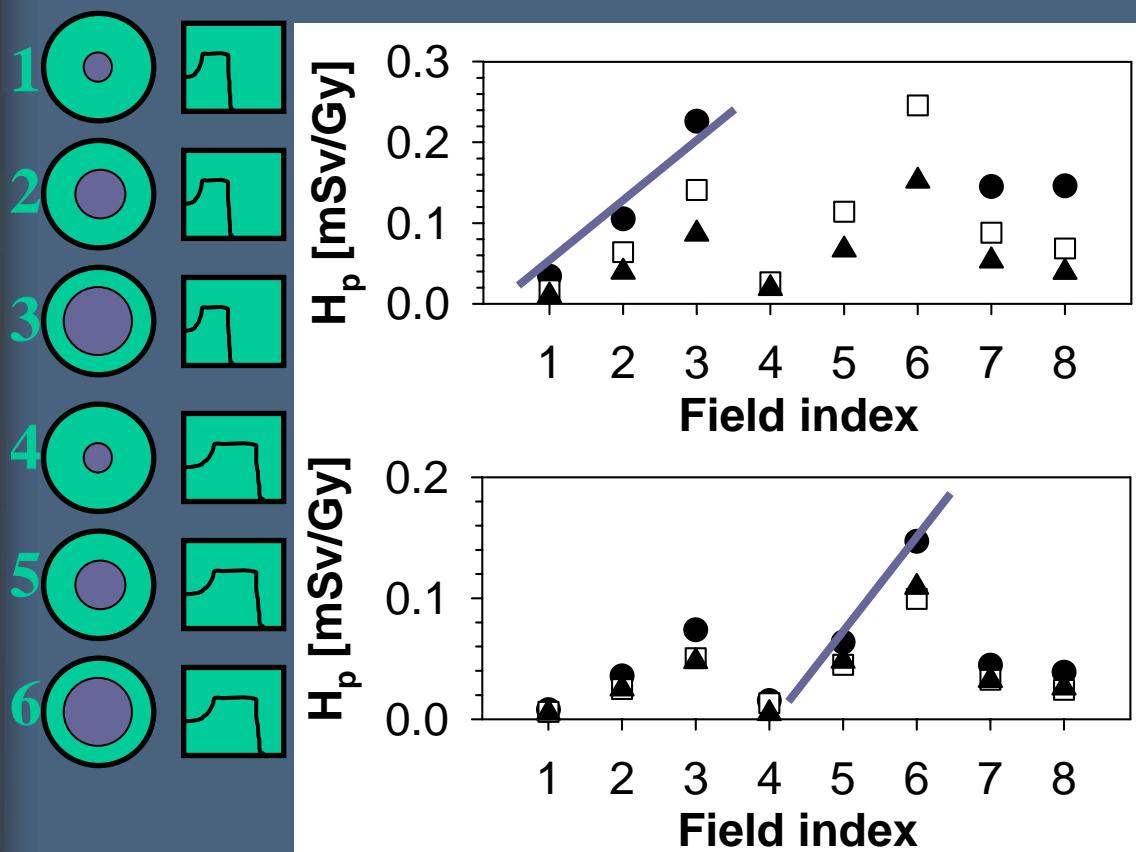


9-mo old (circles)
4-yr old (squares)
8-yr old (triangles)

11-yr old (circles)
14-yr old (squares)
adult (triangles).



Internal equivalent dose for the lungs

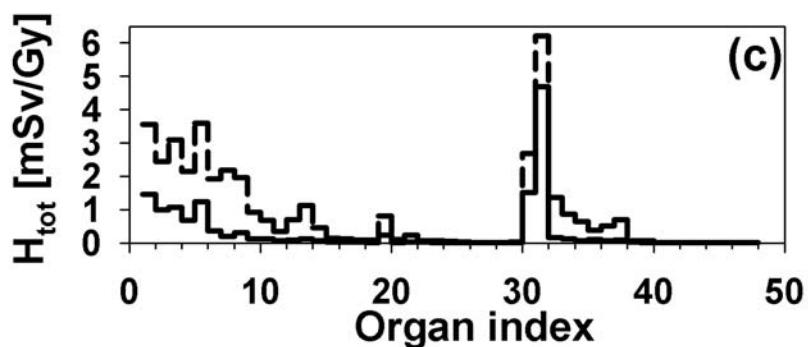
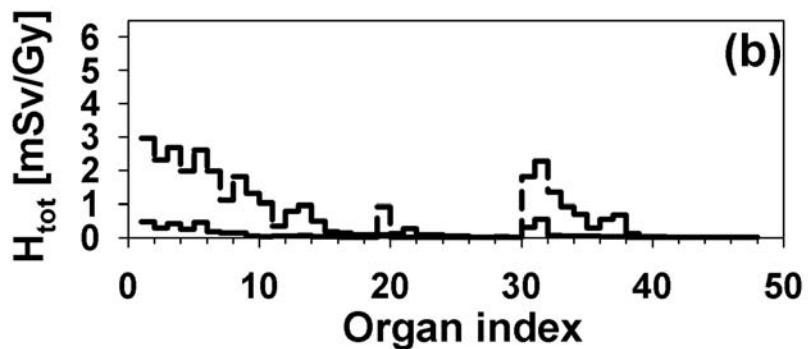
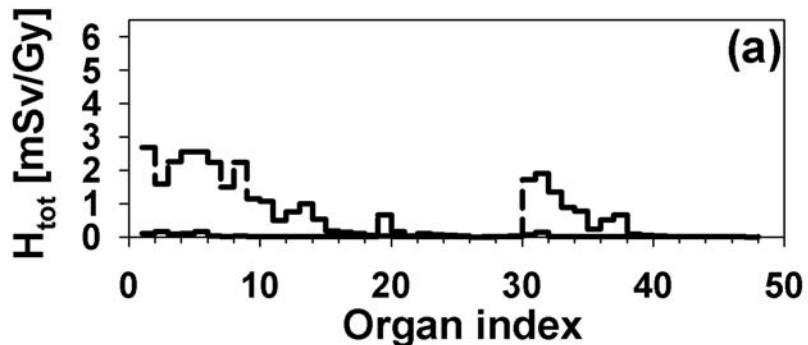


9-mo old (circles)
4-yr old (squares)
8-yr old (triangles)

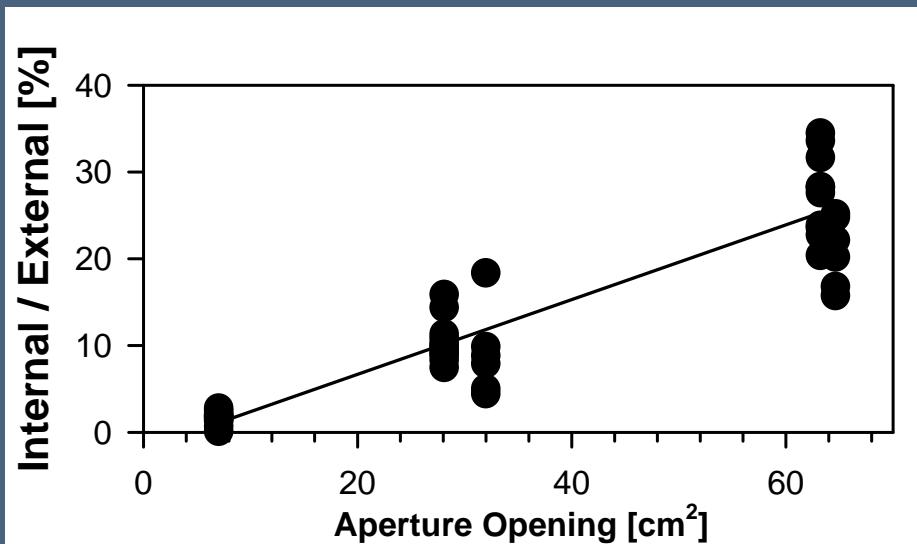
11-yr old (circles)
14-yr old (squares)
adult (triangles).



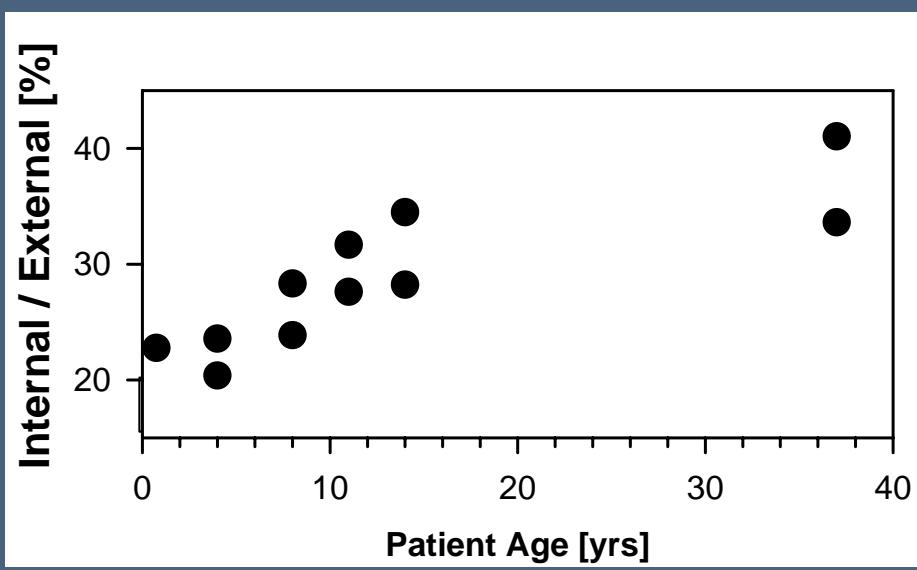
Total equivalent dose (dashed histograms)
Internal equivalent dose (solid histograms)
(8-year-old phantom)



Internal versus external neutrons as a function of aperture opening



Internal versus external neutrons as a function of phantom age
(large apertures)

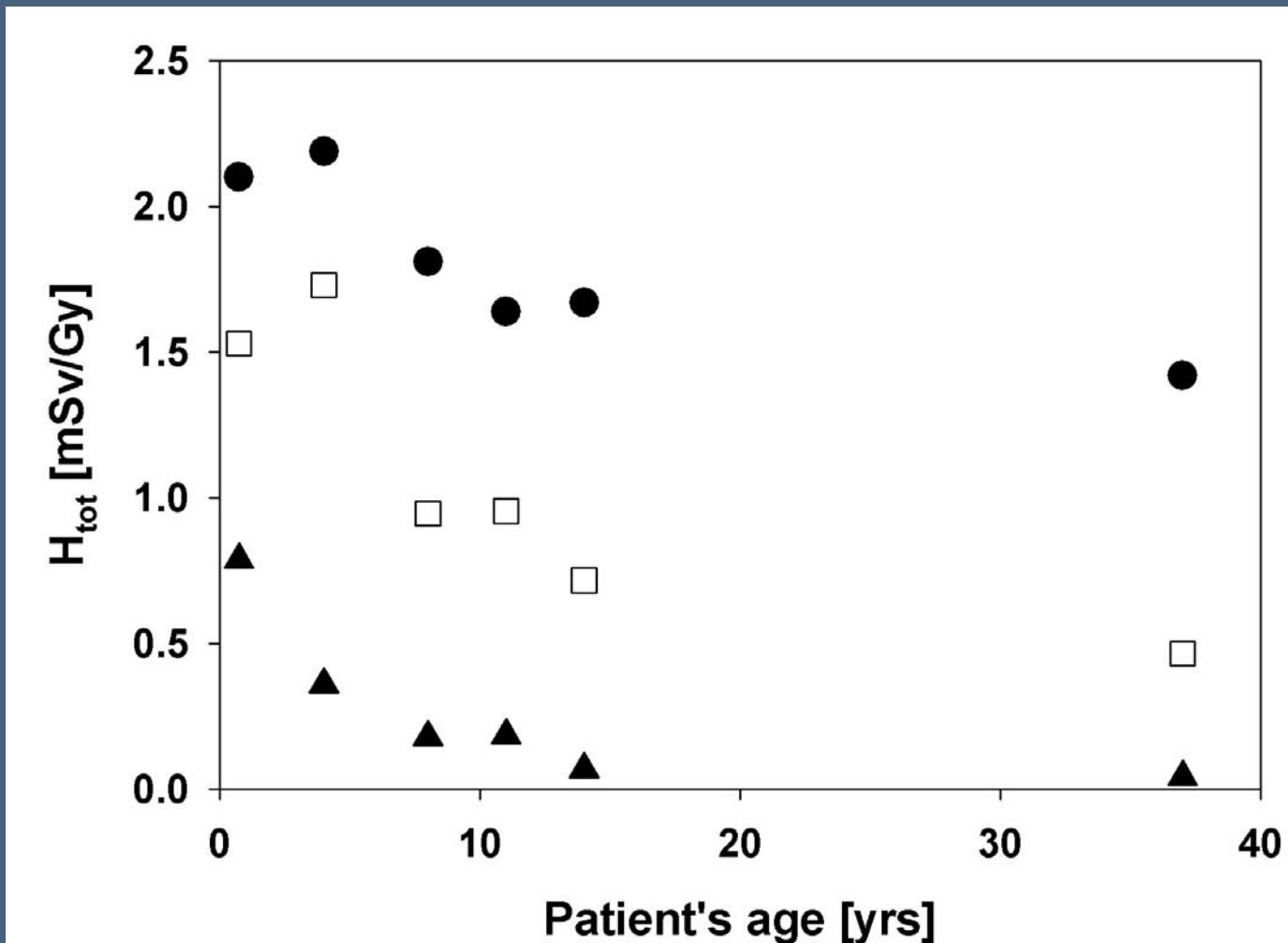


Organ equivalent dose

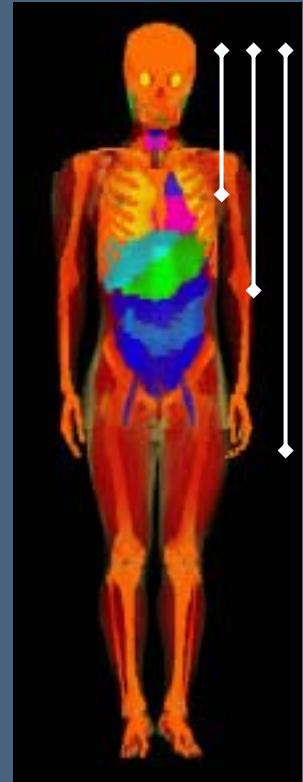
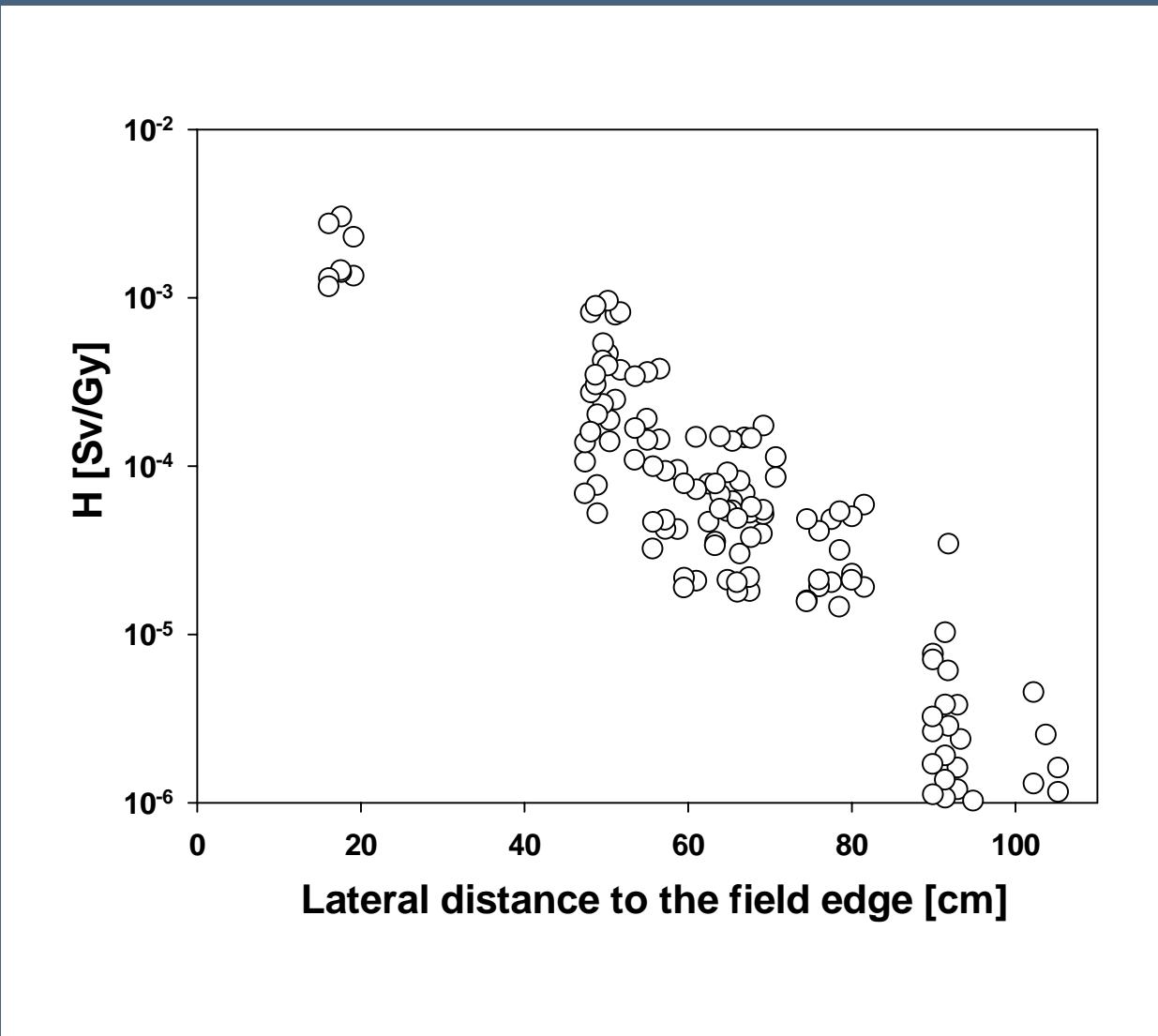
thyroid (circles)

lung (squares)

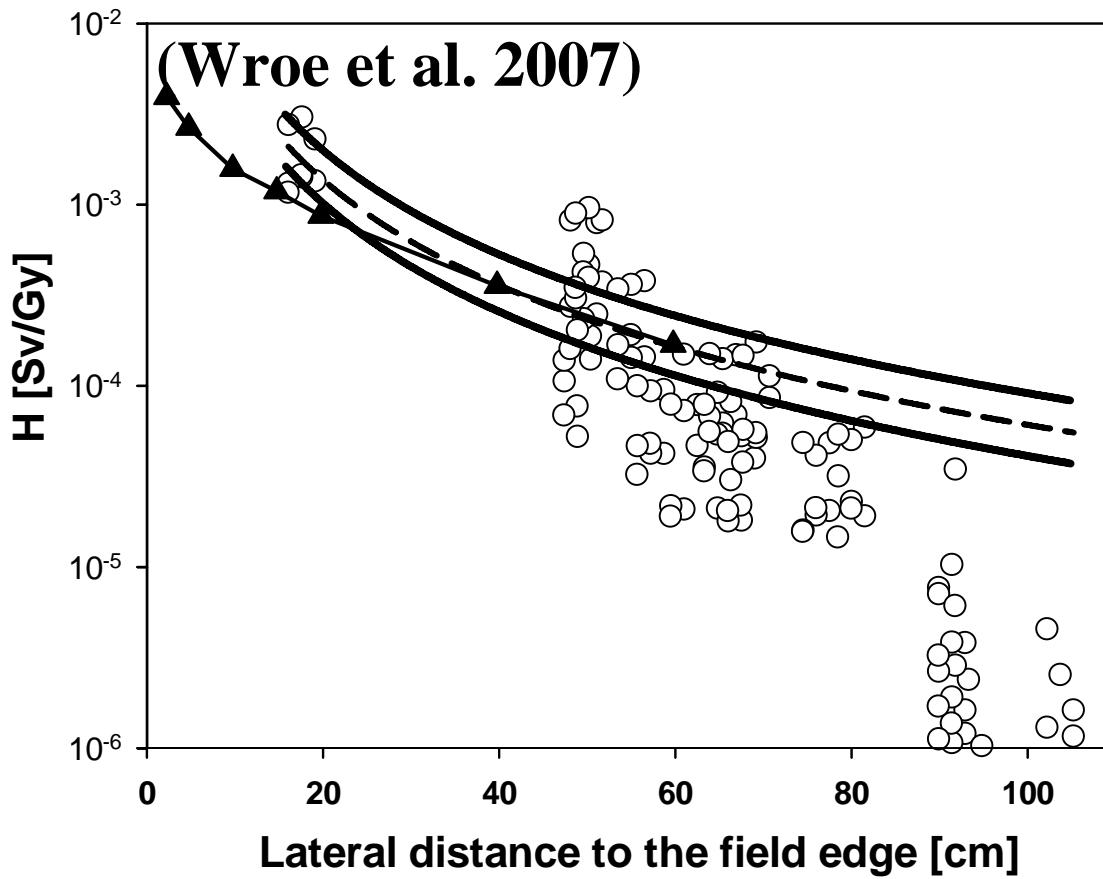
liver (triangles)



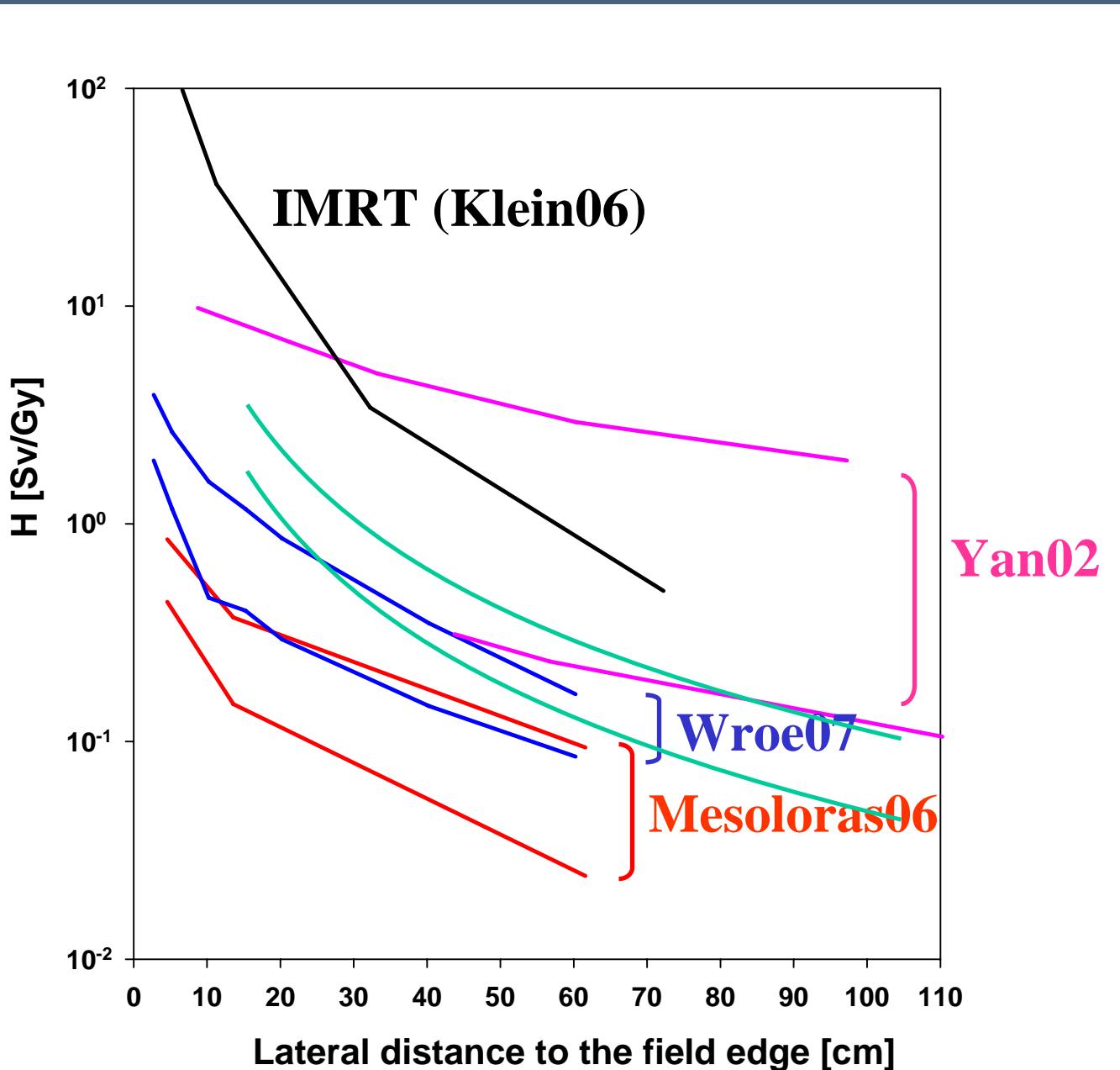
Organ equivalent dose as a function of distance (adult phantom)



Fit $H = (366.2 \times \text{distance}^{-1.861})$



Neutron dose as a function of lateral distance



CONCLUSION (Part I)

- Neutron dose is mainly caused by neutrons from the treatment head
- The neutron dose increases with increasing R/M
- The neutron dose increases with decreasing aperture
- Younger patients are subject to higher neutron doses
- Typically neutron doses from proton therapy are lower than scattered photon doses in IMRT



BEIR, Health risks from exposure to low levels of ionizing radiation, BEIR VII, Phase 2. National Research Council, National Academy of Science, 2006

BEIR (Biological Effects of Ionizing Radiation) report :

**Recommendation of dose-response relationships to
allow risk assessment**

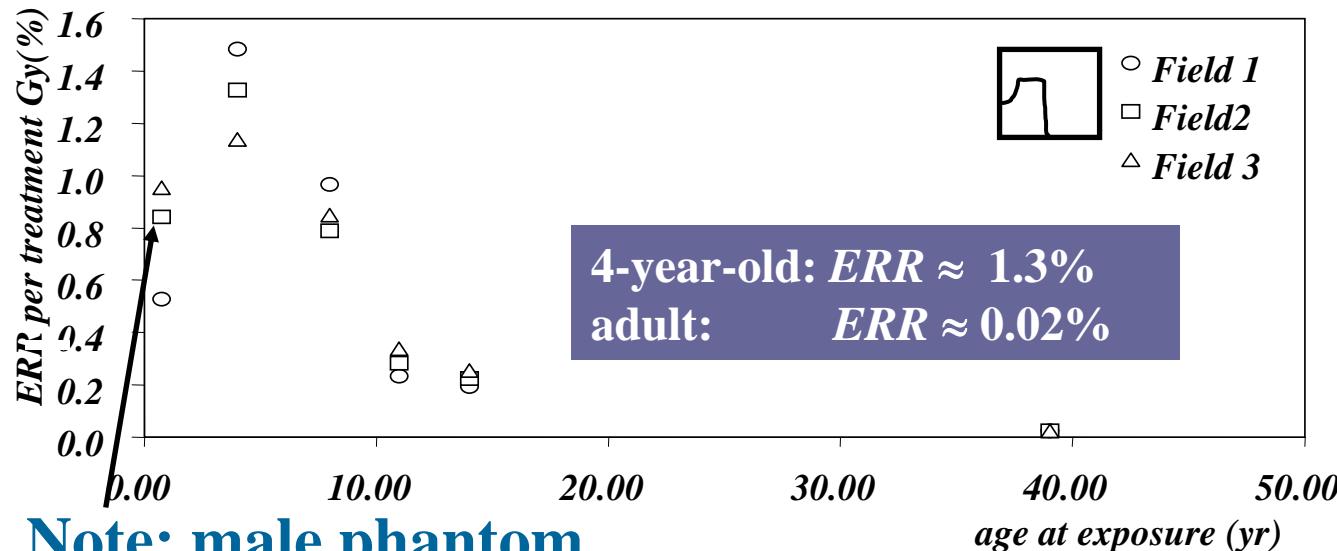
as a function of dose

as a function of patient's age

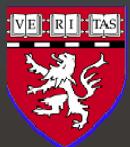
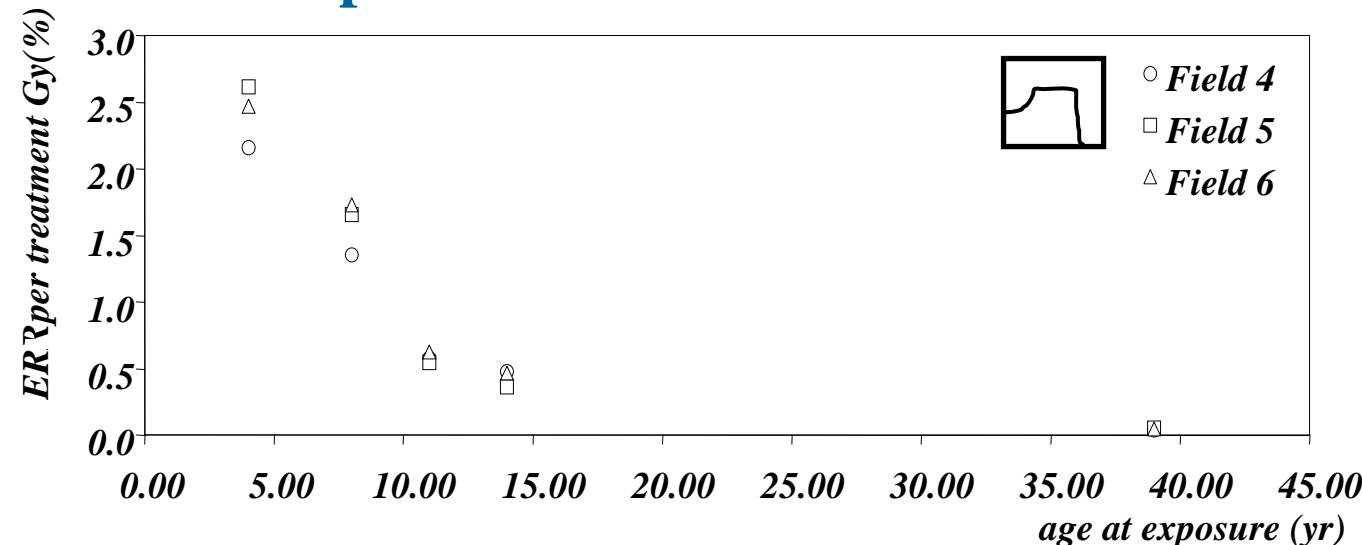
as a function of organ



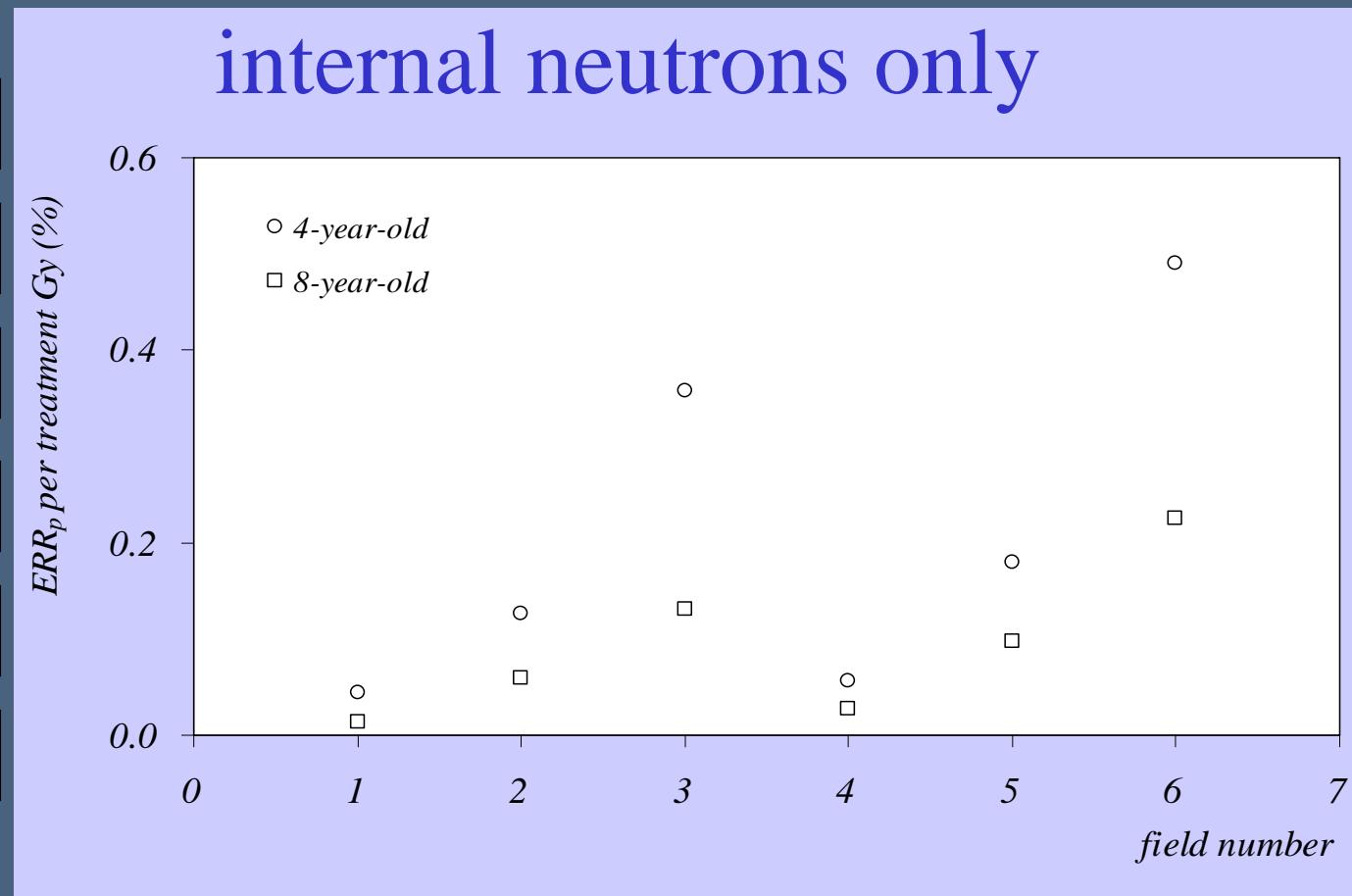
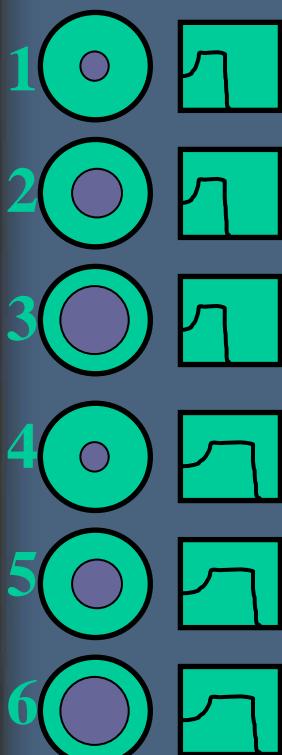
Excess Relative Risk for Thyroid Cancer



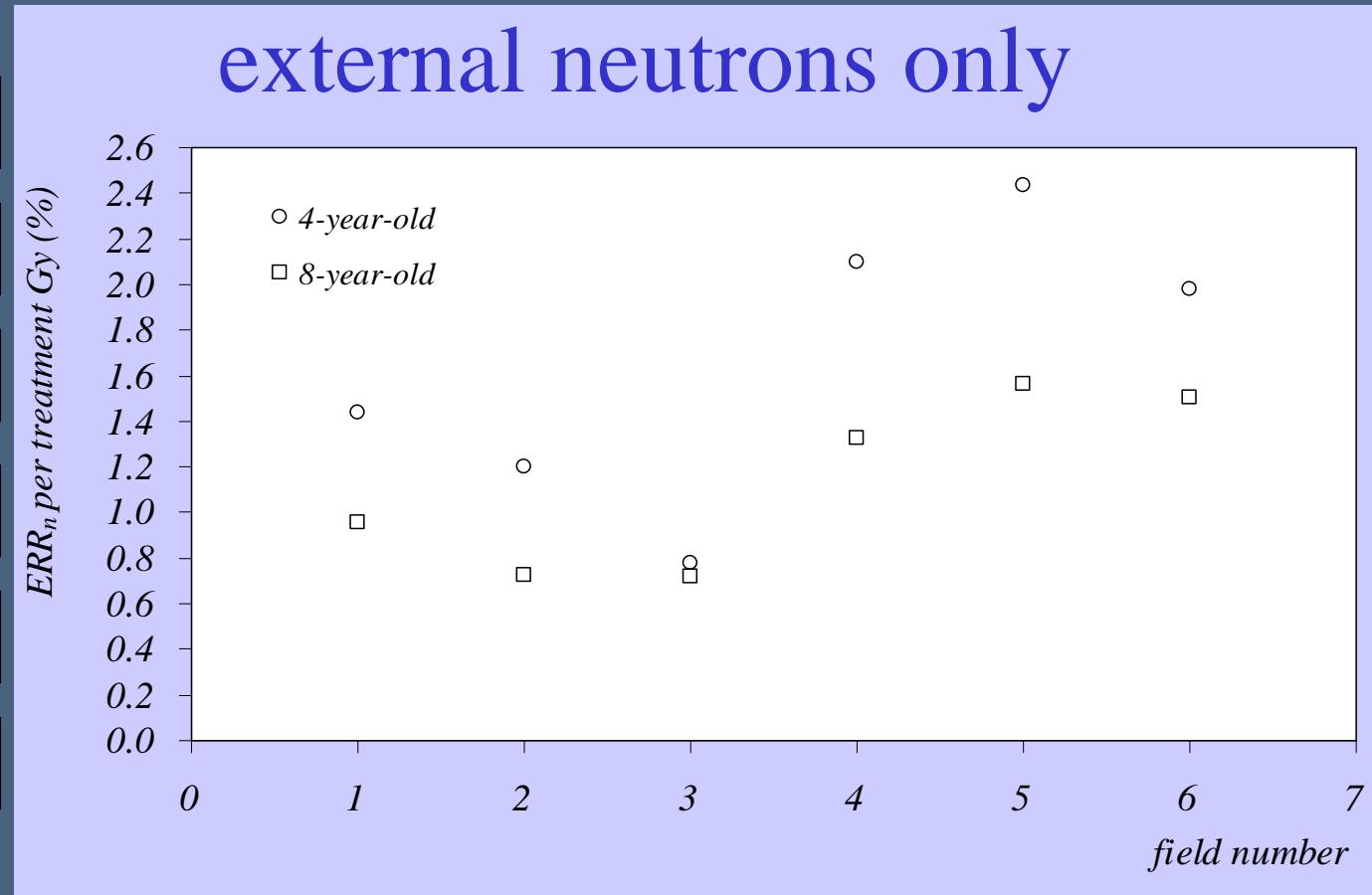
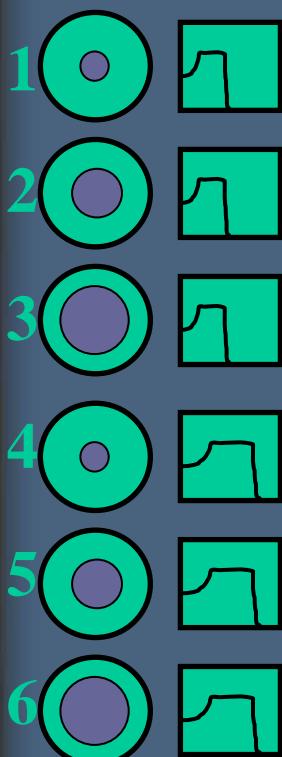
Note: male phantom



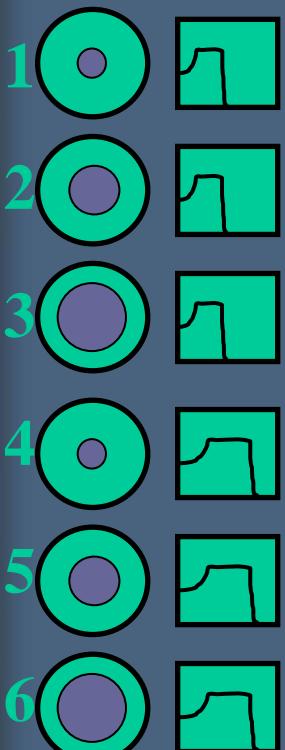
Excess Relative Risk for Thyroid Cancer



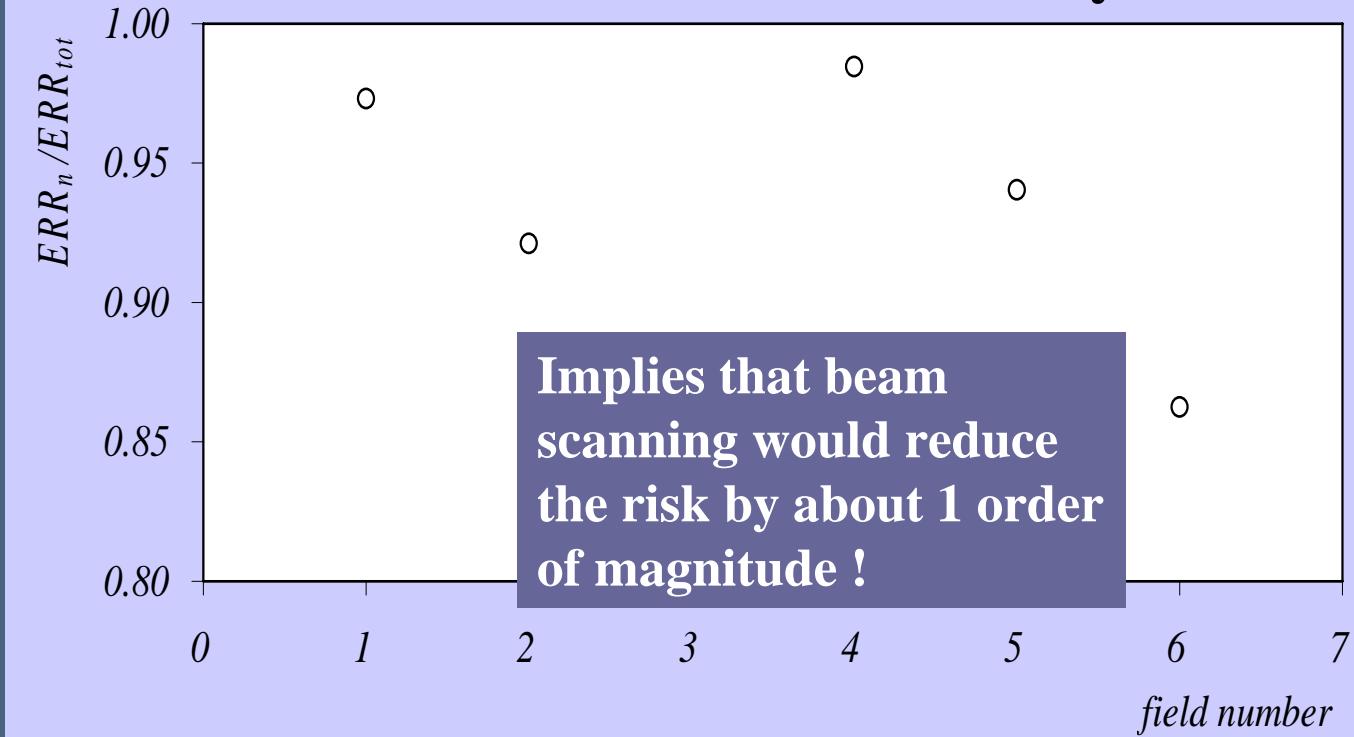
Excess Relative Risk for Thyroid Cancer



Excess Relative Risk for Thyroid Cancer



external / total neutrons 4 year old



Excess Relative Risk for Thyroid Cancer

Assuming a 70 Gy treatment of a 4-yr old
(worst case field):

$$\text{ERR} \leq 1.2$$

$$(0.026 \text{ Sv/Gy} \times 70 \text{ Gy} / 1.5_{\text{DDREF}})$$

Baseline lifetime incidence for Thyroid:

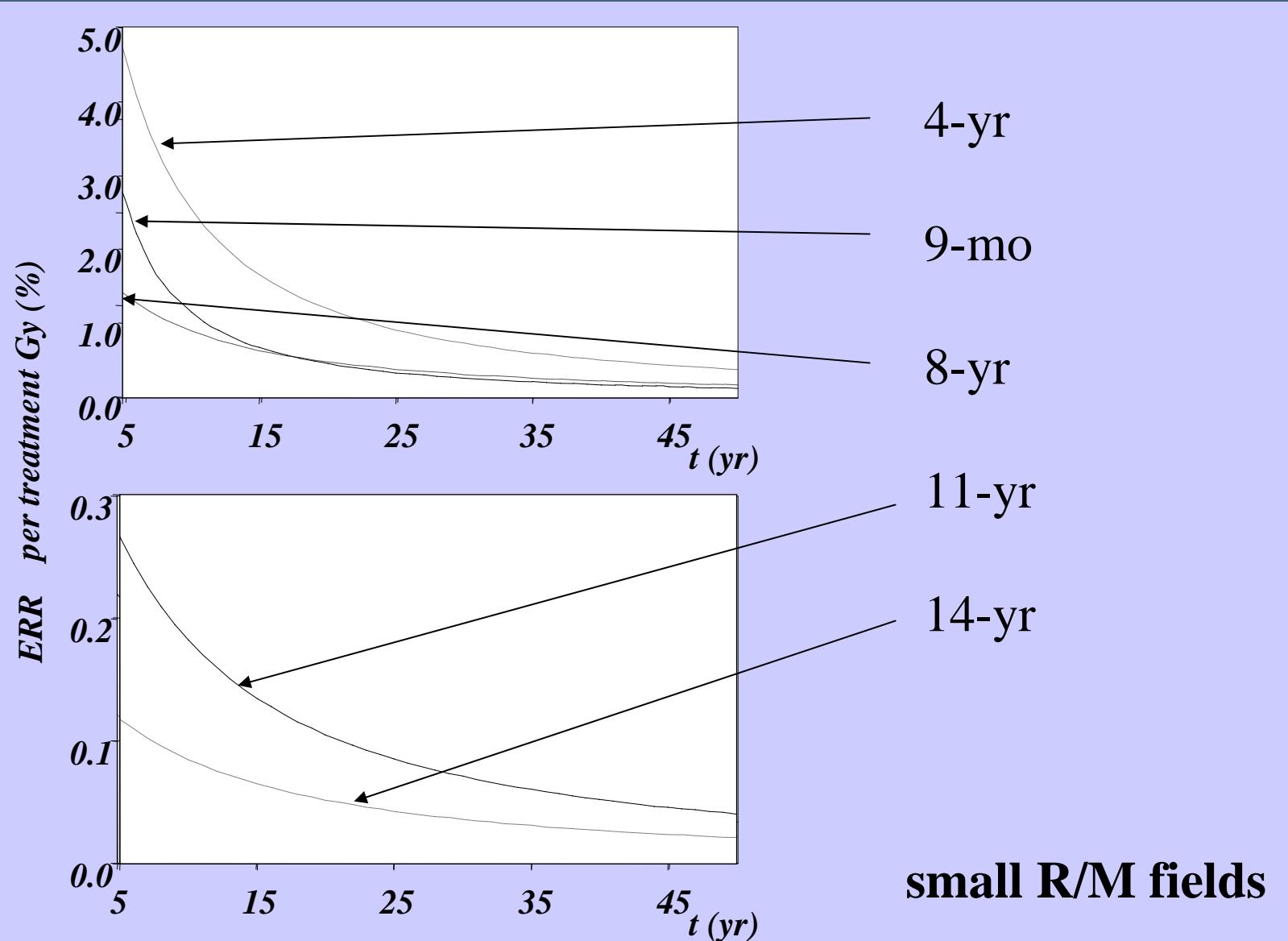
male 0.23 %

female 0.55 %

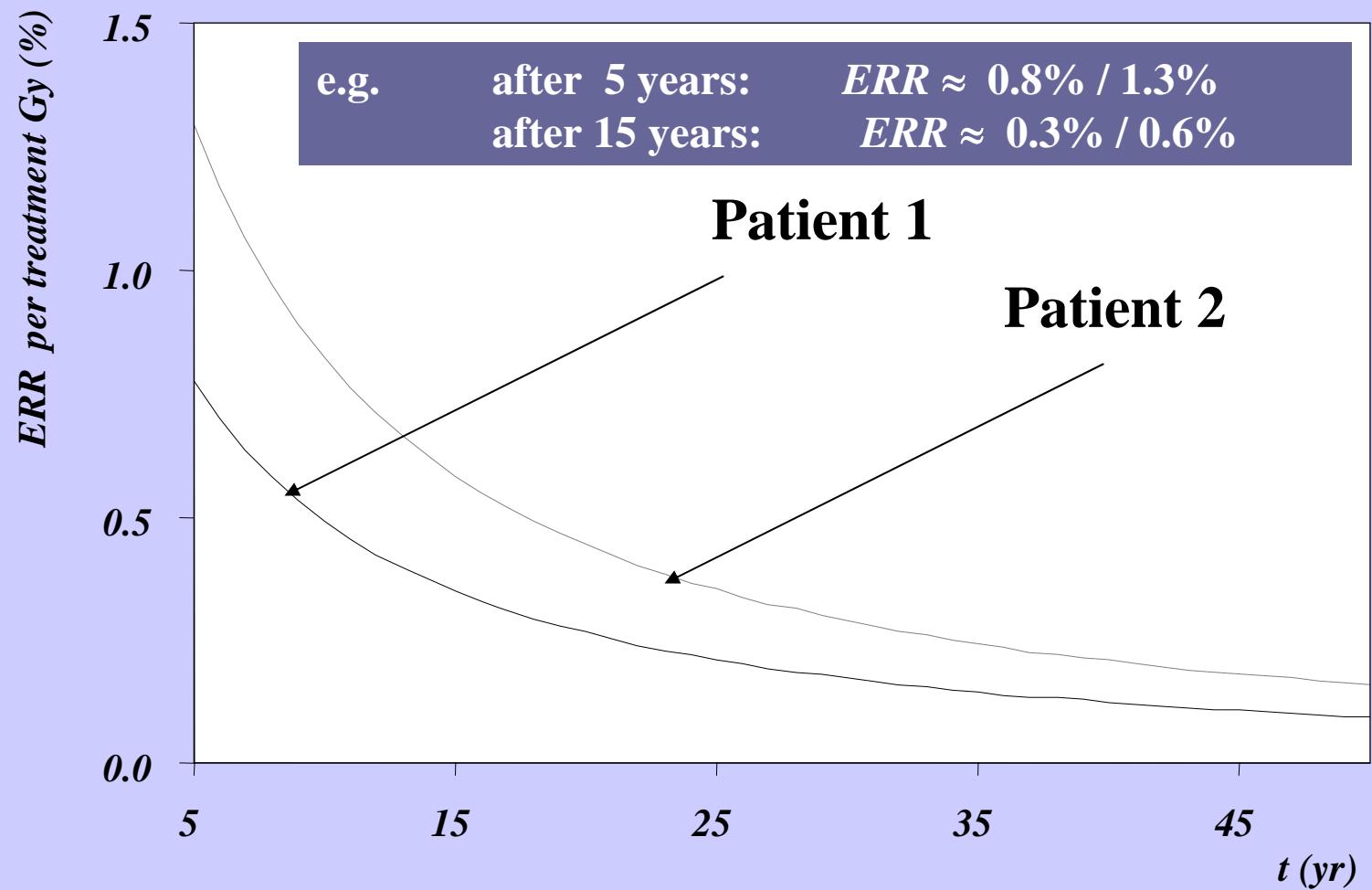
Numbers would increase by up to
a factor of 2.2



Excess Relative Risk for Lung Cancer (depends on time since exposure)



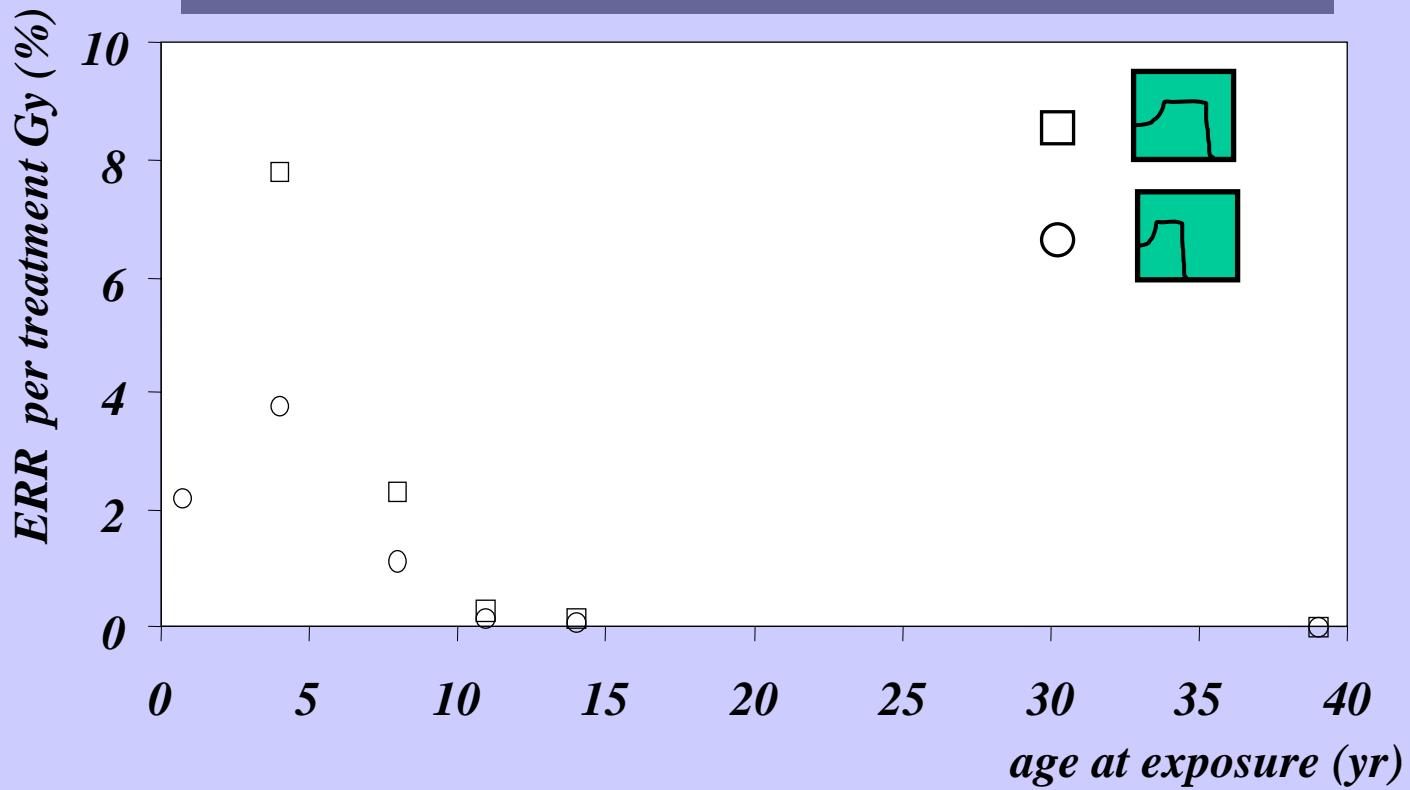
Excess Relative Risk for Lung Cancer



Excess Relative Risk for Lung Cancer

e.g. 10-cm range field:

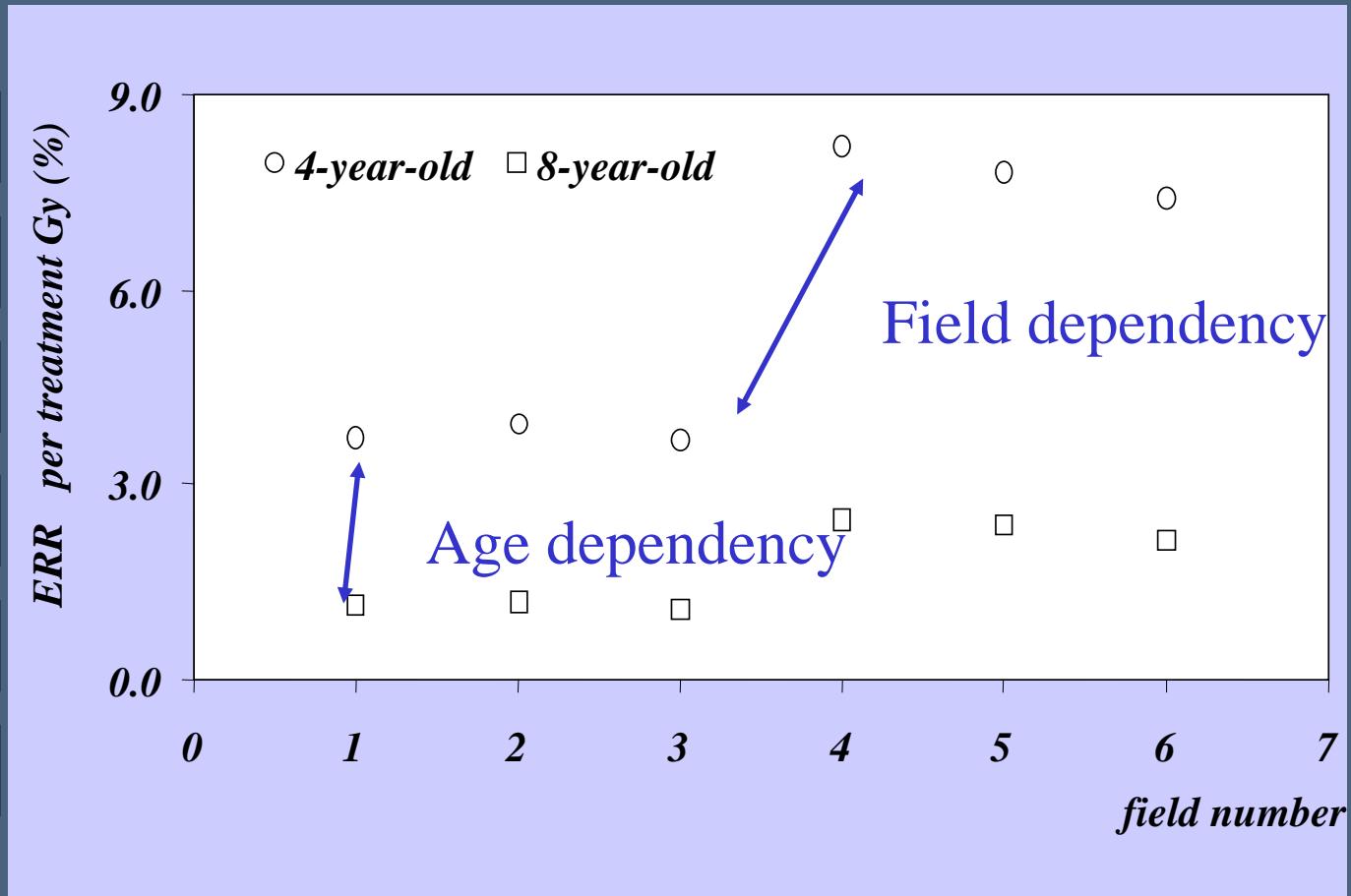
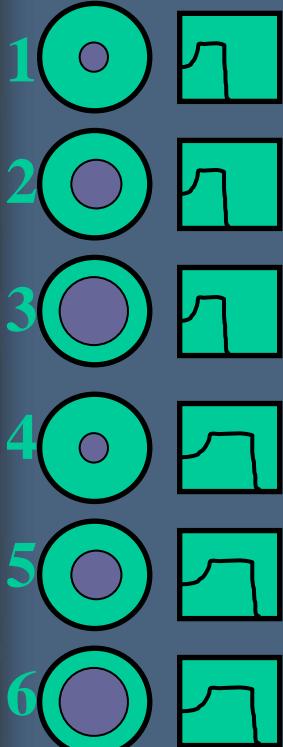
4-year-old: $ERR \approx 3.8\%$
adult: $ERR \approx 0.01\%$



5 years post treatment



Excess Relative Risk for Lung Cancer



5 years post treatment



5-yr Excess Relative Risk for Lung Cancer

Assuming a 70 Gy treatment of a 4-yr old
(worst case field):

$$\text{ERR} \leq 3.6$$

$(0.078 \text{ Sv/Gy} \times 70 \text{ Gy} / 1.5_{\text{DDREF}})$
5-year risk increase: factor of 4.6

Assuming a 70 Gy treatment of a 8-yr old
(worst case field):

$$\text{ERR} \leq 1.1$$

$(0.023 \text{ Sv/Gy} \times 70 \text{ Gy} / 1.5_{\text{DDREF}})$
5-year risk increase: factor of 2.1



CONCLUSION (Part II)

- Neutrons generated during passive scattered proton beam therapy cause a non-negligible risk for the development of second malignancies
- The risk seems to be negligible for adult patients
- Neutron exposure has to be considered when treating pediatric patients
- IMRT is not an option



Nuclear data impact on proton radiation therapy calculations

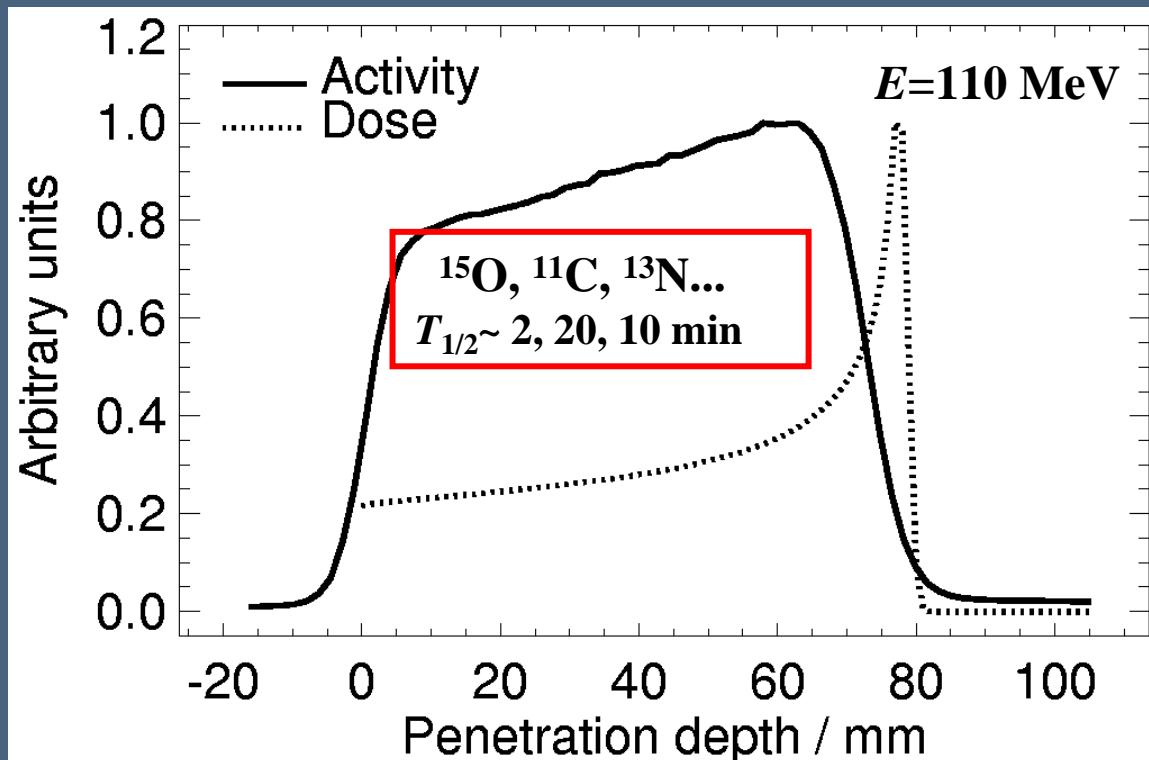
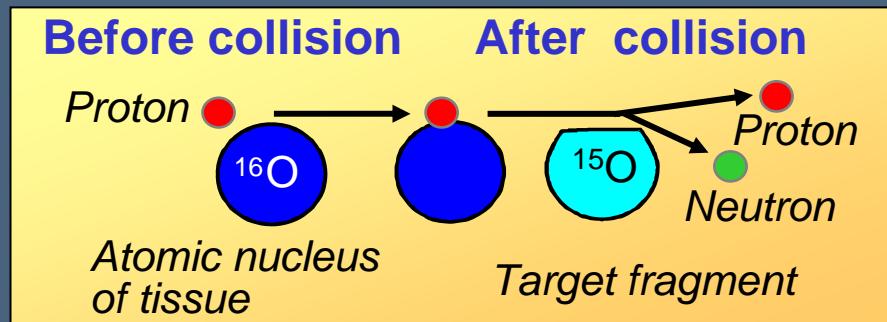
- PET imaging for quality assurance



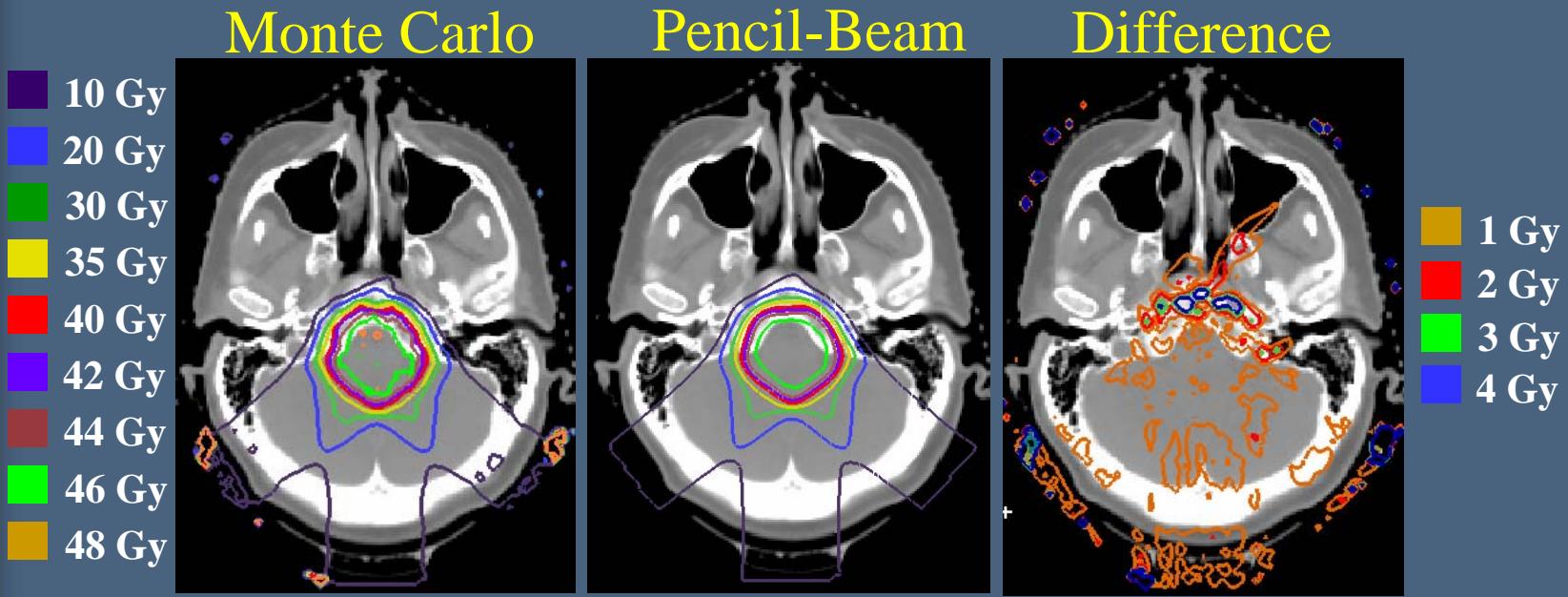
The principle of PET monitoring

In-vivo, non-invasive detection of β^+ -activation induced by irradiation

Mainly ^{11}C ($T_{1/2} = 20.3$ min) and ^{15}O ($T_{1/2} = 121.8$ s)



Monte Carlo dose calculation



Para-spinal tumor
176 x 147 x 126 slices
voxels: 0.932 x 0.932 x 2.5-3.75 mm³
3 fields: ~15.0 Gy each

PET/CT scanning of MGH proton patients



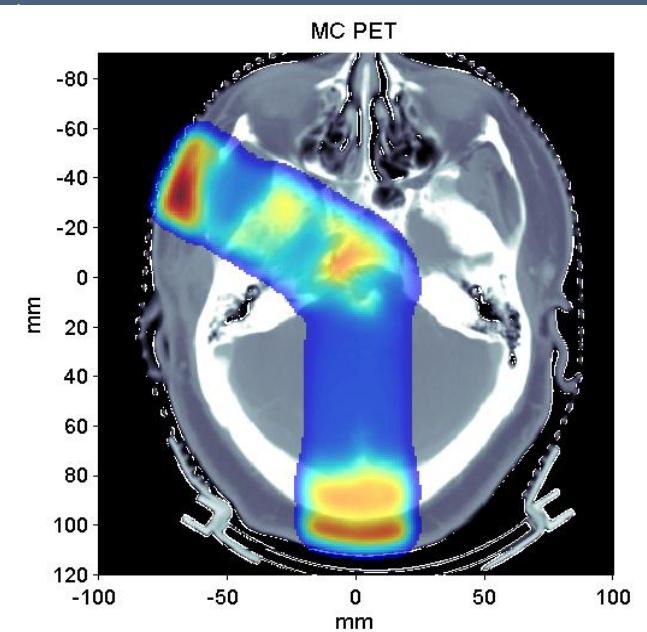
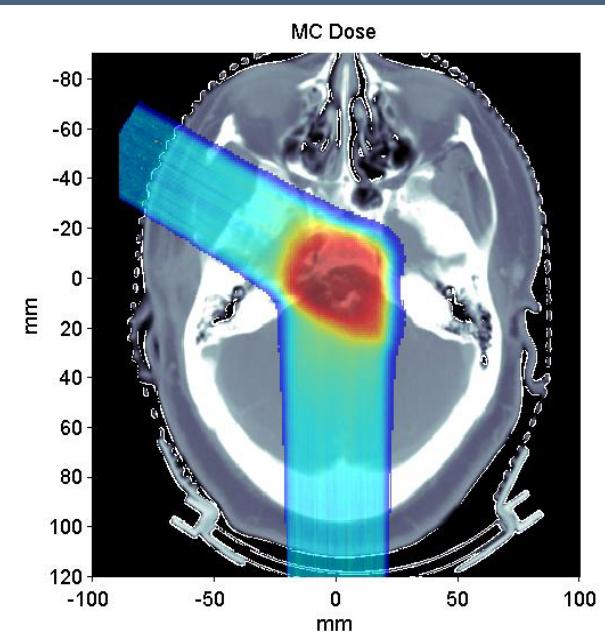
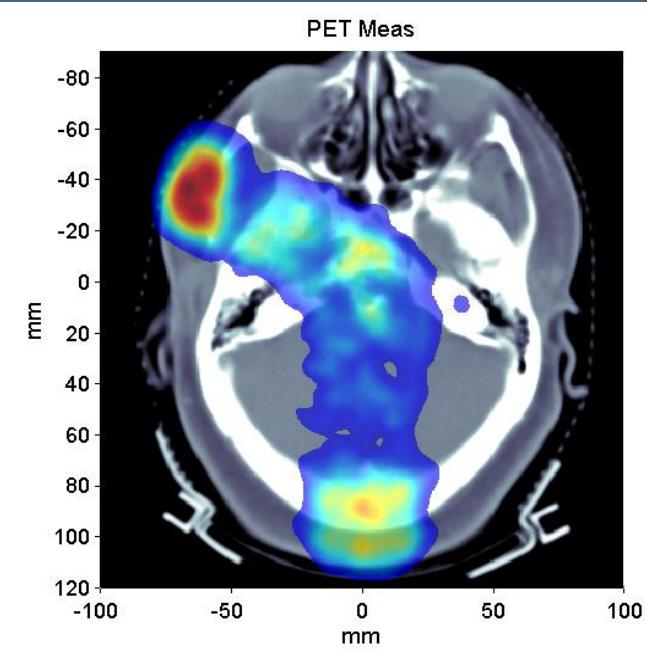
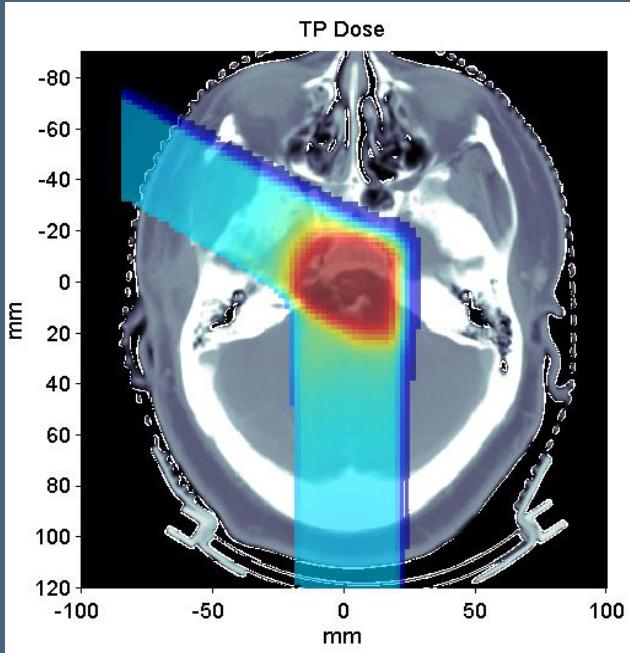
Time delay between
end of treatment and
PET/CT scan: 15 min

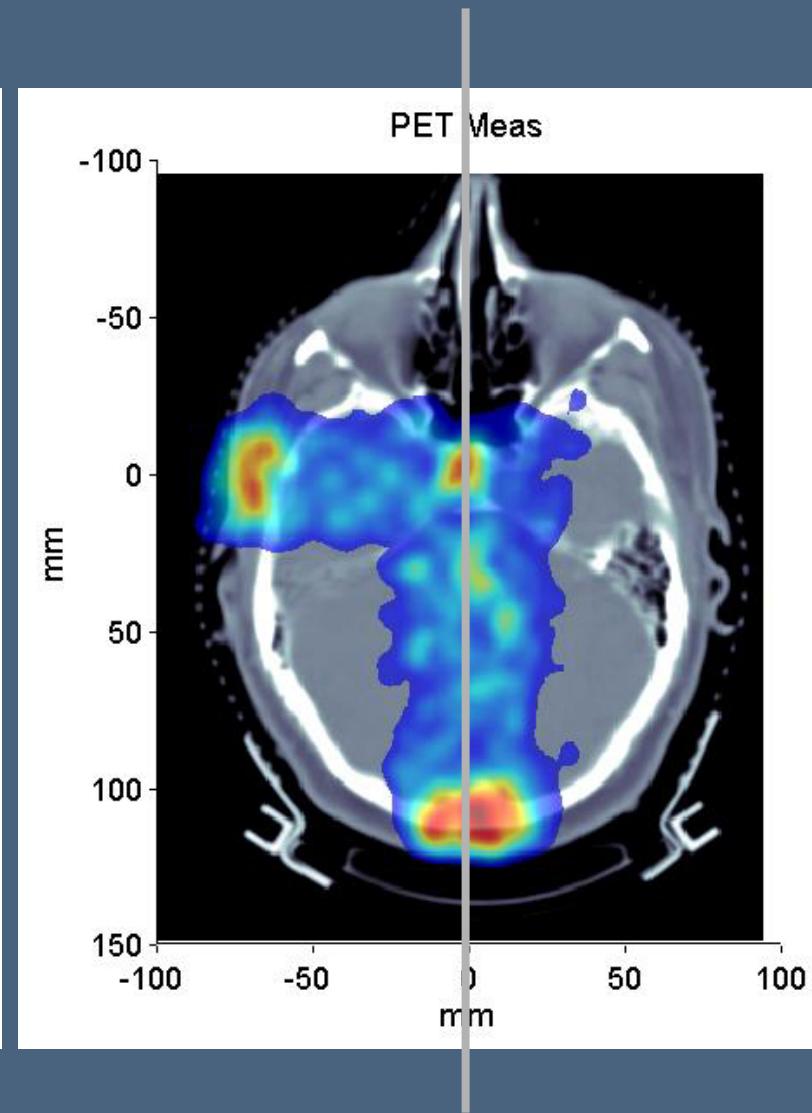
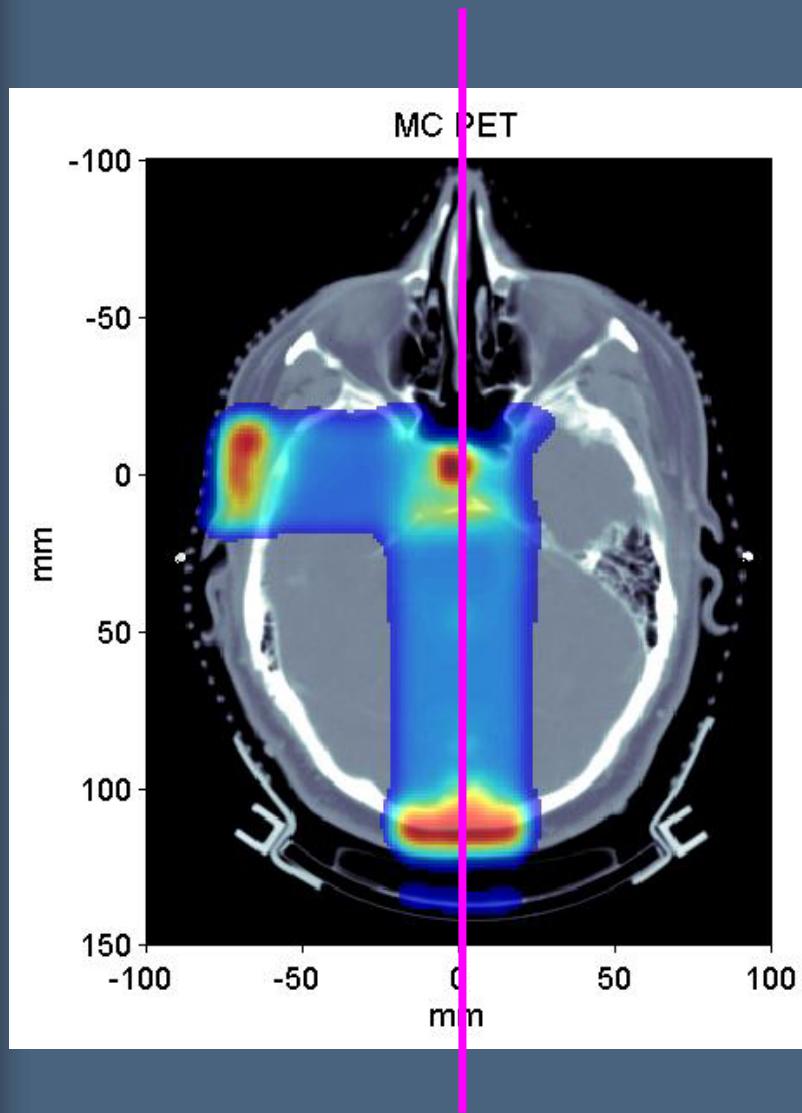
Scan time: 30 min

Siemens Biograph 16

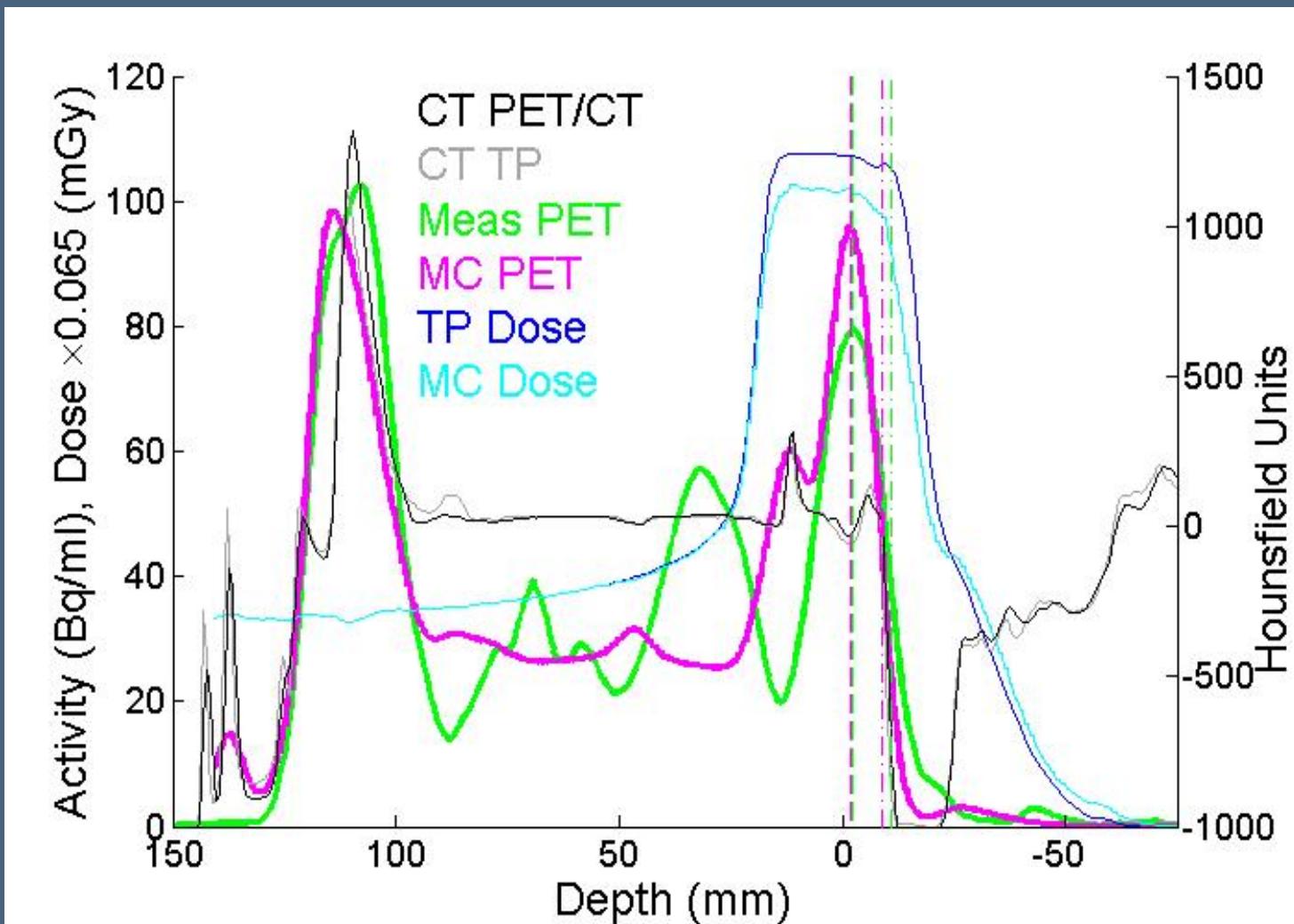


PET imaging for proton therapy QA

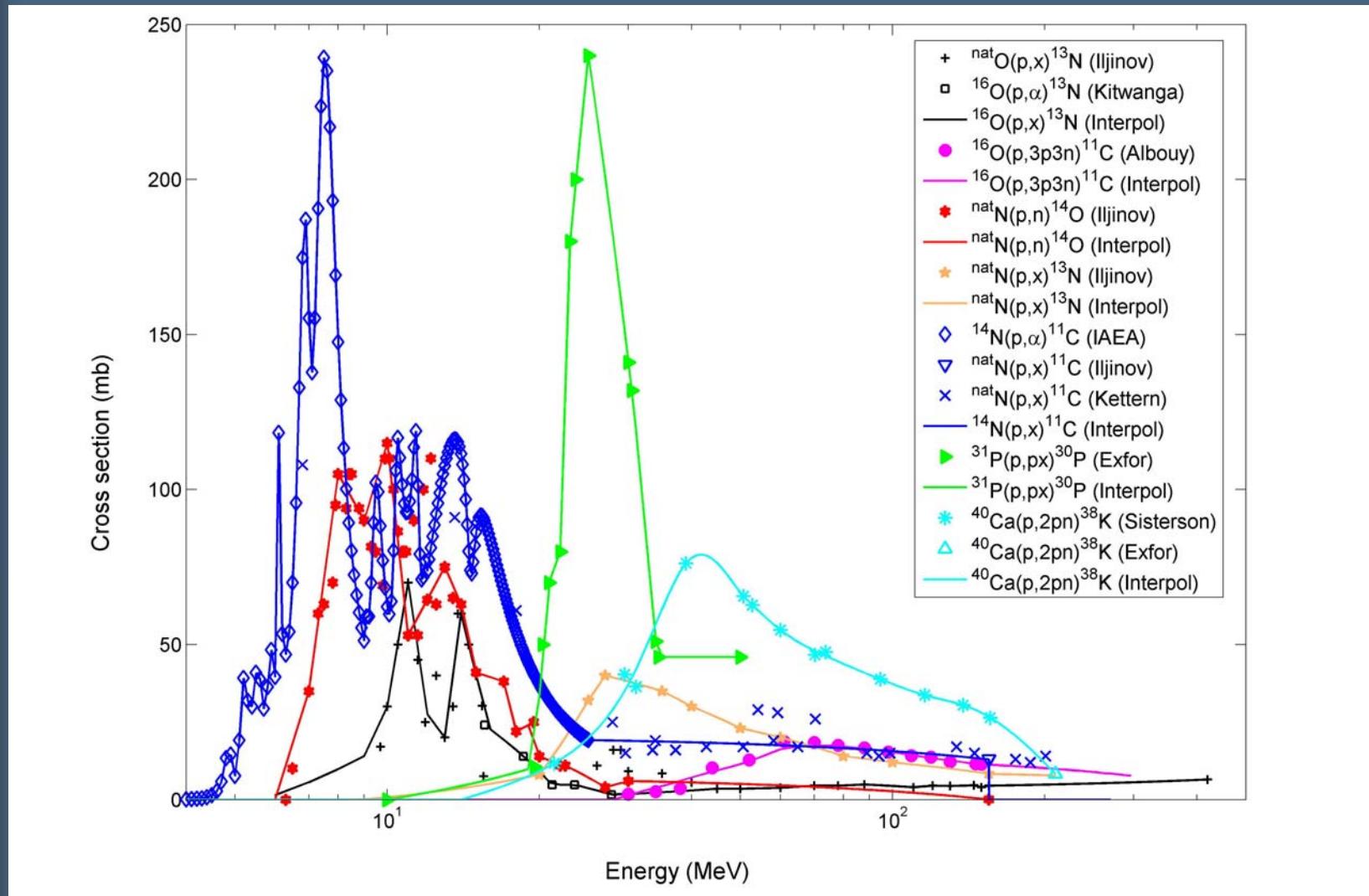




Quantitative Analysis



Nuclear interaction uncertainties



Used additional cross-sections values (lines) interpolated from experimental and evaluated data for proton induced reactions on O, N, P, Ca yielding ^{14}O , ^{13}N , ^{11}C , ^{30}P , ^{38}K positron emitters



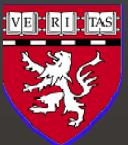
Nuclear data impact on proton radiation therapy calculations

- Monte Carlo benchmarking



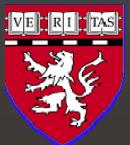
Benchmarking nuclear data

- Patient dose calculation
 - Predict secondary dose (1-3% effect)
 - Needed: Secondary proton yield in tissue -
- Neutron dose assessment
 - Predict cancer risk (20% uncertainty?)
 - Needed: Neutron yield in heavy materials and tissue -
- PET imaging
 - Assess beam range (1-2 mm effect)
 - Needed: Beta-emitter yield in tissue -

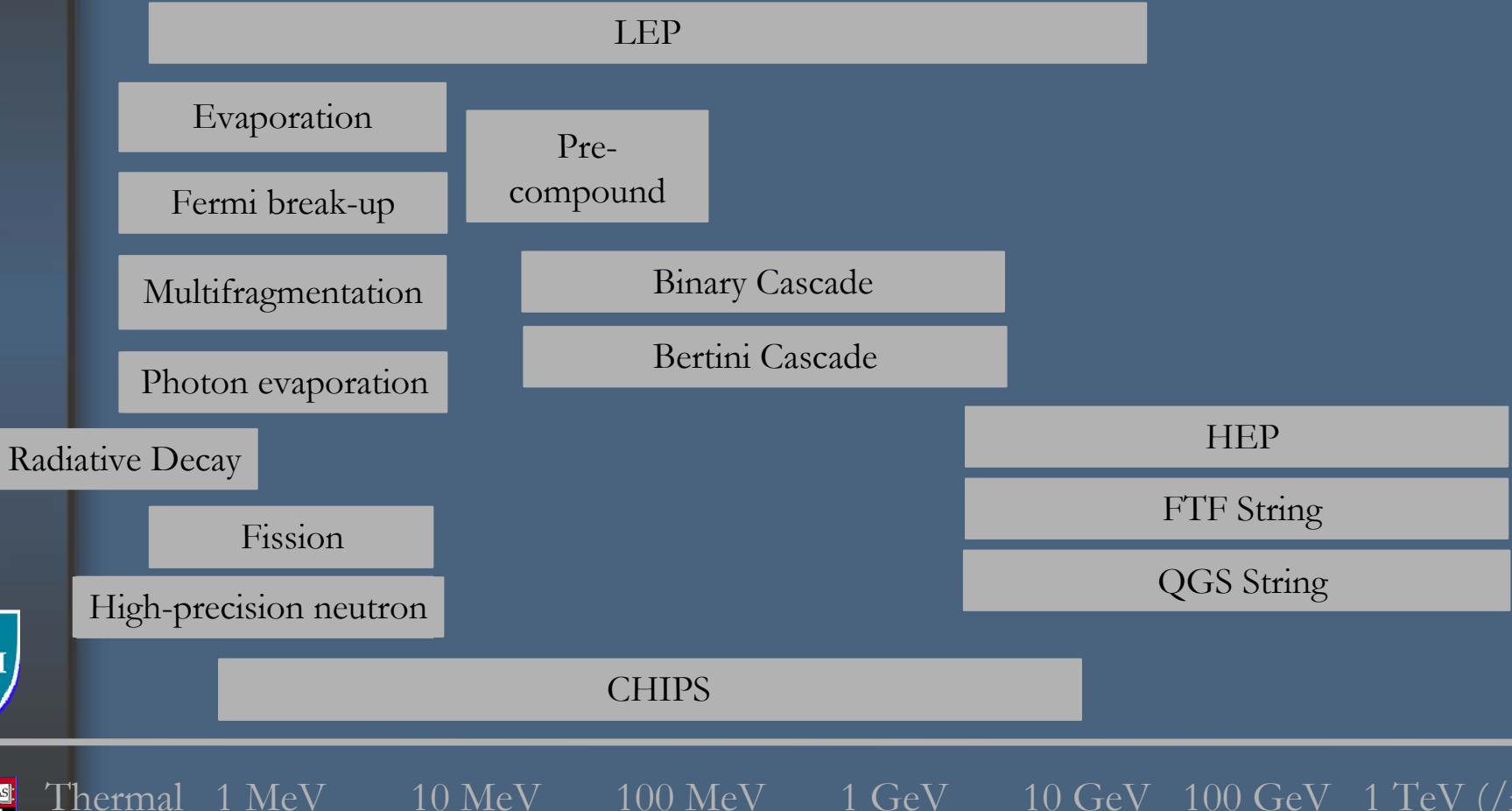


Benchmarking nuclear data

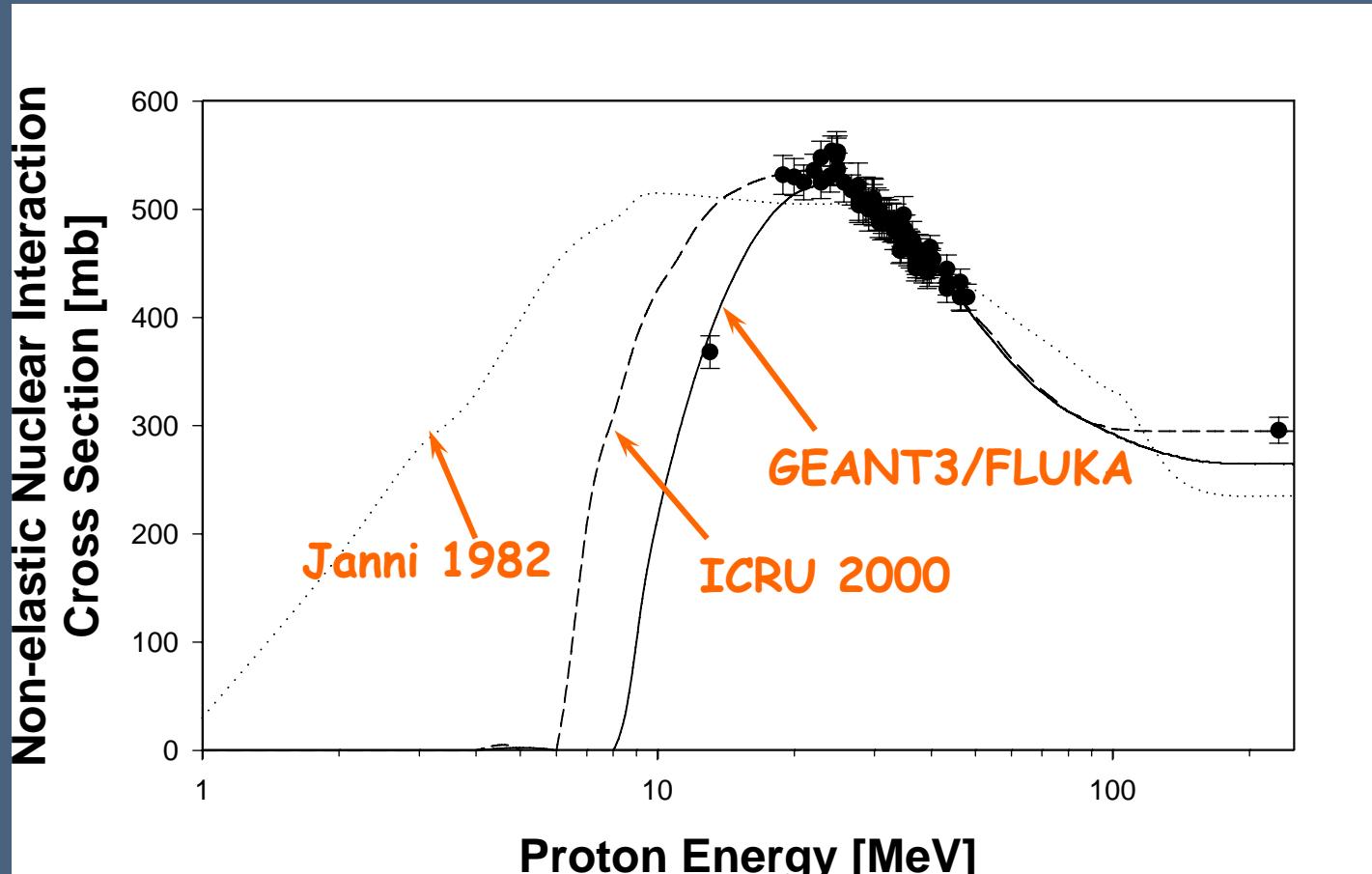
→ Compare Monte Carlo simulations with experiments (directly, if possible, or indirectly)



Geant4 p/n Physics Models



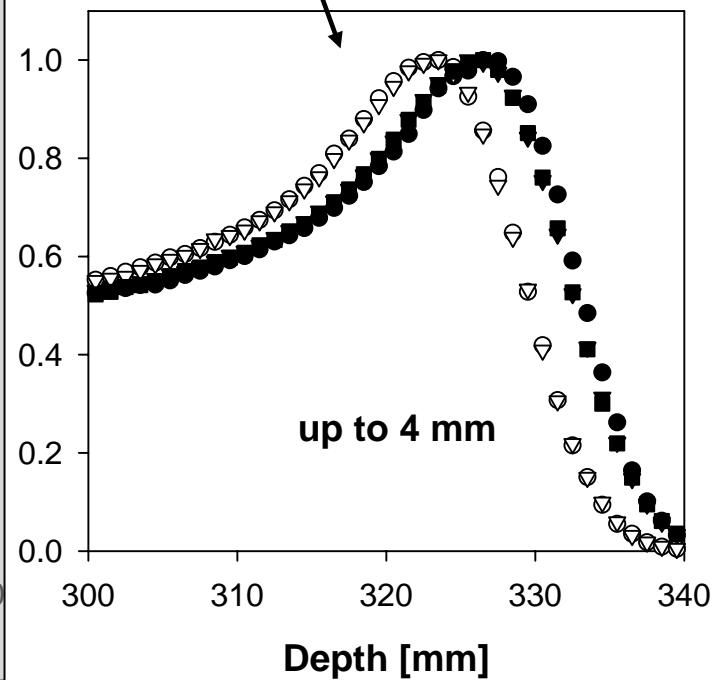
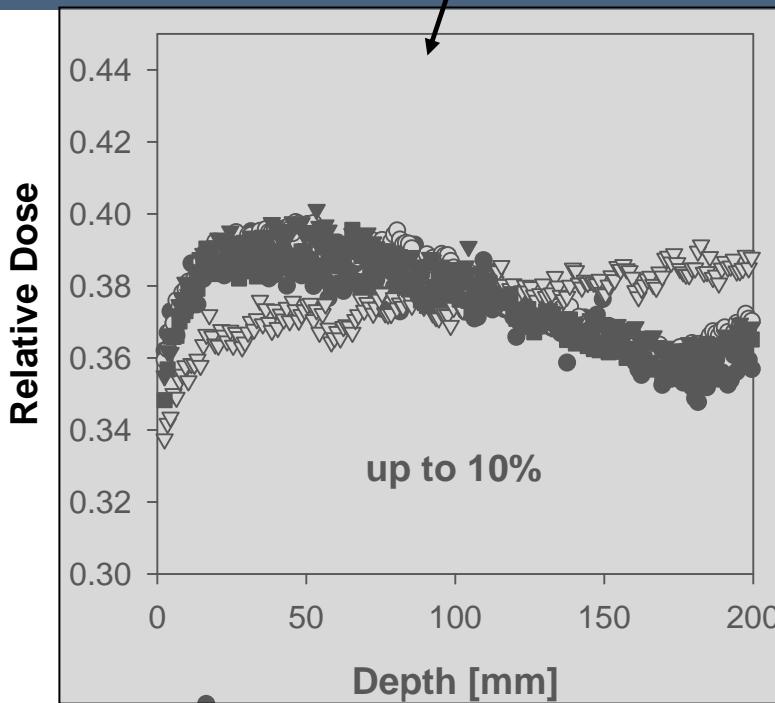
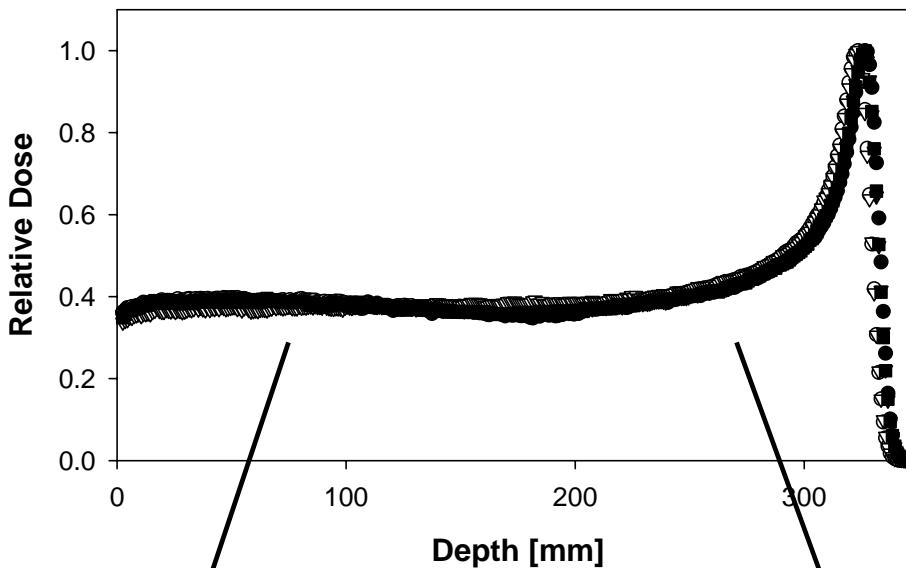
How accurate do we know the cross sections?



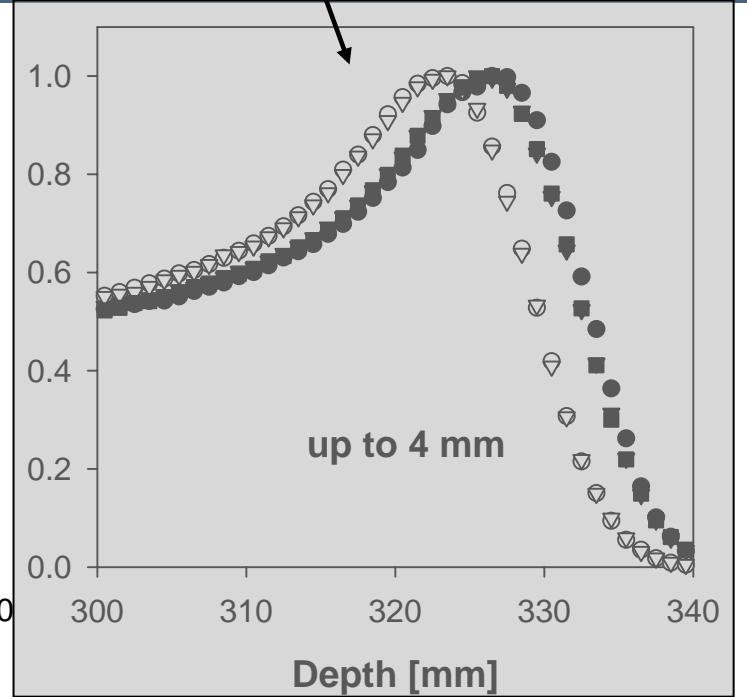
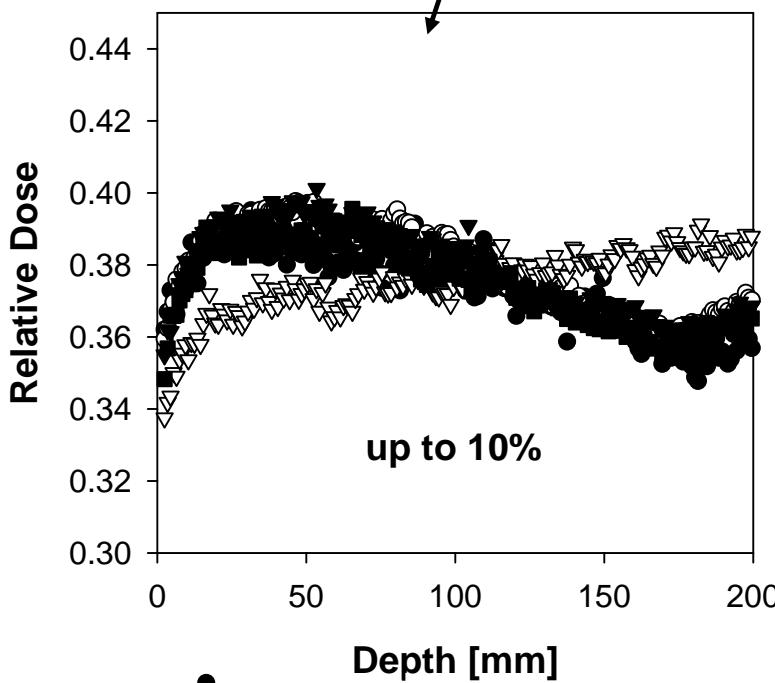
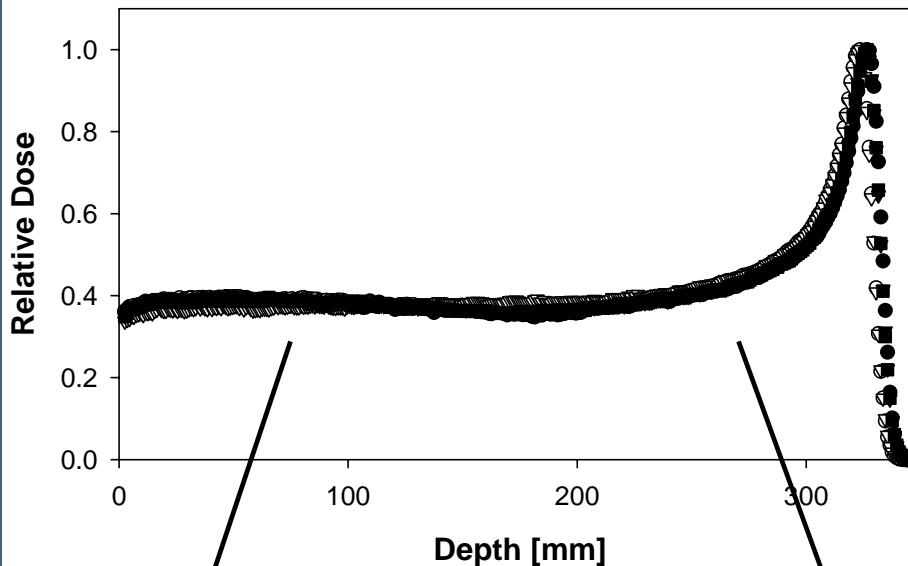
Calculations typically use models,
experimental data or hybrid approaches



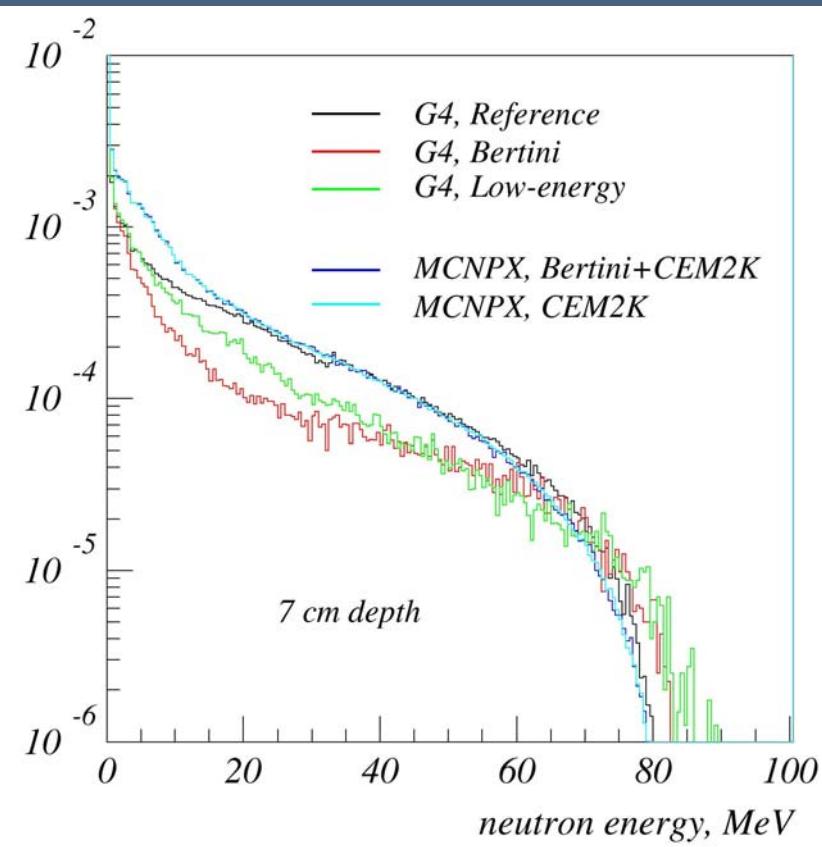
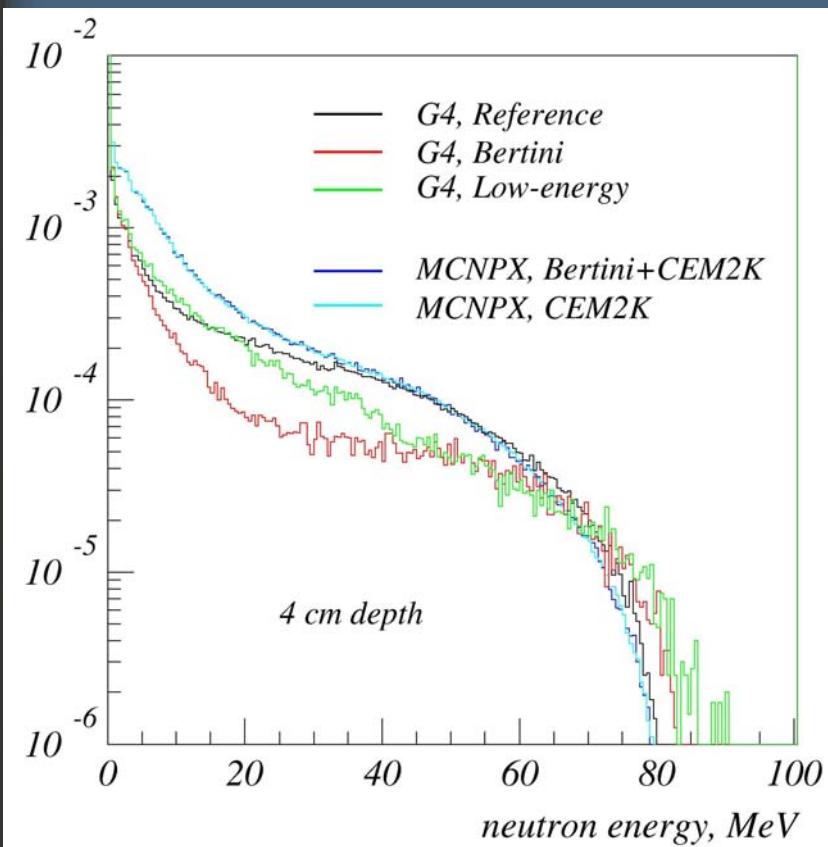
Electromagnetic interaction uncertainties



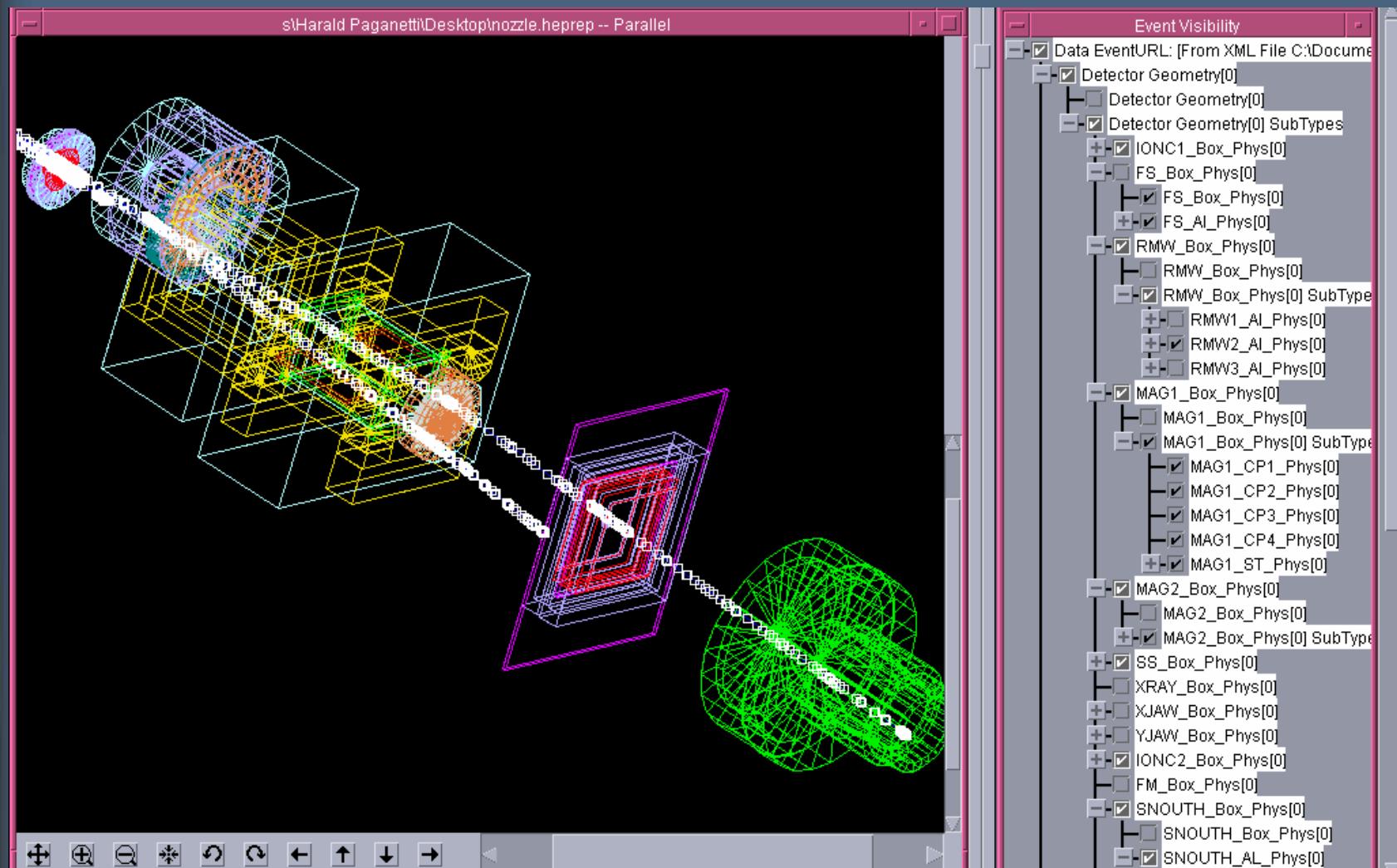
Nuclear interaction uncertainties



Water Phantom – Neutron Energies

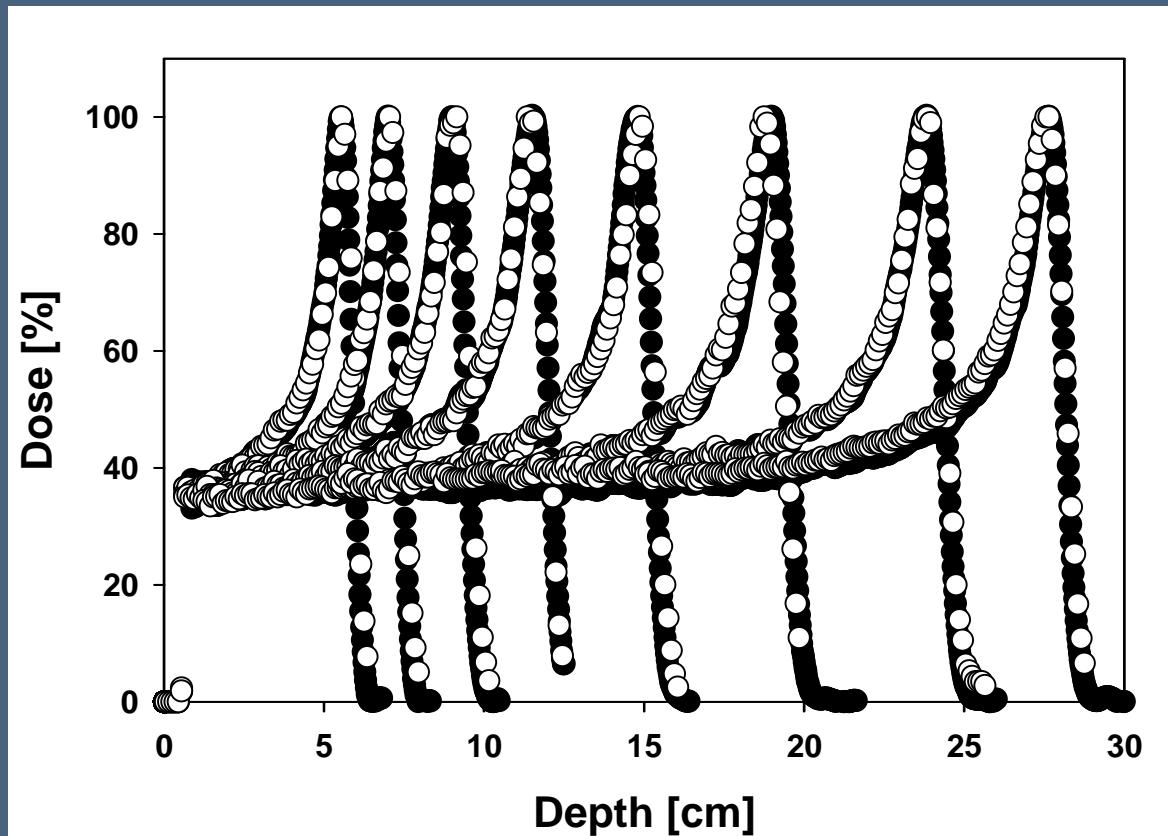


Benchmarking requires treatment head simulation

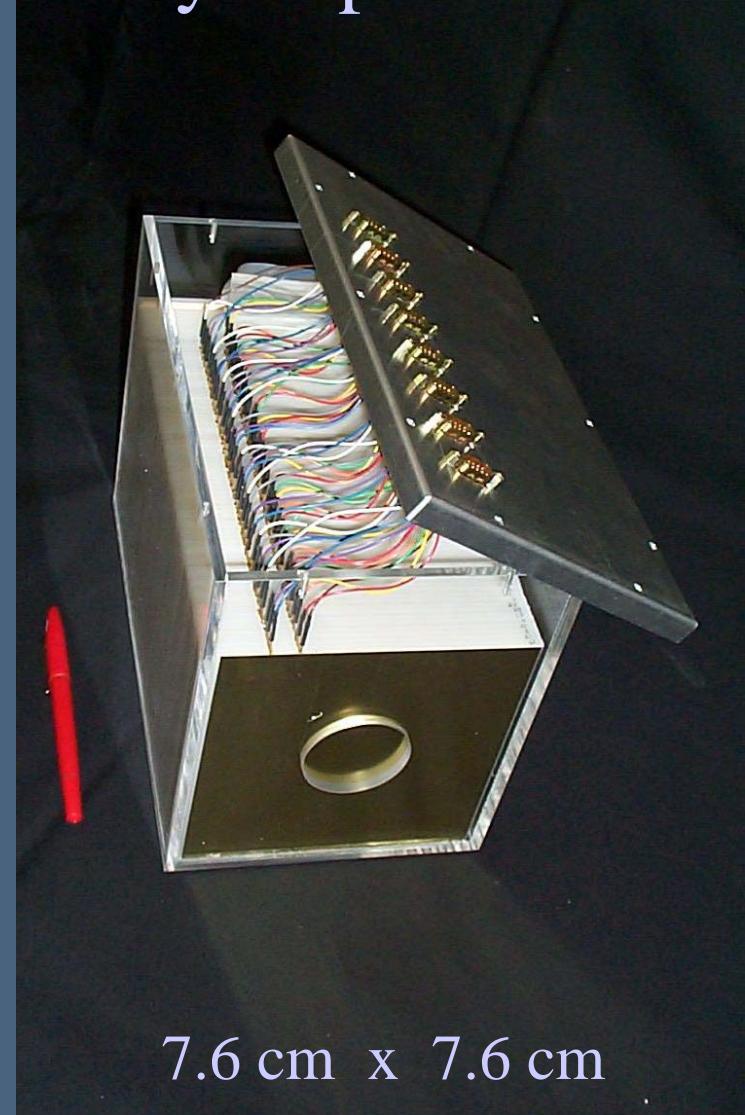
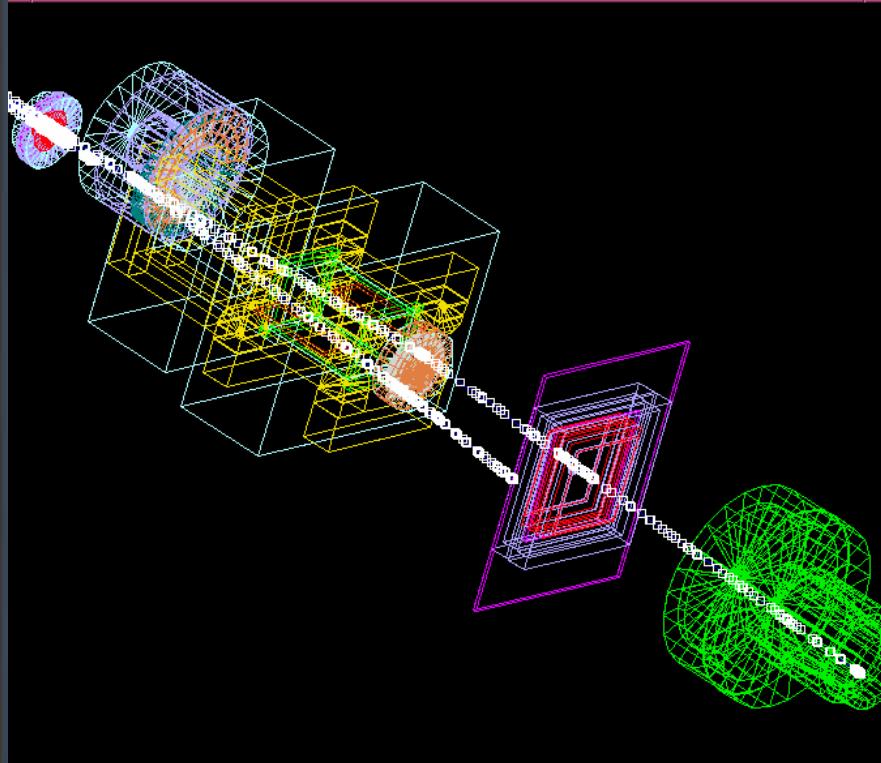


Beam characterization at nozzle entrance:

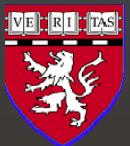
1. Beam size and spread (measured)
2. Beam angular spread (manufacturer info)
3. Beam energy (control system)
4. Beam energy spread (indirectly measured)



Multi-Layer Faraday Cup



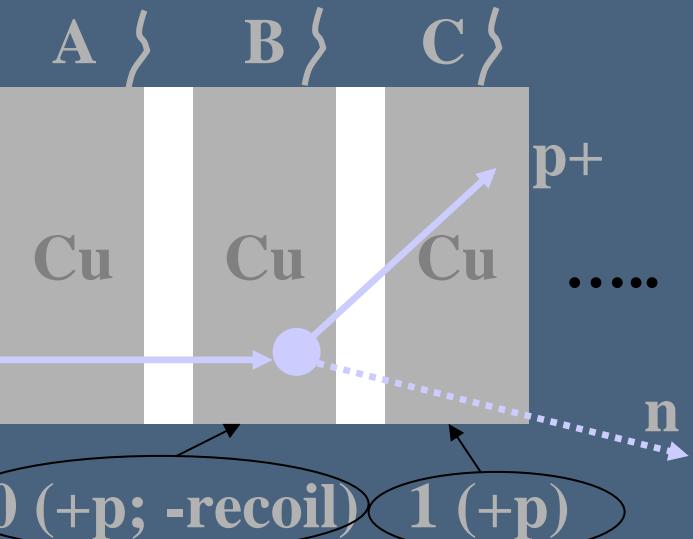
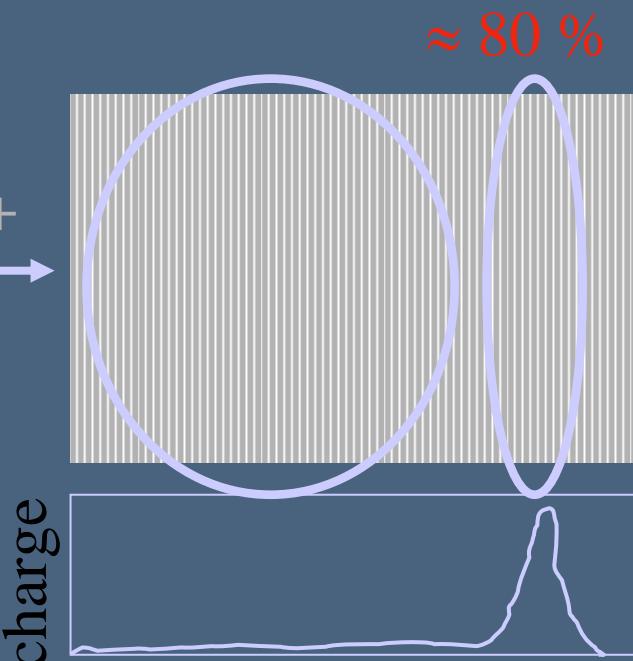
Gottschalk; Platais and Paganetti: Nuclear interactions of 160 MeV protons stopping in copper: a test of Monte Carlo nuclear models. *Medical Physics* 1999: 26, 2597-2601
Paganetti and Gottschalk: Test of Geant3 and Geant4 nuclear models for 160 MeV protons stopping in CH₂. *Medical Physics* 2003: 30, 1926-1931



Multi-Layer Faraday Cup (MLFC)

Clean benchmark for nuclear models:

- separated nuclear buildup region
- device has 100% acceptance for charged secondaries
- technique measures charge, not dose (no problems of dosimeter linearity and response to particle types) (secondary electrons have no effect (will bind the ion left behind))



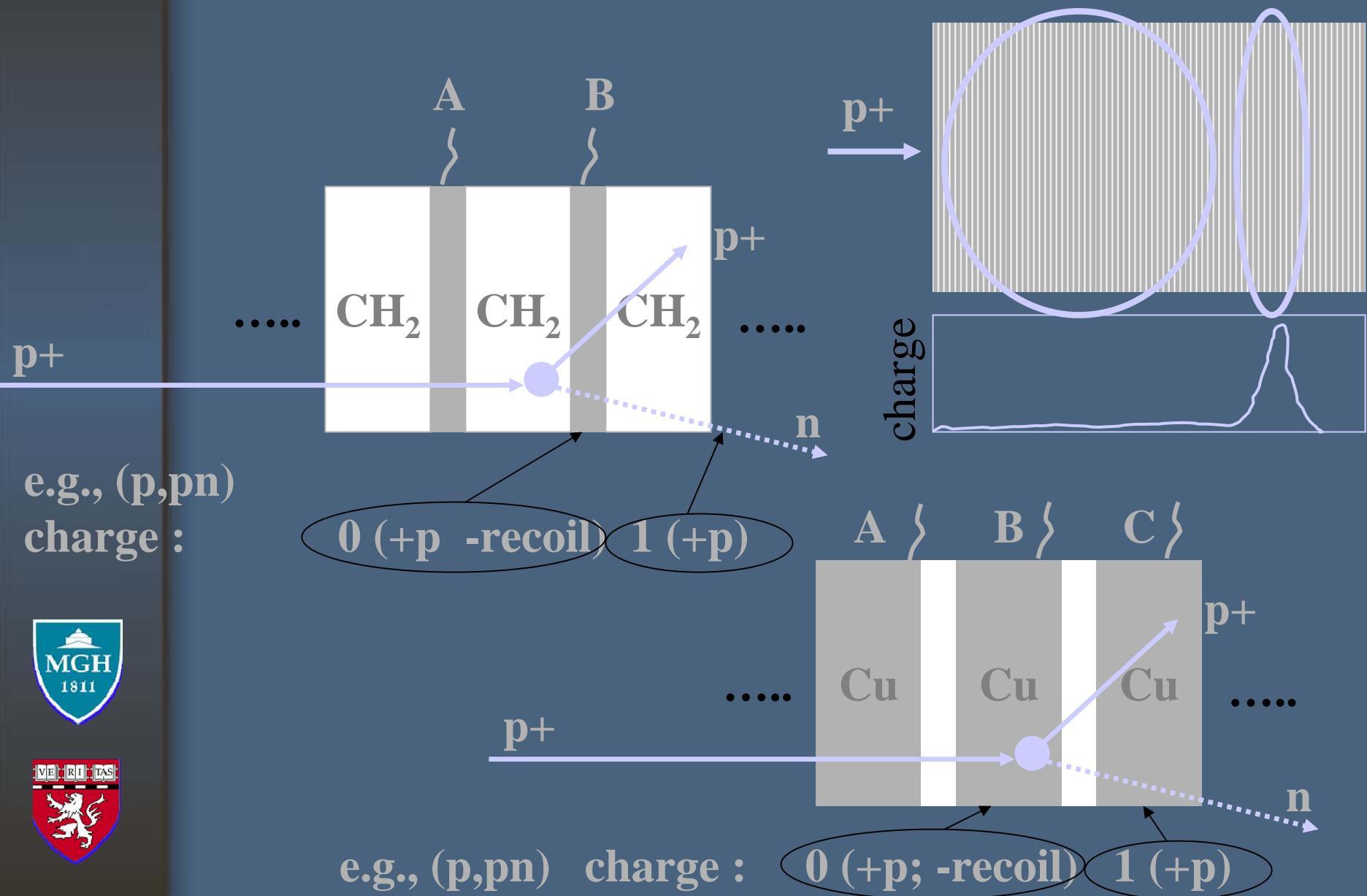
e.g., (p,pn) charge :

0 (+p; -recoil)

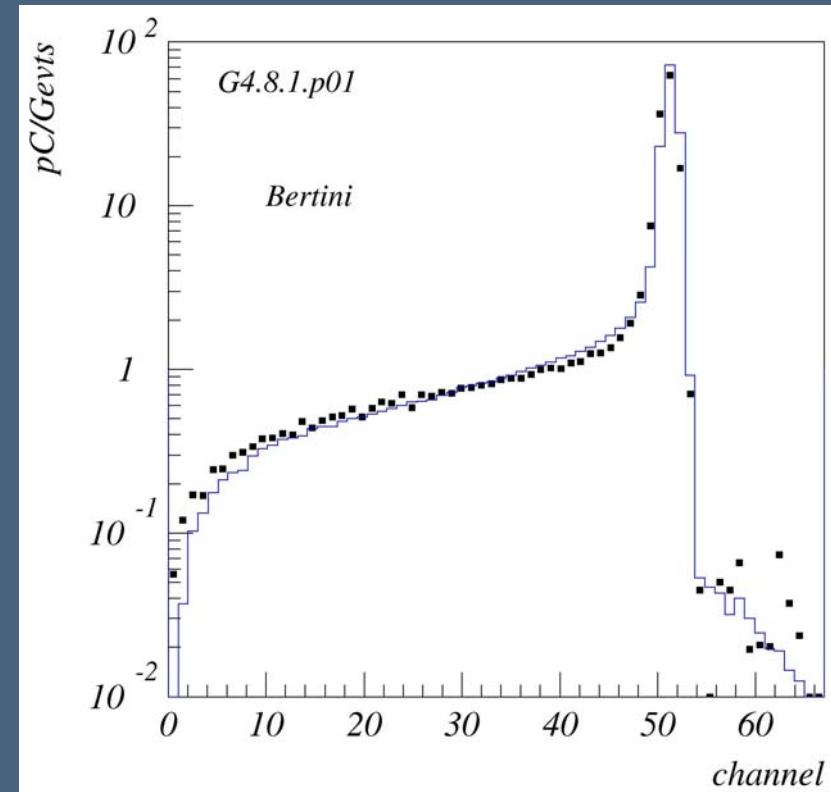
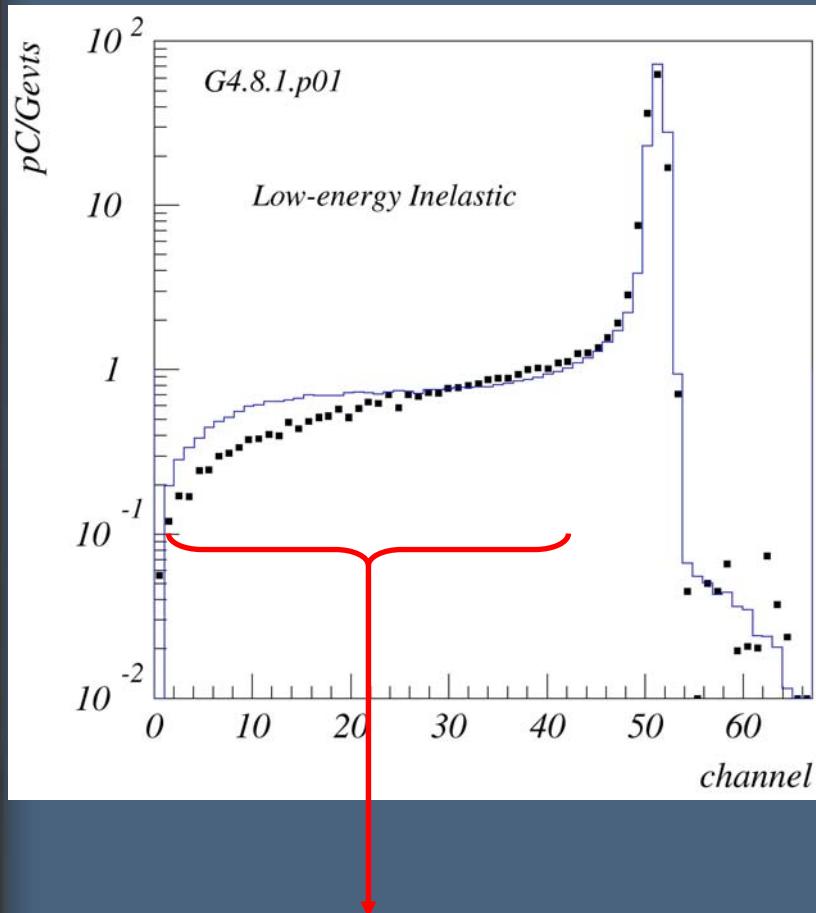
1 (+p)



Multi-Layer Faraday Cup (MLFC) can be used for high and low-Z !



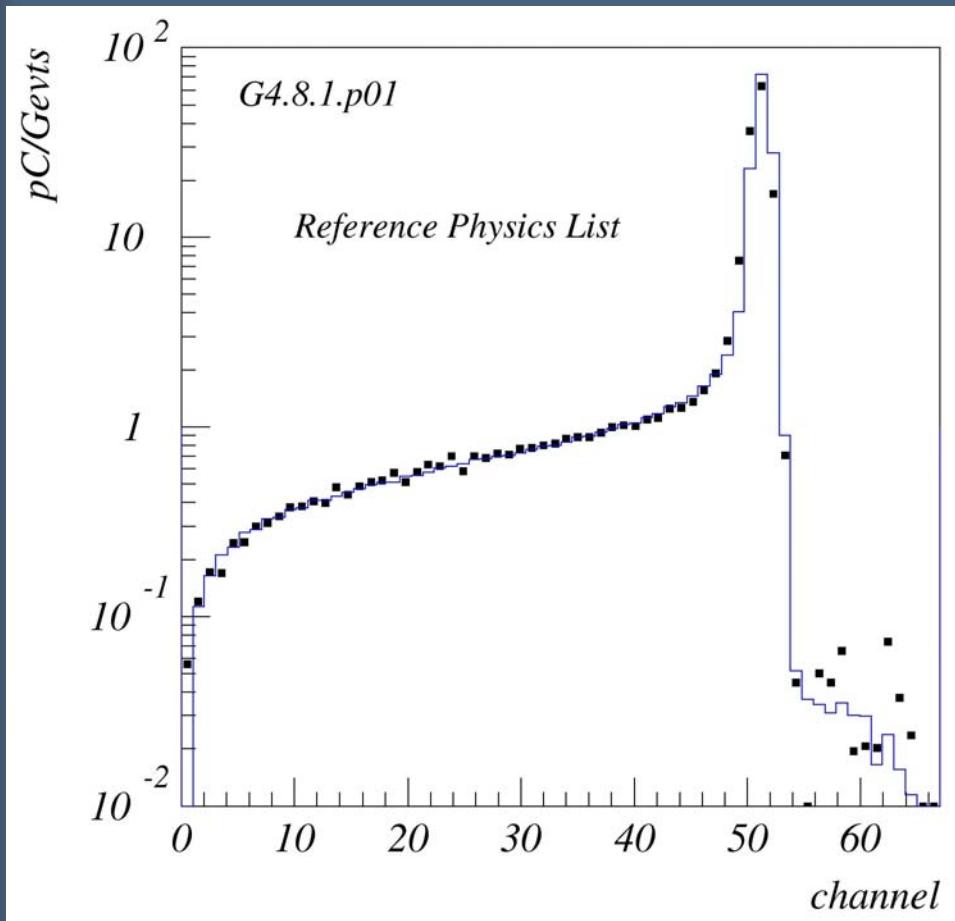
MLFC – Charge Distribution



Nuclear interactions only



MLFC - Reference Physics

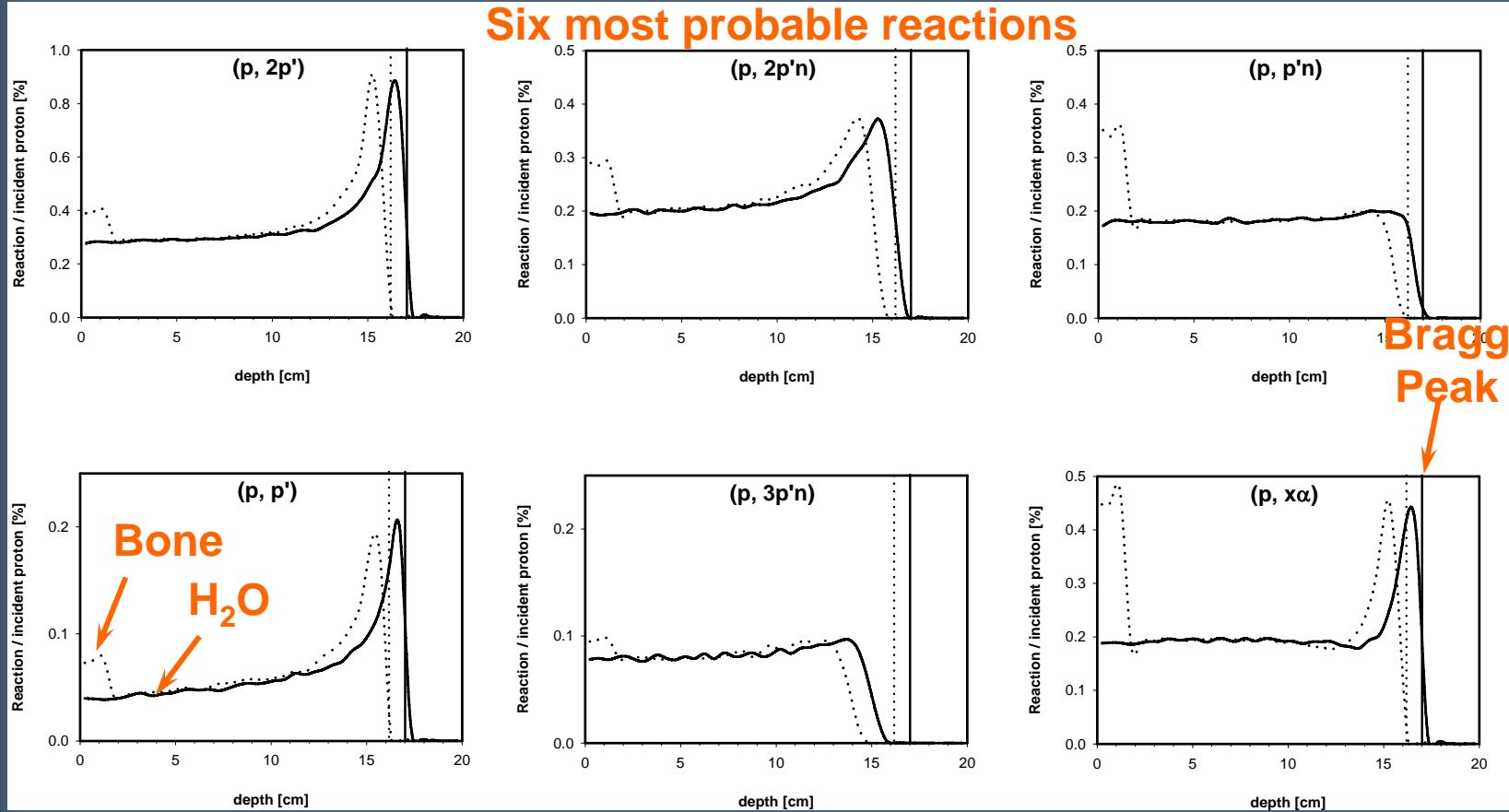


- Standard EM
- Binary cascade
- G4LElastic
- G4HadronElastic Process
- High-precision neutron



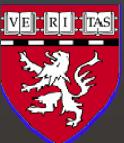
Nuclear Interactions: Branching Ratios

Six most probable reactions



160 MeV p beam

Water
Bone



Nuclear data impact on proton radiation therapy calculations

TAKE-HOME MESSAGES

- **Impact of nuclear interactions on dose**
Small effect in the organs at risk / beam path
- **Neutron dose in proton beam therapy**
Important issue / uncertainties can be large
- **PET imaging for quality assurance**
Uncertainties for PET emitters
- **Monte Carlo benchmarking**
Difficult to do for reaction channels



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Christina Z Jarlskog

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Choonik Lee

Katia Parodi

George Xu

