IFMP WORKSHOP IN IONIAN UNIVERSITY, CORFU, GREECE

Friday 10/11/2017 11:00

INNOVATION IN BIOENGEENERING

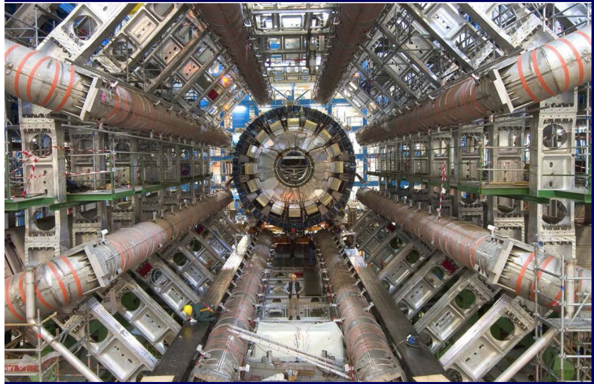
Patrick Ledu, PhD

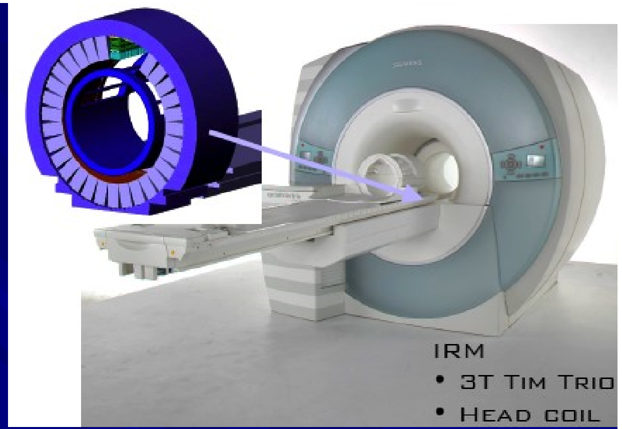
INP Lyon and IEEE

Using my own experience during the last 47 years of working on radiation detectors in particle physics experiments, I will try to give an overview of what were the evolution and the application of the recent developments in the biomedical field especially in tomography (TEP) and Xray imaging.

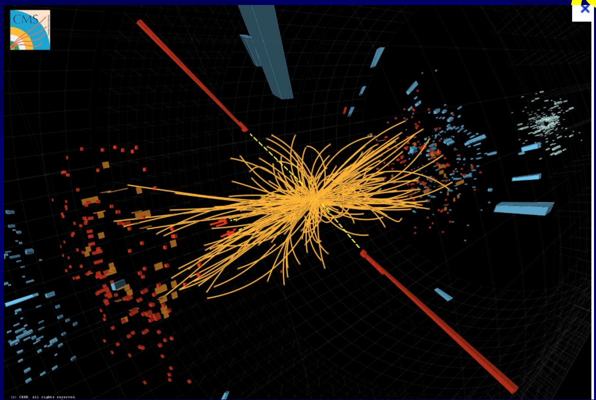
The topics developed are :

- Radiation detectors material
- Photodetectors
- Electronics
- Data acquisition
- Computing , simulation and data sciences





Innovation in bioengineering



P. Le Dû

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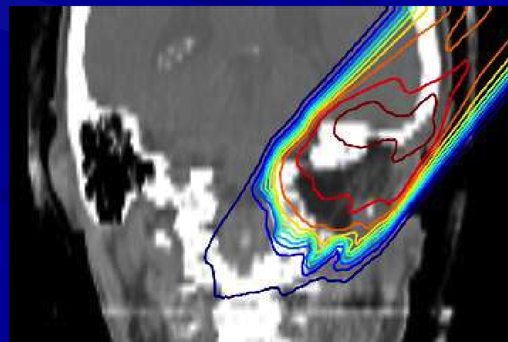
IEEE NPSS
NUCLEAR & PLASMA SCIENCES SOCIETY

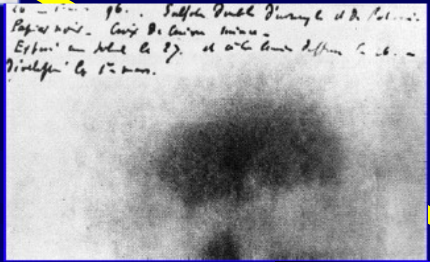


Goals of this presentation

- Using my own experience during the last 47 years of working on RI detectors → try to give a flavor of what could be the application of the recent evolution and developments in the biomedical field

How physics discoveries have impacted our life (1)

1895
W.C. Rontgen
Discovery of X Ray



1896 - Discovery of the natural radioactivity by Henri Becquerel

First image of potassium uranyl disulfide

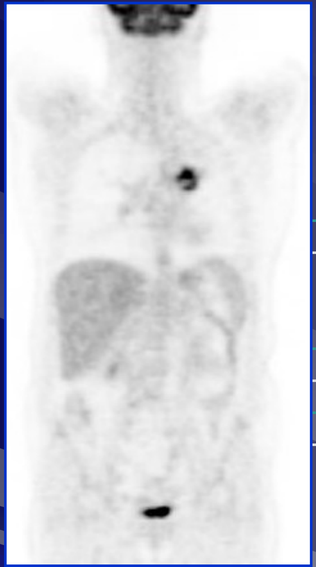
1898
Pierre and Marie Curie
the Radioactivity
Polonium,Radium

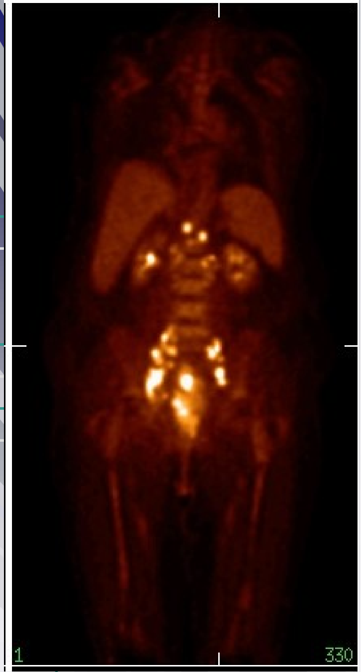
1910

X Ray Radiography

1923 - The Tracer principle
`G.V.Hevesy- the father of nuclear medicine

Tracer

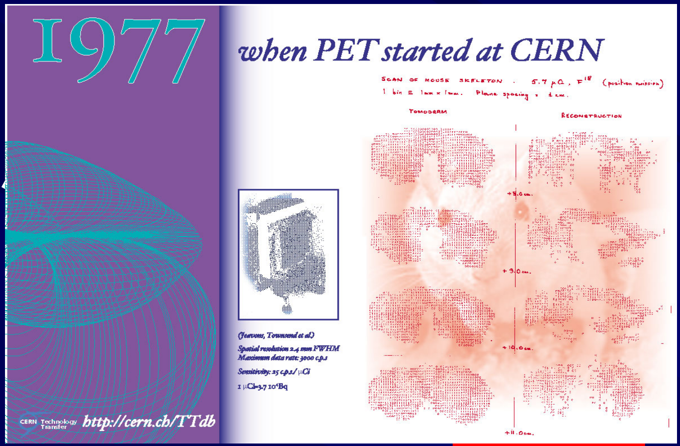




The best 'typical example → The PET

PET imaging
From past, present to future

Historical Evolution of PET

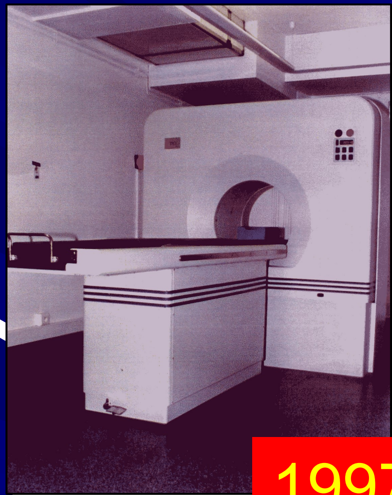


1977

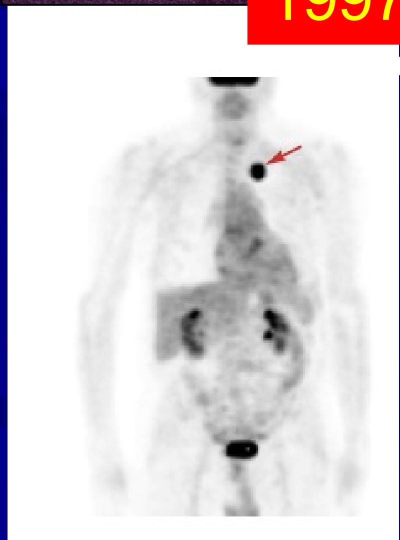
First Steps
Townsend & Jeavons

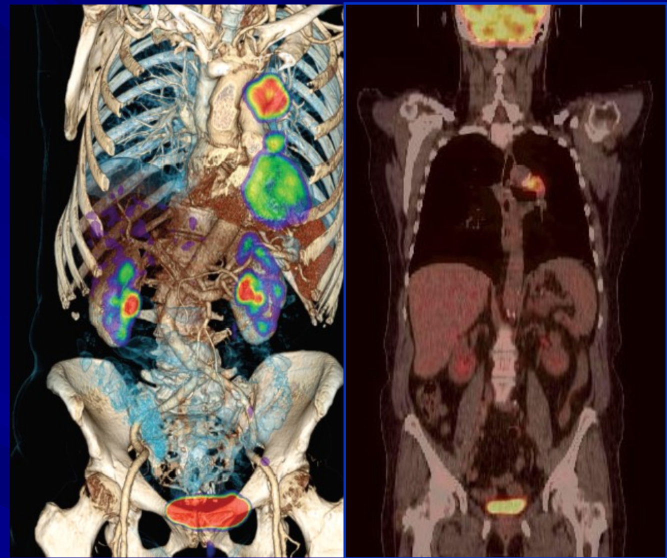
First mouse imaging with ^{18}F

C-PET Philips



1997





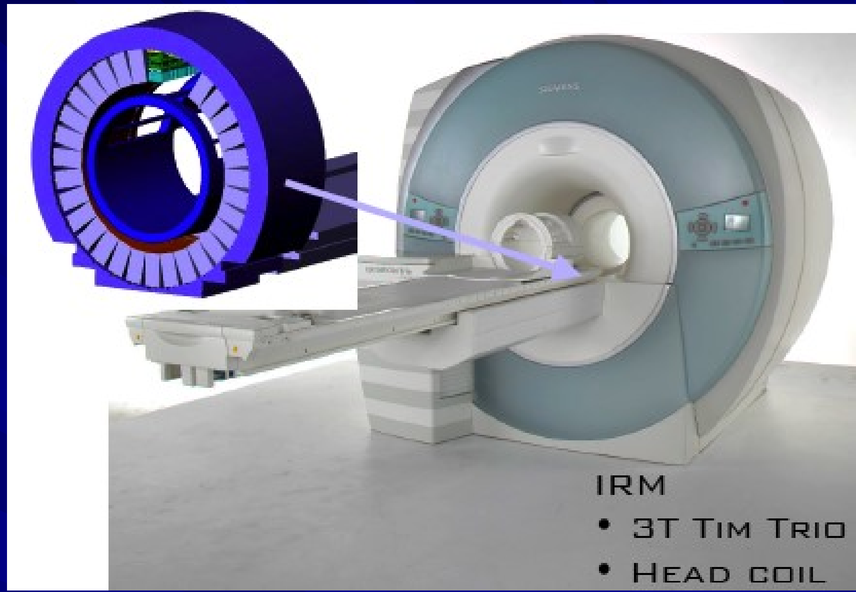
2007

Biograph PET + X ray-CT

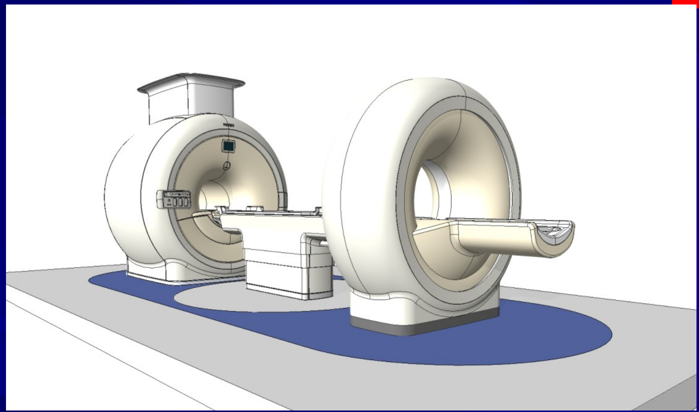
From Today ---> Tomorrow Challenge

TDM/PET-TOF (300 psec)

Today
2017



Siemens



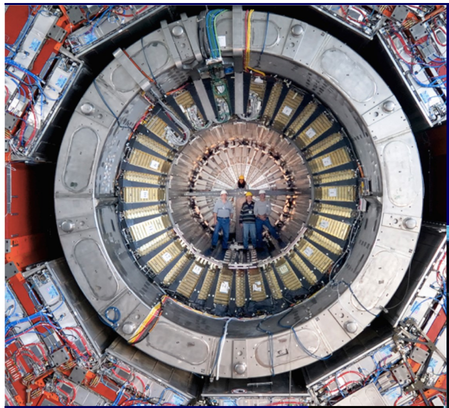
Philips

PET-MRI

2027 ?

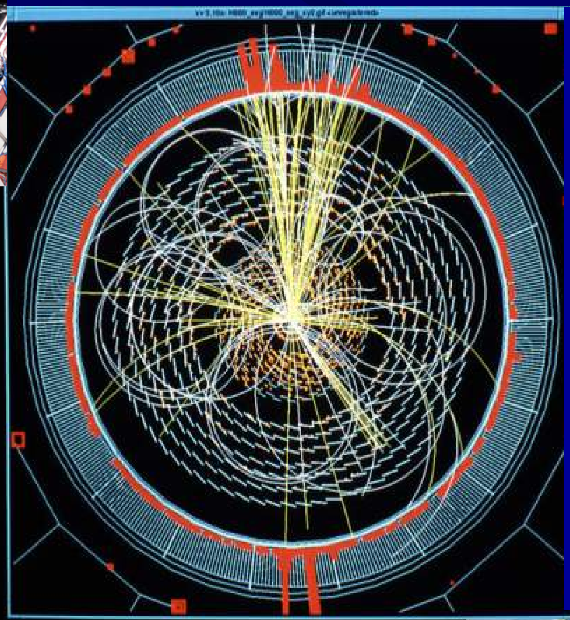
HEP & PET

Similarities and differences

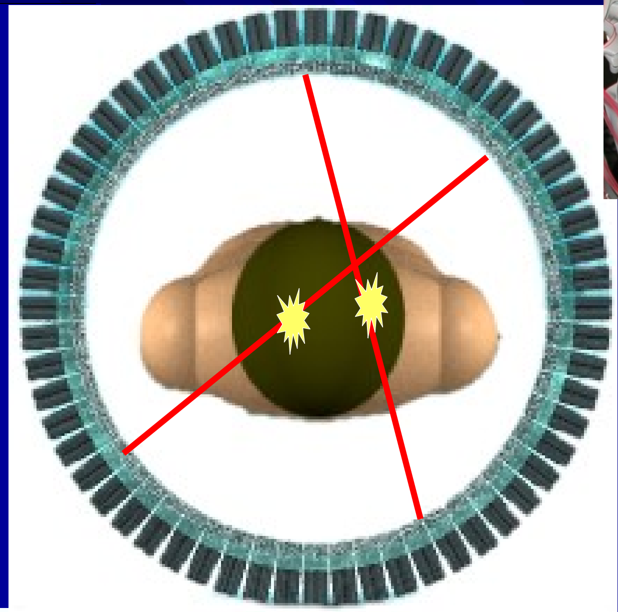


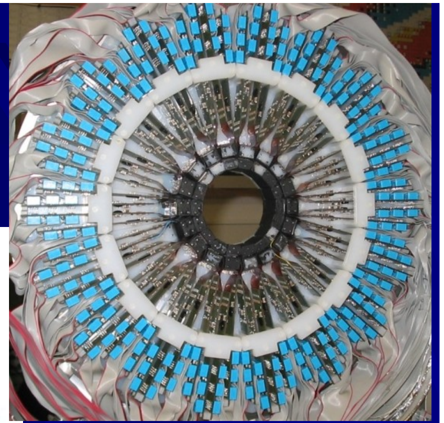
Calorimeter

HEP



M_{Higgs} = 100 GeV





PET Camera

Biomedical Imaging

Similarities

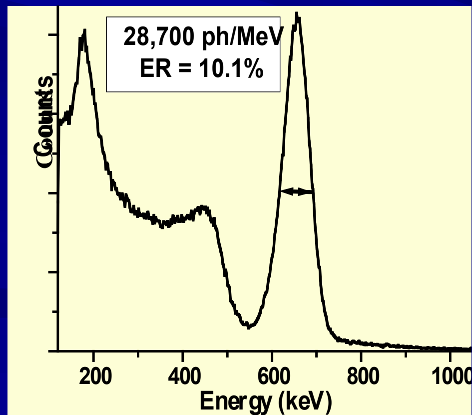
Geometry and granularity

Detector (Crystals & scintillator)

Sensor Photodetectors (PMT,APD)

Digitizers: ADC,TDC,

Data volume (Gbytes)



Differences

Energy range

(10GeV → -511keV)

Event Rate 40 → 10 MHz

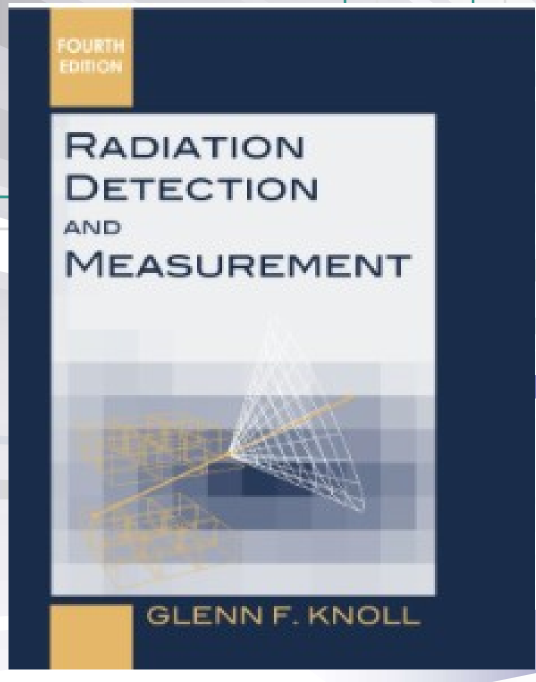
No synchronization

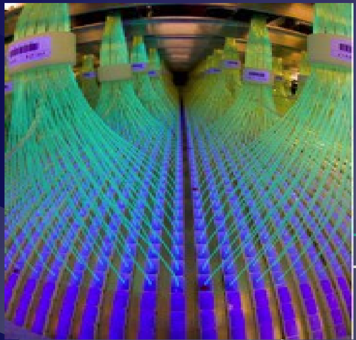
Self triggered electronics

Multiple vertices

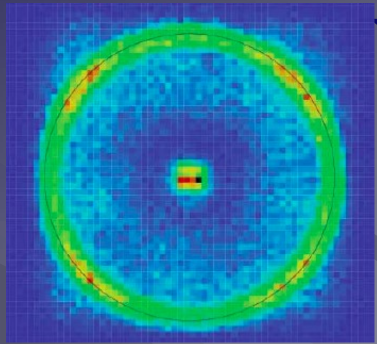
Few words about Particle Physics Detector

Radiation
Instrumentation
The Bible
Glenn Knoll

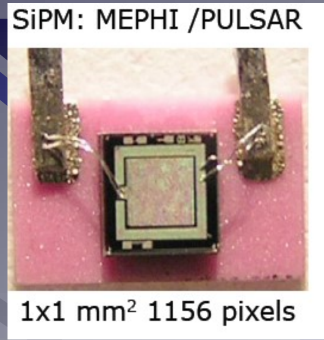




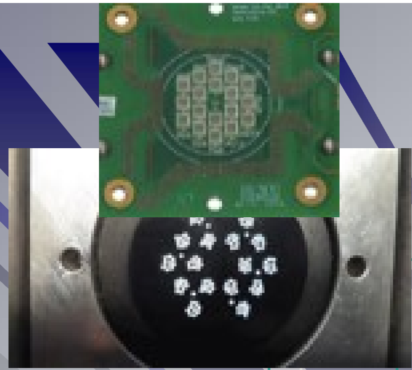
T2K
scintillators
WLS fiber
60000 SiPM



Belle2 RICHs
single γ

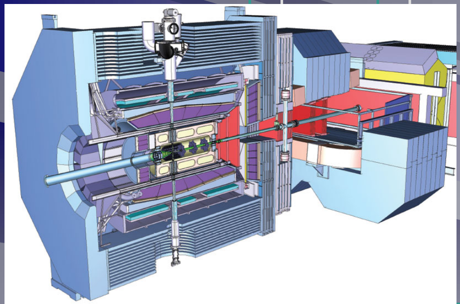


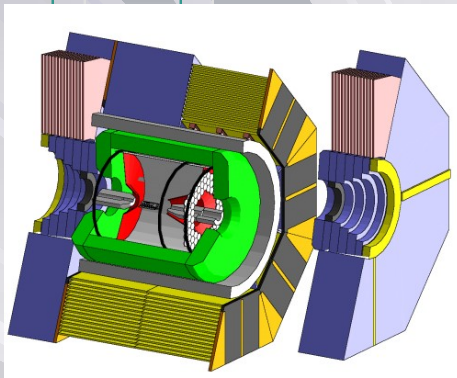
ILC - CALICE
$8x10^6$ SiPM

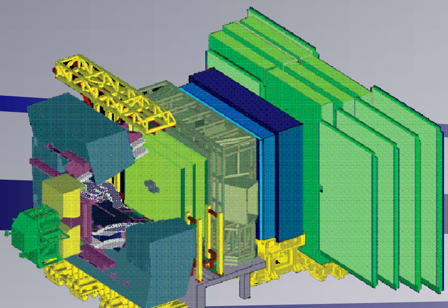


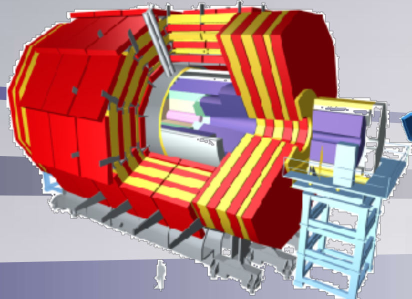
CMS HCAL
$2 x10^3$ SiPM

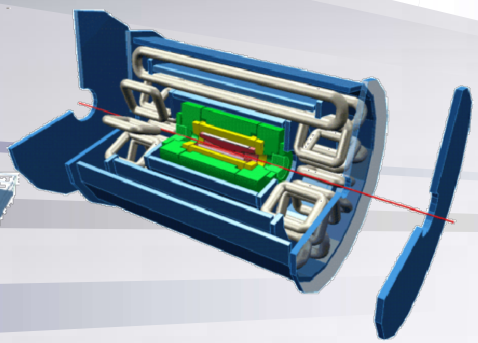
Some technologies that can make a breakthrough

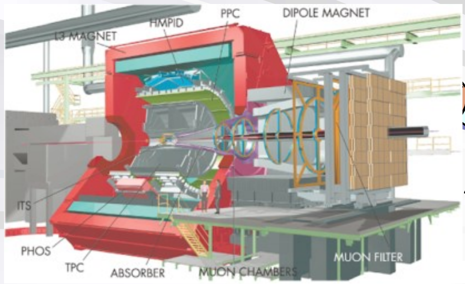


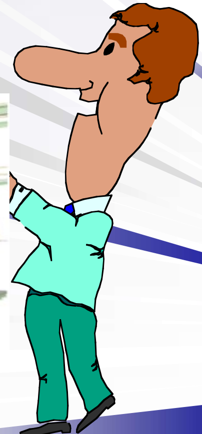








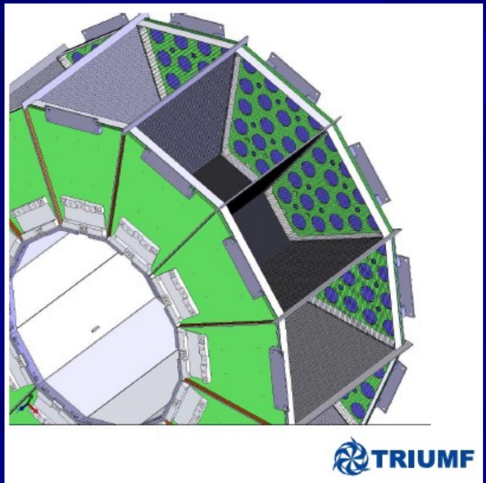




Material for photon detection

LSO

- Standard : Crystal
  - From LEP/ L3 BGO ,LHC/ CMS PbO4
  - → Crystal Clear Collaboration.
- Possible 'exotics alternatives: LXenon, MG-RPC's … ????



Liquid Xenon

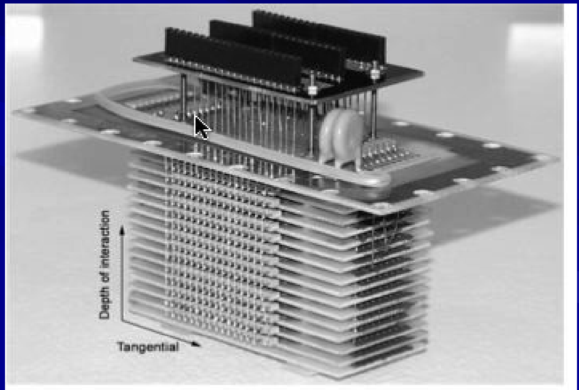


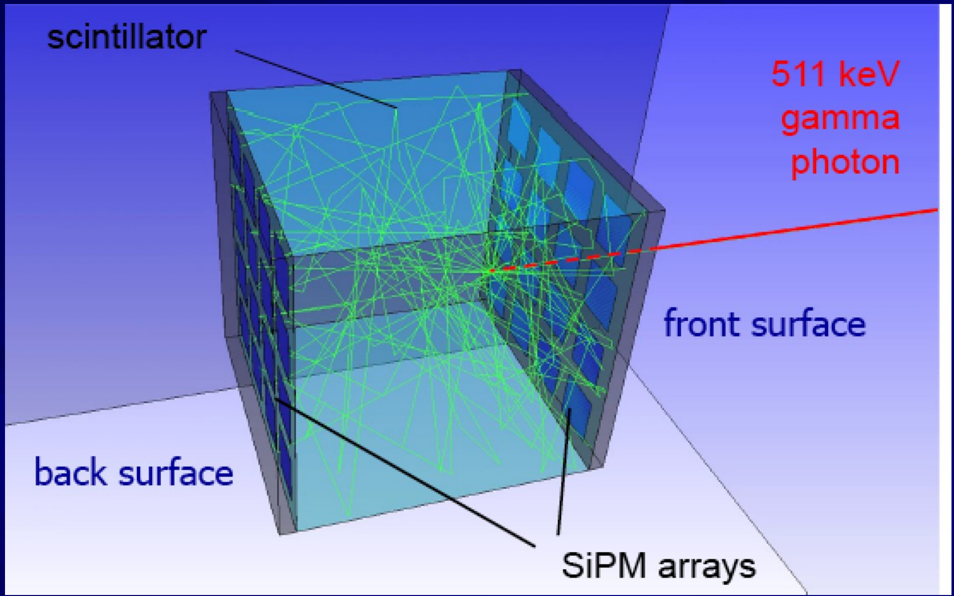
Fig. 2. Detecting element built with 17 identical stacked plates, which define 16 independent sensitive gas gaps, being able to measure the photon interaction point in two dimensions: the tangential dimension and the DOI.

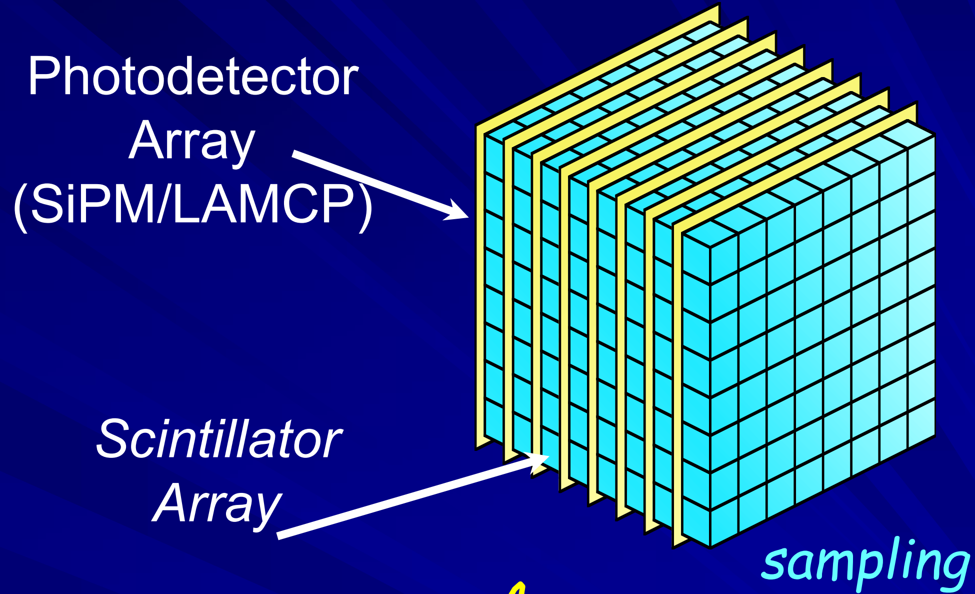
Scintillators for PET

	1962	1977	1995	1999	2001	2003	2007
	NaI	BGO	GSO:Ce	LSO:Ce	LuAP:Ce	$LaBr_3$:Ce	LuAG:Ce
Density (g/cm³)	3.67	7.13	6.71	7.40	8.34	5.29	6.73
Atomic number	51	75	59	66	65	47	63
Photofraction	0.17	0.35	0.25	0.32	0.30	0.13	0.30
Decay time (ns)	230	300	30-60	35-45	17	18	60
Light output (hν/MeV)	43000	8200	12500	27000	11400	70000	>25000
Peak emission (nm)	415	480	430	420	365	356	535
Refraction index	1.85	2.15	1.85	1.82	1.97	1.88	1.84

- No Scintillator with Superior Properties in All Aspects

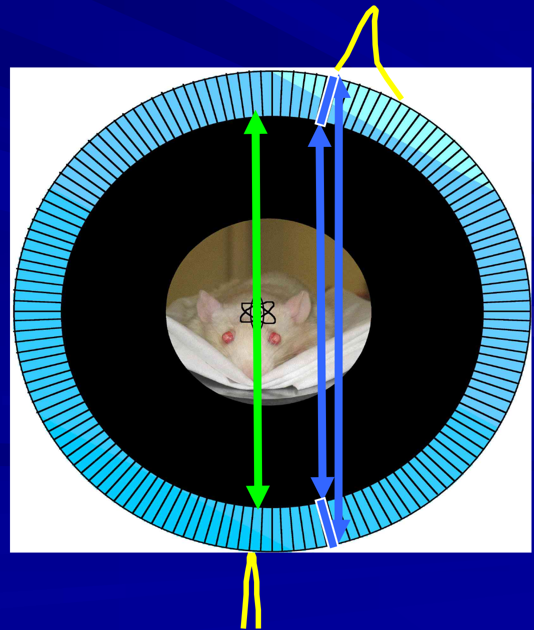
On going DOI development





Monolithic scintillator
D;Shaart TUDelf

- Goal
  - TOF: 100 psec resolution
  - Position : 1 mm
  - DOI* capability



*Depth Of Interaction

What is the limit for TOF ?

Hardware	Δt (ps)	TOF Gain
BGO Block Detector	3000	0.8
LSO Block (non-TOF)	1400	1.7
LSO Block (TOF)	550	4.2
$LaBr_3$ Block	350	6.7
LSO Single Crystal	210	11.1
LuI_3 Single Crystal	125	18.7
$LaBr_3$ Single Crystal	70	33.3

~350 ps Intrinsic Detector Resolution today

New 'picosecond development → 100 psec goal

Photodetectors

Photomultipliers tubes (PMT)

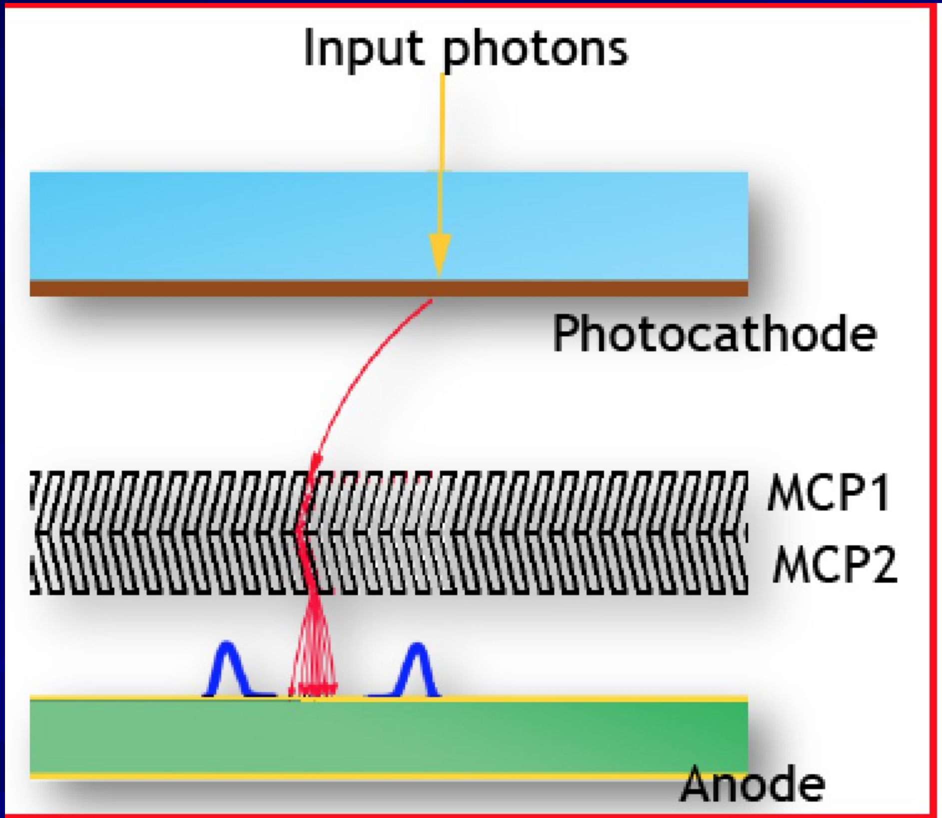
- Standard : PMT → Use since 75 years (RCA 1936)
  - Large gain, high QE,and stability.
  - But bulky, sensitive to magnetic field
- In 70"s → > 10 manufacturers (EMI,RCA ....)
- 2000's → 75% production for medical (Spect/,PET)
- Today only 2 (Hamamatsu & Photonis)
  - -> **closing their main PMT factories**

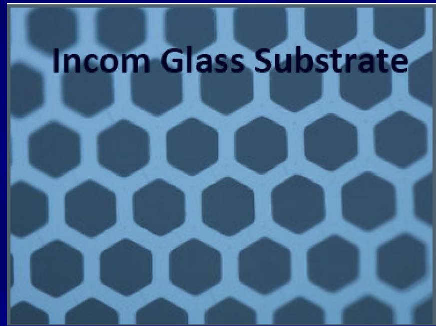
- However → New technological developments
  - LAPPD (UC Chicago & Argonne)
  - Tynode (H. Van Der Graaf)

Micro Channel Plate → How does it work ?

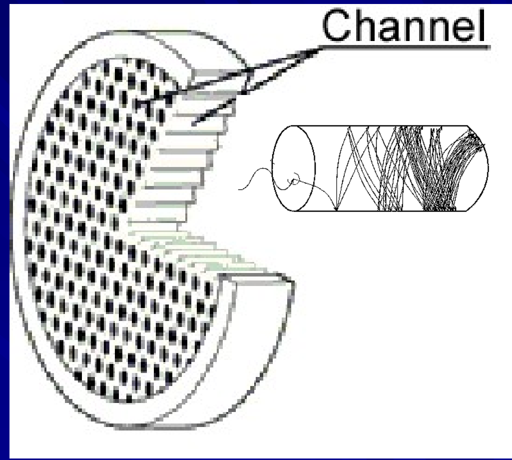
- High,gain>10^7,low noise,low power, $\sigma(t)<10$ psec, $\sigma(x)<\$1$mm
- Goal → large area, low cost:

(since intrinsic time and space scales are set by the)

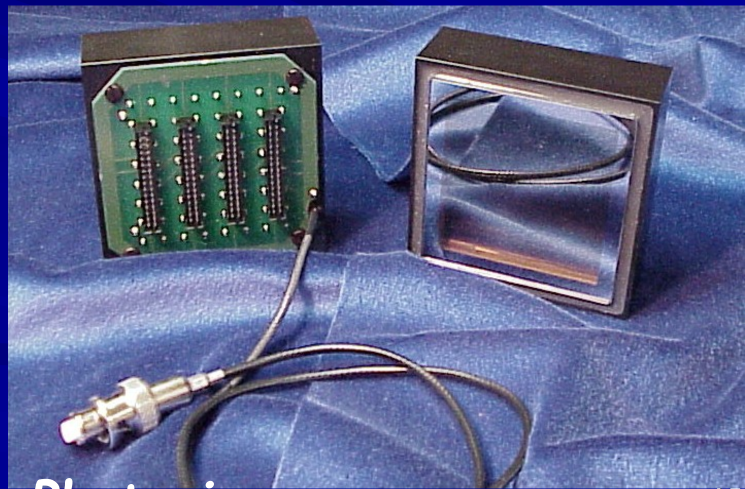




Atomic Layer deposition (ALD)

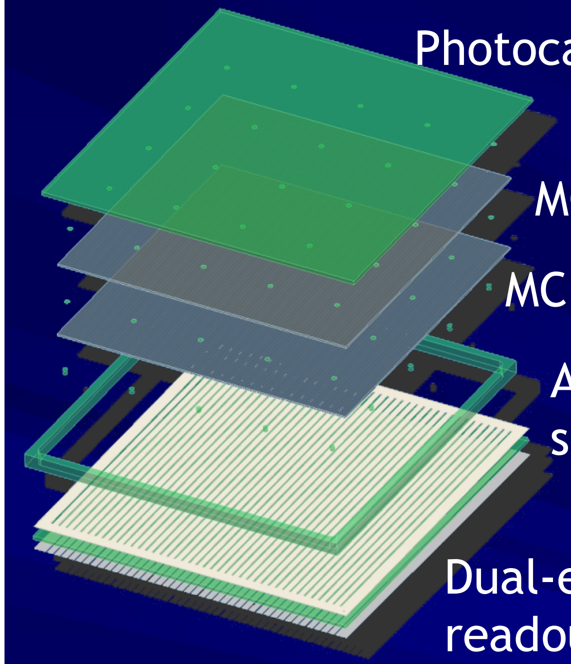


pore sizes 2-20μm



Photonis

Large Area Micro-Channel Plates Devices



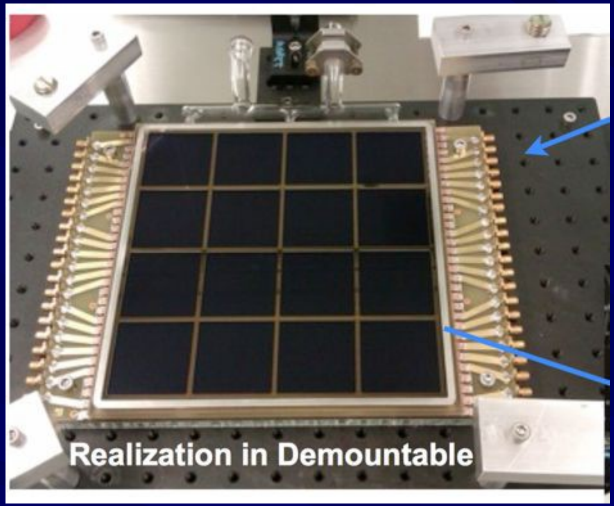
LAPPD project : *Chicago-ANL-Hawaii*
Large Area: 200 x 200 mm2
- *Flat Geometry*
- *PMT Sensitivity: QE >20% w/bi-alkali photocathode*
- *Picosecond Timing: resolution <60 pS,*
- *Sub-mm spatial resolution*
- *Lower Cost per Unit Area*

Transmission lines 2D readout:

limits the number of electronic channels compared to pixels

Electronics

- GigaSample/s Waveform Sampling and Digital Processing



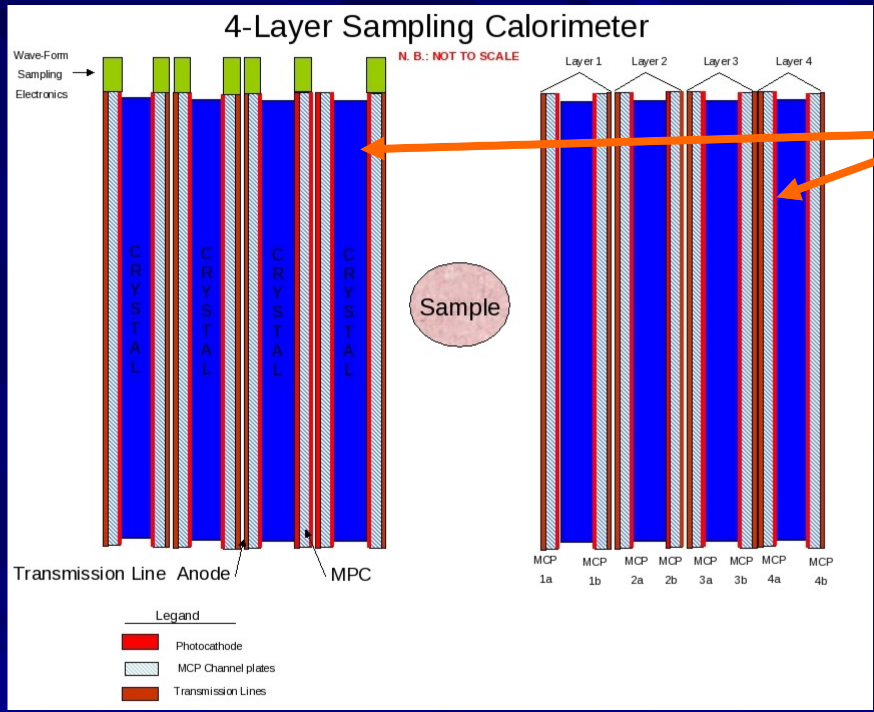
Coming soon

A Super Module holds 12 tiles in 32 rows.15 waveform sampling ASICS on each end of the tray Digitze 90 strips. 2$layers of local Processing (Altera) measuer extract Charge,time,positon,goodnessof fit

http://psec.uchicago.edu/

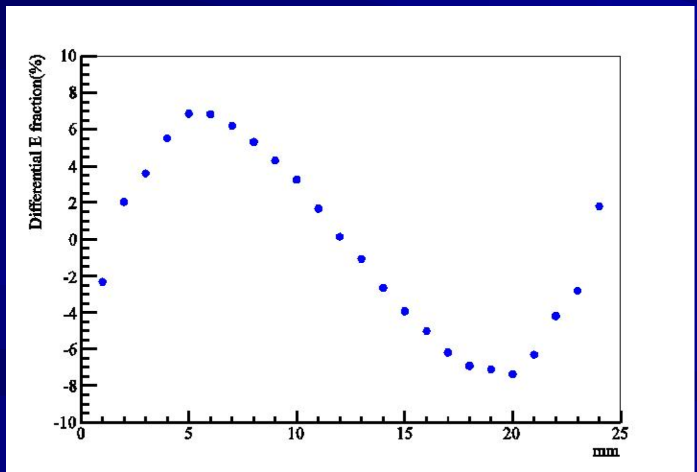
Application in Medical Imaging (PET)

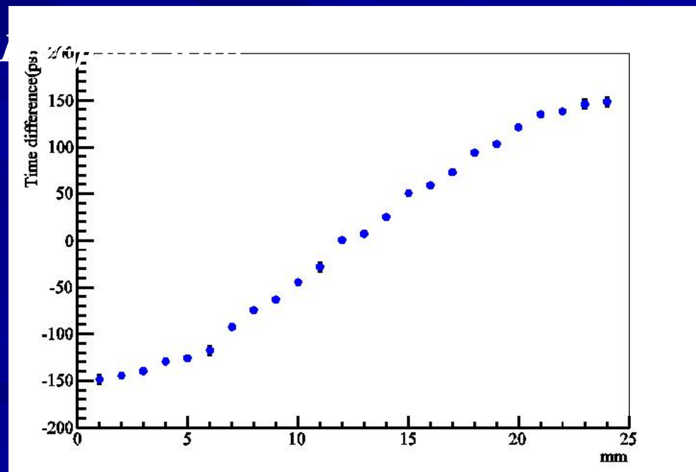
Can we solve the depth-of-interaction problem and also use cheaper faster radiators?



Alternating radiator and cheap 30-50 psec planar mcp-pmt's on each side

Simulations by Heejong Kim (Chicago)

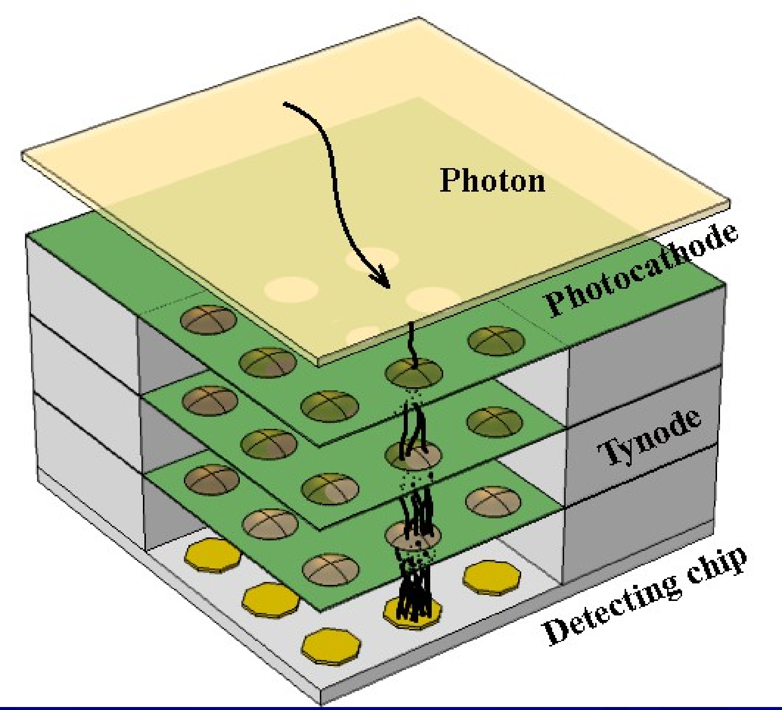




Depth in crystal by time-difference

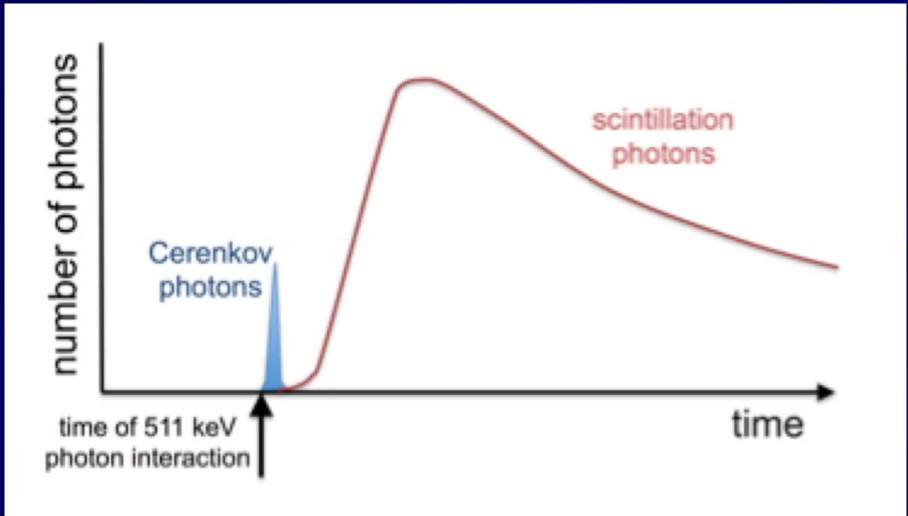
Depth in crystal by energy-asymmetry

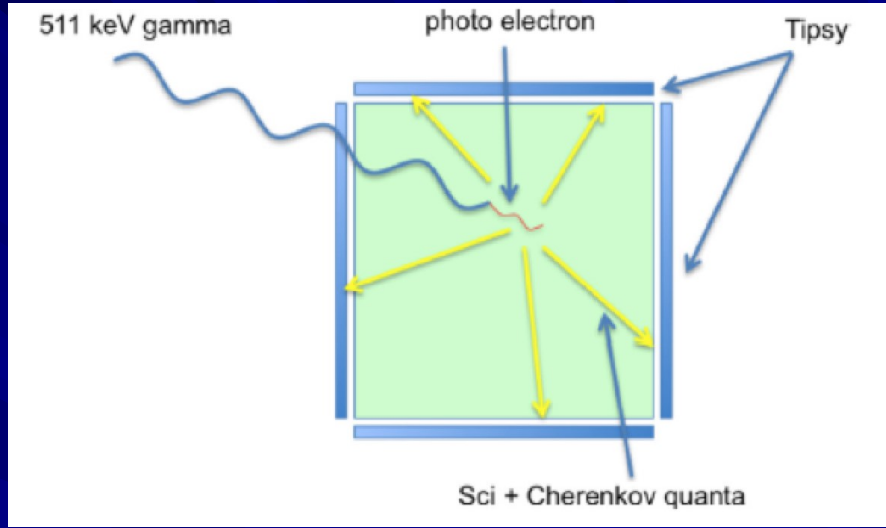
TYNODE:typsi Membrane Project (H.Van Der Graaf) Nikhef-TUDelf-BNL-Photonis



- **detection efficiency: Quantum Efficien**
- **single (digital) soft photon detectors**
- **time resolution**
- **2D spatial resolution**
- **Principle = active photocathode**
- → drift field pushing electrons to emission vacuum surface
- electric field created in between by potential defining graphene planes
- all layers build up individually by *atomic layer deposition* ALD
- electron emission stimulated by negative electron affinity by *termination*
- First designed after *ab initio* simulations of 3D atomic building blocks
- http://dx.doi.org/10.1016/j.nima.2016.11.064.

Principle of Cherenkov PET-TOF with Large MCP or Tynode





- Cherenkov photons created after the absorption a 511 Kev annihilation photon in a lead glass cube are read out all the sides
- 4D (X,Y,Z,t) measurement of conversion point of 511 keV quantum
- Needs:
- • Dense materials with high index of refraction and high transparency in blue/UV like PbF2 → **single photondetection**
- • Photodetectors with high blue/UV sensitivity and low noise

Solid State Photodetectors

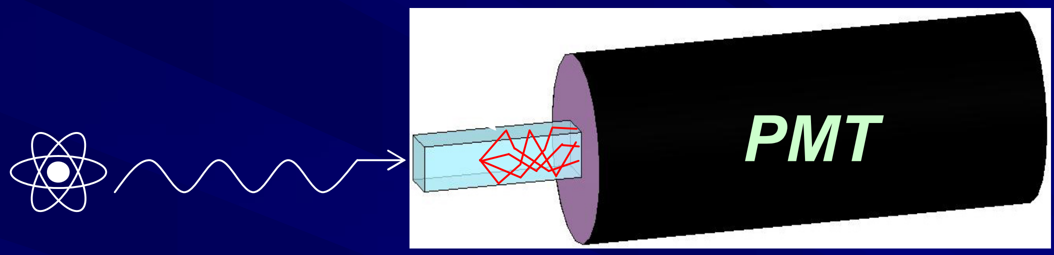
- 1980 → PIN diode for SLAC SLD calorimeter
- 1985 → APD's EGG (McIntyre)
  - First Sherbrooke animal PET (Roger Lecomte)
  - SDC and CMS EM calorimeter read out
- 2000 → SIPM (MPPC ..) arrays in Geiger mode
- 2005 -→ DSIPM
- Today → Many providers & development (Philips, Hamamatsu,RMD ....)
- **New commercial whole body PET use intensively SiPM & DSiPM**

Photodetector Technologies: A Comparison

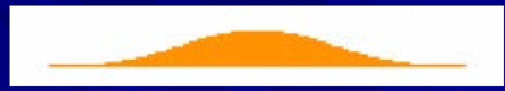
Photo detector	PMT	PIN	APD	SiPM
Technology	Vacuum-Based	Solid-State	Solid-State	Solid-State
Gain	High	Poor	Moderate	High
Detection Efficiency	Low to Moderate	High	High	Moderate to High
Noise	Low	Moderate	Moderate	Moderate
Timing Response	Moderate to Fast	Slow	Slow	Fast
Packaging	Bulky	Compact	Compact	Compact
Sensitivity to Magnetic Field	Yes	No	No	No
Bias Voltage	>1kV	~50V	100–1000V	~50V

Scintillation Detectors vs Solid-State Detectors

Scintillator



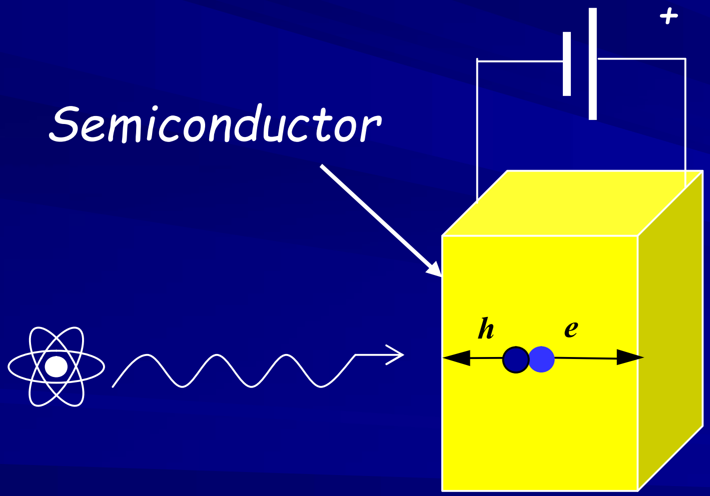
~1,500 e$^-$
@ 140 keV



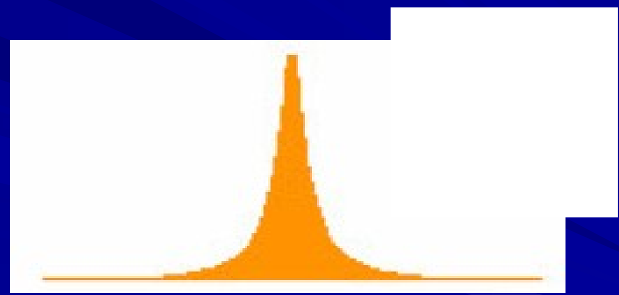
Energy per e$^-$ ~ 10 – 200 eV

Gamma Ray --> Visible Light --> Electrical Signal (Indirect Detection)

Semiconductor



~30,000 e$^-$
@ 140 keV

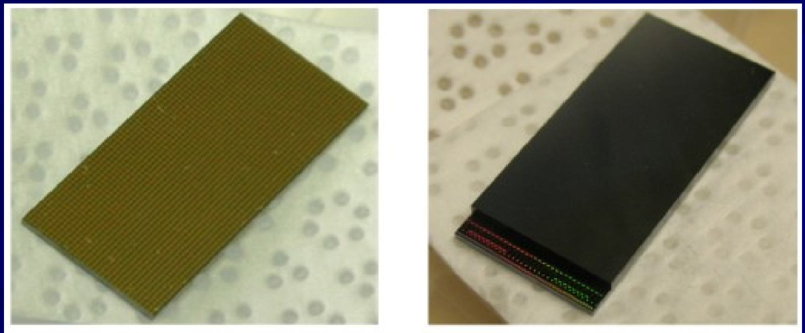


Energy per e$^-$ ~ 3 – 5 eV

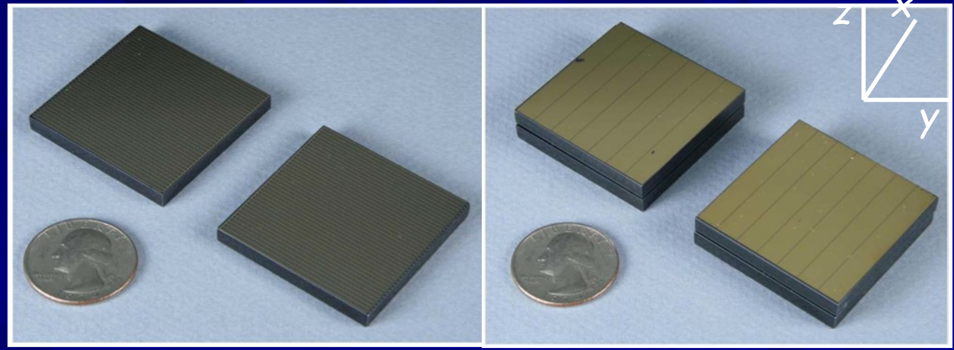
Gamma Ray --> Electrical Signal (Direct Detection)

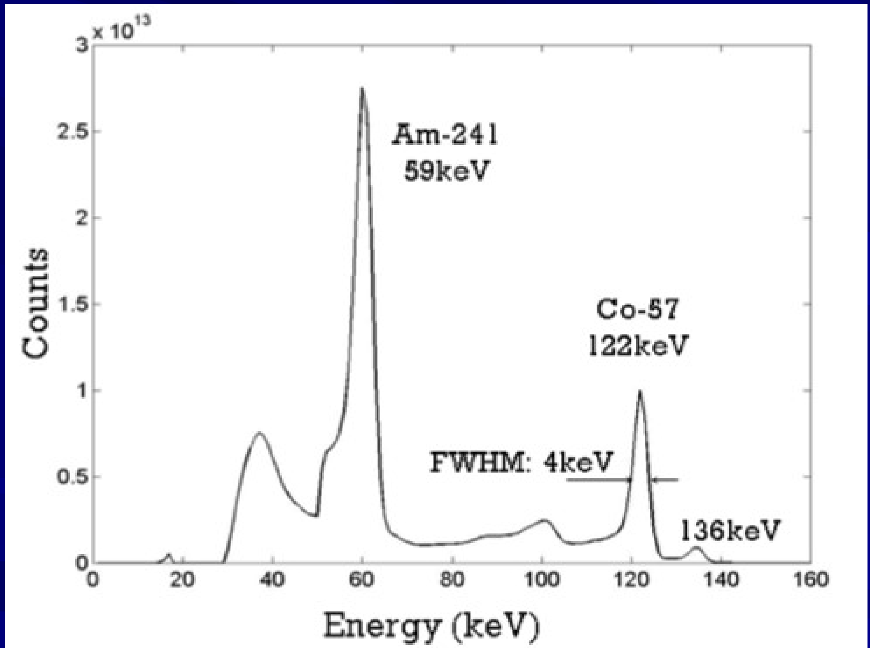
Examples of CdTe/CdZnTe Detectors for SPECT and PET

CdTe: 11x22x1 mm^3, 350 μm pixels

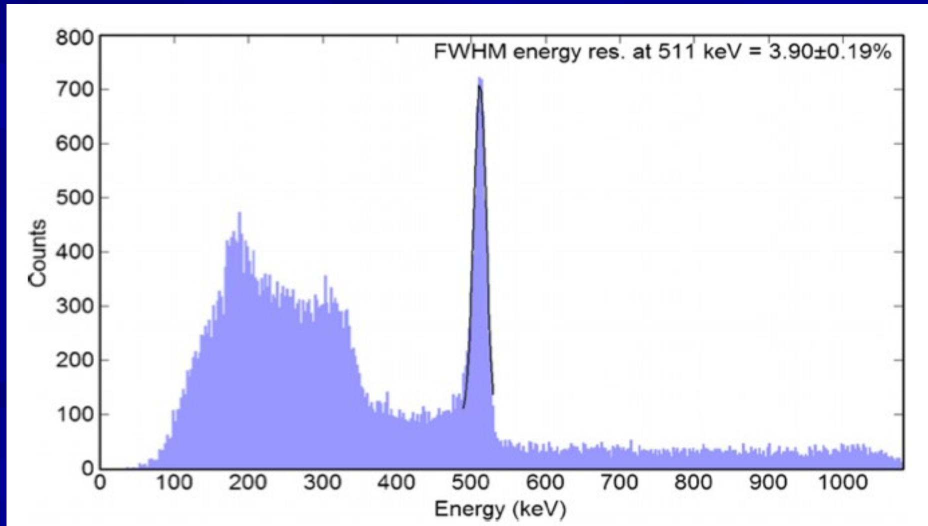


CdZnTe: 39x39x5 mm^3, double-sided strip



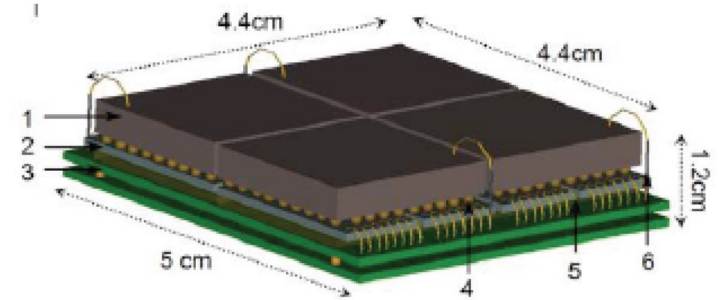


Edge-on geometry, 3-D positioning
X position: anode strip, 1 mm pitch
Z position: cathode-anode ratio, ~1 mm
Y position: cathode strip, 5 mm pitch

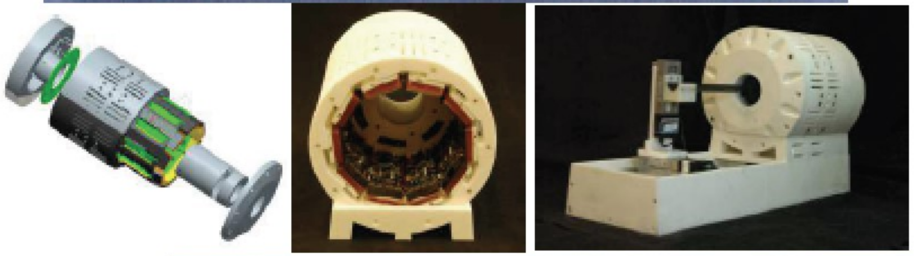


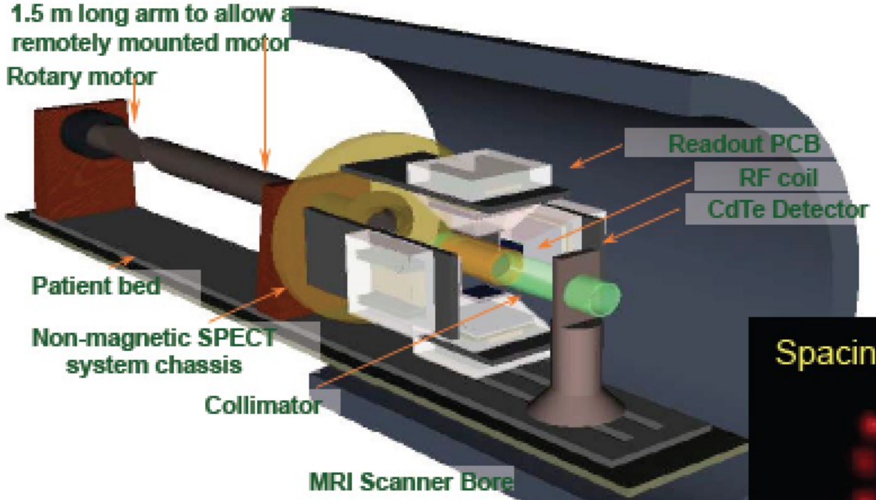
Source: L.J. Meng, et al., Nucl. Instr. Meth., vol. A604, 548 (2009)
Y. Gu, et al, Phys. Med. Biol., vol. 56, 1563 (2011)

CZT/CdTe SPECT insert for MRI

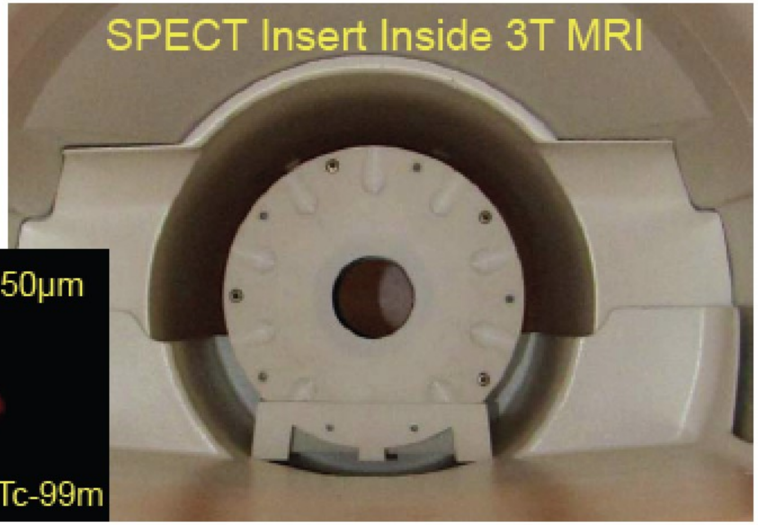


The proposed energy-resolved photon-counting (ERPC) detector. (1) CZT crystals of 4.4cm × 4.5 cm × 2-4 mm in size, (2) ERPC ASICs, (3) Readout PCBs, (4) indium bump-bonding between CZT detector to the ASIC, (5) wire-bonds between the ASIC and the PCBs and (6) Cathode signal out.





Cai et al, NIMA, 2014
UIUC-Meng et al & UC-Chen et al



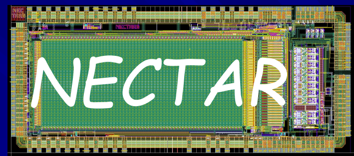
Courtesy of Chin Tu Chen (Universitty of Chicago

Electronics

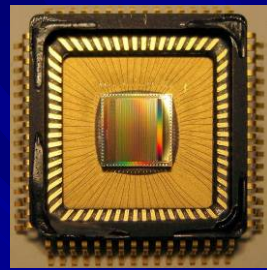
A survey of common area (cont't)

- Front end electronics & signal treatment
  - Fast shaping, integrated, low noise, low power, self trigger
  - Digital filtering and signal analysis

    --> Waveform Digitizer :SCA



Giga sampling chip
LAL-Saclay)

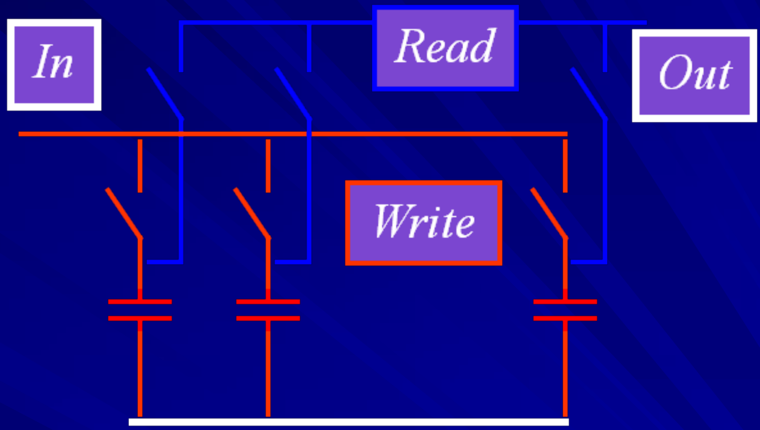


DRS4 (PSI)

- Read Out, Trigger & DAQ
  - Pipeline and parallel read-out → FPGA
  - Feature extraction techniques →like Time Of Flight (TOF)
  - Real Time selection → GPU's image processing
  - High bandwidth networks → new telecom standard (xTCA)
- Computing & software : handling high quantity of data
  - Reconstruction, simulation & modelling --> GATE
- Global design
  - Compact integration of large number of channels

Analog memories → Waveform digitizers

Switched Capacitor Arrays (SCA)
Store signal on capacitors (~pF)
High speed (up to 5 GHz)
Slower readout (~10MHz)
High channel density
9 channels on 5x5 mm^2
Dynamic range : 10-13 bits
Depth : 100-2000 cells
Low power (10-40 mW / channel)
Low cost (~ 10€ / channel)

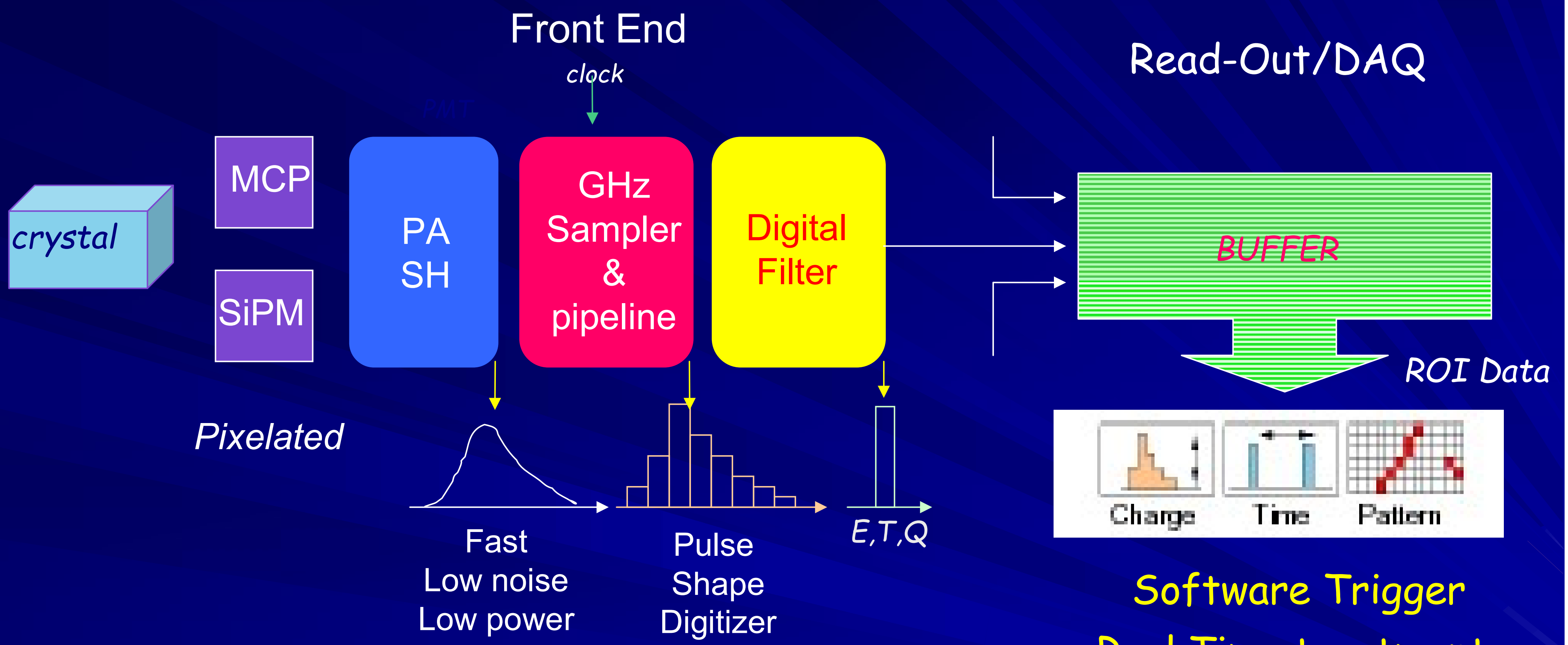


DRS4

PSI Zurich

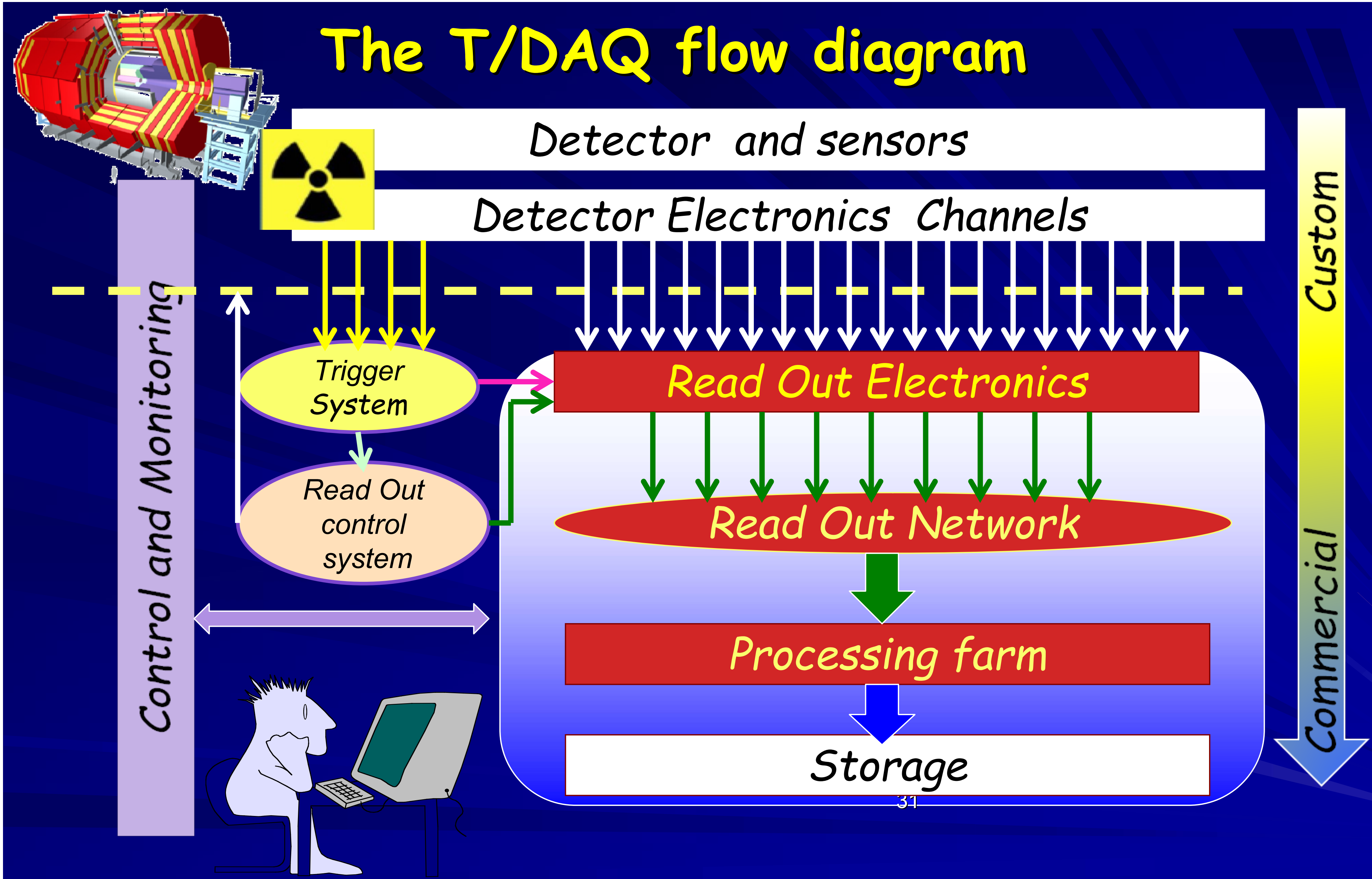
But possible loss of data integrity
limited deeph
leakage current,
non linear timing

Exemple of Conceptual TOF-PET architecture model

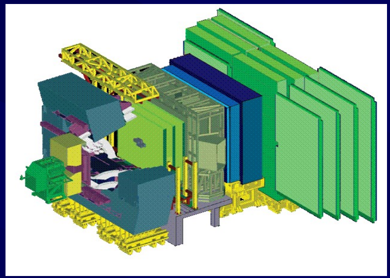


- ♦Free-running analog waveform sampling and digitizer (SCA)
- ♦ Digital filter used to extract pulse amplitude and high resolution timing (FPGA)
- ♦ Pipelined processing architecture to avoid deadtimes (GPU's)
- ♦Parallel digital read out
- ♦Terabit network for communication and processing (xTCA)

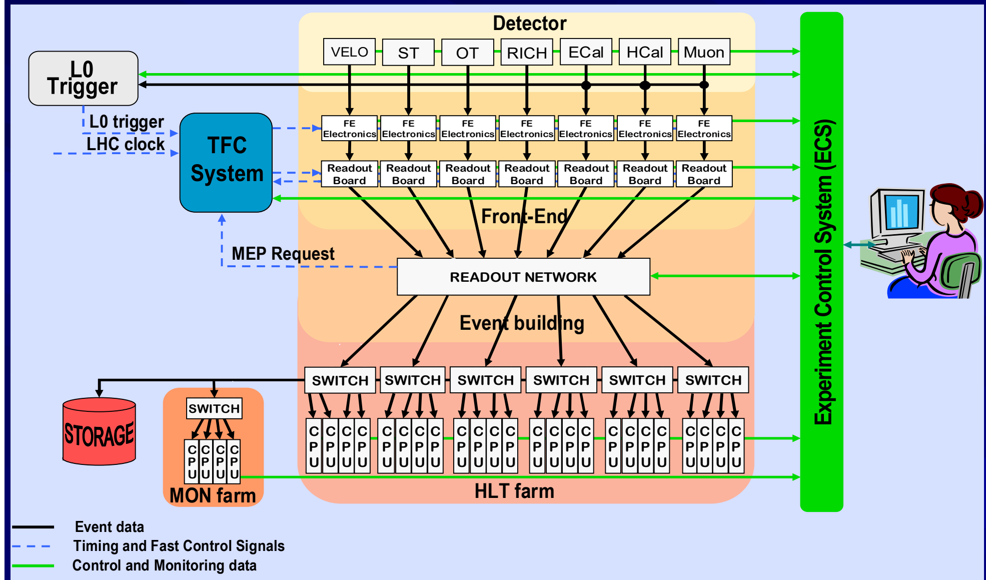
The T/DAQ flow diagram



DAQ = The evolution of architecture

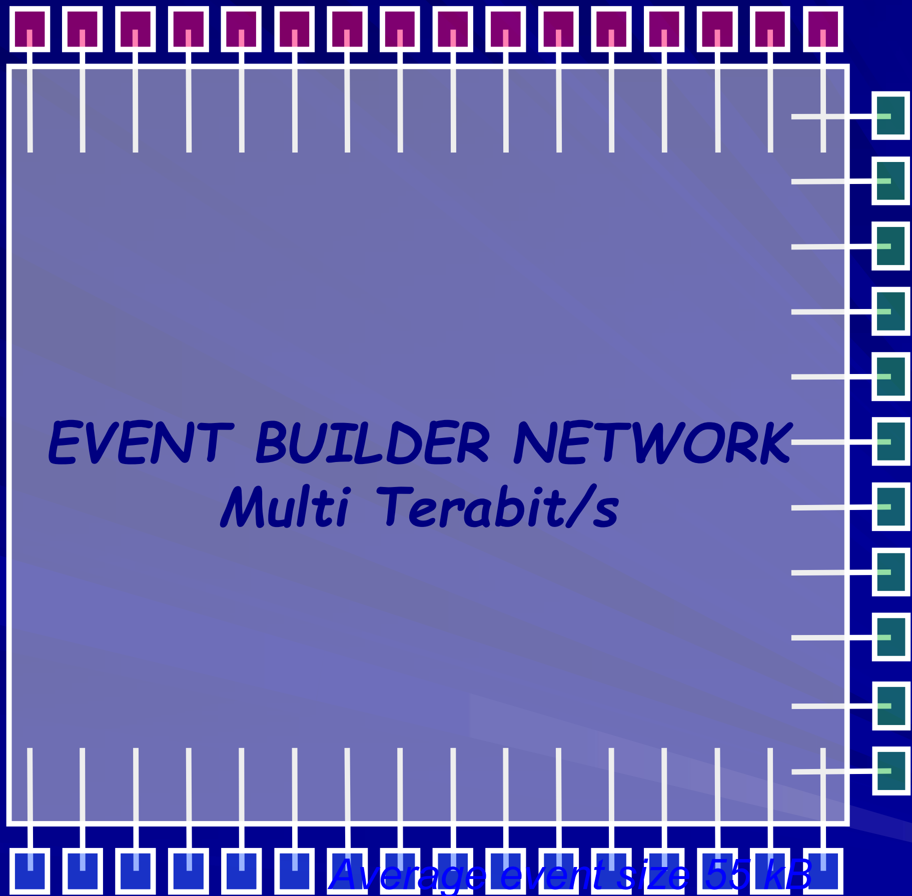


LHCb



Average event size 55 kB
Average rate into farm 1 MHz
Average rate to tape 4 – 5 kHz

Direct network access From Detectors and Machine



Controls & Storage servers

Average event size 55 kB
Average rate into farm 1 MHz
Average rate to tape 4 – 5 kHz

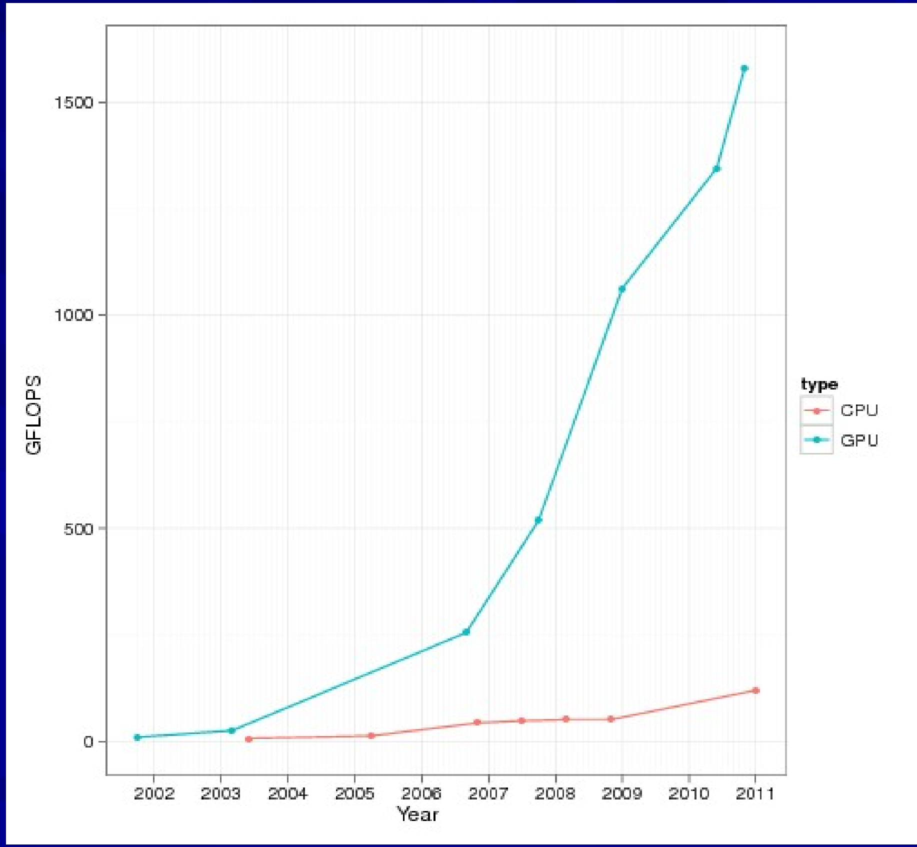
Trigger Farms & Analysis

Computer farm evolution → GPU's

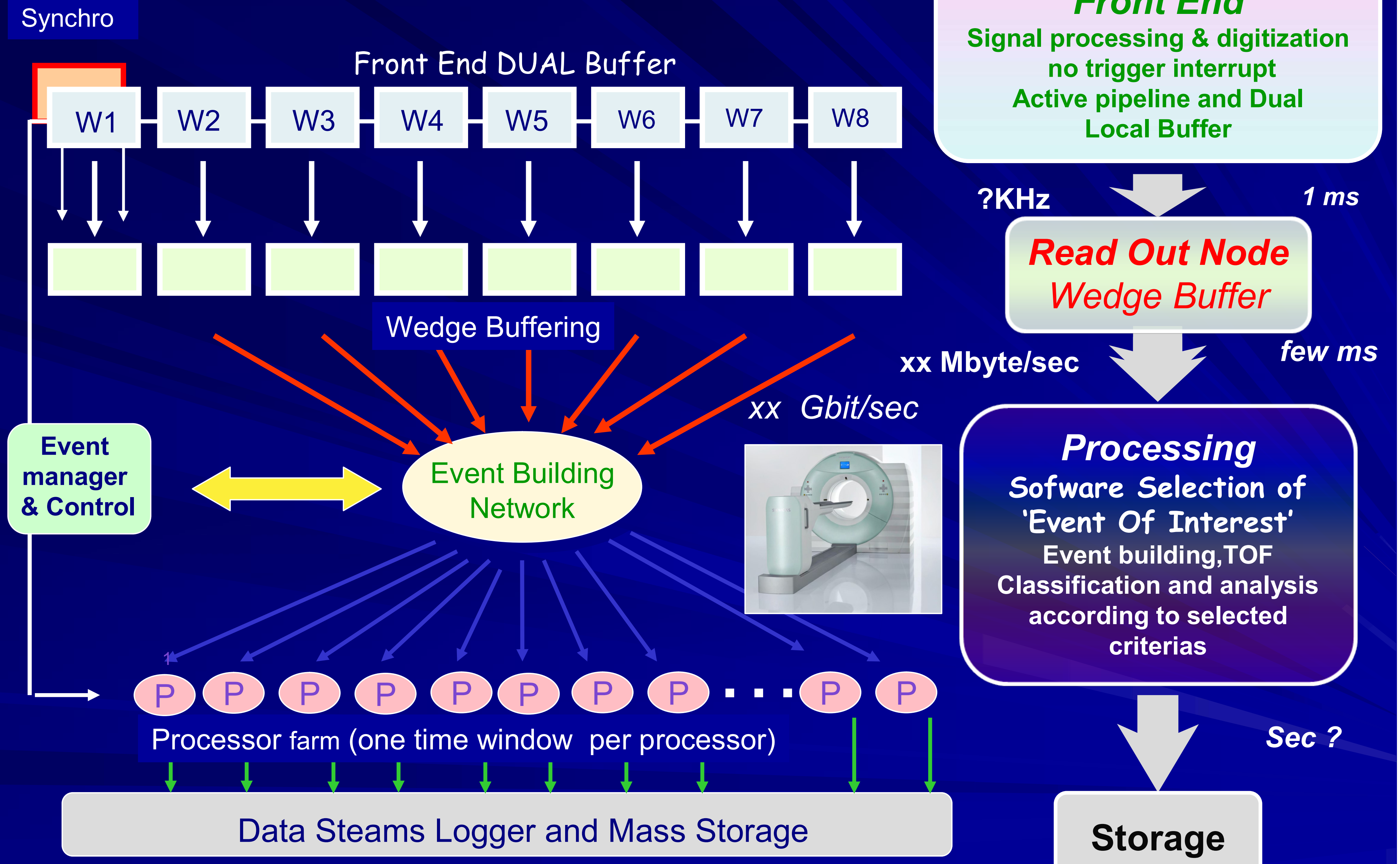
- GPUs: Graphical Processor Units :

highly parallel, multi-threaded, multicore processors with remarkable computational power and high memory bandwidth: promising candidate for fast track fitting at high luminosity

From the video game world

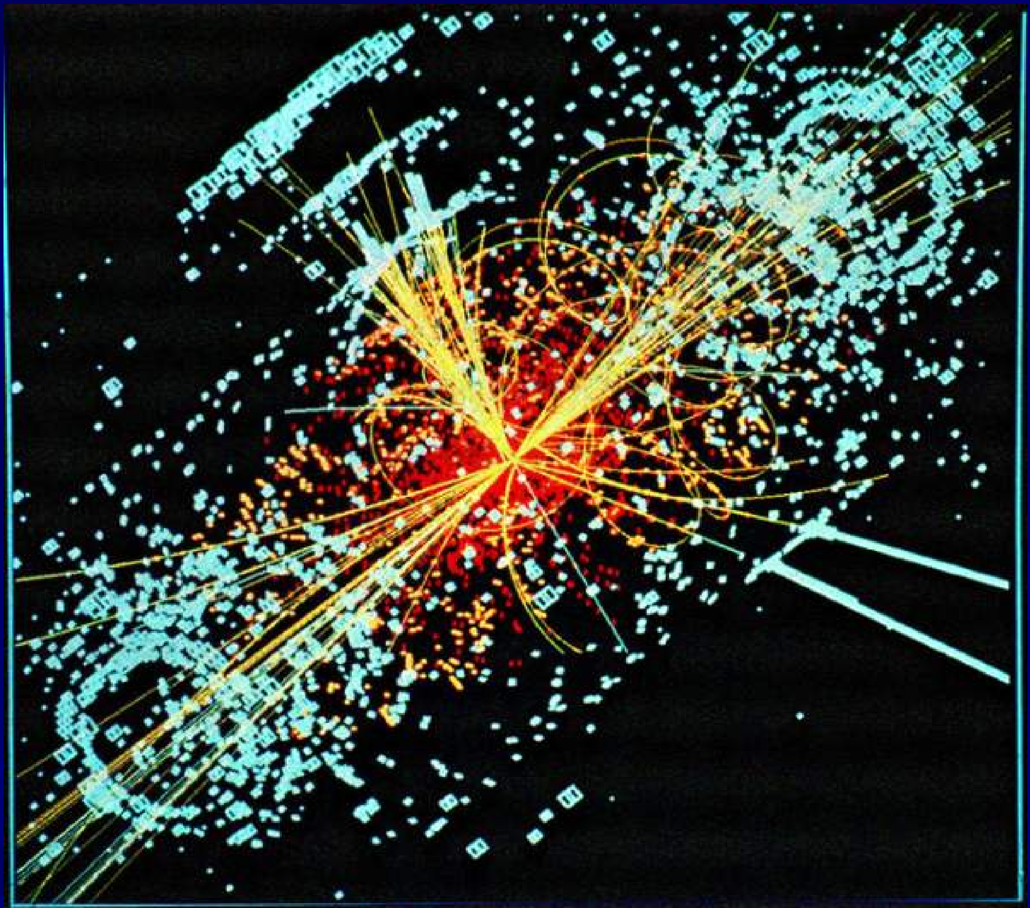


« Advanced » TEP Data Flow

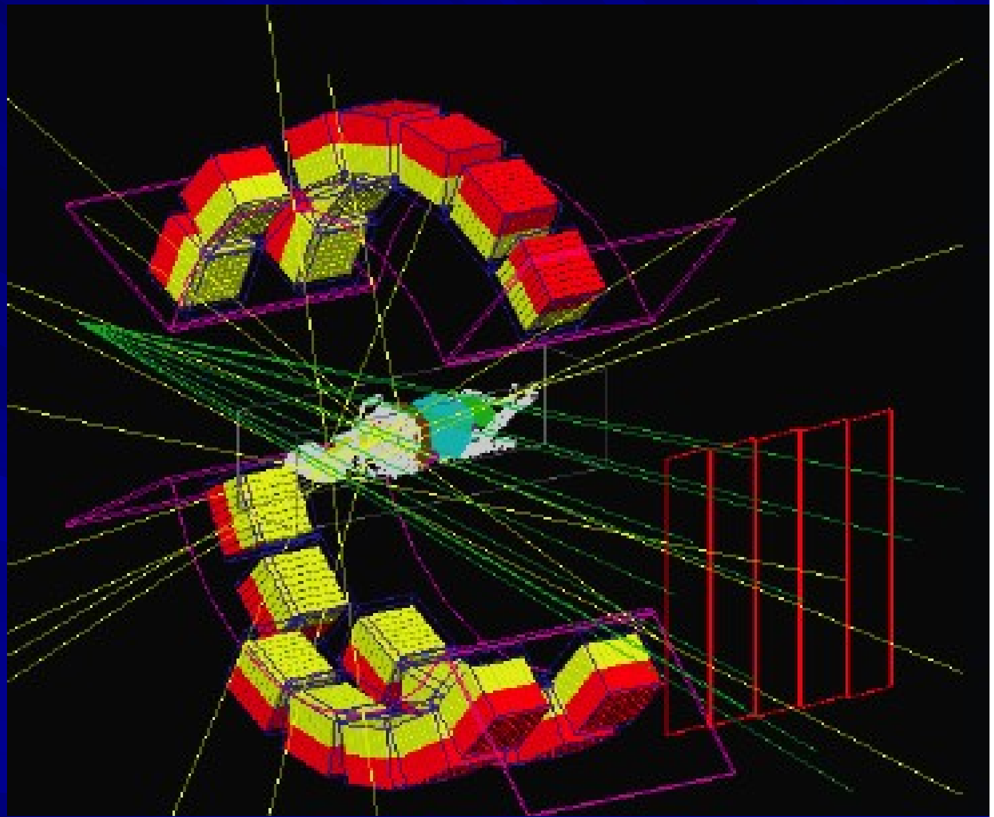


Simulation

Higgs event at LHC (*CMS*) with Geant4



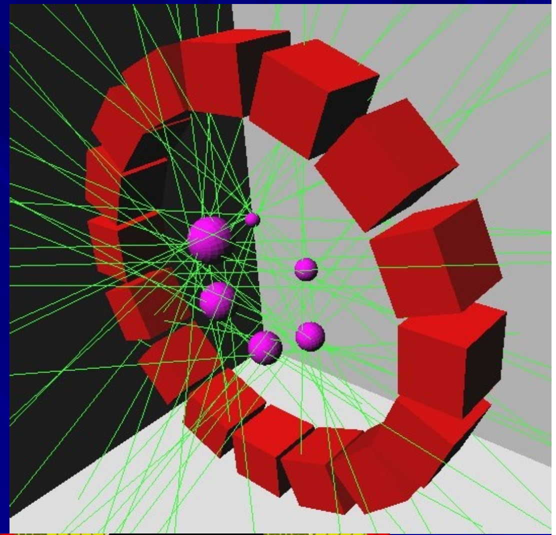
PET with GATE: Geant4 Application for Tomographic Emission

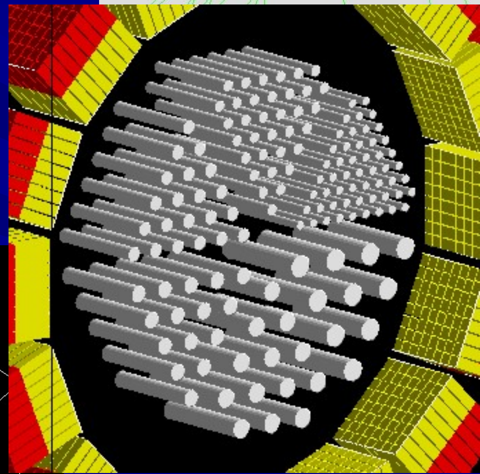


GATE : Geant4 Application for Tomographic Emission

Monte-Carlo simulation allowing to :

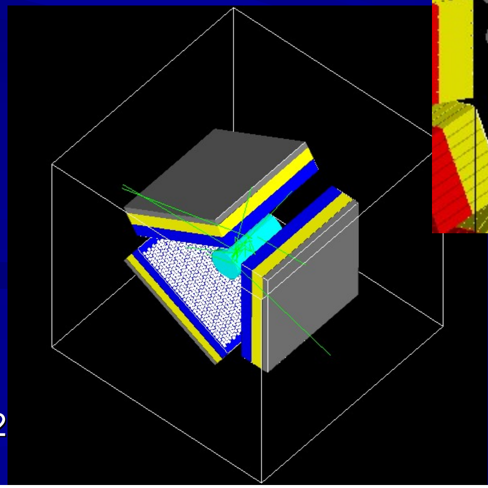
- ✓define geometries
  (size, materials,…)
- ✓ define sources
  (geometry, nature, activity)
- ✓ choice of physical process
  (low energy package of G4)
- ✓ follow track point by point





GATE specificities:

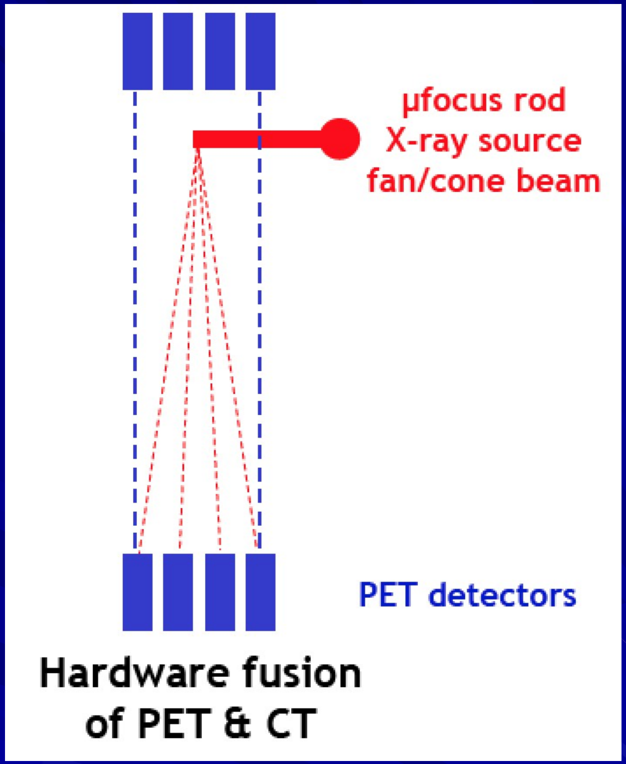
- ✓CERN GEANT4 libraries
- ✓Time modellign
  (sources , movement,random…)
- ✓Script language(avoid C++)
- ✓Code interactivity
- ✓Sharing development



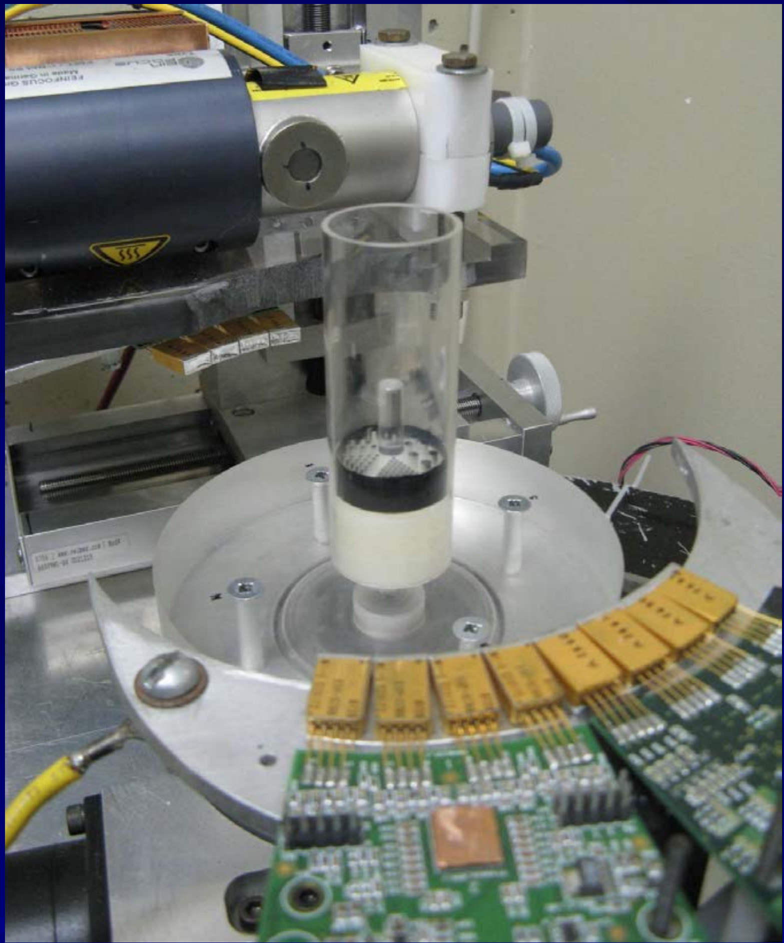
Some ' exotic ideas'

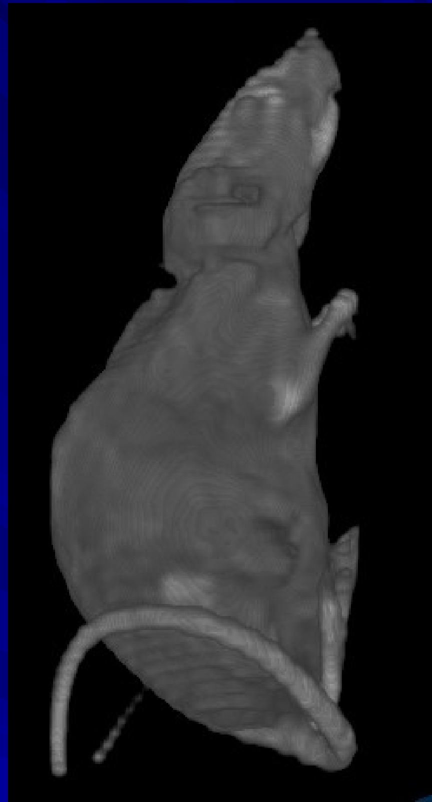
Using PET detector for CT

- **Motivation**
  - Common detection system
  - Reduce cost
  - Concurent (simultaneous,)imaging of anatomy
  - Perfect co-registration of PET and CT image in space and time
    - Correction of motion in CT image
    - Co-registred dynamic image series
- **Challenges**
  - ? Compromise on PET,CT or both
- **Opportunity**
  - PET detector are **photon counting**



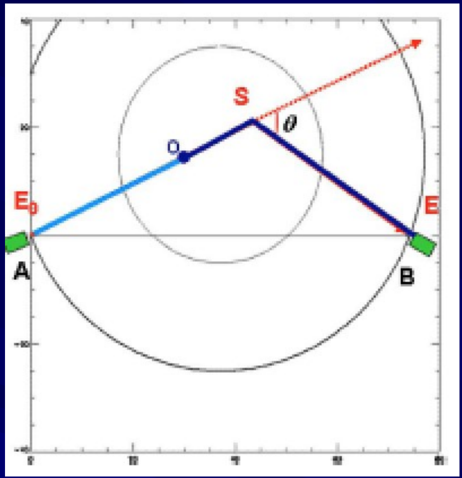
Counting CT imaging - Proof of principle

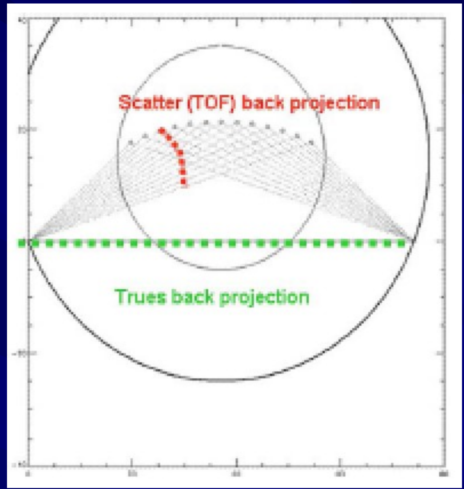


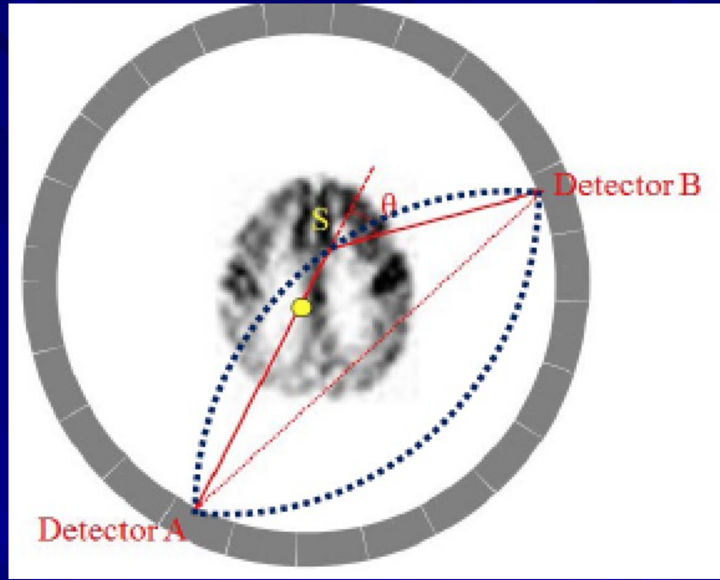


Sherbrook LABPET detector and electronics
R Lecomte courtesy

Scater recovery in TOF-PET







- Backprojection along circular arc
- Iterative reconstruction of both unscattered and scattered events
- Image of trues (unscattered) can be used as *a priori* information
- •Object boundaries allows rejection of one arc
- •LE threshold ~250 keV
- •Very high *energy resolution* required

Some 'today' State of art project

Nuclear Magnetic Resonance

X-rays

MRI

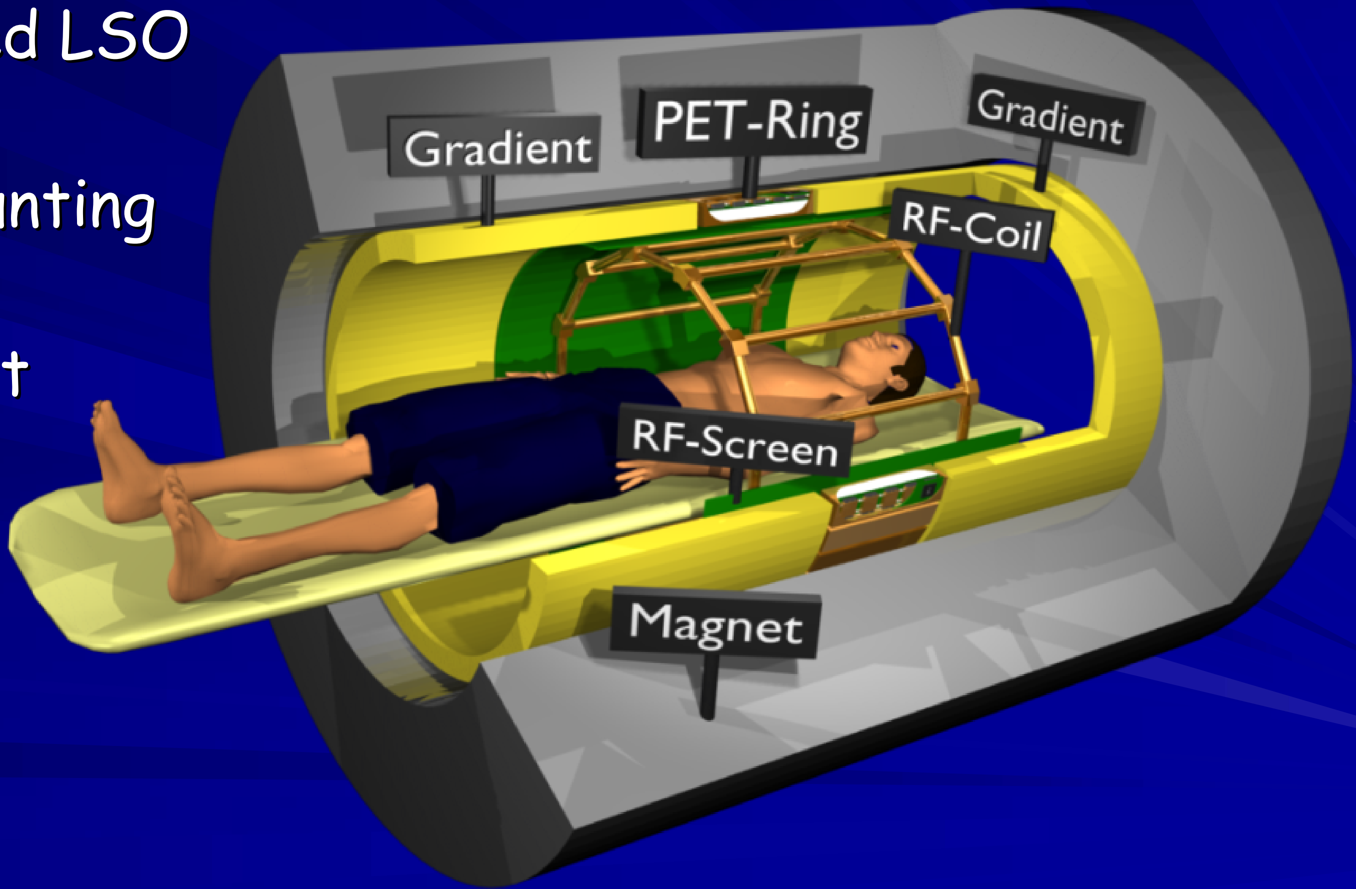
CT

PET

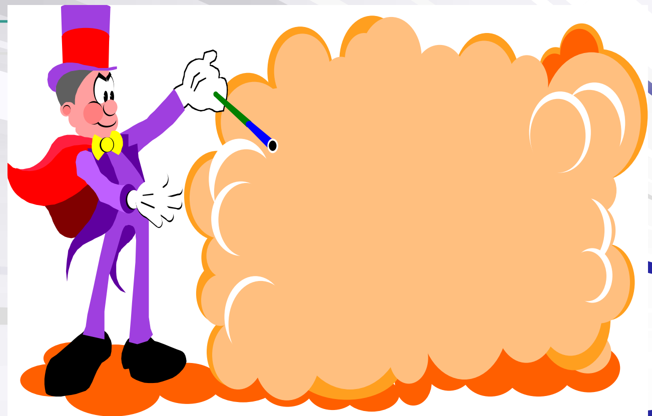
The SUBLIMA project: High resolution TOF-PET / MRI

www.sublima-pet-mr.eu

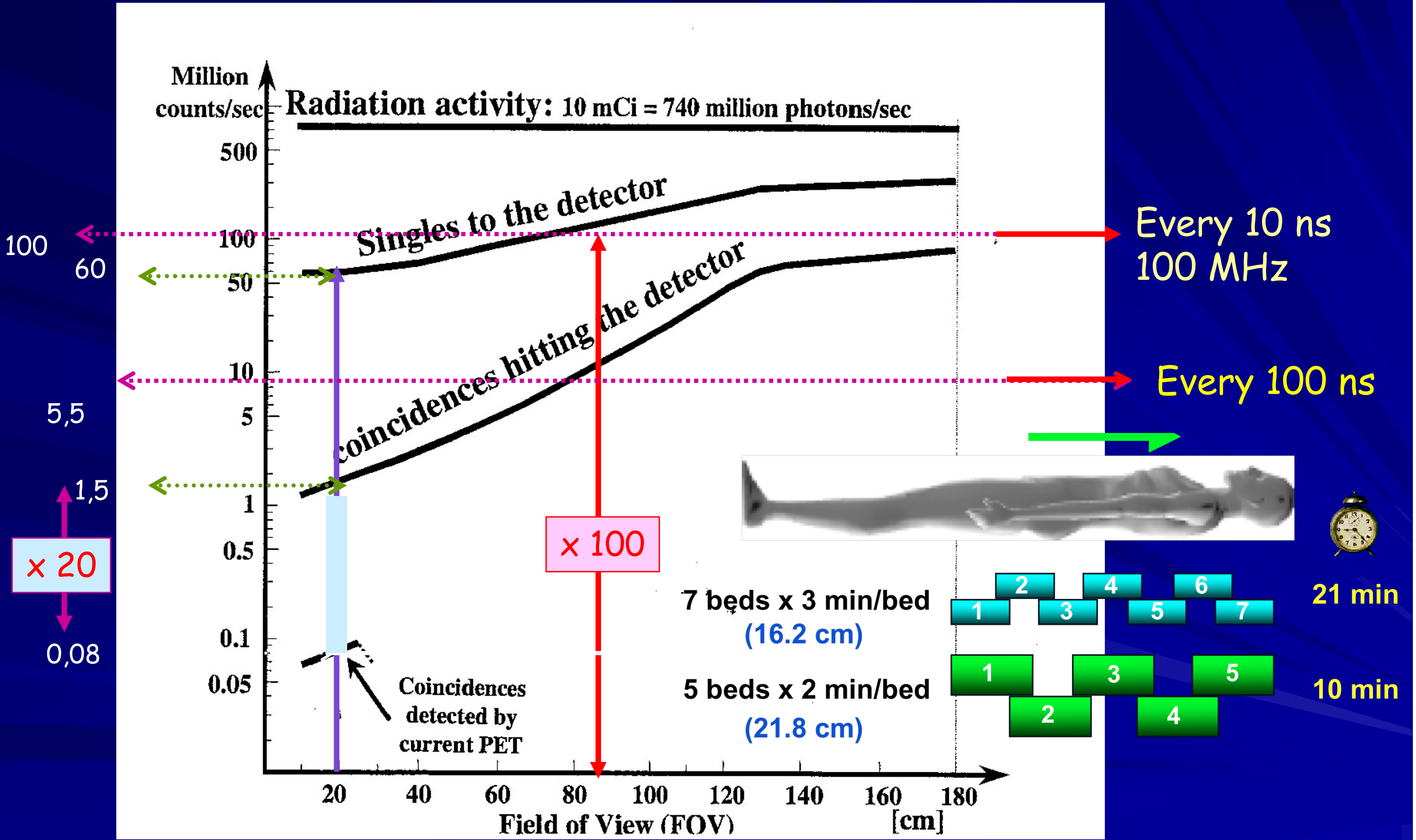
- Monolithic TOF/DOI detector
- Improved performance due to Ca co-doped LSO scintillator,
- Digital photon counting (dSiPM)
- Optimized readout algorithms



The Physician dream
' the minute PET'



Counting rate estimate



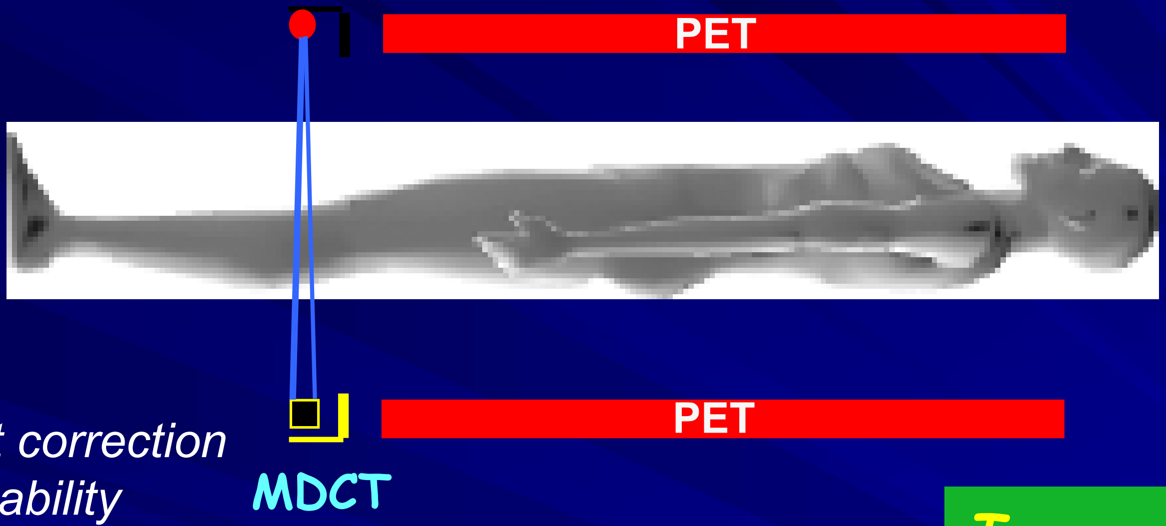
The Physician Dream

Courtesy of D.Townsend

Combined whole-body PET/CT or PET/MR…..

Minute PET/CT

Less dose
Less movment correction
Screaning capability



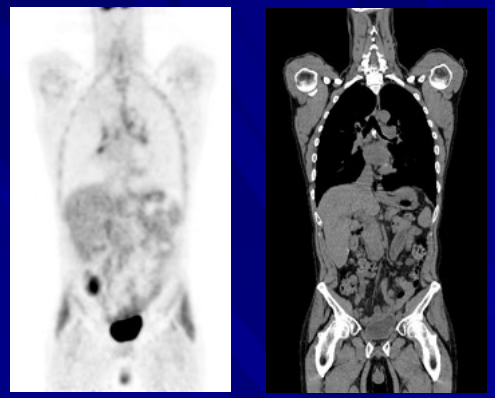
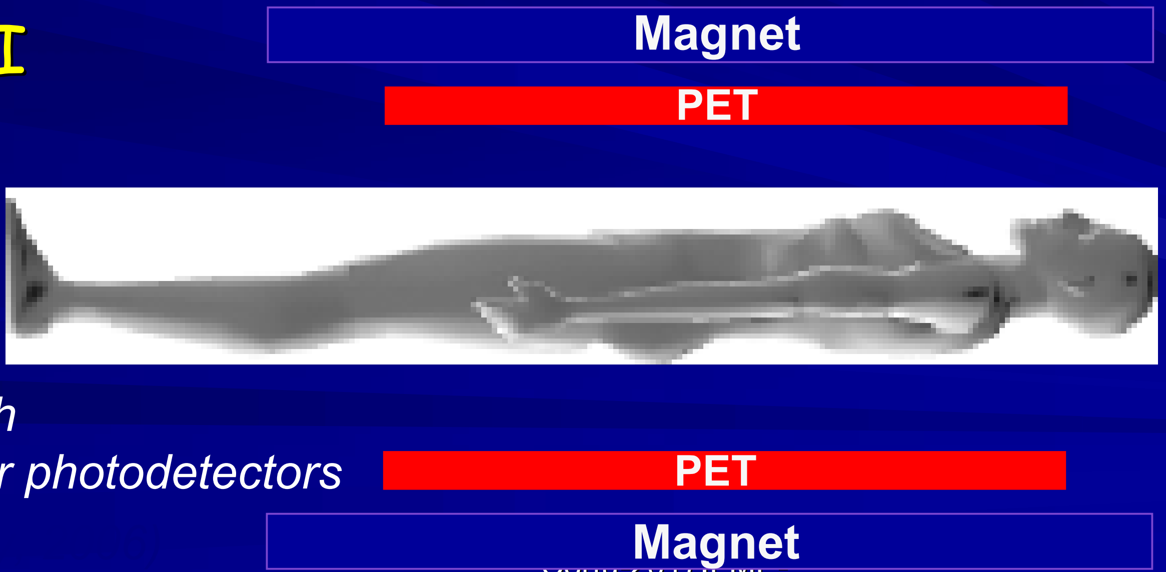
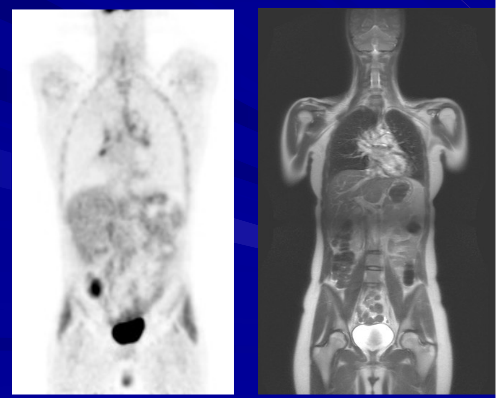


Image In Real Time !

PET/MRI



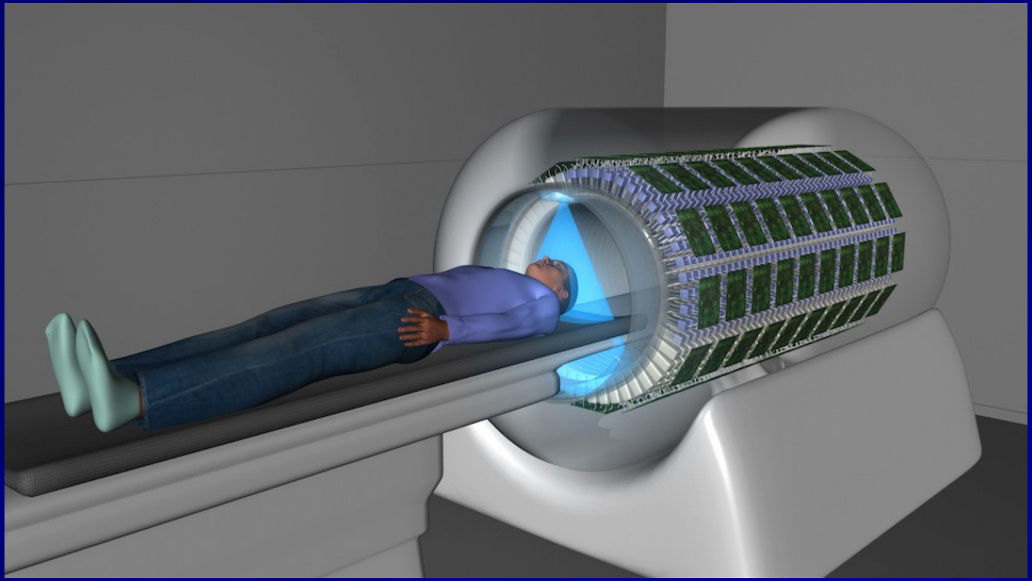
PET Insert with
Semiconductor photodetectors

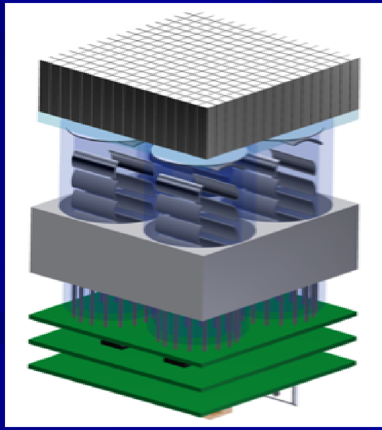


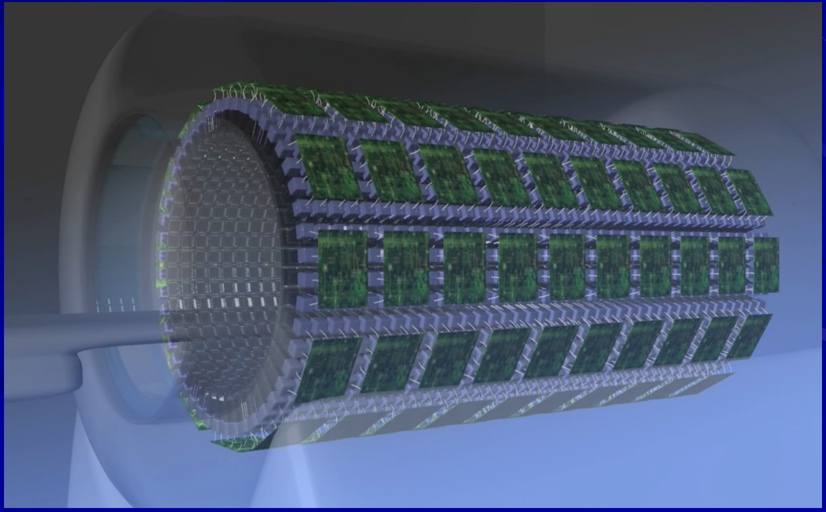
The total body 'explorer' project

Davis,LBL,Upenn

- Modular "Block" Detectors
- ~3.1 x 3.1 x 20 mm L(Y)SO
  - 880 kg of L(Y)SO!
- PMT (possibly SiPM) readout
- Time of flight and 1-bit DOI
- 40 rings, 48 detectors/ring
- ~78.6 cm ring diameter
- 215 cm axial FOV
- OpenPET electronics

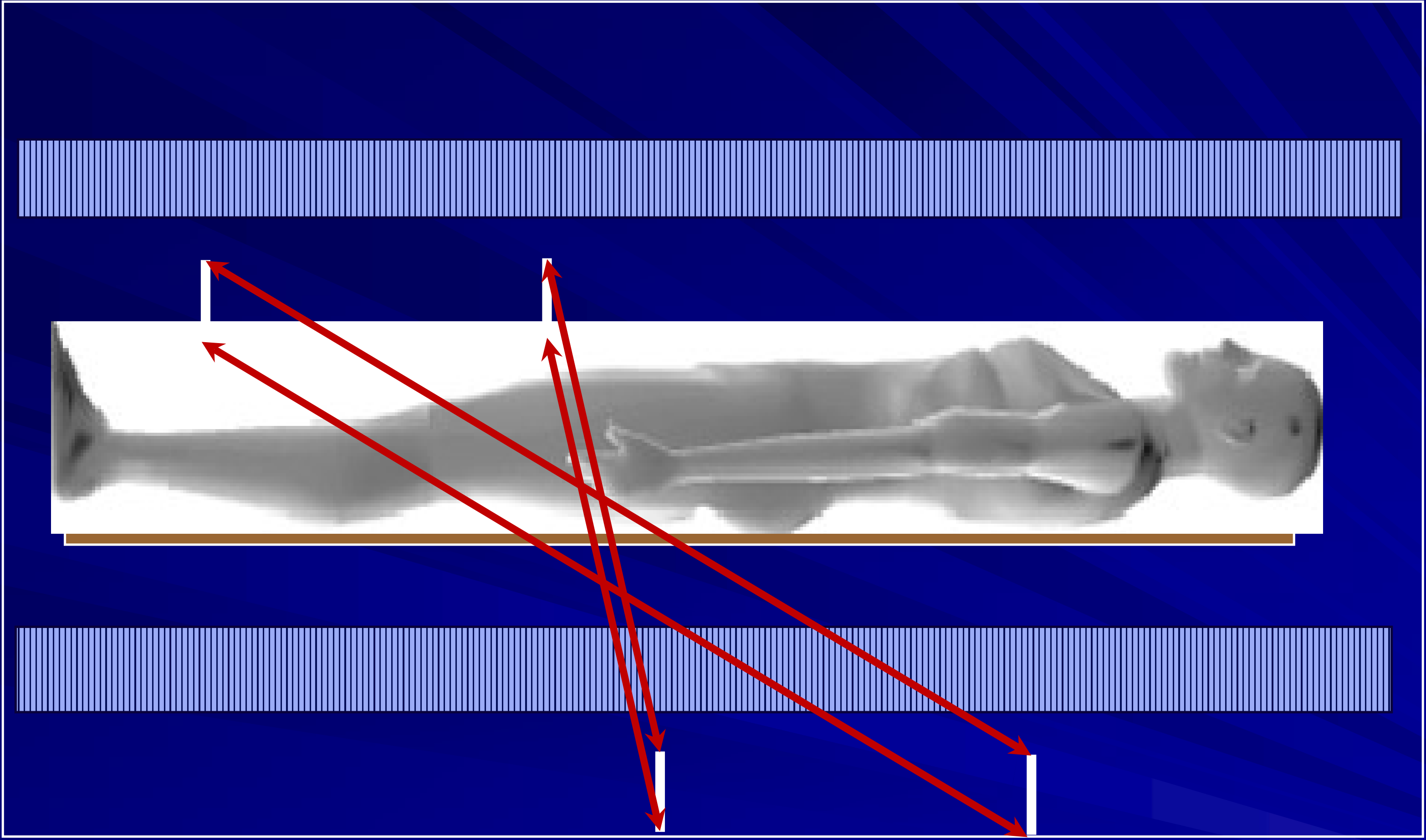






S. Cherry, J3-7
NSS-MIC 2013 Seoul

Estimated data production



Singles: 164 MHz
Prompts: 47 MHz
Randoms: 34 MHz

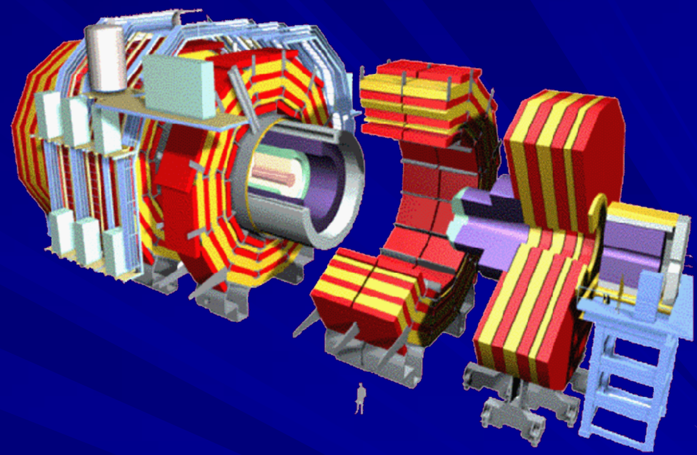
DOI needed

The Challenge

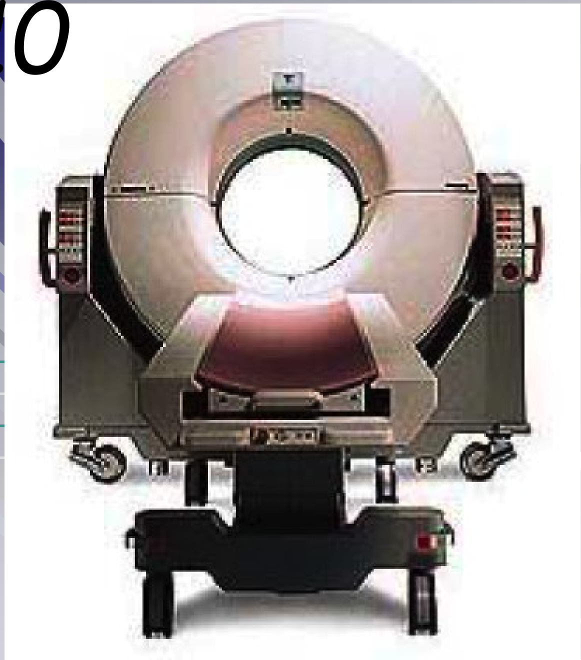
Total-Body "Explorer" Project

- Very large number of channels (20 → 2m FOV)
  ~ 500 k channels (2x2 mm2 pixels)
- High trigger rate ~ 10 MHz
  (10 mCi, 20% sensitivity)
- High data rate
  ~ 10 Gbyte/s (1 kbyte event size)
- Large number of events
  - *160 x 160 x 1000 image matrix*
  - Large data volume per image
  - 1 billion events

  Real Time analysis
- Simultaneous merging of multimodality data
  – CT- MRI



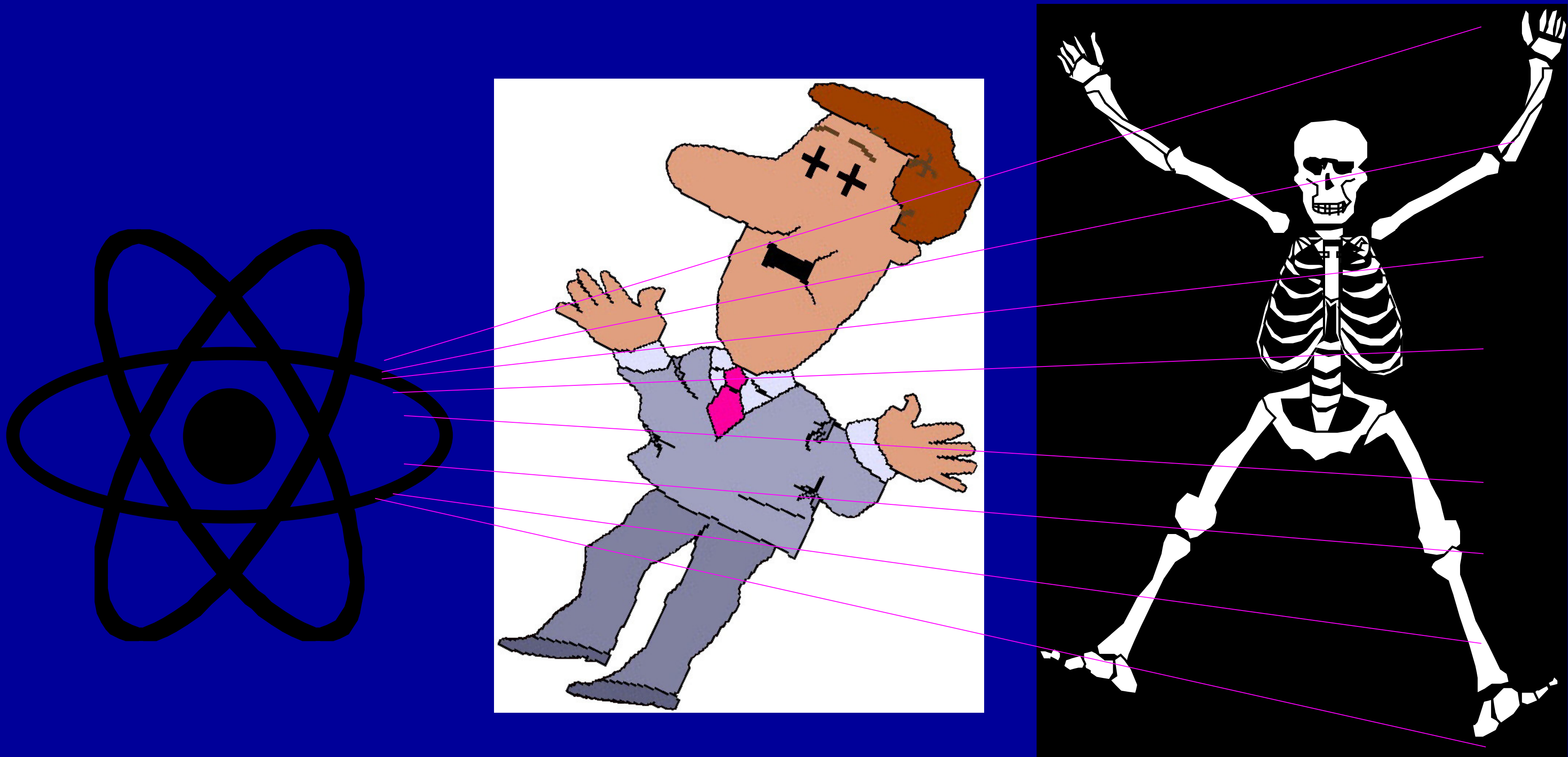
Looks like



Radiography
X Ray imaging

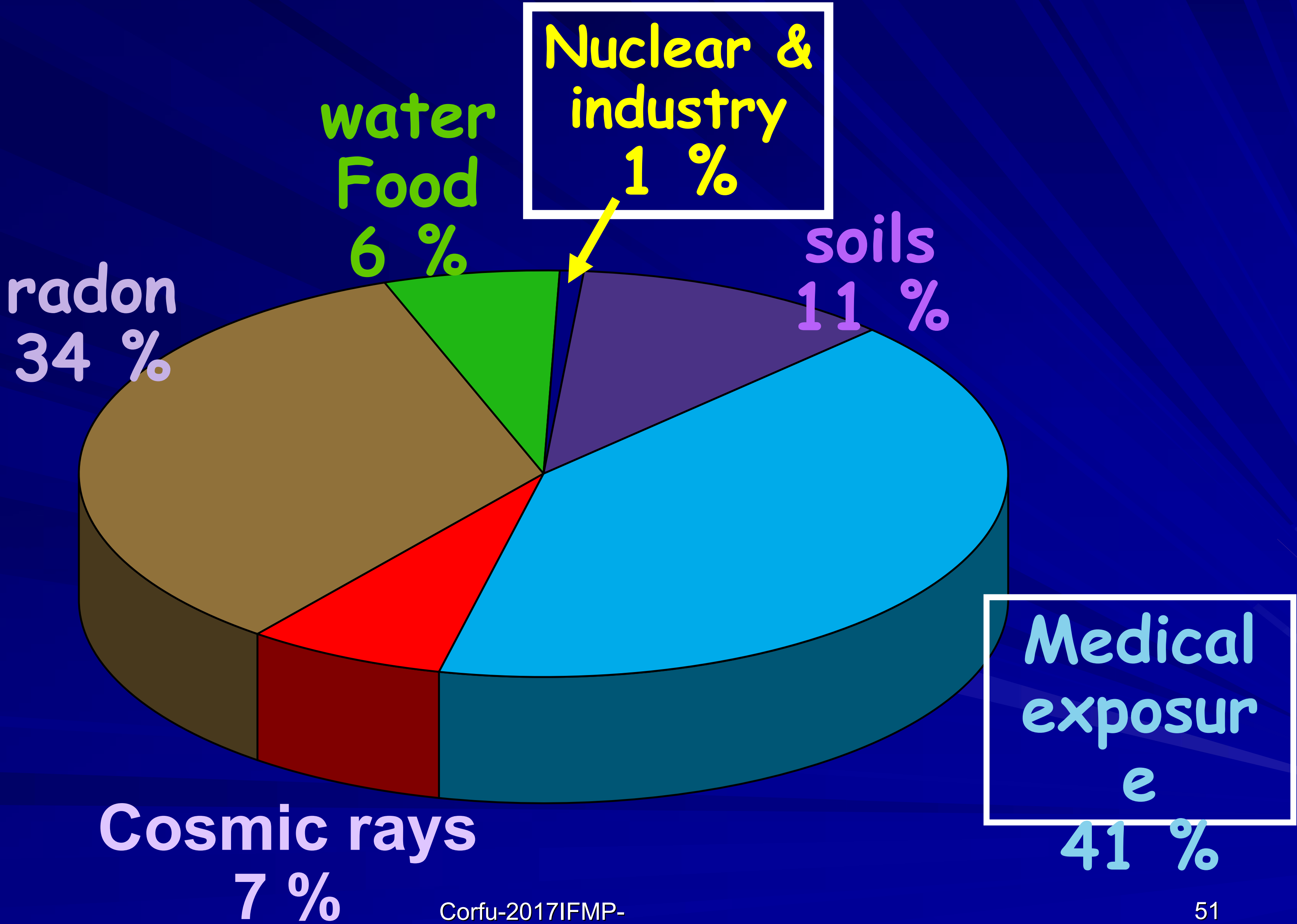
CT

Patient Radiation Dose is Limited!



- Image Noise Is Limited by Counting Statistics
- Cannot Increase too much Source Strength

Natural versus medical irradiation



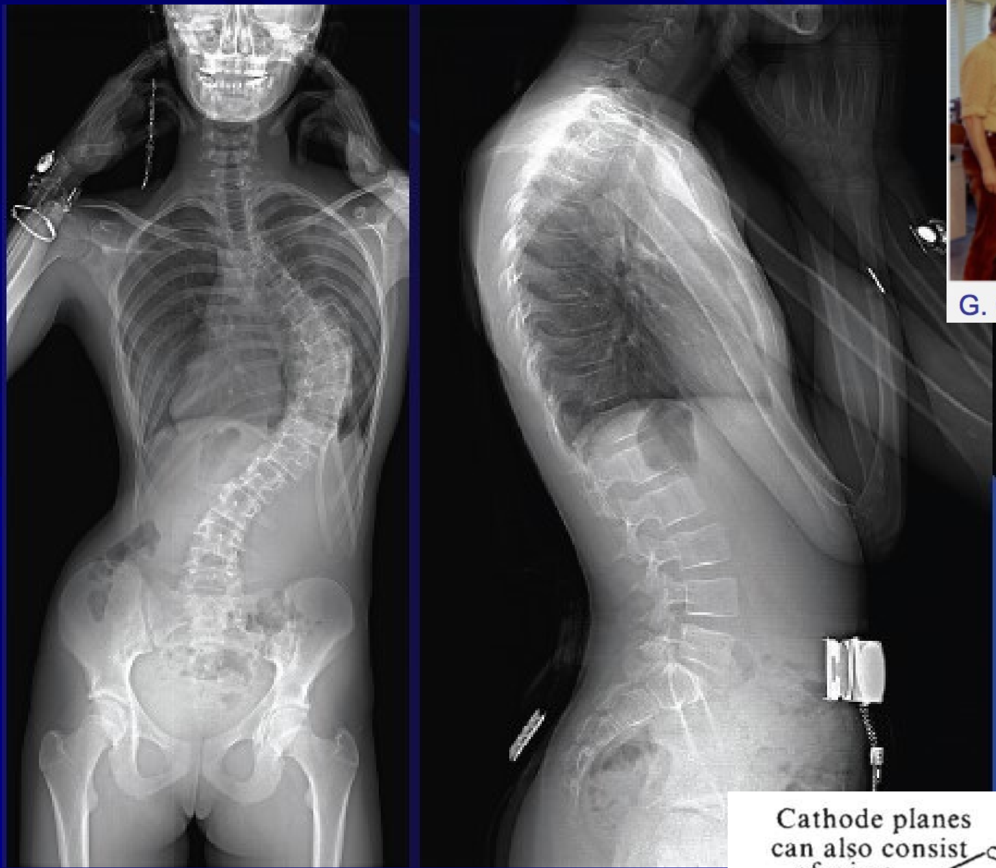
Exposure for radiological exams

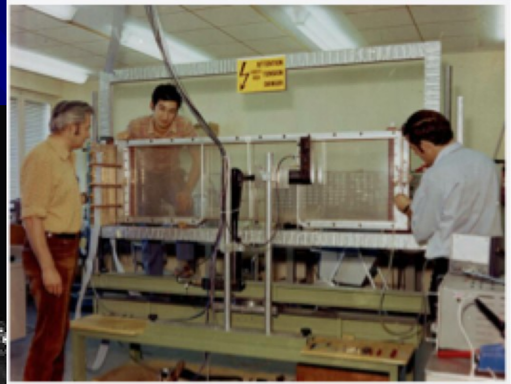
- Some examples

organ	dose skin mGy	effective dose mSv
Thorax, face	0,2 - 0,5	0,015 - 0,15
Lumbar region	4 - 28	1,5
Urography	40 - 60	3
Brain scan	7 - 78	1
Whole Body scan	30 - 60	4 - 10
Mammography	7 - 25	0,5 - 1

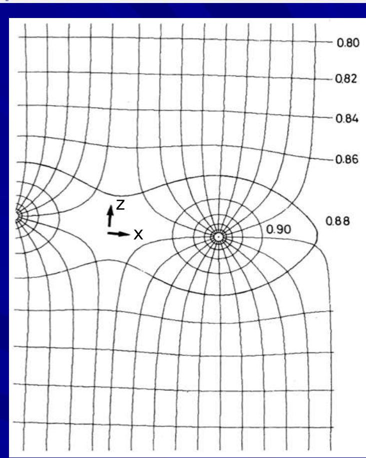
The 1970's dream : Digital radiography with MWPC
A tribute to George Charpak

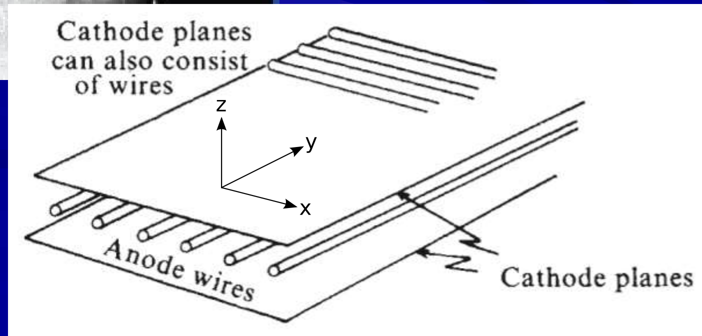
- With 10 time less dose





G. Charpak, F. Sauli and J.C. Santiard



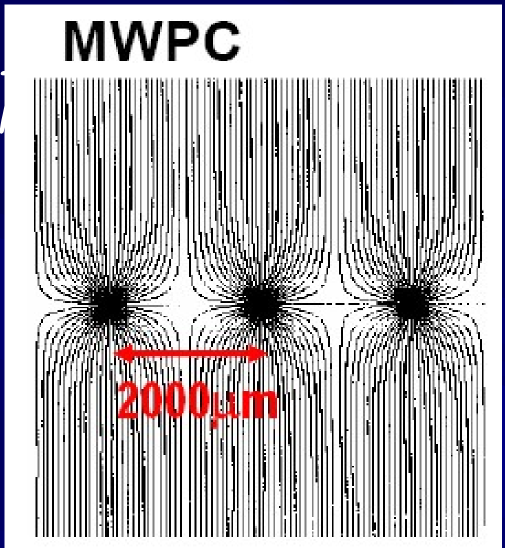


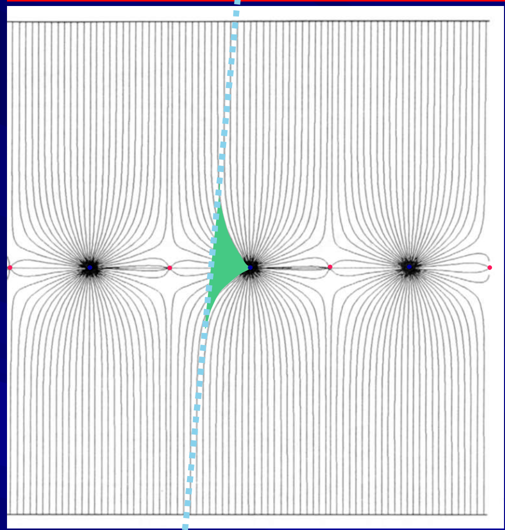
From MWPC's to MGPD's

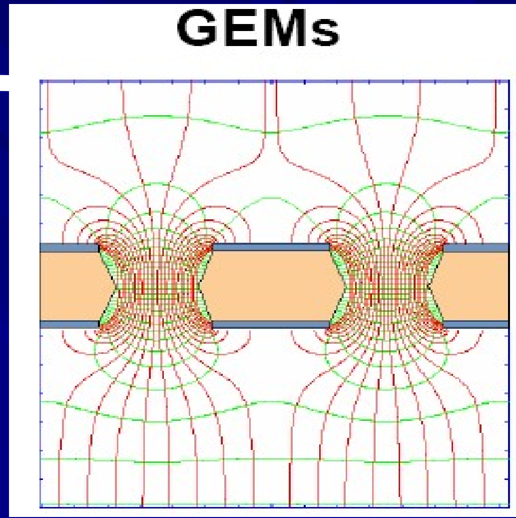
MGPD

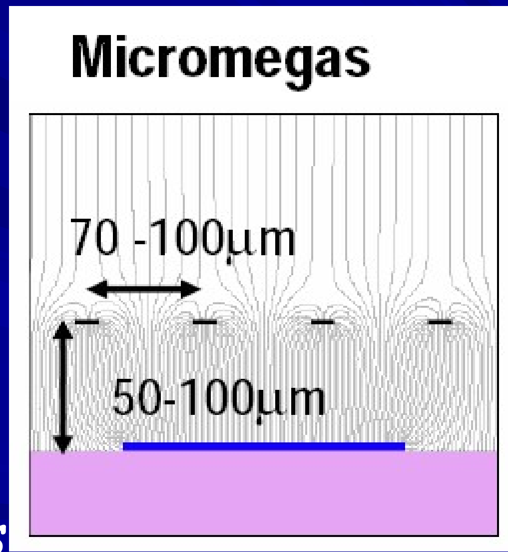
MWPC

Drift Chamber









1975 - 1995

UA2-LEP

Multiwire Proportional Chamber

Georges Charpak 1968

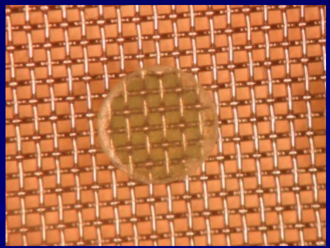
1990 -

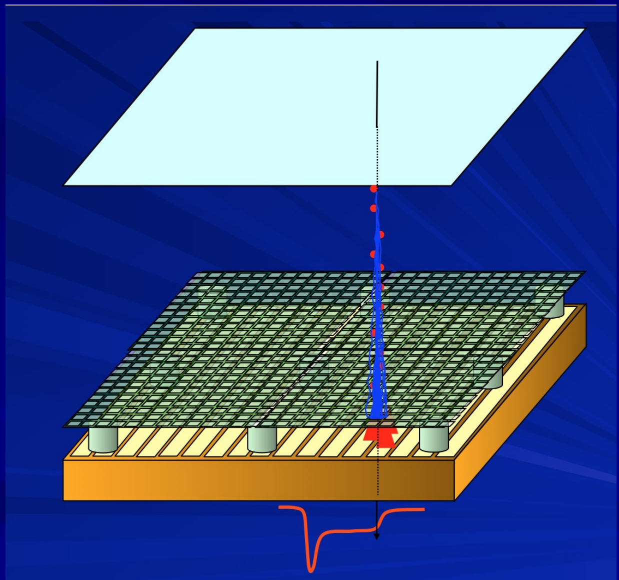
GEM F.Sauli)

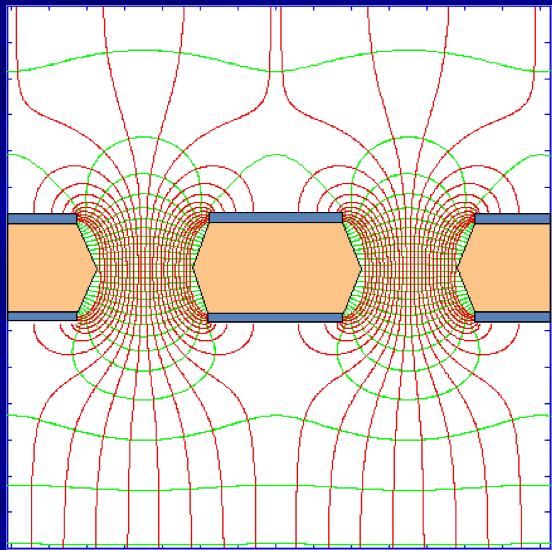
Micromegas Y. Giomataris

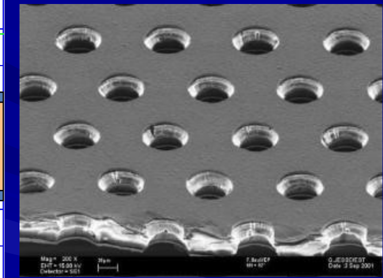
MPGD

- From 1988-1998 Micro-technologies and etching techniques allowed development of Micro Pattern Gaseous Detectors
  - MICROMEsh GASeous Structure (MICROMEGAS)
    - Thin gap Parallel Plate Chamber: micromesh stretched over readout electrode.
  - Gas Electron Multiplier (GEM)
    - Thin, metal-coated polymer foil with high density of holes, each hole acting as an individual proportional counter.









To summarize X Ray imaging

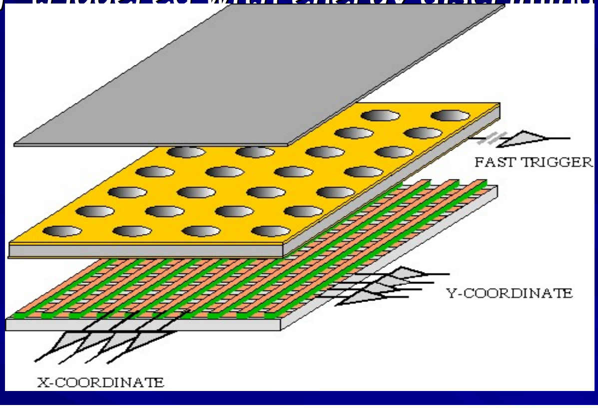
Wire Chamber Radiography:

Position resolution ~ 250 μm

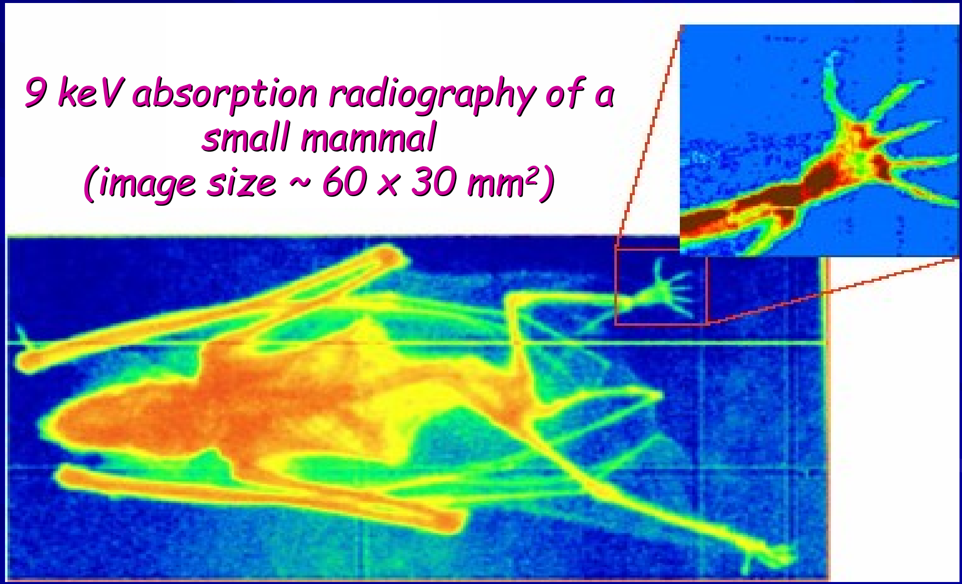
A. Bressan et al, Nucl. Instr. and Meth. A 425(1999)254
F. Sauli, Nucl. Instr. and Meth.A 461(2001)47
G. Charpak, Eur. Phys. J. C 34, 77-83 (2004)
F. Sauli, http://www.cern.ch/GDD

GEM for 2D Imaging:

Using the lower GEM signal, the readout can be self-triggered with energy discrimination:



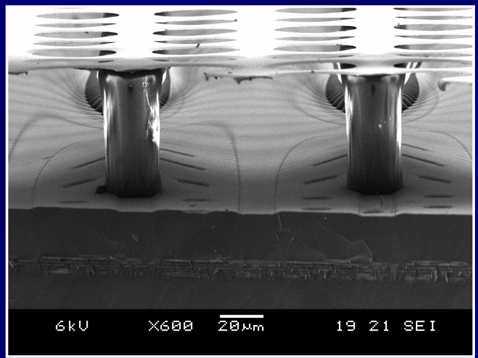
9 keV absorption radiography of a small mammal
(image size ~ 60 x 30 mm²)



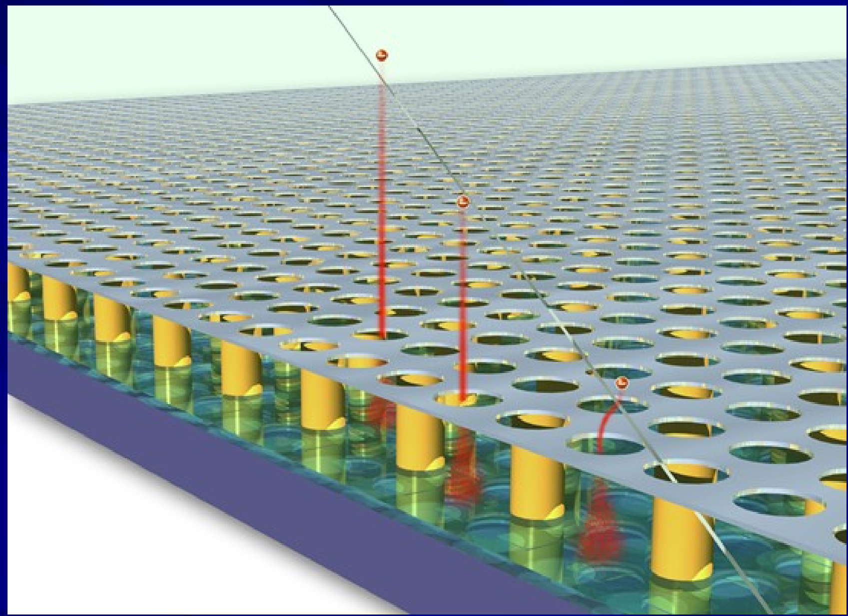
Position resolution ~ 100 μm
(limited by photoelectron range in the gas)

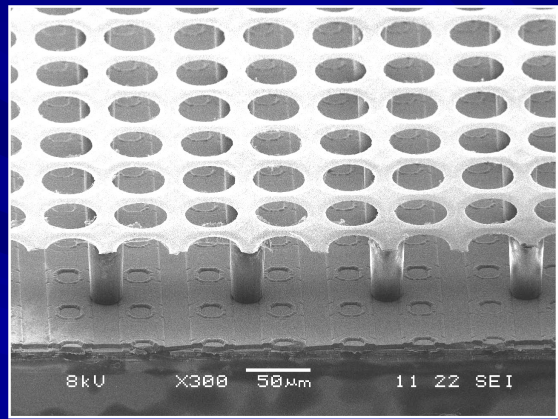
Next → INGRID

- InGrid :integrate the Micromegas/GEM concept on top of a MediPix pixel CMOS chip (Timepix)
  - pixel size: 55 x 55 μm^2
  - per pixel: preamp – shaper – 2 discr. –
  - Thresh. DAQ - 14 bit counter



metalized foil
~100 µm ~1mm





57Cmos Medipix chip

- Use → Large Trackers - Calorimeters @ MI devices

Summary & Conclusions (1)

- HEP has considerable acquired knowledge, expertise and resources that can, when transferred properly, significantly impact the practice of medical imaging and therapy
- A lot of exciting ideas and developments!
  - Should attrack young 'experimentalists'
- Activity that need to be 'promoted' actively outside our community for the benefit of us…in these hard time !
  - HEP is not only hunting the Higgs !

Summary & Conclusions (2)

- It take sometime between the discovery and initial ideas.
- But when the technology is mature, it can make a gigantic breakthrough in the development of a technical device or system
- Collaboration between various scientists and expert is fundamental and the key factor for success.
- Building a community (network) about a specific subjects is the way to integrate students and experts

Final Conclusions

There is a lot to do
Particularly
for students

References
Proceedings
of NSS-MIC
conferences
Transaction on Nuclear Sciences (TNS)
http://www.nss-mic.org/2016/NSSMain.asp

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- D.Townsend (U. Singuapor)
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Thank you for your attention

Photodetector Technologies: A Comparison

Photo detector	PMT	PIN	APD	SiPM
Technology	Vacuum-Based	Solid-State	Solid-State	Solid-State
Gain	High	Poor	Moderate	High
Detection Efficiency	Low to Mo			Low to Moderate
Noise	Low		ate	Moderate
Timing Response	Moderate t			Fast
Packaging	Bulky		act	Compact
Sensitivity to Magnetic Field	Yes	No	No	No
Bias Voltage	>1kV	~50V	100–1000V	~50V

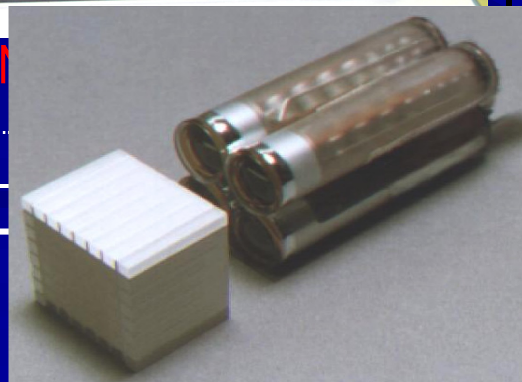
Good choice for both TOF PET, PET/MRI & SPECT/MRI

Photodetector Technologies: A Comparison

Photo detector	PMT		
Technology	Vacuum-Based		
Gain	High		
Detection Efficiency	Low to Moderate		
Noise	Low	Mod	
Timing Response	Moderate to Fast	Sl	
Packaging	Bulky	Con	
Sensitivity to Magnetic Field	Yes	No	N
Bias Voltage	>1kV	~50V	100–

Conventional SPECT & PET detectors has been dominated by the use of PMT.


Courtesy of L. Shao, Philips Medical Systems



Photodetector Technologies: A Comparison

Photo detector	PMT	PIN	APD	SiPM
Technology	Vacuum-Based	Solid-State	Solid-State	Solid-State
Gain	High			
Detection Efficiency	Low to Moderate			
Noise	Low			
Timing Response	Moderate to Fast			
Packaging	Bulky			
Sensitivity to Magnetic Field	Yes	No	No	No
Bias Voltage	>1kV	~50V	100–1000V	~50V

Cannot be used in PET/MRI & SPECT/MRI. The timing response is fast, but may be the limiting factor in next generation TOF PET.

Photodetector Technologies: A Comparison

Photo detector	PMT	PIN	APD	SiPM
Technology	Vacuum-Based	Solid-State	Solid-State	Solid-State
Gain	High	Poor	Moderate	High
Detection Efficiency		n	High	Moderate to High
Noise		ate	Moderate	Moderate
Timing Response		v	Slow	Fast
Packaging	Bulky	Compact	Compact	Compact
Sensitivity to Magnetic Field	Yes	No	No	No
Bias Voltage	>1kV	~50V	100–1000V	~50V

Has low SNR and not suitable for TOF PET.