# “A” Quantitative Approach in Radiotherapy

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&

SOKENDAI: The Graduate University for Advanced Studies

# Who are we?

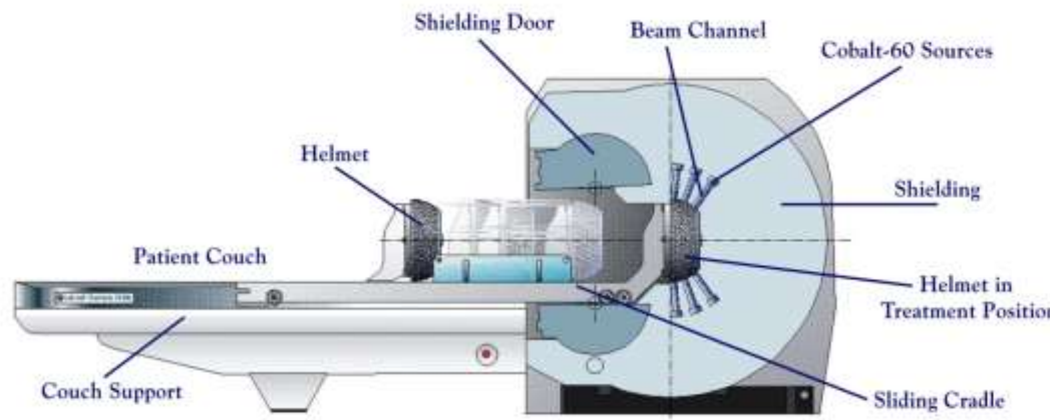
- KEK = High Energy Accelerator Research Organization
  - K: Kou: 高:   High
  - E: Enerugi: エネルギー: Energy
  - K: Kasokuki Kenkyu Kikou: 加速器研究機構: Accelerator Research Organization
- KEK is a multi disciplinary laboratory
  - HEP, Nuclear Physics, Life Science, Material Science and etc
  - KEKB, J-PARC and photon factory
- SOUKENDAI is the graduate university hosted by national laboratories under MEXT

# Radiotherapy

- Radiotherapy is a treatment of tumors(mostly)
- Various methods are available
  - External beam radiation therapy
    - e/γ, p, n, C…..
  - Brachytherapy
  - Intraoperative radiotherapy
  - Radioisotope therapy

# Gamma knife

http://cdn.images.express.co.uk/img/dynamic/11/590x/secondary/Gamma-knife-machine-217370.jpg

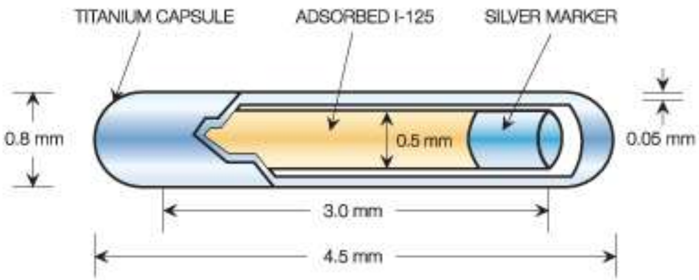



http://www.universityneurosurgery.com/clientuploads/GK_illustJpg.jpg

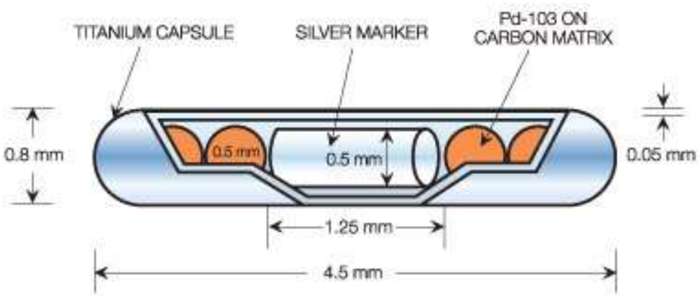
# Linac


https://www.varian.com/sites/default/files/Tx_Delivery_Truebeam_006_960x500.jpg

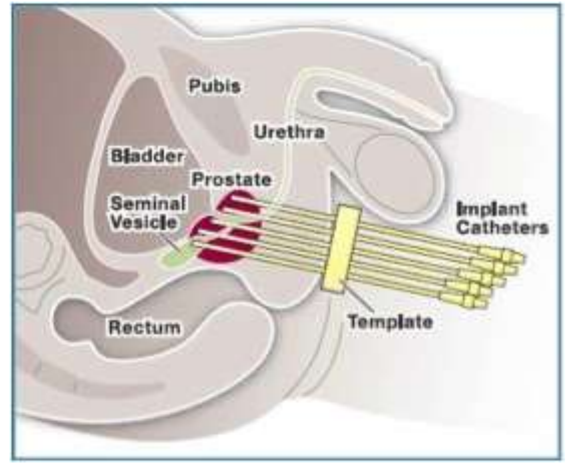
# Brachytherapy

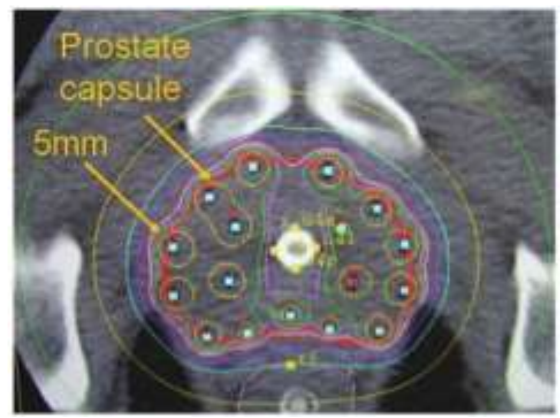



IsoAid Advantage™ (model IAI - 125A) I-125 source



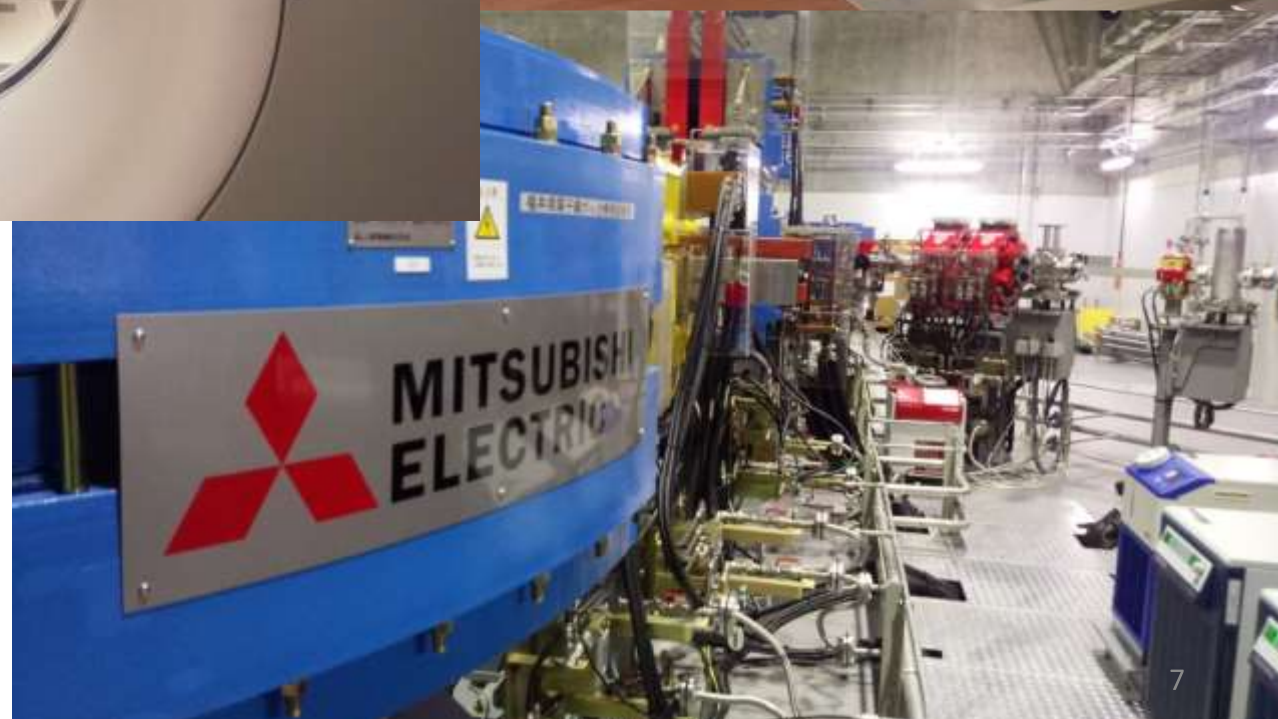

IsoAid Advantage™ (model IAPd - 103A) Pd-103 source




https://isoaid.com/site/assets/images/radioactive-seeds.jpg

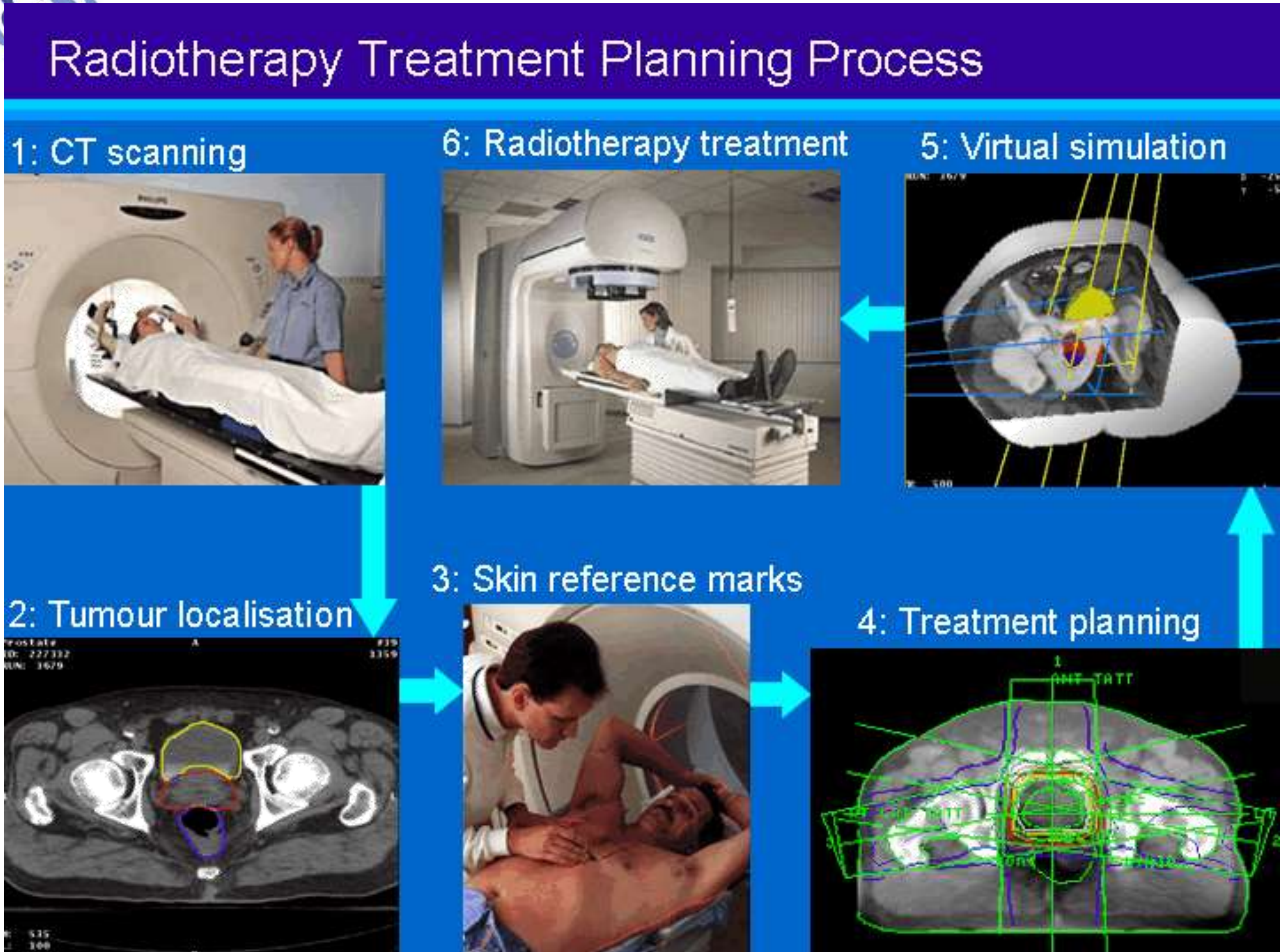
http://hdrprostatebrachytherapy.com/hdr-method/




Nagoya proton therapy center

# Treatment planning

- MDs tend to make a decision for the choice of the treatment method based on their past experiences and the facilities available
- Treatment planning and ex post facto assessments are done just for the decided method
- Fair comparison among the different methods never done quantitatively before the treatments
- Commercial treatment planning systems are based on approximations not full MC




http://www.impactscan.org/slides/impactcourse/introduction_to_ct_in_radiotherapy/img3.html

# A Quantitative Approach in Radiotherapy

- The first step of radiotherapy, the choice of the method, should be done based on a scientific evidence
- Necessary tools for pre assessments to compare different treatment methods qauntitatively in radiotherapy are available
  - Monte Carlo
- Patients definitely want to have the evidence-based best practice

# Radiation simulation in medicine

- Key physical quantities in medical simulation
- Physics, chemistry and biology of radiation absorption in biological materials
- Molecular Mechanisms of DNA damage and repair
- Linear energy transfer and relative biological effect
- Dose distributions: Depth dose curves, profiles, isodose distributions, dose-volume histograms


1. Eric J. Hall, Amato J. Giaccia, “Radiobiology for the radiologist,” 7th ed, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012
2. F.H. Attix, “Introduction to Radiological Physics and Dosimetry,” Wiley-VCH
3. P.N. McDermott and C.G. Orton, “The Physics and Technology of Radiation Therapy,” 2010, Medical Physics Publishing, Madison, WI.

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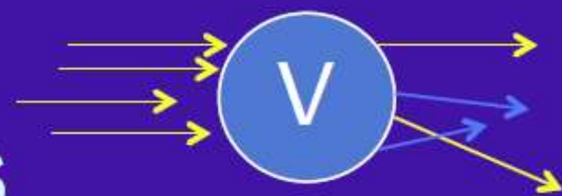
Bruce Faddegon, UCSF

# Physical Quantities




## Fluence

$$\Phi = \frac{dN_e}{da}$$

## Spectrum

$$\Phi = \int_{\theta=0}^{\pi} \int_{\beta=0}^{2\pi} \int_{E=0}^{E_{max}} \Phi'(\theta,\beta,E) \sin\theta \, d\theta \, d\beta \, dE$$

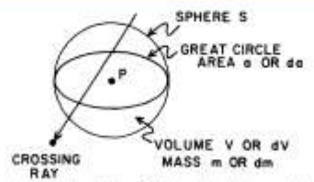



FIGURE 1.1. Characterizing the radiation field at a point $P$ in terms of the radiation traversing the spherical surface $S$.

## Attenuation

$$N = N_o e^{-\mu t}$$

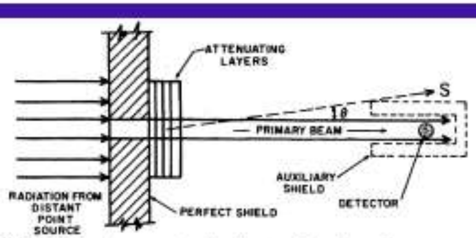



FIGURE 3.2. Narrow-beam geometry. The diameter of the primary photon or neutron beam is made just large enough to cover the detector uniformly. The detector is placed at a large enough distance from the attenuator that the number of scattered or secondary particles ($S$) that reach the detector is negligible in comparison with the number of primary rays.

## Kinetic Energy Released per Unit Mass

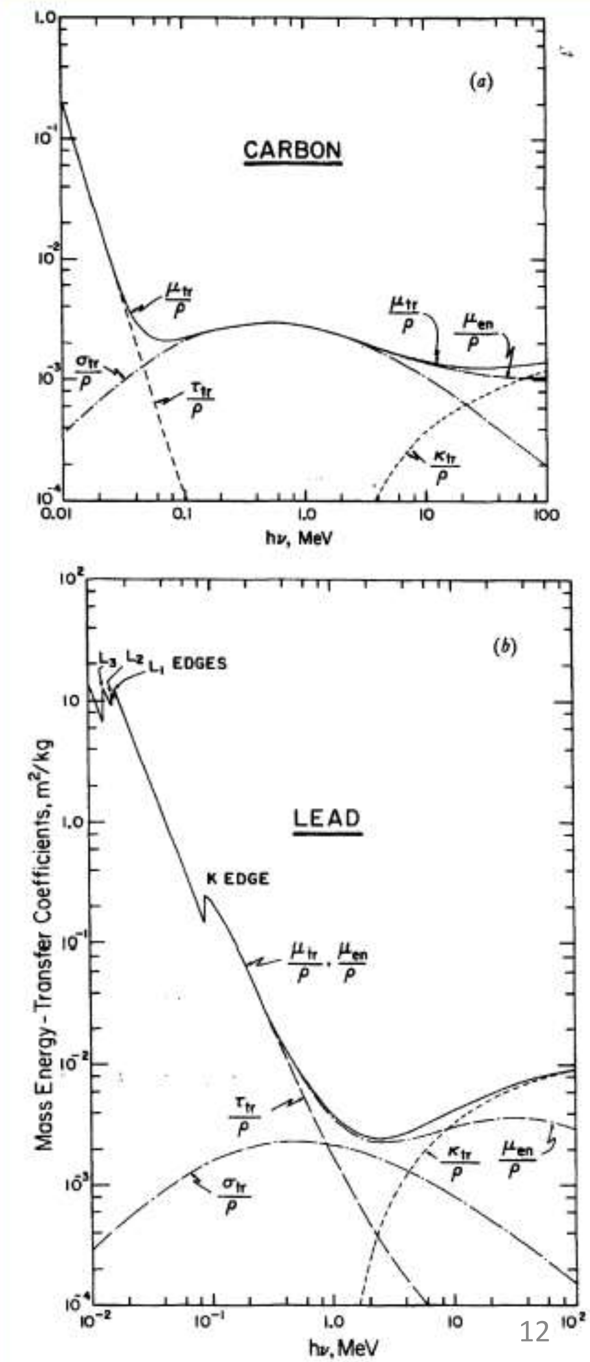
$$\text{Kerma}, K = \frac{d<\varepsilon_{tr}>}{dm}$$

$$K = \Psi\left(\frac{\mu_{tr}}{\rho}\right)_{E,Z} = K_c + K_r$$

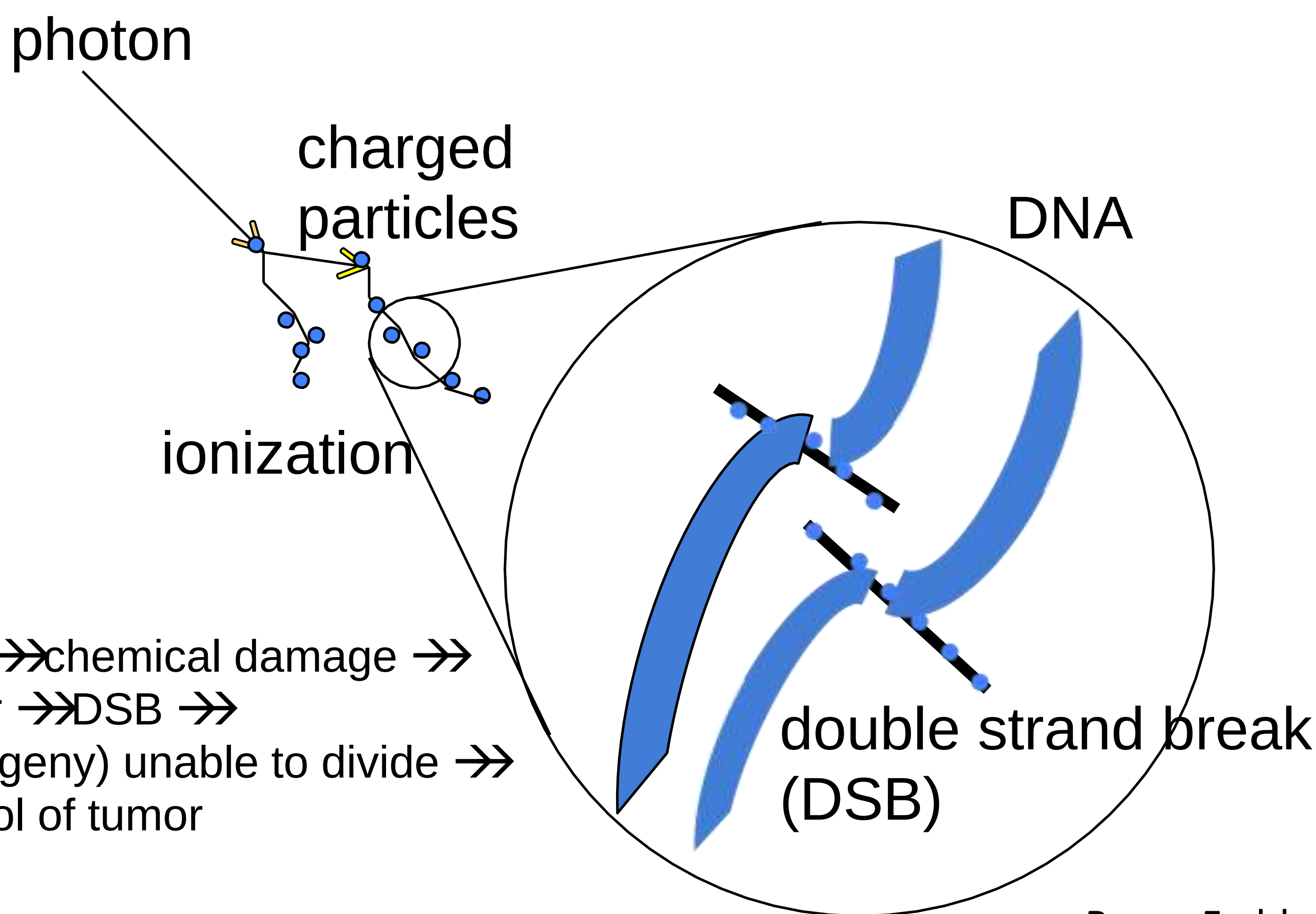
$$\text{Dose, D} = \frac{d<\varepsilon>}{dm} \underset{\text{CPE}}{=} K_c$$

## Mass energy absorption coefficient, $\mu_{en}/\rho$

$$\left(\frac{\overline{\mu_{en}}}{\rho}\right)_{\Psi'(E),Z} = \frac{K_c}{\Psi} = \frac{\int_E \Psi'(E)\left(\frac{\mu_{en}}{\rho}\right)_{E,Z} dE}{\int_E \Psi'(E)\, dE}$$



# The therapeutic effect of ionizing radiation: physics, chemistry and biology




ionization ↠ chemical damage ↠
DNA repair ↠ DSB ↠
cell (or progeny) unable to divide ↠
local control of tumor



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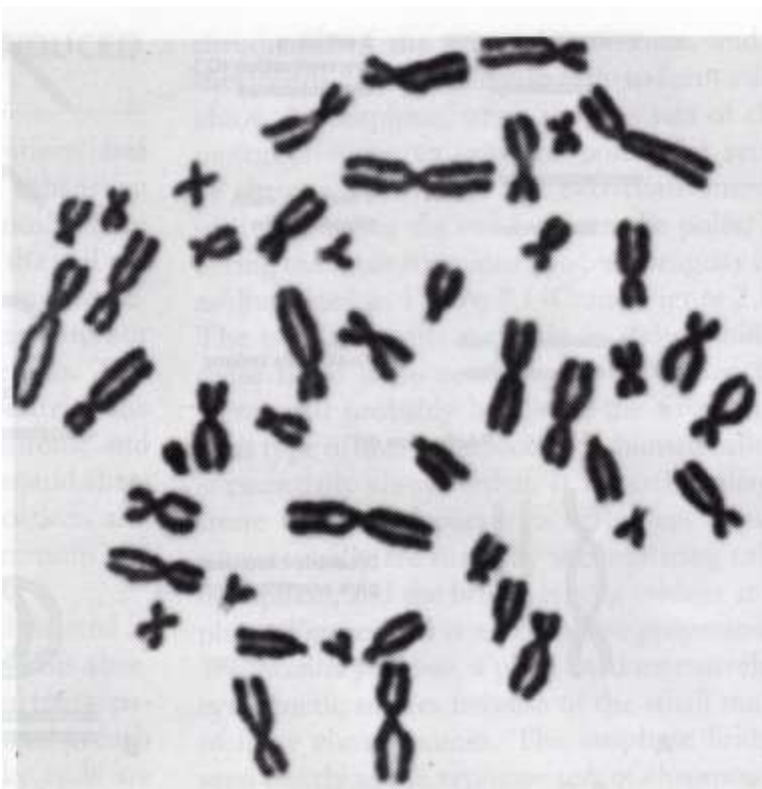
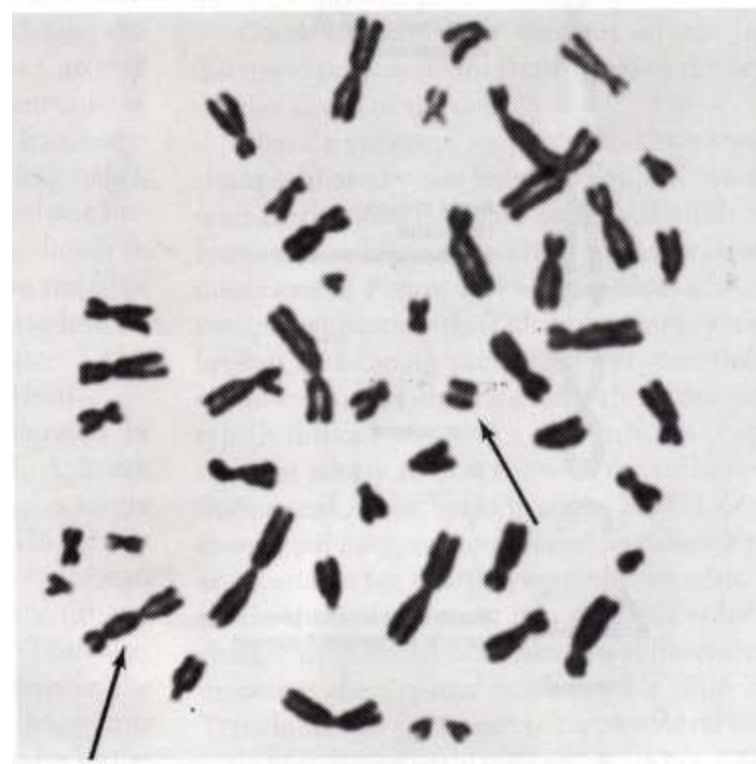
# Molecular Mechanisms of DNA damage and repair

Normal human leukocyte



Dicentric chromosome with fragment





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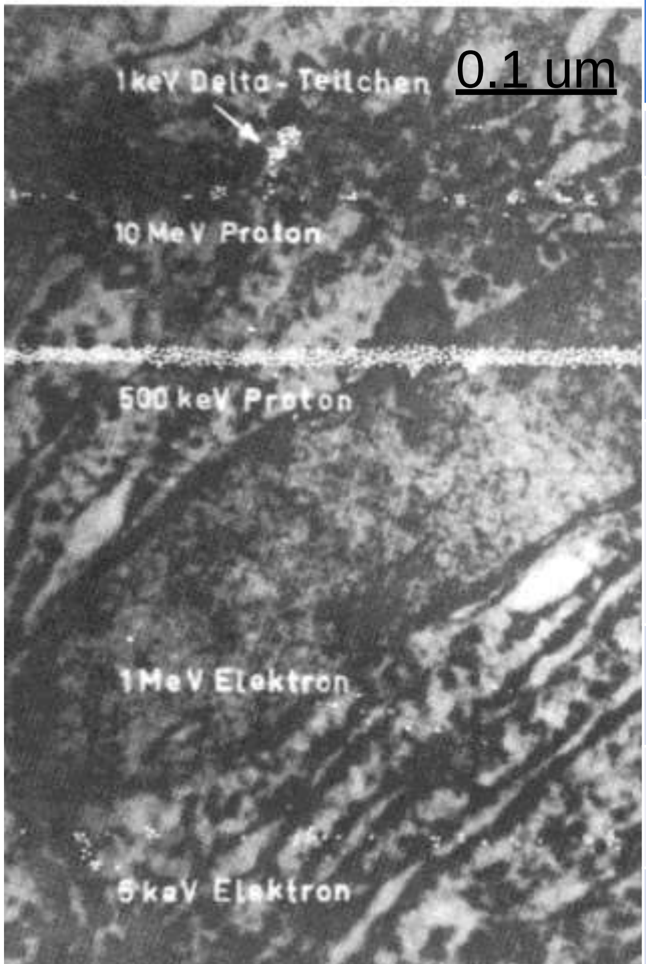
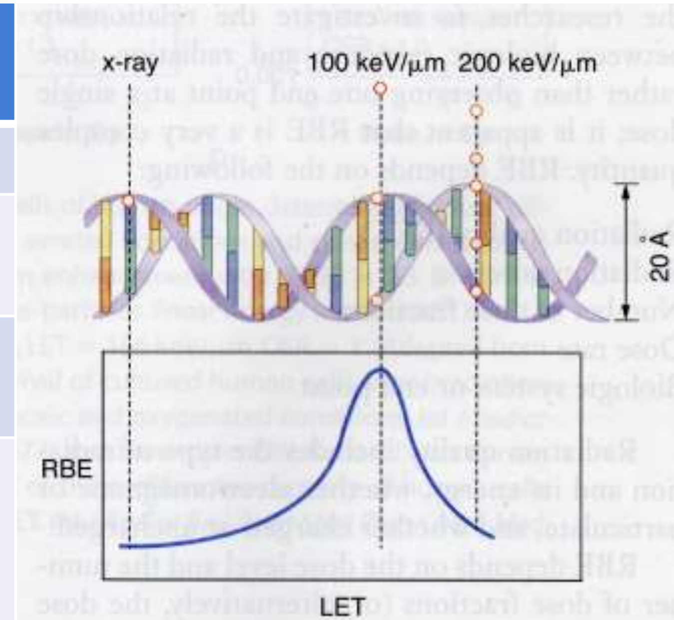
# Linear energy transfer and relative biological effect




| Radiation | LET (keV/um) |
|---|---|
| $^{60}Co$ | 0.2 |
| 250 kV x-rays | 2.0 |
| 10 MeV protons | 4.7 |
| 150 MeV protons | 0.5 |
| 14 MeV neutrons | 12-100 |
| 2.5 MeV alphas | 166 |
| 2 GeV Fe ions | 1000 |




RBE= $D_{xray}/D_{particle}$ for same survival

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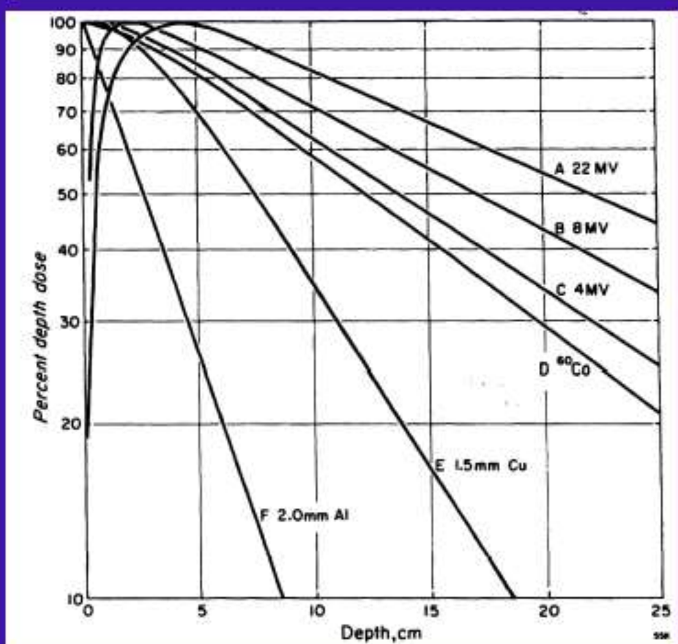
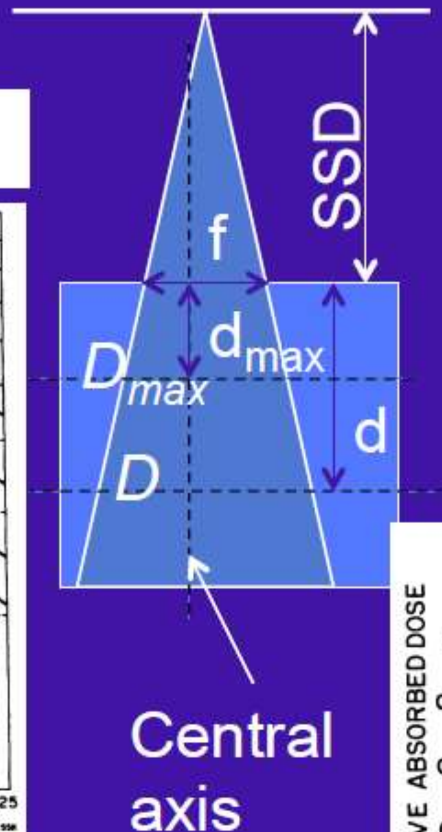
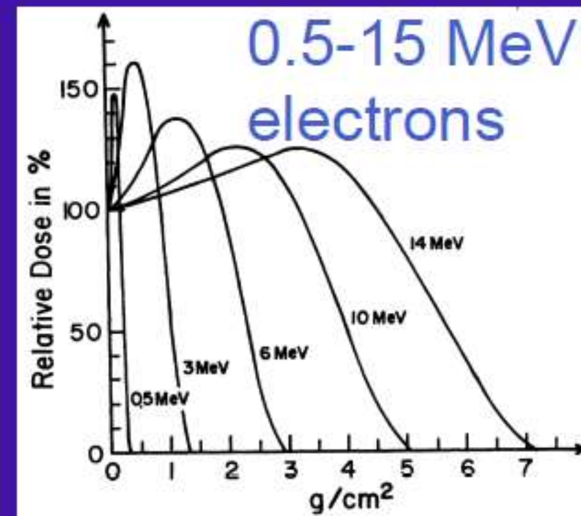
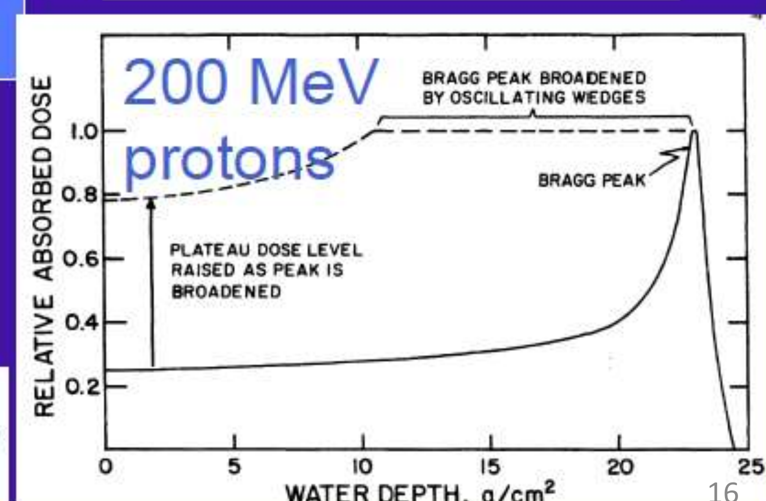
# Source-surface distance (SSD)
# Central axis percent depth dose (PDD)

100 kV-22 MV x-rays




$$PDD(d, f, SSD) = \frac{D(SSD + d, f)}{D(SSD + d_{max}, f)} \times 100\%$$

# We've been ready

- Tools are available
  - Geant4: A toolkit to simulate interactions between particles and matter
  - PTSIM: A toolkit for radiation therapy simulation
    - Modeling of treatment devices and facilities
  - Geant4-DNA: A cell level simulation toolkit based on Geant4
  - MPEXS: GPU accelerated simulation toolkit
    - More than 200 times faster than Geant4 today

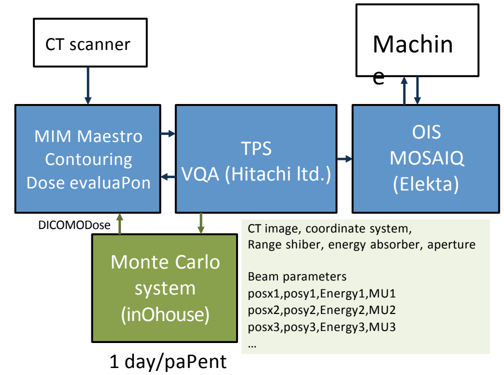
# Geant4

- A toolkit for simulating interactions between particles and matter
- The development was started in 1992 based on independent KEK and CERN R&D
- Widely used in particle physics, space, medicine and so on
- The two main reference papers for Geant4 are published in Nuclear Instruments and Methods in Physics Research A 506 (2003) 250-303, and IEEE Transactions on Nuclear Science 53 No. 1 (2006) 270-278.
- The first paper was cited more than 6,000 times
- http://geant4.org for the detail

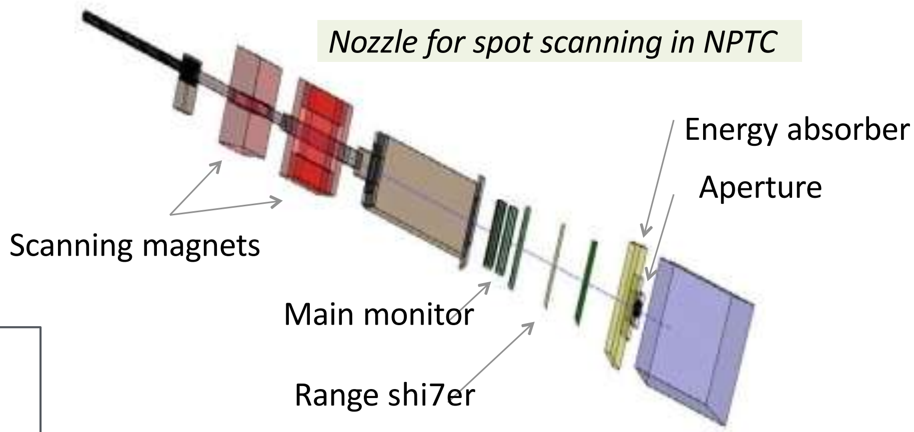
# Toolkits for radiotherapy

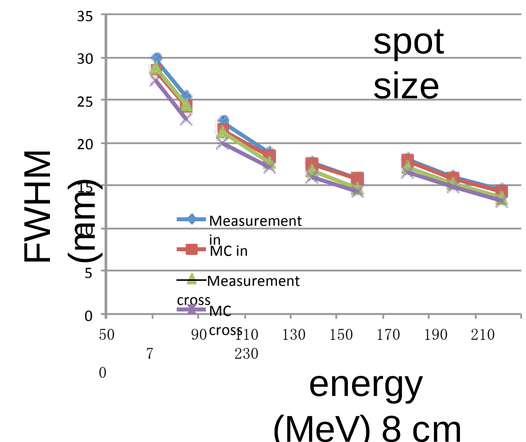
- PTSIM: originally developed for particle therapy, but also X-ray therapy (Japan)
  - Funded by CREST during 2003-2008
- TOPAS: Proton therapy simulation toolkit inspired by PTSIM (US) 2010-
- GAMOS: Geant4 based Architecture for Medical Oriented Simulations (Spain) inspired by PTSIM 2006-
- GATE: Geant4 Application for Tomographic Emission (France)
- Many of attempts have been done independently

# Nagoya Proton Therapy Center

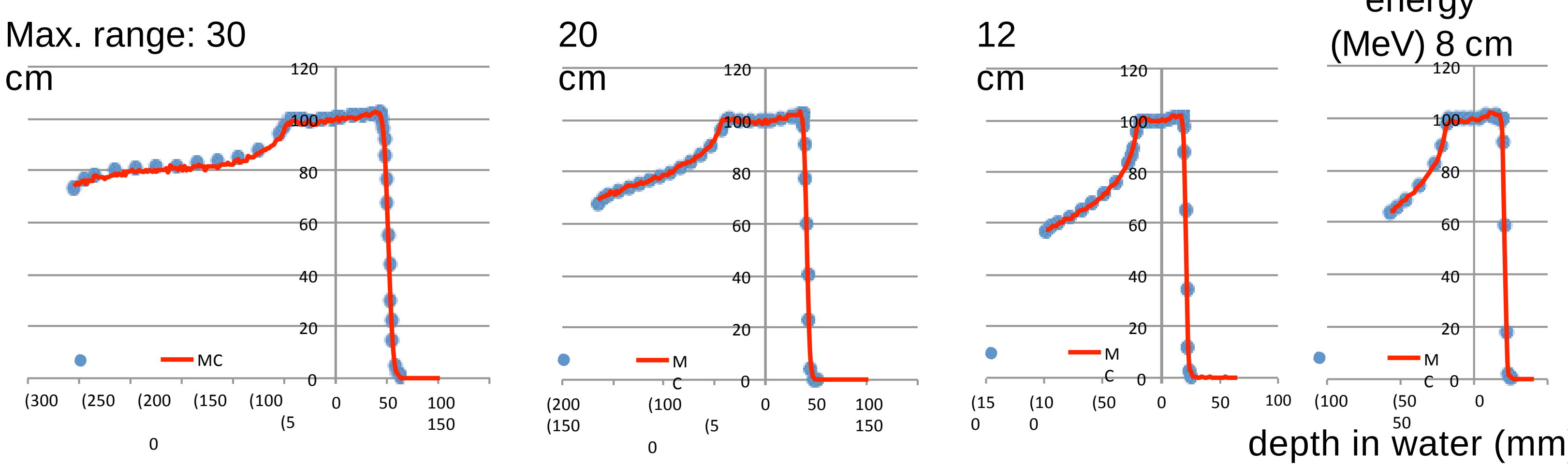



An example of PTSIM



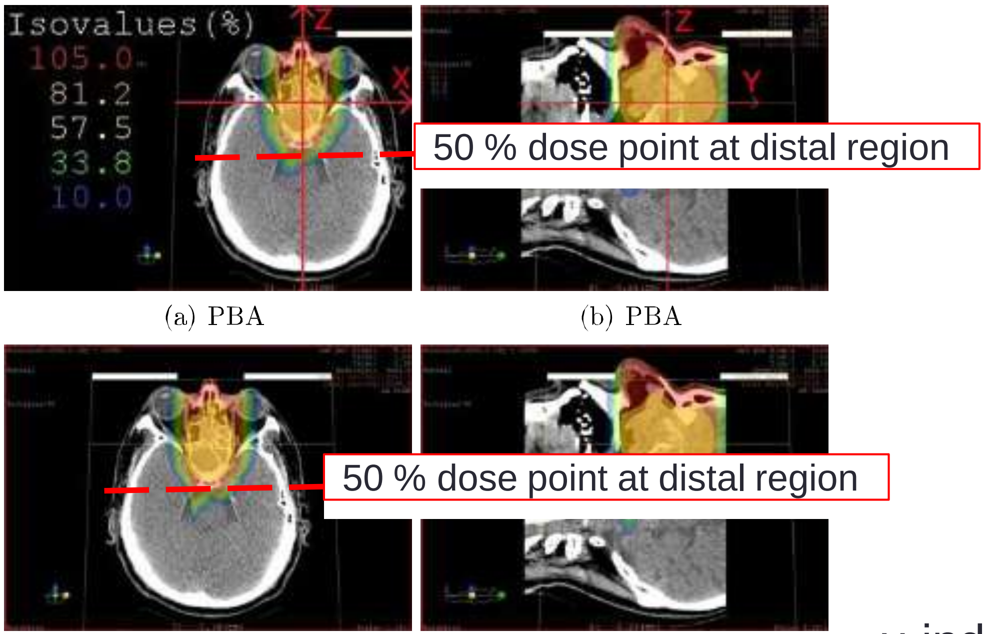

SOBP: 10cm
Field size: 10cm



# Hyogo Ion Beam Medical Center

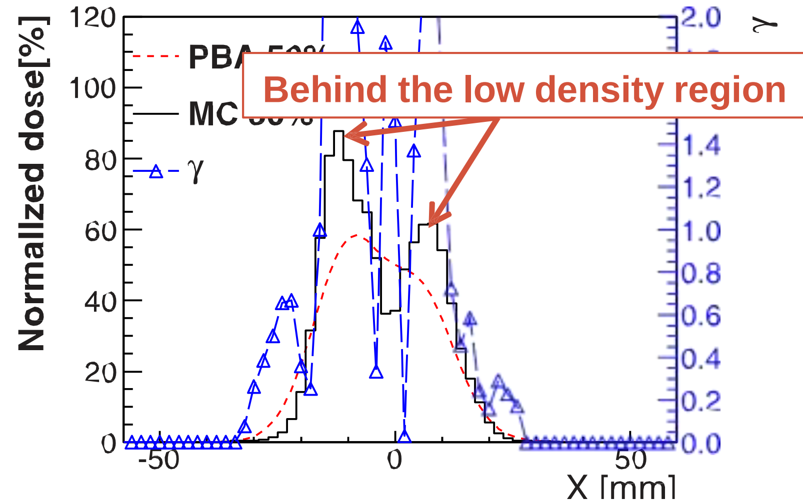
- PTSIM(Geant4) vs TPS

T.Yamashita et al., Phys.Med.Biol.57(2012)7673-7688.



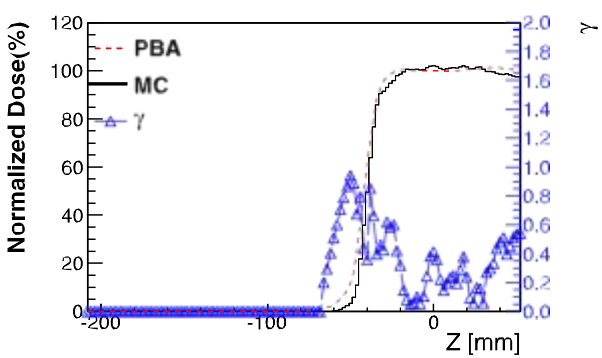

(a) PBA (b) PBA

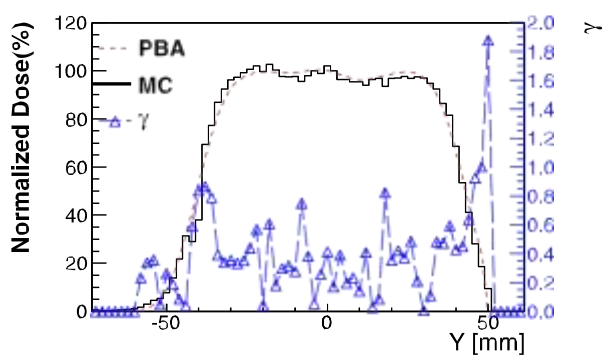
(d) MC (e) MC

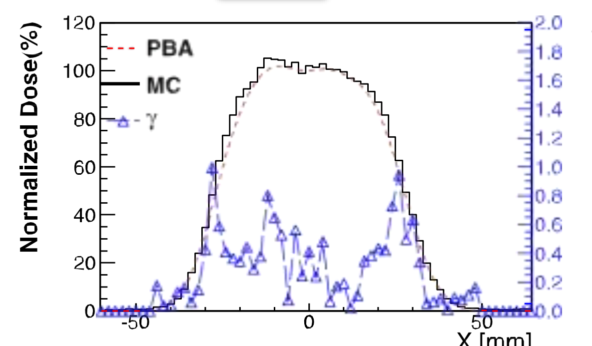



50 % dose point at distal region

γ-index 5%/6mm






Dose in the isocenter plane

See Int. J. Model. Simul. Sci. Comput. 1 (2010) 157-178 (link)

# The Geant4-DNA project

**Main objective**

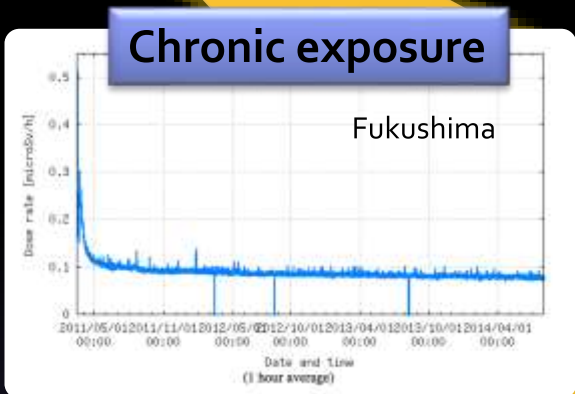
Extend the general purpose Geant4 Monte Carlo toolkit for the simulation of interactions of radiation with biological systems at the cellular and DNA level in order to predict early DNA damage in the context of manned space exploration missions (« bottom-up » approach).

Designed to be developed and delivered in a FREE software spirit under Geant4 license, easy to upgrade and improve.

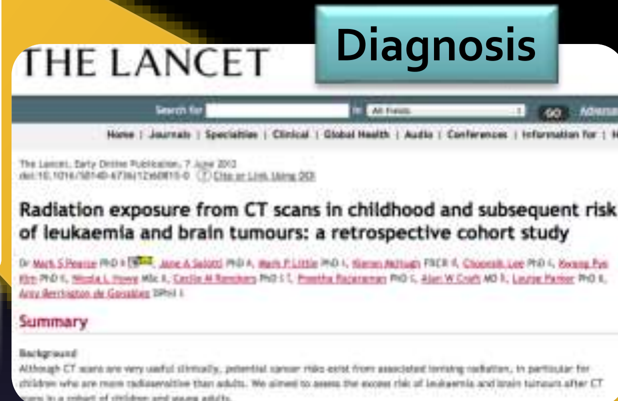
**Evolution**

- **2001:** Initiated in 2001 by Dr Petteri Nieminen at the European Space Agency/ESTEC
- **2007:** First prototypes of physics models added to Geant4
- **Since 2008:** Development coordinated by CNRS in Bordeaux, France
- **December 2014:** Chemistry stage extension ready for end users

# Modelling biological effects of ionising radiation remains a major scientific challenge




http://rcwww.kek.jp/norm/index-e.html







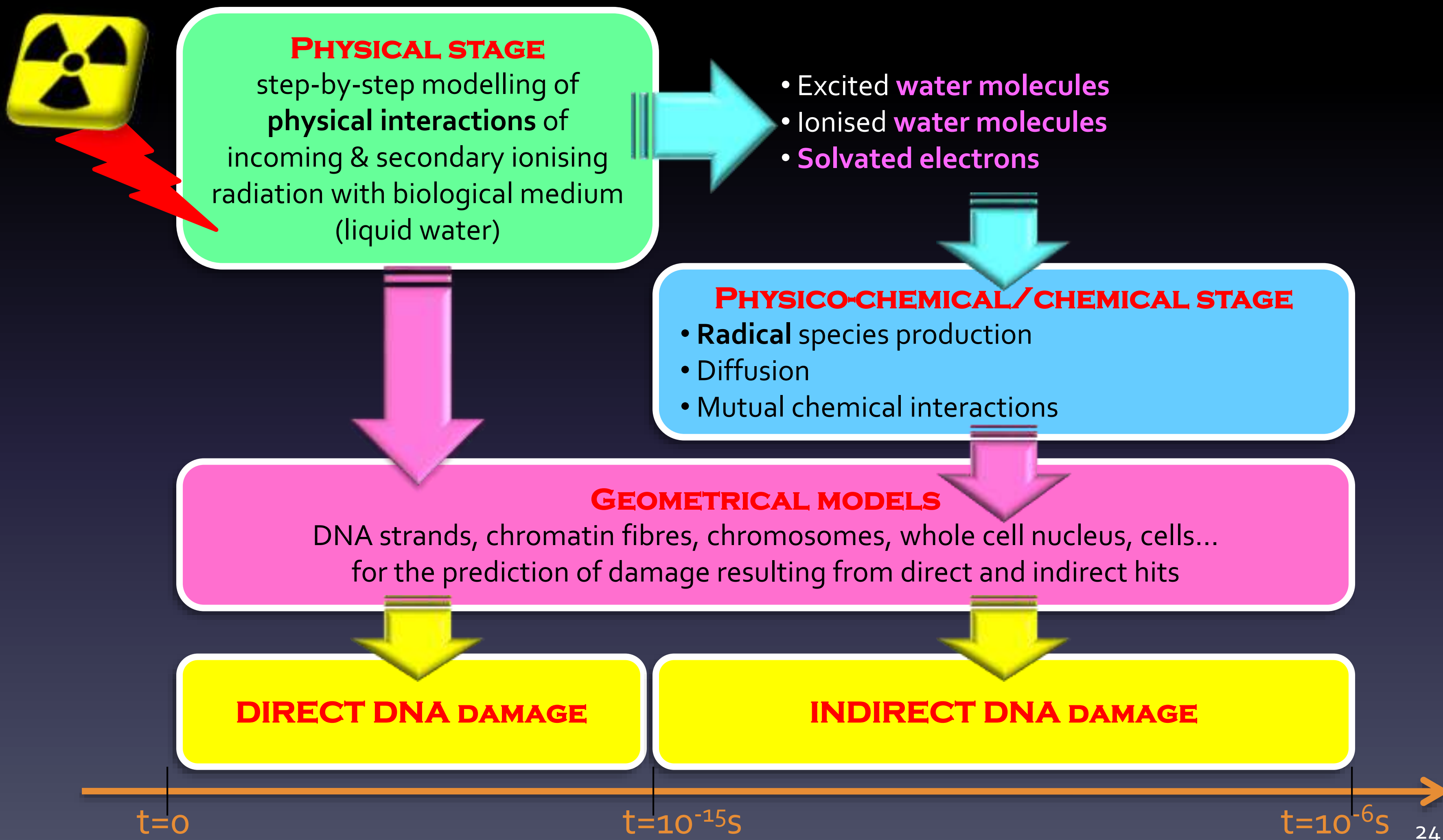
« A major challenge lies in providing a sound mechanistic understanding of low-dose radiation carcinogenesis »

L. Mullenders *et al.*

Assessing cancer risks of low-dose radiation

Nature Reviews Cancer (2009)

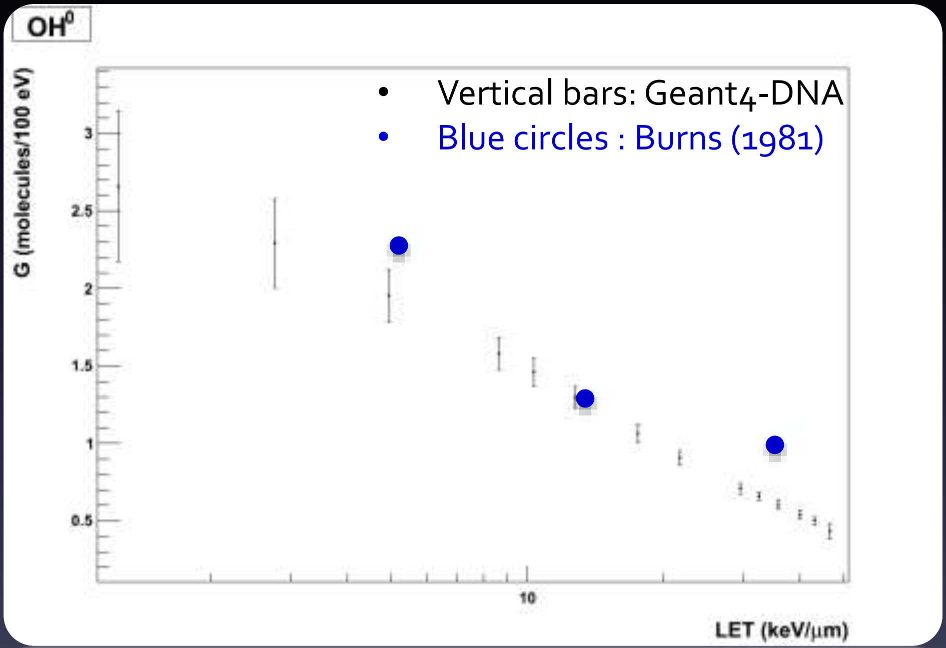
# How can Geant4-DNA model early DNA damage ?

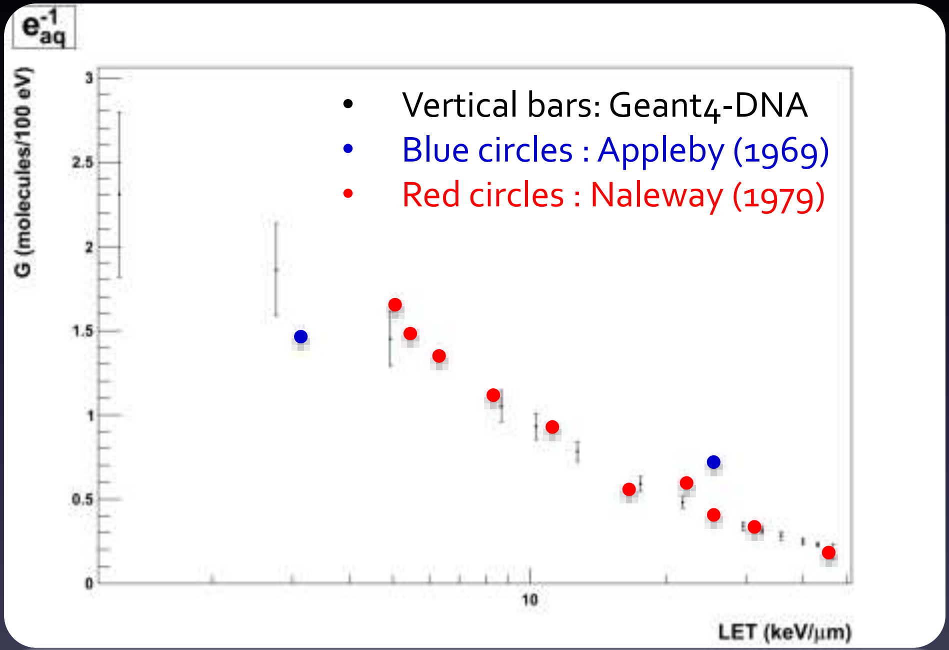


# Radiochemical yields VS LET

•OH radicals

Solvated e-

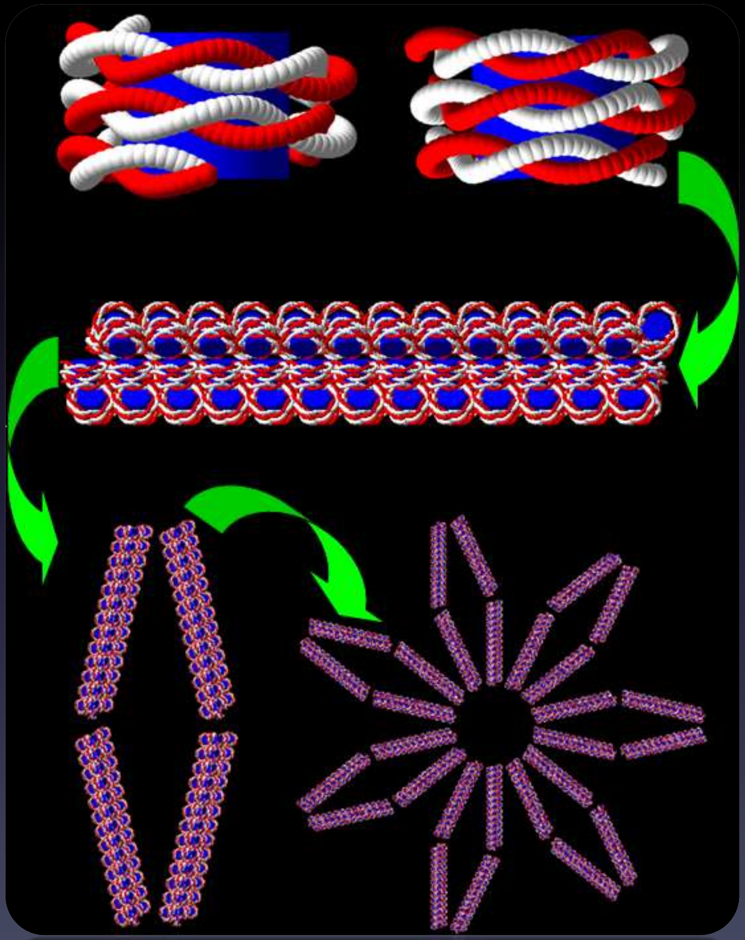



See J. Comput. Phys. 274 (2014) 841-882 (link)

# « dnageometry » advanced example

Morgane Dos Santos PhD thesis (link)



## Nucleosome

- 200 bp / nucleosome
- DNA diameter = 2.16 nm
- Histone = cylinder of 6.5 nm in diameter and 5.7 nm in height

## Chromatin fiber

- 90 nucleosomes / fiber
- 7 nucleosomes / turn
- D = 31 nm
- L = 161 nm

## Chromatin fiber loop

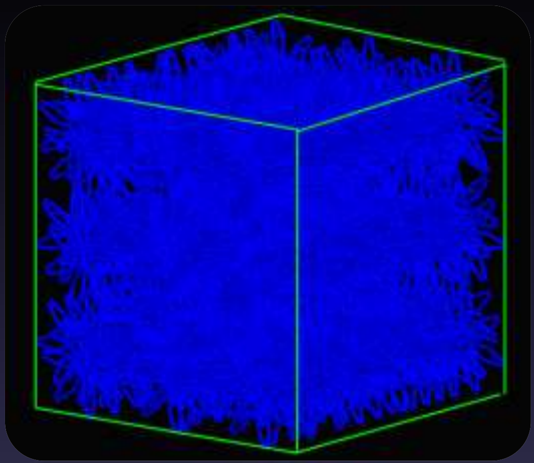
- 4 fibers / loop assembled in a diamond shape
- 7 loops to form a "flower"*

* W. Friedland et al, Rad. Res 59 (2003), 401-410

# « dnageometry » advanced example

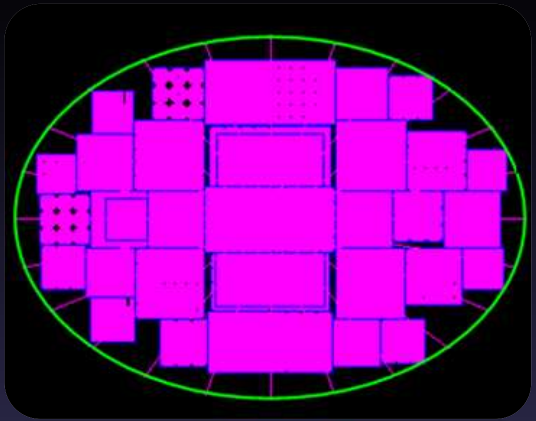
« DetectorConstruction » class: implementation of an elliptical cell nucleus with similar dimensions of fibroblast grown on a microscopic plate at confluence

## Chromosome domain example



Per nucleus
- 23 pairs of chromosomes
- 11875 flowers or 83125 loops
- 332 500 chromatin fibers
- 29 925 000 nucleosomes
- ~ 6 Gbp

## « Fibroblast » cell nucleus



- Nucleus-shape: ellipsoid
- Dimensions: 19.7 * 14.2 * 5 $\mu m^3$
- V = 732 $\mu m^3$
- 0.42 % of DNA / nucleus

**Output**: a ROOT file containing an n-tuple with the following values only for energy transfer points located in the backbone region:
-**Particle type** at the origin of the energy deposition
-**Process type** **(ionization, excitation)**
-Information on the **DNA strand** (flag 1 / 2)
-**Coordinates** **of the energy deposition** (x,y,z)
-**Energy deposition** amount

**See NIMB 298 (2013) 47-54 (link)**

http://pdb4dna.in2p3.fr
http://geant4-dna.org

# A new interface to describe geometries in Geant4-DNA

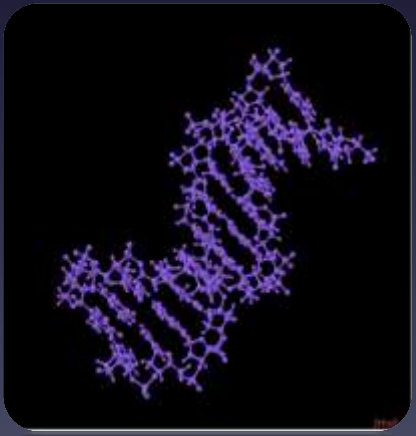
- PDB : Protein Data Bank

  http://www.rcsb.org/pdb/

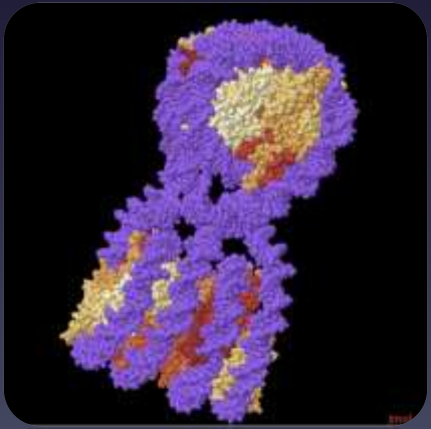
  - 3D structure of molecules
  - Proteins
  - Nucleic acids

- Description of DNA molecules
  - 1FZX.pdb
    - Dodecamer
    - 12 DNA base pairs
    - (2,8 x 2,3 x 4,01 $nm^3$)
  - 1ZBB.pdb
    - Tetranucleosome
    - 2 nucloosomes : 347 pairs of bases
    - (9,5 x 15,0 x 25,1 $nm^3$)

```
HEADER   STRUCTURAL PROTEIN/DNA            08-APR-05  1ZBB
TITLE    STRUCTURE OF THE 4_601_167 TETRANUCLEOSOME
...
ATOM    1 O5' DA I  1    70.094 16.969 123.433 0.50238.00   O
ATOM    2 C5' DA I  1    70.682 18.216 123.054 0.50238.00   C
ATOM    3 C4' DA I  1    69.655 19.289 122.776 0.50238.00   C
...
TER  14223     DT J 347
...
HELIX   1  1 GLY A  44  SER A  57  1                 14
HELIX   2  2 ARG A  63  ASP A  77  1                 15
...
SHEET   1  A 2 ARG A  83  PHE A  84  0
SHEET   2  A 2 THR B  80  VAL B  81  1  O  VAL B  81   N  ARG A  83
```



1FZX.pdb



1ZBB.pdb

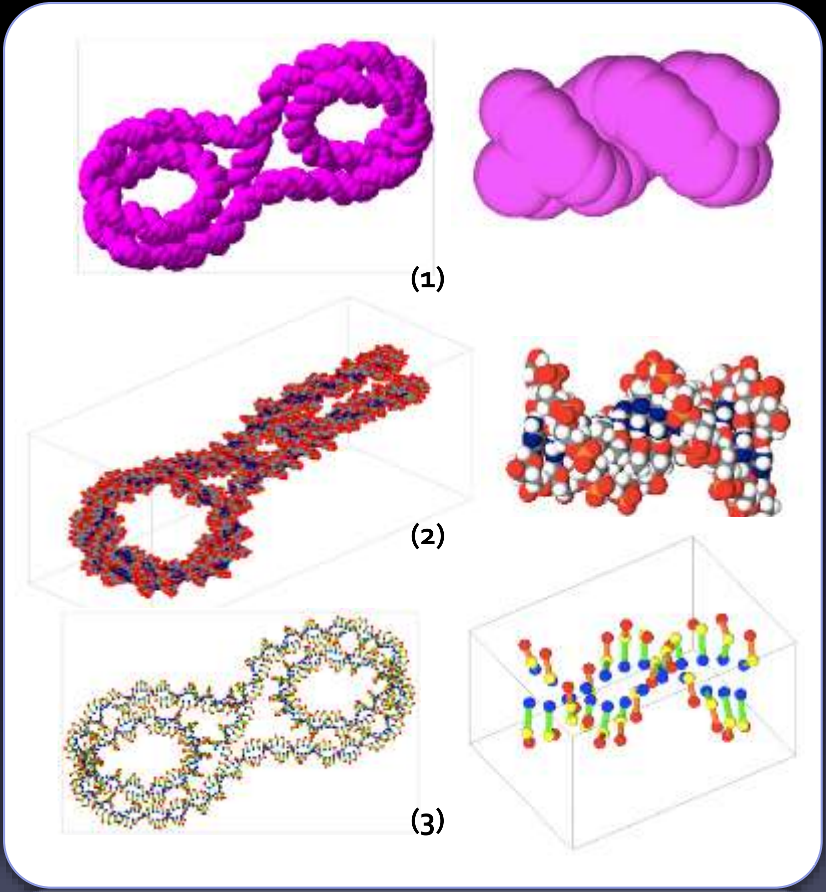
**Trung Pham PhD thesis (soon)**

Emmanuel DELAGE
Yann PERROT
Quang Trung PHAM
LPC-Clermont Ferrand

http://pdb4dna.in2p3.fr
http://geant4-dna.org

# « PDB4DNA » suite

- 1) A C++ library
  - Reading of PDB files
  - Build bounding boxes from atom coordinates
  - Search for closest atom from a given point
  - Geometry and visualization : 3 granularities
    - (1) Barycenter of nucleotides
    - (2) Atomistic
    - (3) Barycenter of nucleotide components
- 2) A Geant4-DNA example
  - Water box surrounding the molecule
  - The output results consists in a ROOT file, containing for each event:
    - energy deposit in bounding boxes
    - number of single strand breaks (SSB)
    - number of double strand breaks (DSB)
- Available on-line under Geant4 license



# Geant4 in medicine

- Geant4 has been proved that it has enough accuracy to simulate the treatments
- Geant4-DNA is promising
  - Further R&D needs yet
- Still clinical usages are limited but for research
  - Why?

Speed!

# New step

**Geant4**

- Single code for the everything approach
- Validation of physics results are well done
- Highly accurate but slow
- Covers eV to PeV
  - Geant4-DNA: meV - eV
- Open source license

**Tailor maid simulator**

- Just for the particular application
- Validation has done in Geant4
  - The same algorithm and data from Geant4
- Accurate enough and fast
- Covers meV to a few 100 MeV
- New software license

# MPEXS

- GPU powered acceleration
  - aka G4CU
  - Coded in CUDA
- Industrial and bio-medical applications are the targets
  - HEP applications are still in our mind
- Currently only EM physics
- Not an open source project
- Collaboration among KEK, SLAC and Stanford

# MPEXS-DNA

- Collaboration with CENBG, Bordeaux, France
- aka G4CU-DNA
  - Coded in CUDA
- Based on MPEXS
- All of physics processes have been implemented in Geant4-DNA
  - 200 times faster
- Chemical processes follows soon

# MPEXS-N

- For BNCT simulation
  - Neutron energy up to 30MeV
- Needs sponsors and collaborators

# MPEXS-ION

- For ion therapy (protons and carbons)
  - Below 500 MeV
- Still in plan
- Needs sponsors and collaborators

# MPEXS Benchmarking

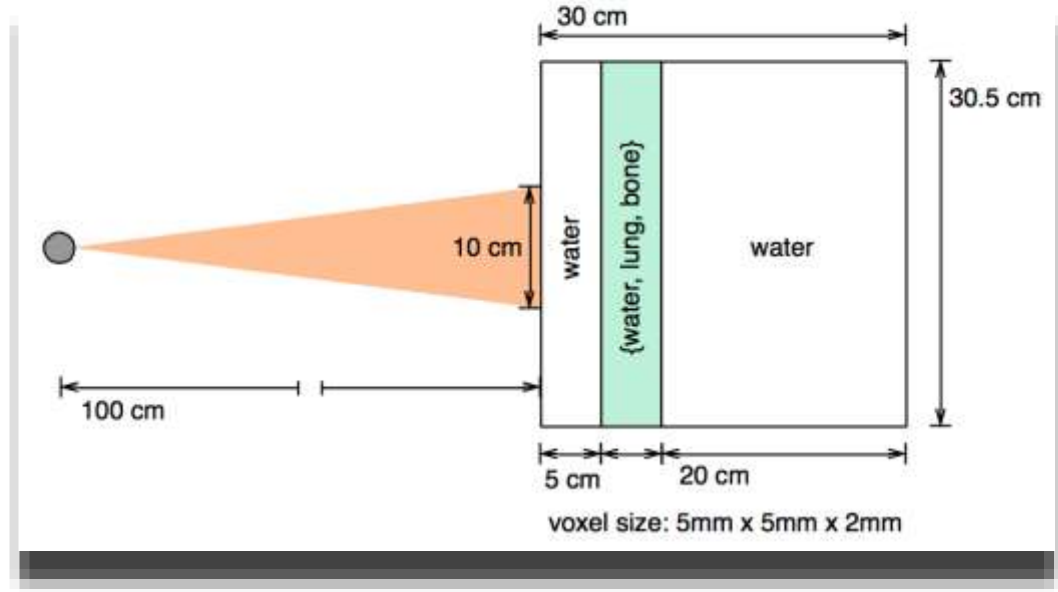
size: 30.5 x 30.5 x 30 cm

- Voxel size: 5 x 5 x 2 mm
- Field size: 10 $cm^2$
- SSD: 100 cm
- Slab materials (30.5 x 30.5 x 5 cm):
  - Water, Lung, Bone

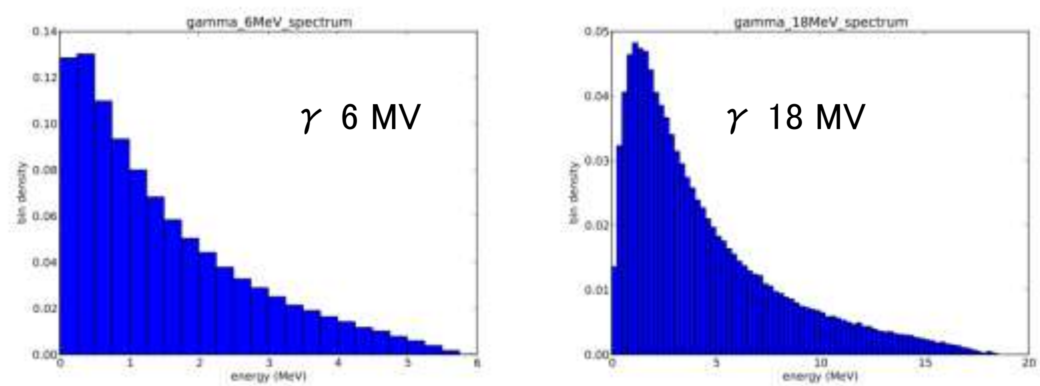
| | Density |
|---|---|
| **Water** | 1.0 $g/cm^3$ |
| **Lung** | 0.26 $g/cm^3$ |
| **Bone** | 1.85 $g/cm^3$ |
| **Air** | 0.0012 $g/cm^3$ |

- Beam particles:
  - Electrons (20 MeV)
  - Photons (6, 18 MV)

Simulation model

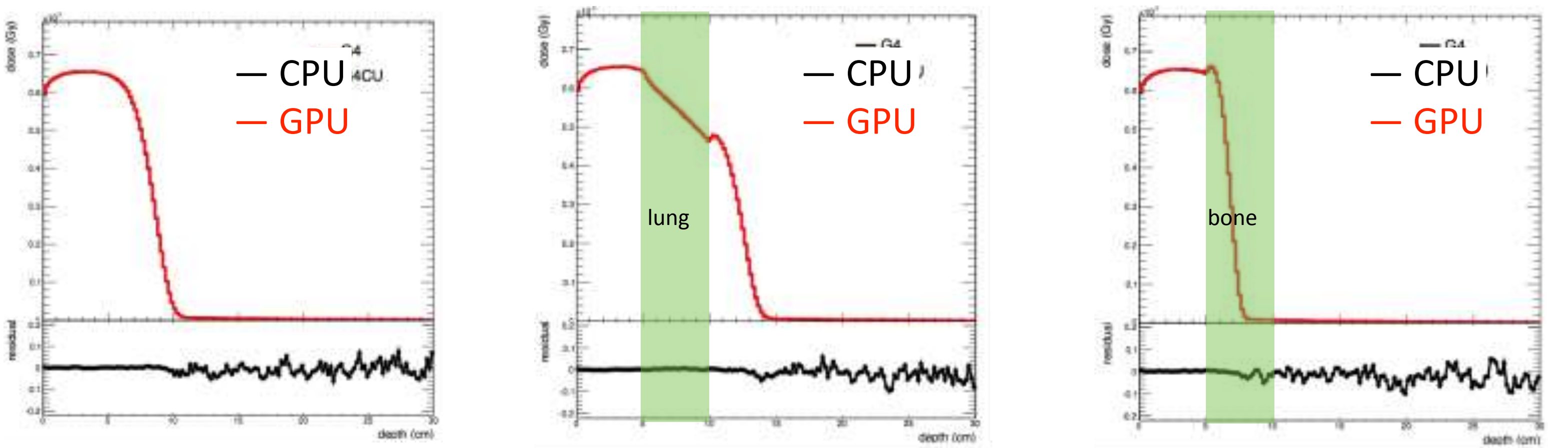



Energy spectrums for photons

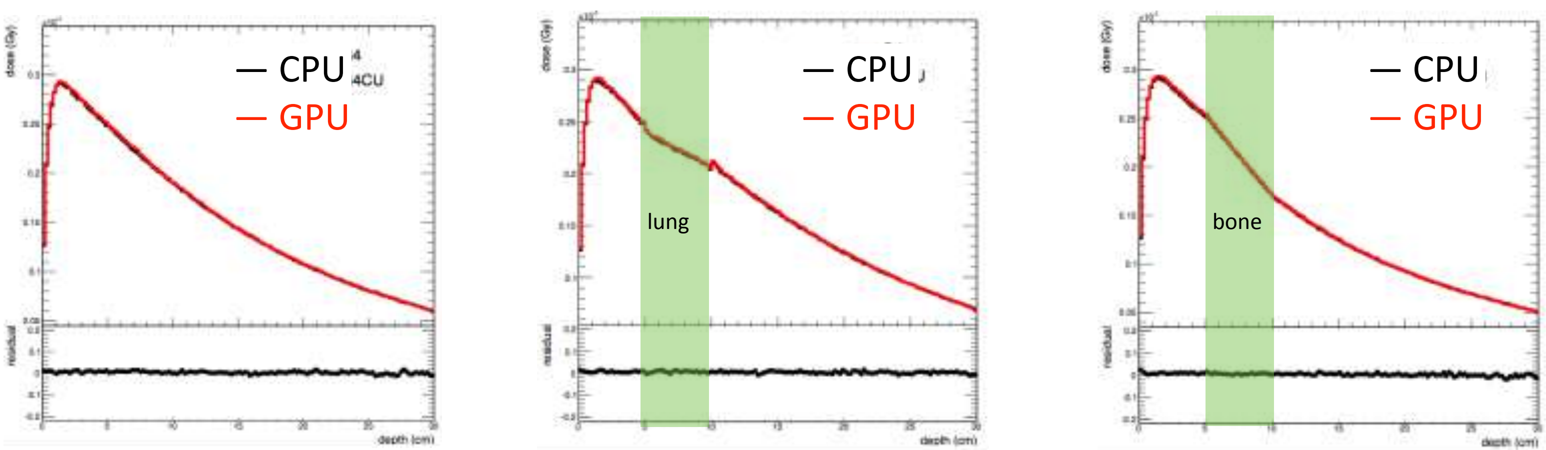


# Physics Performance for MPEXS

## Electrons, 20 MeV




## Photons, 6 MV



# MPEXS performance

**250 times faster against one single CPU core**

| | e– beam with 20MeV | | |
|---|---|---|---|
| | Water | Lung | Bone |
| Geant4 [msec/particle] | 1.84 | 1.87 | 1.65 |
| G4CU [msec/particle] | $8.81 \times 10^{-3}$ | $9.58 \times 10^{-3}$ | $8.85 \times 10^{-3}$ |
| × speedup factor( = G4 / G4CU ) | ***208*** | ***195*** | ***193*** |

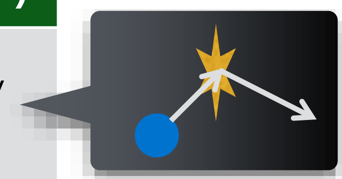
- GPU
  - Tesla K20c (*Kepler architecture*)
  - 2,496 CUDA cores, 796 MHz
  - 4096 blocks x 128 threads /block
- CPU
  - Intel Xeon E5-2643 v2 3.50 GHz
- Preformance comparison (e– 20 MeV, 50M, water)

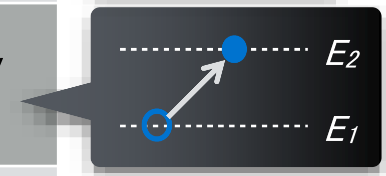
*~25 hr. (single-core CPU) → <u>~7 min.</u> (GPU)*

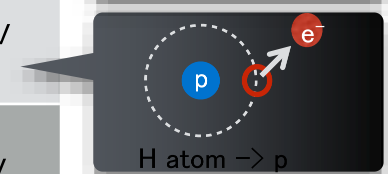
| | γ beam with 6MV | | | γ beam with 18MV | | |
|---|---|---|---|---|---|---|
| | Water | Lung | Bone | Water | Lung | Bone |
| Geant4[msec/particle] | 0.780 | 0.822 | 0.819 | 0.803 | 0.857 | 0.924 |
| G4CU [msec/particle] | $3.36 \times 10^{-3}$ | $3.31 \times 10^{-3}$ | $3.41 \times 10^{-3}$ | $4.33 \times 10^{-3}$ | $4.25 \times 10^{-3}$ | $4.43 \times 10^{-3}$ |
| × speedup factor( = G4 / G4CU ) | ***232*** | ***248*** | ***240*** | ***185*** | ***201*** | ***208*** |

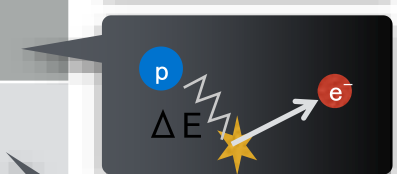
# DNA Physics Processes

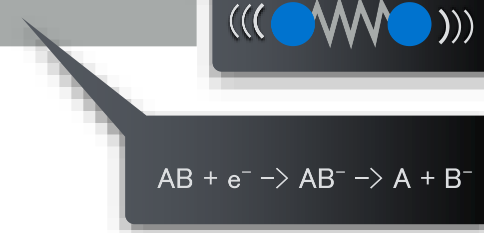
| Physics Processes / Particles | Electrons | Protons | Hydrogen atoms | Helium atoms ($He^{++}$, $He^{+}$, $He^{0}$) |
|---|---|---|---|---|
| **Elastic scattering** | 9 eV - 10 keV *Uehara* 10 keV - 1 MeV *Champion* | 100 eV - 1 MeV *Hoang* | | 100 eV - 10 MeV *Hoang* |
| **Excitation** | 10 eV - 10 keV *Emfietzoglou* 10 keV - 1 MeV *Born* | 10 eV - 500 keV *Miller Green* 500 keV - 100 MeV *Born* | 10 eV - 500 keV *Miller Green* | 1 keV - 400 MeV *Miller Green* |
| **Charge change** | – | 100 eV - 10 MeV *Dingfelder* | 100 eV - 10 MeV *Dingfelder* | 1 keV - 400 MeV *Dingfelder* |
| **Ionization** | 10 eV - 10 keV *Emfietzoglou* 10 keV - 1 MeV *Born* | 100 eV - 500 keV *Rudd* 500 keV - 100 MeV *Born* | 100 eV - 100 MeV *Rudd* | 1 keV - 400 MeV *Rudd* |
| **Vibrational excitation** | 2 - 100 eV *Michaud et al.* | – | – | – |
| **Disociative attachment** | 4 - 13 eV *Melton* | – | – | – |



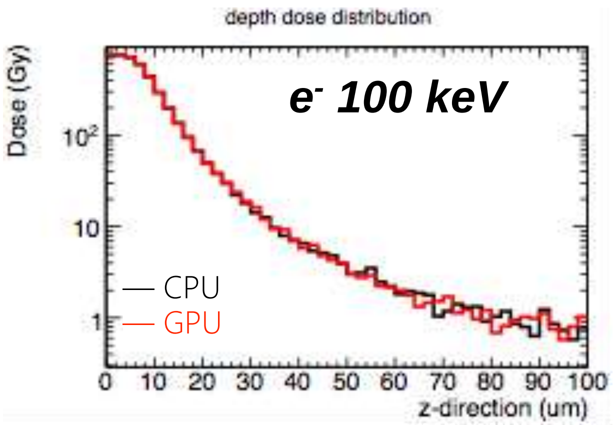


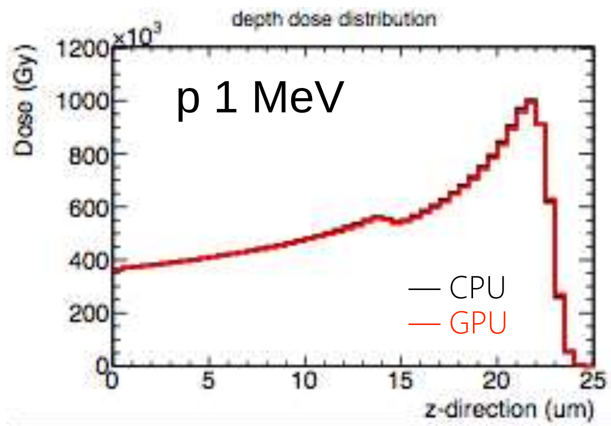



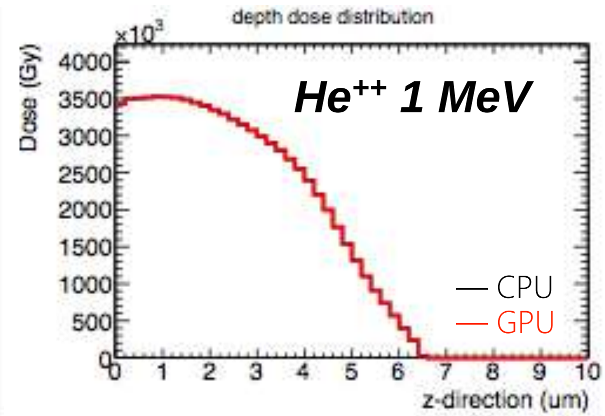



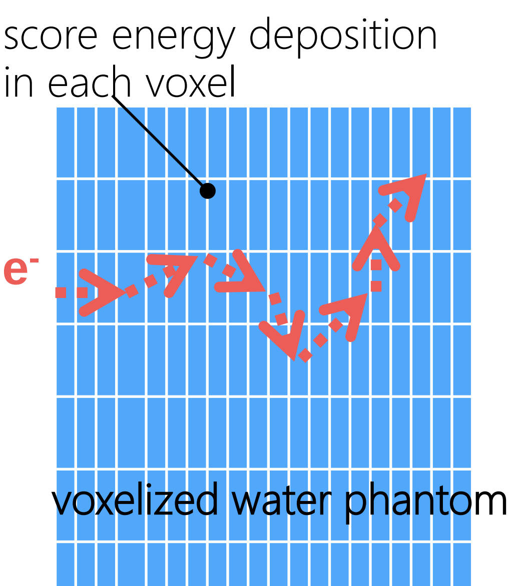



# MPEXS-DNA Physics Performance




| incident particle | initial energy | phantom size | # of voxel cells (voxel size) |
|---|---|---|---|
| e- | 100 keV | 102 x 102 x 100 um | 51 x 51 x 50 (2 x 2 x 2 um) |
| p | 1 MeV | 25.5 x 25.5 x 25 um | 51 x 51 x 50 (0.5 x 0.5 x 0.5 um) |
| He++ | 1 MeV | 10.2 x 10.2 x 10 um | 51 x 51 x 50 (0.2 x 0.2 x 0.2 um) |

# Computing Performance (MPEXS-DNA)

MPEXS-DNA is 200 times faster than Geant4-DNA

For ~16k protons with 1 MeV

***~ 53 hr. (single-core CPU) → <u>~ 16 min.</u> (GPU)***

| | Incident particle | Initial energy | G4CU-DNA Total thread numbers ($N_{blk}$ x $N_{thr/blk}$) | G4CU-DNA Process time (sec/particle) | Geant4-DNA Process time (sec/particle) | speedup factor (=G4/G4CU) |
|---|---|---|---|---|---|---|
| DNA Physics | $e^-$ | 100 keV | 524,288 (4,096 x 128) | $3.53 \times 10^{-3}$ | 0.764 | ***216*** |
| | p | 1 MeV | 524,288 (4,096 x 128) | $5.97 \times 10^{-2}$ | 11.8 | ***198*** |
| | $He^{++}$ | 1 MeV | 524,288 (4,096 x 128) | $6.10 \times 10^{-2}$ | 12.3 | ***202*** |
| Standard EM Physics | $e^-$ | 20 MeV | 524,288 (4,096 x 128) | $8.81 \times 10^{-6}$ | $1.84 \times 10^{-3}$ | ***208*** |

# The achievements

- Geant4: 20years history for developments and maintenance
  - Stable and reliable in the all range of incident energy for all of the particles
- Medical applications: Tools and examples are available
- Cell level simulation: Geant4-DNA is available and further developments will come
- MPEXS series: GPGPU powered acceleration
  - Very promising with next generation  hardware

# Toward real EBM

- Simulation of treatment devices and facilities are already available
  - They are well utilized in clinics
  - We do not see any major problems except the calculation time
- Fair comparison among the different technique can be done, but nobody have done
  - Barrier of commercial secrets
    - Design and implementation of devices and facilities are concealed
  - No motivation in the supplier company side
  - Patients' voice will change the situation
- Cell level simulation needs more improvements and enhancements yet
- Computing speed problems to be solved by GPU

# Borders of disciplines

- New frontiers of science “where no man has gone before”
  - "*Space the final frontier. These are the voyages of the starship Enterprise. It's continuing mission, to explore strange new worlds, to seek out new life and new civilizations, to boldly go where no man has gone before*.“ –StarTrek
- There will be lots of new findings to help people’s real life not in the far future, but tomorrow
- Modern cow boys/girls are invited to start their voyages for discovering a treasure in science


“where no man has gone before”
U.S.S. ENTERPRISE
NCC - 1701
New disciplines
Fly, climb or dig?
physics
biomedicine
chemistry
medical physics
Borders of disciplines

# Summary

- Necessary tools to establish a quantitative approach in radiotherapy have been ready almost
  - Geant4 and MPEXS for dose calculation
  - Geant4-DNA for cell level radiation simulation
  - MPEXS, a new simulation toolkit to use GPGPU, will open a new window for radiology
  - Simulation on bio-chemical effects are under development in MPEXS-DNA
- Everybody are invited to come to the new frontiers in the borders of the disciplines
  - "*boldly go where no man has gone before*"
- Mutual respect among people in the different fields is the key to start a good collaboration