PET Instrumentation and Innovation

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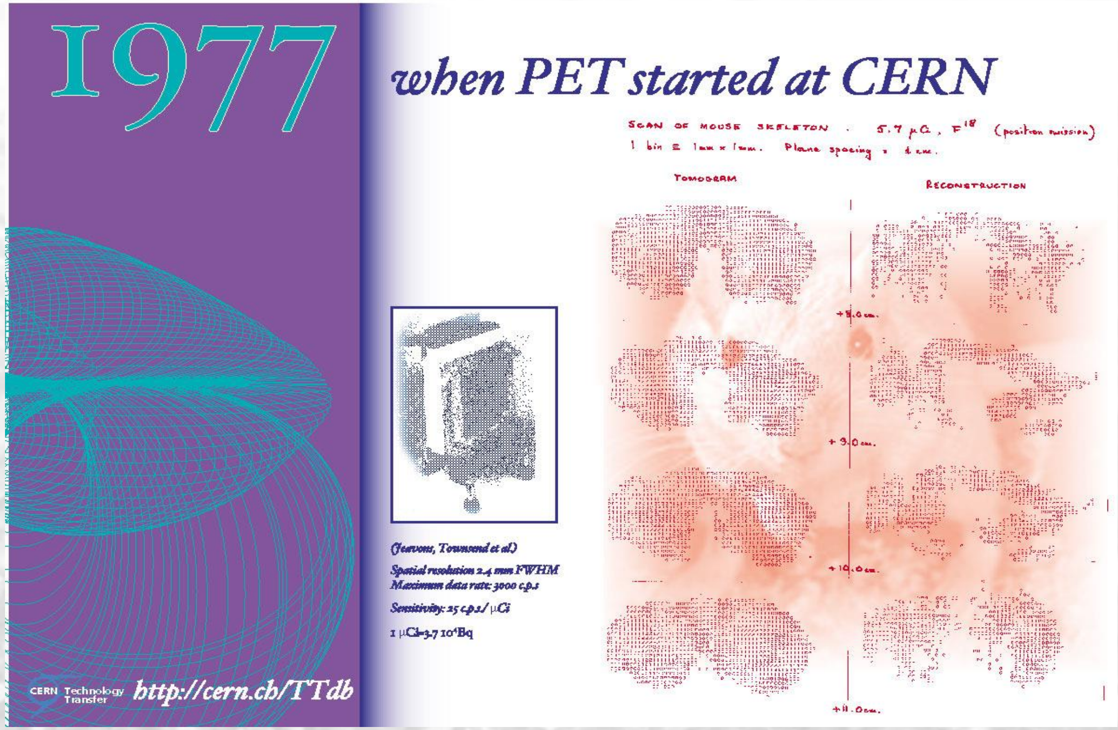
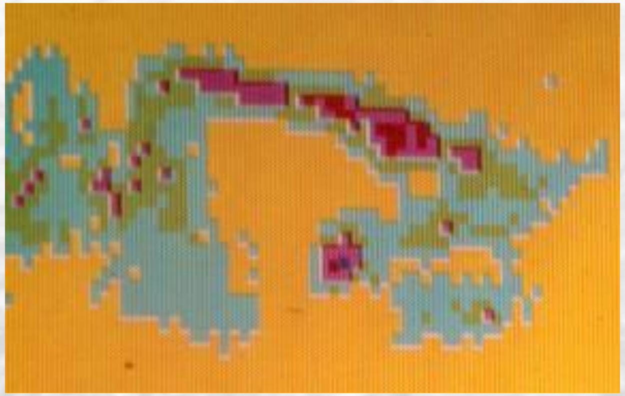
Overview:

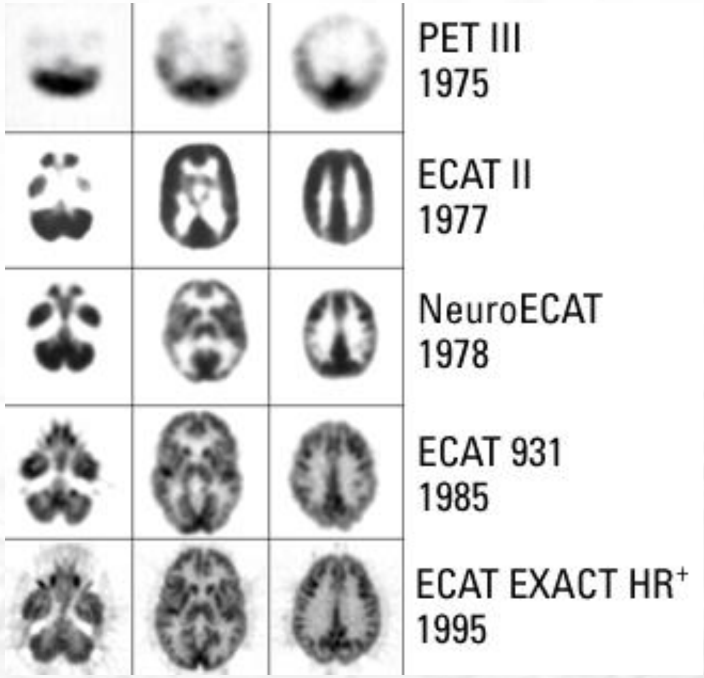
a brief survey of influential advances and changes in PET instrumentation and methods that are a foundation for current and future advances in hybrid medical imaging using Positron Emission Tomography





First mouse image with ^{18}F

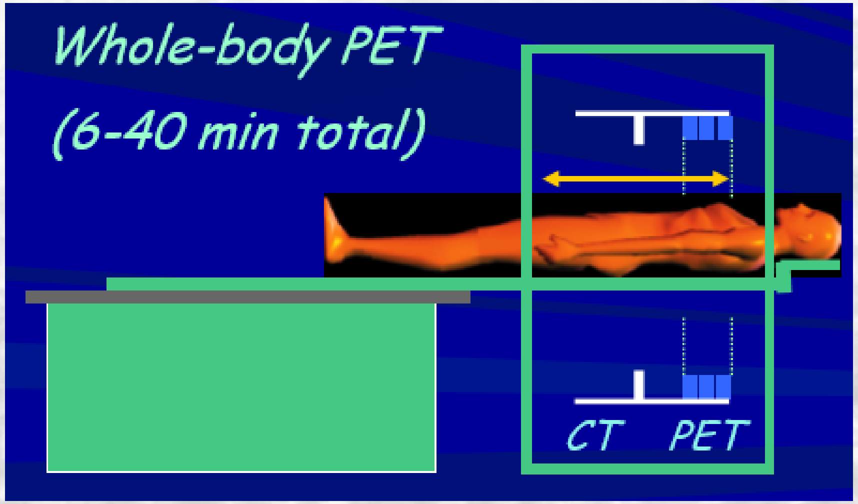
Julie Haglund, haglundj@aol.com, september 2019



1980s: PET studies focused on brain or heart

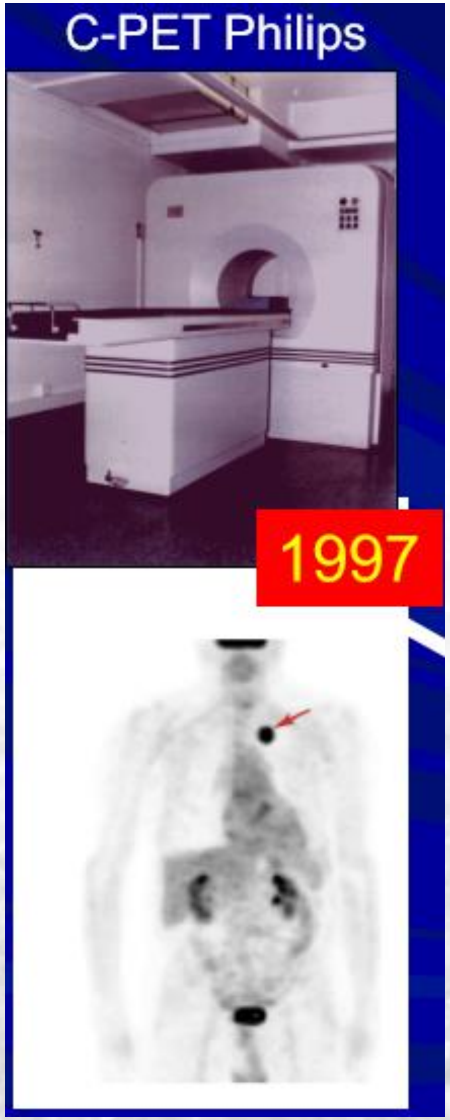
- Design of most PET scanners with axial FOV just large enough for these organs
- One bed position

Influential advance #1:
Move the bed through the scanner and acquire data at a set of contiguous or overlapping bed positions = Whole-body PET



Viewing the whole body opened clinical applications that we know today:

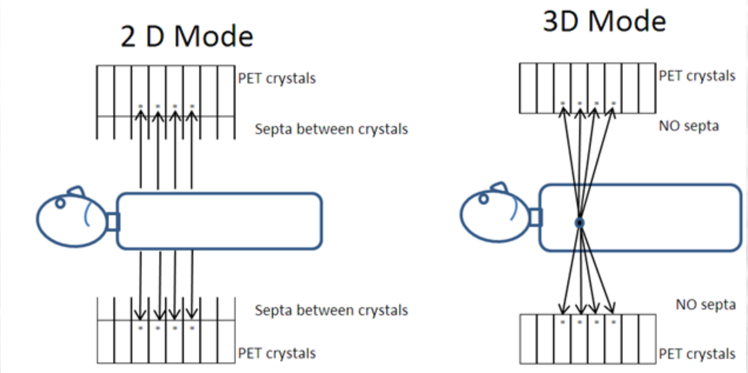
- disseminated disease
- whole-body surveys to find primary tumors & metastasis
- monitoring response to chemotherapy



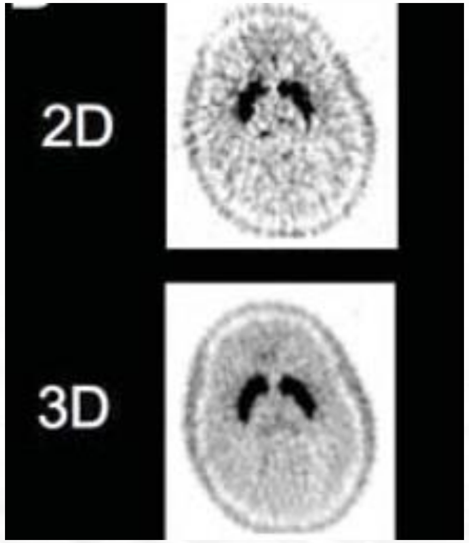
From whole-body imaging to better whole-body imaging

- Detectors are expensive… How can we improve sensitivity?

Influential advance #2:
Remove slice-collimating septa = 3D PET



3D PET means that coincidences can be formed between any detector ring in the PET scanner → ~ 5- to 7-fold increase in sensitivity without (an expensive) increase in the number of detectors



3D acquisition = immediate benefit for brain PET

+/- higher counting rates

- higher scatter fractions

- higher numbers of random coincidences

→ Mild whole-body benefit with slow, low light yield scintillators (BGO)

Even with 3D mode, human PET is limited

- 8 - 12mm resolution for SNR acceptable for diagnostic interpretation
- Really we want 4-6mm resolution, full potential for 3D PET

Workshop Day 5 means we know that BGO is not the end of the story...

Influential advance #3:
New detector materials

1990s: Choosing a detector material for PET

Properties of PET Scintillators

Scintillator	Relative light output (NaI(Tl) = 100)	Decay time (ns)	Thickness for 90% efficiency at 511 keV (cm)
NaI(Tl)	100	230	6.6
BGO	15	300	2.4
LSO, LYSO	70	40	2.7
GSO:Ce	25	60	3.3
BaF_2	28	0.8 (15%), 640 (85%)	5.1
CsF	5	2.5	5.4
$LaBr_3$	150	35	4.9

GSO = gadolinium oxyorthosilicate.

- NaI(Tl) known from γ-camera
- BGO

Dead-time limits 3D applications!

LSO/LYSO

+ dense
+bright
+fast timing resolution
+reasonable energy resolution
+good stopping power for 511keV

LSO/LYSO improved the performance of 3D PET... and is cost-effective because...
(a bright scintillator allows more cyrstal elements to be decoded per PM tube)

Commonly Used PET Scintillators

Material	λ Max. (nm)	Density (g/cm³)	Atten. Length (mm)	Photo-electric fraction	Decay Time (ns)	Light Yield (ph/MeV)	Initial Rate (ph/ns/MeV) I_0 / τ_d
BGO	480	7.1	11	43%	300	8,200	27
LSO:Ce[2]	420	7.4	12	34%	40	32,000	800
LYSO:Ce[2]	420	7.1	12	34%	40	32,000	800
GSO:Ce	440	6.7	15	30%	60	9,000	150
LuAP:Ce[2]	365	8.3	11	30%	17	11,000	647
$LaBr_3$:Ce[1]	380	5.3	22	14%	16	63,000	3,938
LuI_3:Ce[1,2]	470	5.6	18	29%	36	76,000	2,111
LuAG:Pr[2]	310	6.7	13	28%	22	23,000	1,045

[1] *Is hygroscopic*

[2] *Has natural radioactivity*

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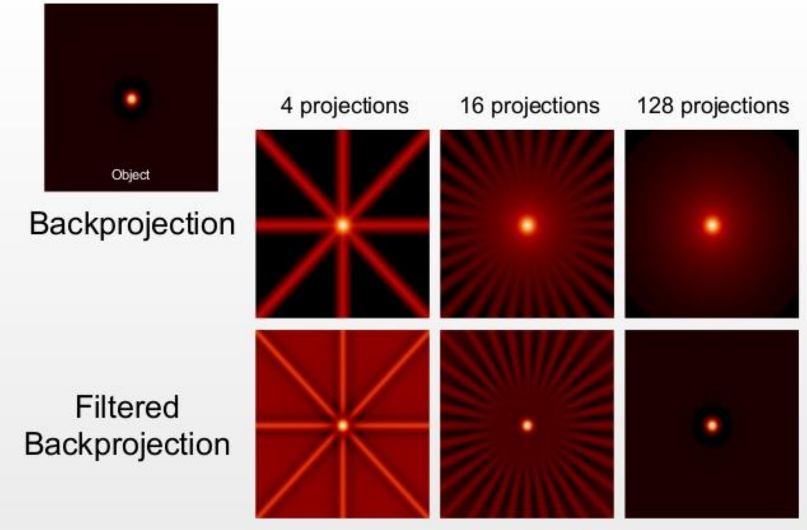
Evolution of Data Reconstruction in PET

Making PET clinically robust generates data

- single organ → whole-body
- 2D → 3D
- Fast, bright crystal materials acquire more counts



Filtered backprojection methods

+ linear
+ computationally fast
- artifacts caused by a low statistics (both in the original emission data and possible contributions from normalization, attenuation correction, and randoms correction)
- artifacts caused by sampling

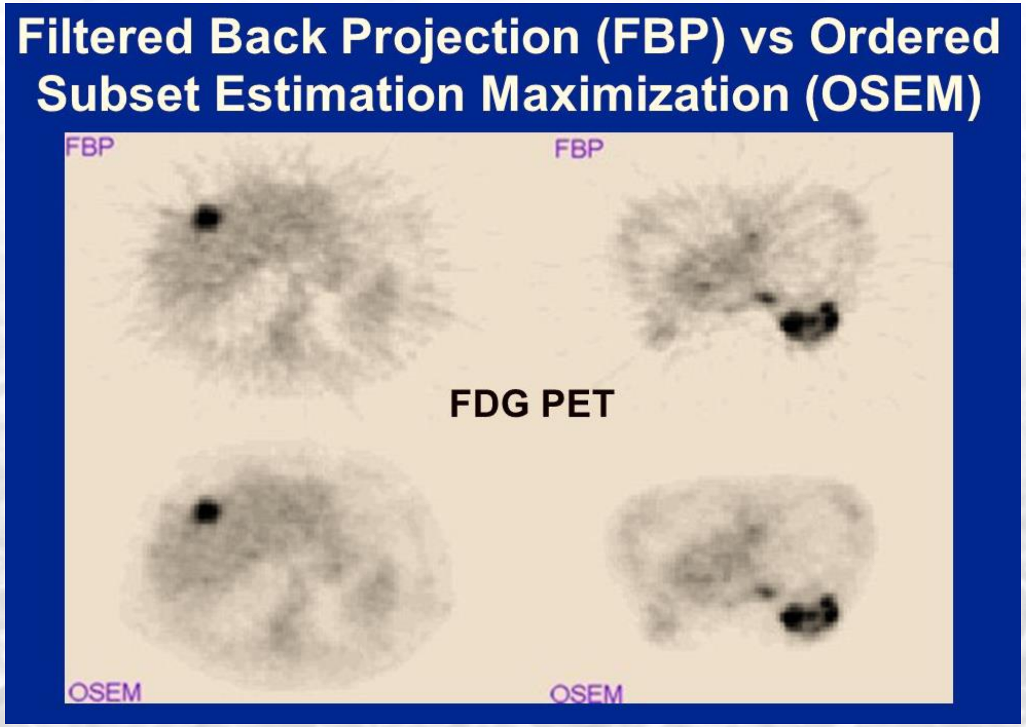
+/- simplistically model the scanner geometry with perfect point-like detectors

+/- give the same weight to projection elements containing large numbers of counts as to those containing few counts

Influential avane #4:
Iterative Reconstruction Algorithms

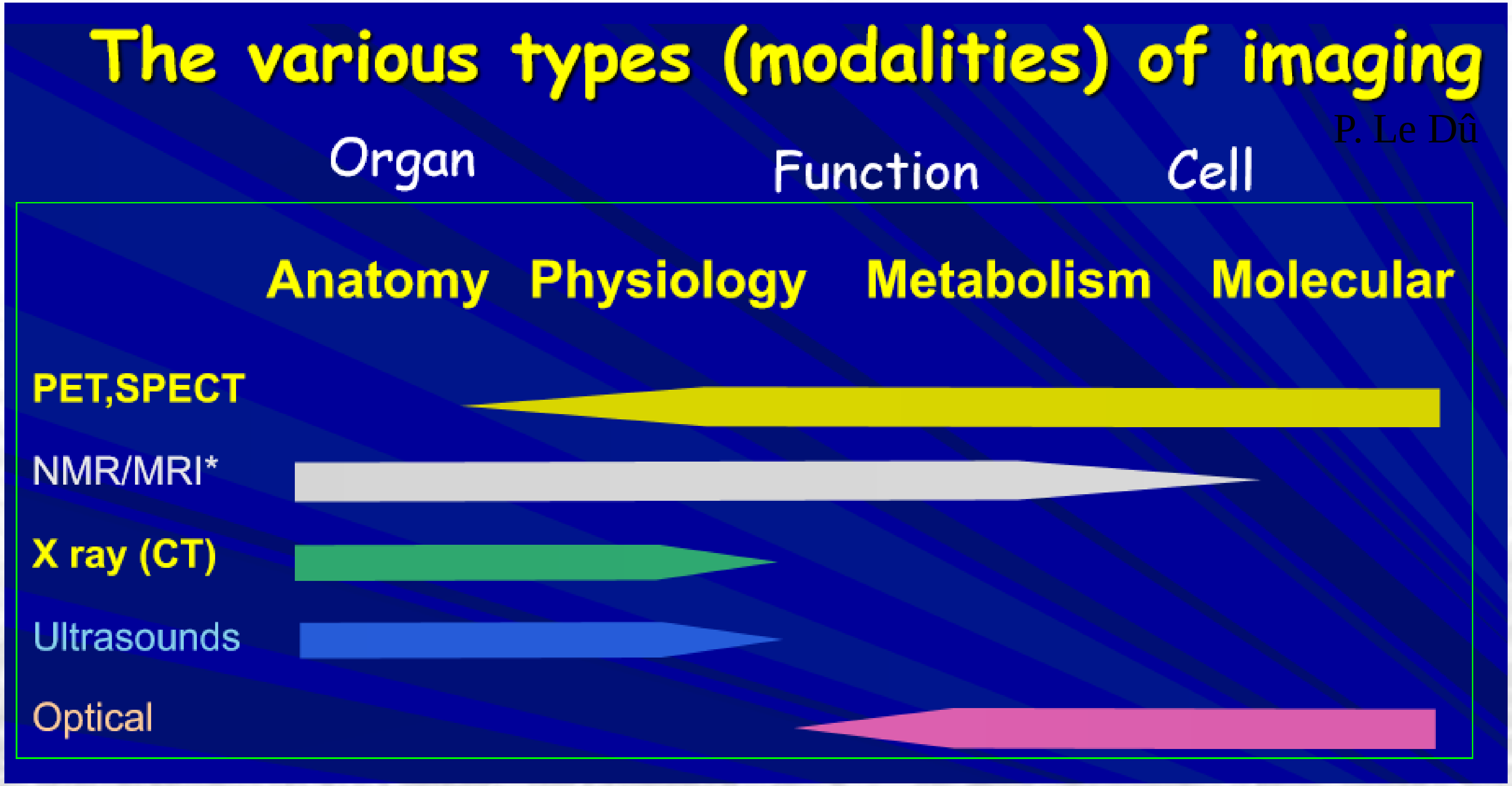
Favorable tradeoff between SNR and spatial resolution

- Weight data according to statistical quality
- Accurately model the geometry of the
- imaging system
- Account for inter-crystal scatter, DOI,
- nonuniform sensitivity along LOR
- Corrections for attenuation and normalization
- Eliminate streak artifacts



"Acceptably" computationally expensive
Practical for routine use

The workshop is Hybrid Imaging, but do remember our humble origins!



PET is functional imaging that sees metabolism with 5mm resolution

- ***Molecular Imaging:*** *in vivo, non-invasive, functional.*
- ***What Can PET Measure?***
  - *Blood flow ($H_2{}^{15}O$)*
  - *Oxygen metabolism ($^{15}O_2$)*
  - *Glucose metabolism (^{18}FDG)*
  - *Fatty acid metabolism (^{11}C-acetate)*
  - *Protein synthesis (^{11}C-methonin*
  - *DNA synthesis / Gene expression (^{18}F-FLT)*
  - *Neurotransmitter synthesis (^{18}F-FDOPA)*
  - *Receptor/ protein concentration (^{11}C-AFM)*
  - *Receptor occupancy*

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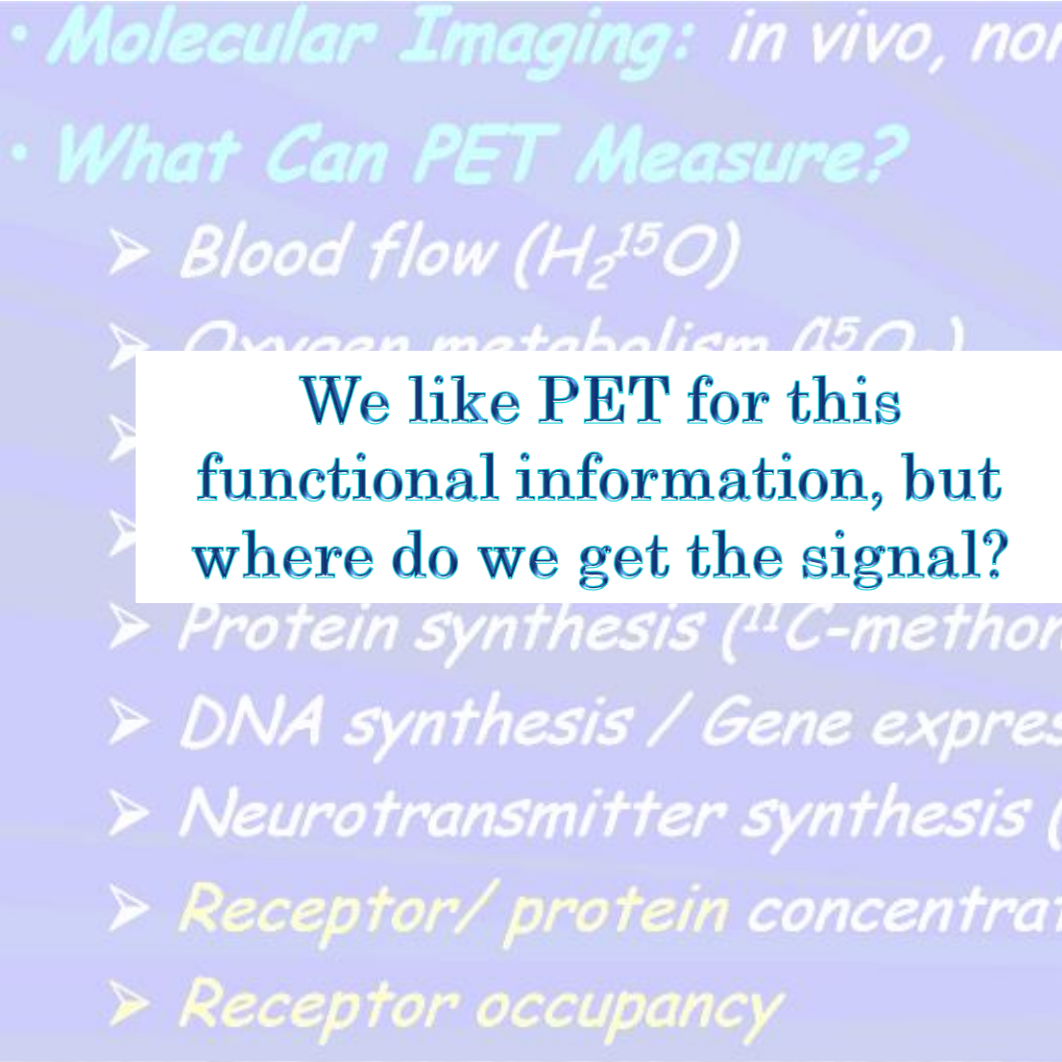
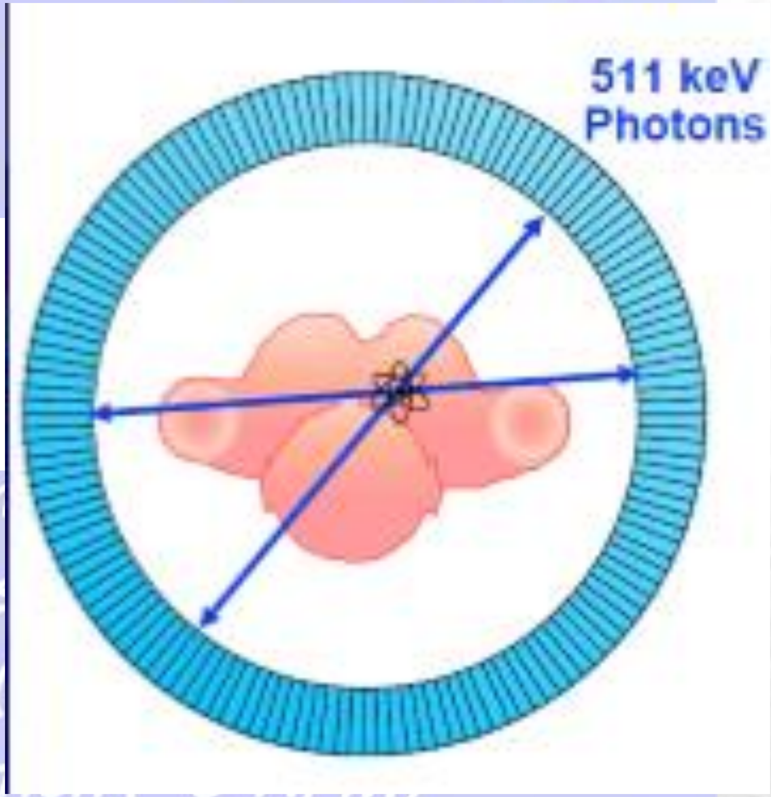
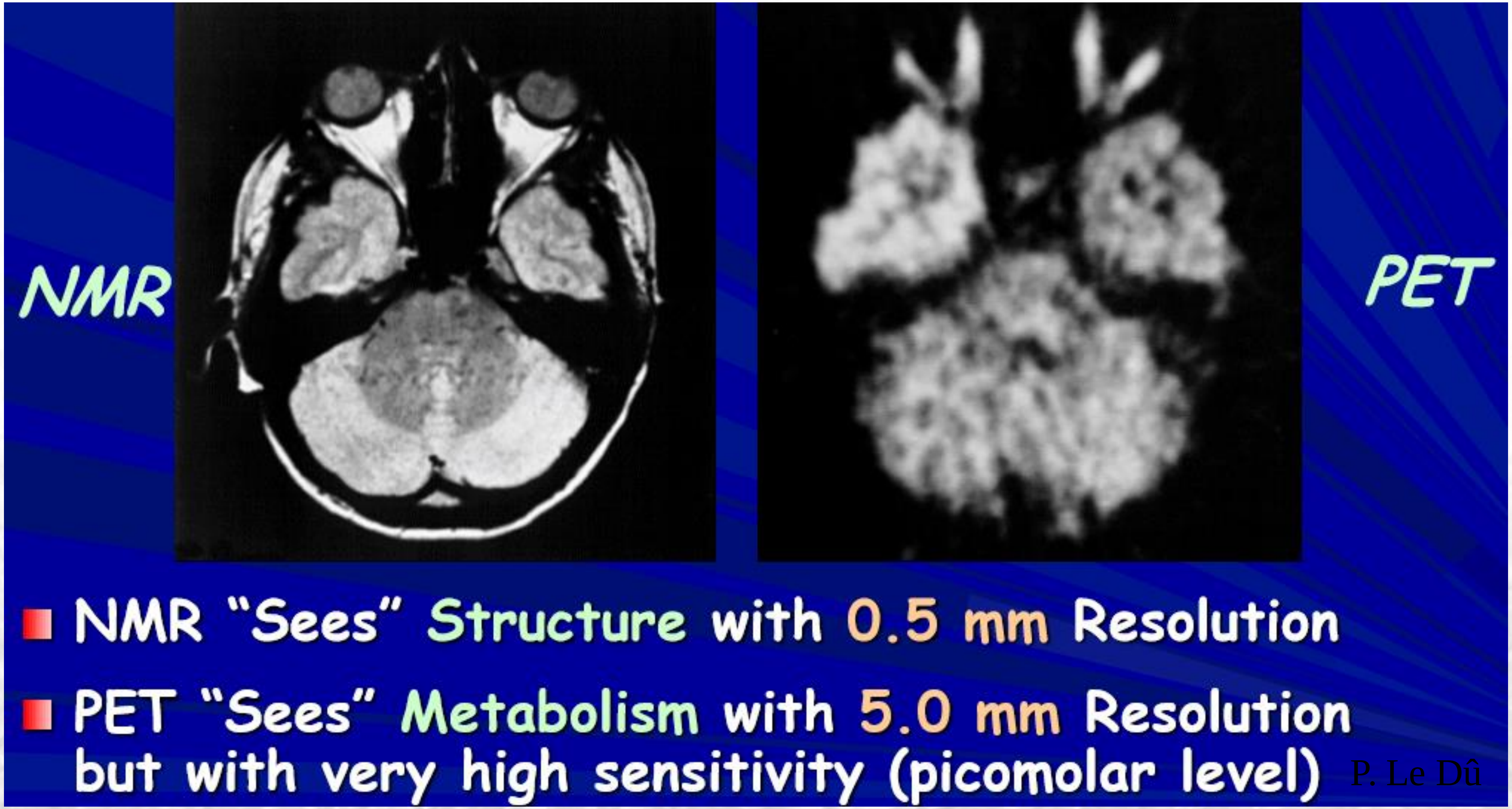


We like PET for this functional information, but where do we get the signal?



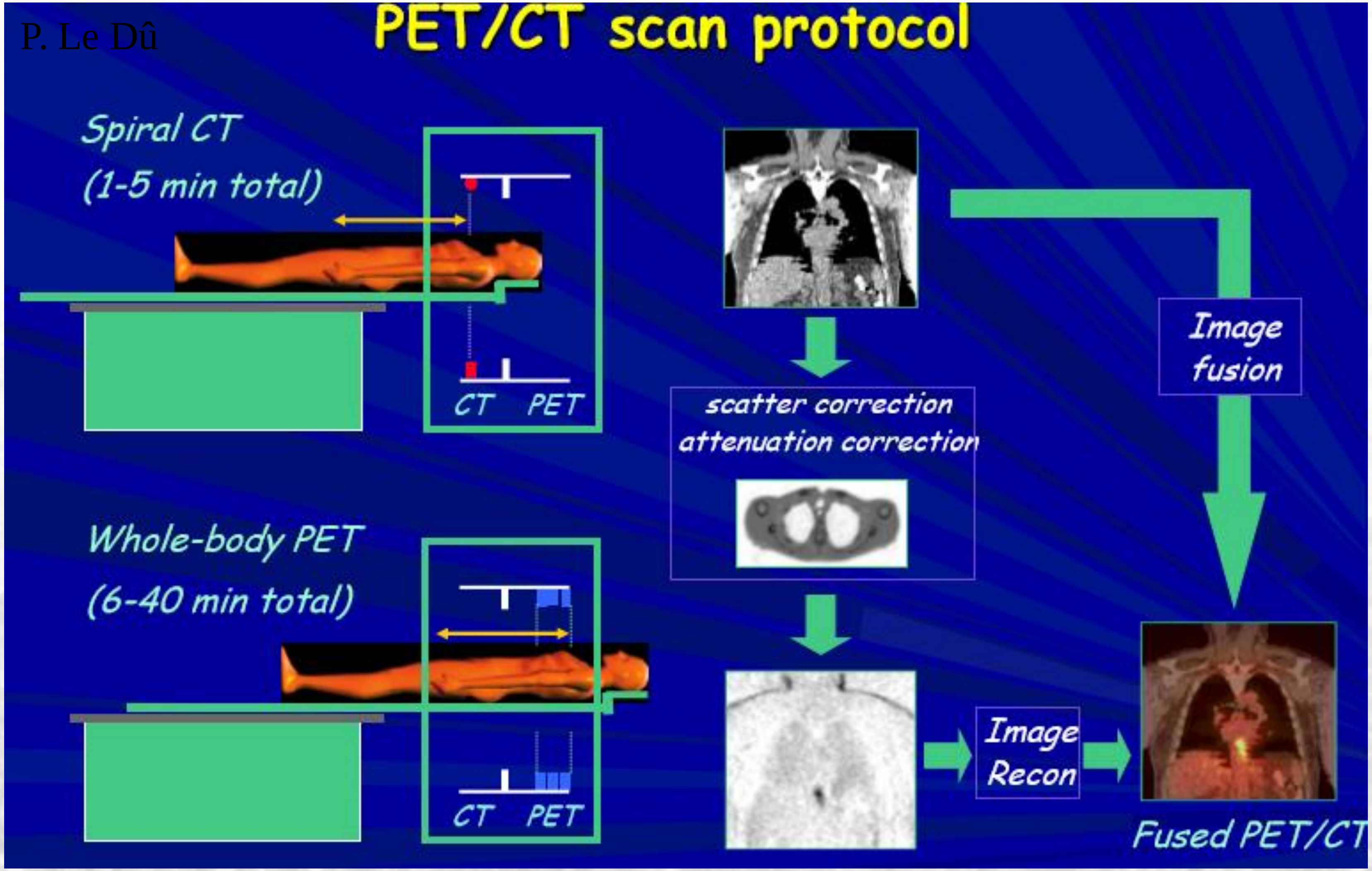
Workshop Day 5… What am I suggesting?

Hint: Functional imaging is not the whole story…



What do we want? → Everything!

Late 1990s: Enter the era of PET + CT



Rapid clinical acceptance of PET/CT

>90% PET sales were PET/CT within 5 years

PET/CT enables regions of increased 18F-FDG accumulation on the PET image to be directly correlated with anatomic locations on the CT scan

- Improved specificity for lesion detection
- CT correction for photon attenuation in PET
- CT estimates scattered events in PET
- CT corrects for partial volume errors

Challenges remain:

- Motion effects between the acquisition protocols
- CT contrast agents can affect PET attenuation correction

Shall we take the Day 1 quiz again?

PET as a research tool

Small detector rings and animal studies:

single organ studies have always existed, but neuroscience research and cardiovascular research began with larger animals on clinical scanners

Influential advance #5: Pre-clinical PET scanners

High-resolution, dedicated animal PET scanners let a new group of researchers play with the PET tool

Pre-clinical PET appliations:

- Biological sciences
- Pharaceutical industry
- Biotechnology

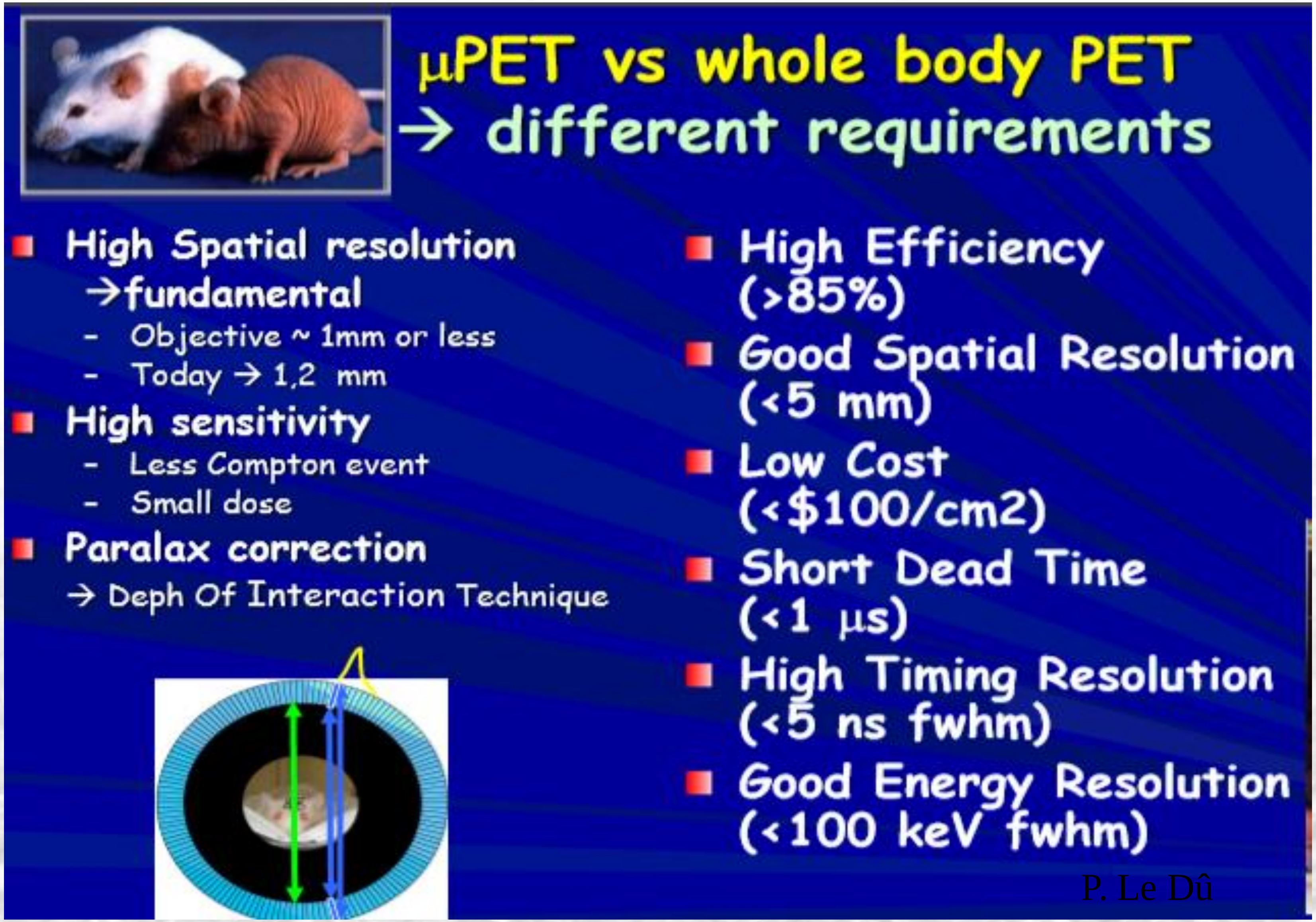
Small animal scanners based on same technologies as clinical scanners, but very different in design tradeoffs

(Pre-clinical) imaging requirements:

- High sensitivity
- High resolution
- Small FOV

Pre-clinical imaging environment:

- Low attenuation
- Low scatter
- Low counting rates


μPET vs whole body PET
→ different requirements
High Spatial resolution
→fundamental
- Objective ~ 1mm or less
- Today → 1,2 mm
High sensitivity
- Less Compton event
- Small dose
Paralax correction
→ Deph Of Interaction Technique
High Efficiency
(>85%)
Good Spatial Resolution
(<5 mm)
Low Cost
(<$100/cm2)
Short Dead Time
(<1 μs)
High Timing Resolution
(<5 ns fwhm)
Good Energy Resolution
(<100 keV fwhm)
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PET milestones are a foundation for the future… What's next?

Time of Flight (again)

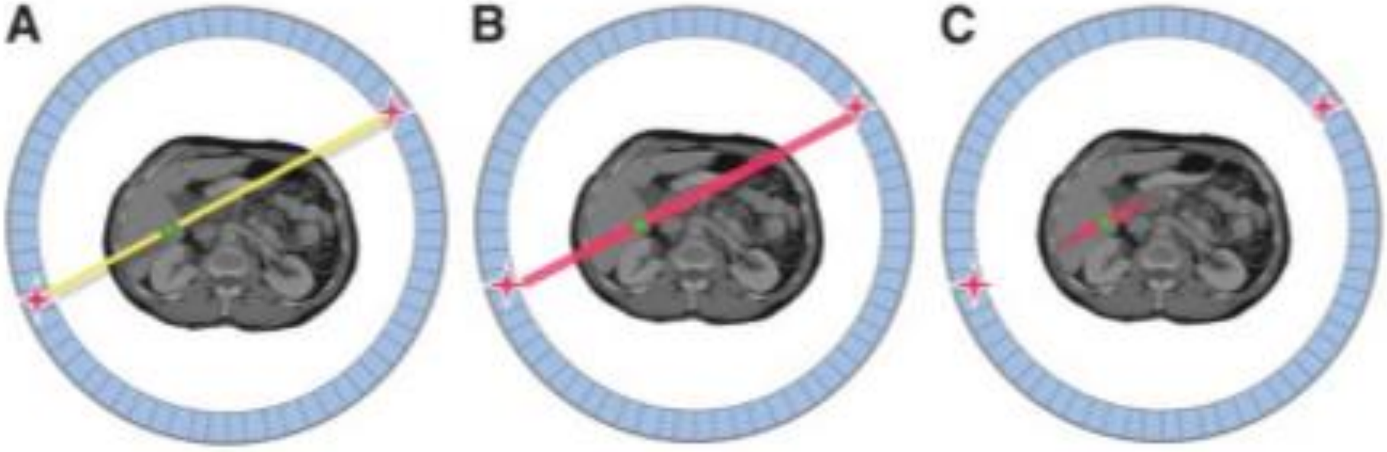

FIGURE 3. Illustration of TOF PET: detection of 2 annihilation photons in PET scanner (A), uniform-probability weighting of annihilation site in standard PET (B), and use of TOF information to constrain location of annihilation site during image reconstruction (C).

ToF always deisred, verified in 1980s, but clinically rejected in 1990s

- Scintillators BaF2 and CsF gave timing resolution 550-750ps, ~1cm spatial resolution, not enough SNR benefit compared to the clinical performance of BGO

Problems With TOF in the 1980's

- CsF & BaF_2 have drawbacks (compared to BGO)
  - Lower density & atomic number (worse spatial resolution & efficiency)
  - "Fast" emission of BaF_2 is in UV (quartz PMTs, no transparent glues)
- Few "fast" PMTs (most 2" diameter, all expensive)
- GHz electronics was "beyond state-of-the-art"
  - Time alignment and stability problems

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Non-TOF PET with BGO Dominates

Conclusions

- *Benefits of TOF are HUGE:*
  - *5x effective efficiency gain w/ 500 ps timing*
  - *Greatest improvement in large patients*
  - *Faster reconstruction algorithm convergence*
- *Rebirth of TOF PET Due To New Scintillators:*
- *550 ps for LSO, 420 ps for LaBr3*
-
- *Still LOTS To Do:*
- *Electronics* • *Photodetectors*
- *Module Design* • *Scintillators*
- *Reconstruction* • *Evaluation*

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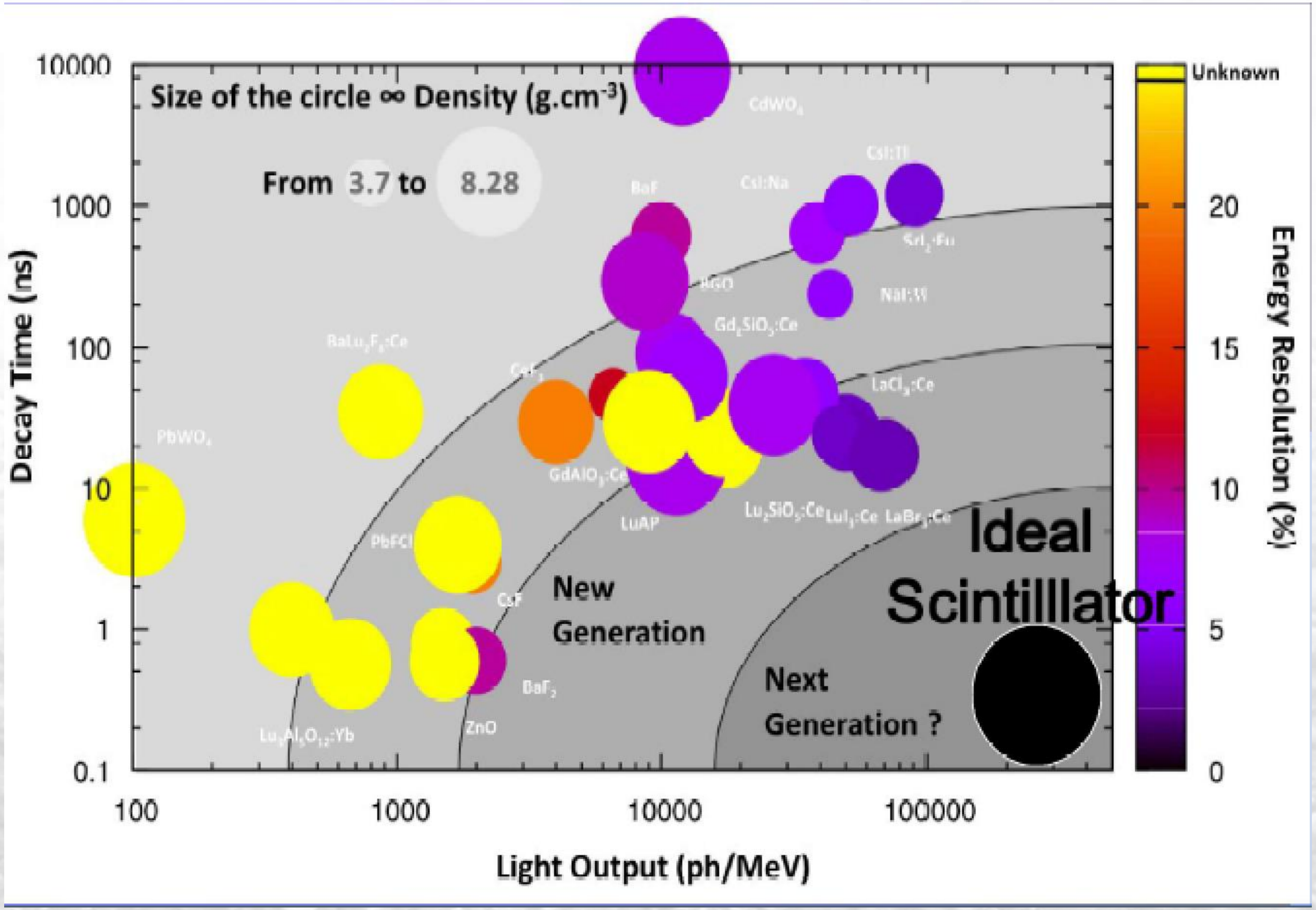
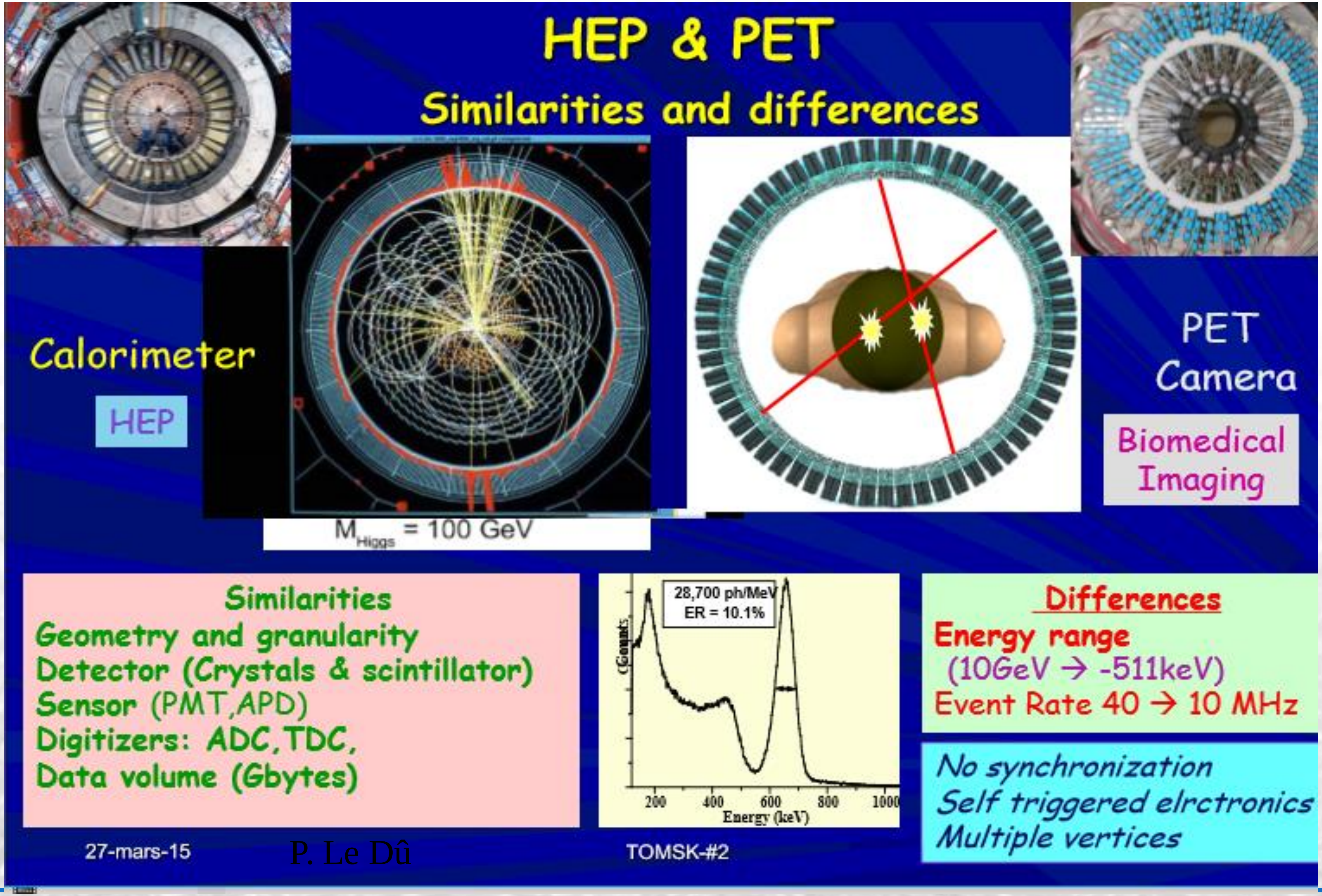
→Workshop day 5: Why?

Is L(Y)SO the end of the story?



No material is ideal, but maybe PET can get help from the corresponding desires of High Energy Physics


HEP & PET
Similarities and differences
Calorimeter
HEP
M Higgs = 100 GeV
PET
Camera
Biomedical
Imaging
Similarities
Geometry and granularity
Detector (Crystals & scintillator)
Sensor (PMT,APD)
Digitizers: ADC,TDC,
Data volume (Gbytes)
28,700 ph/MeV
ER = 10.1%
Counts
Energy (keV)
Differences
Energy range
(10GeV → -511keV)
Event Rate 40 → 10 MHz
No synchronization
Self triggered elrctronics
Multiple vertices
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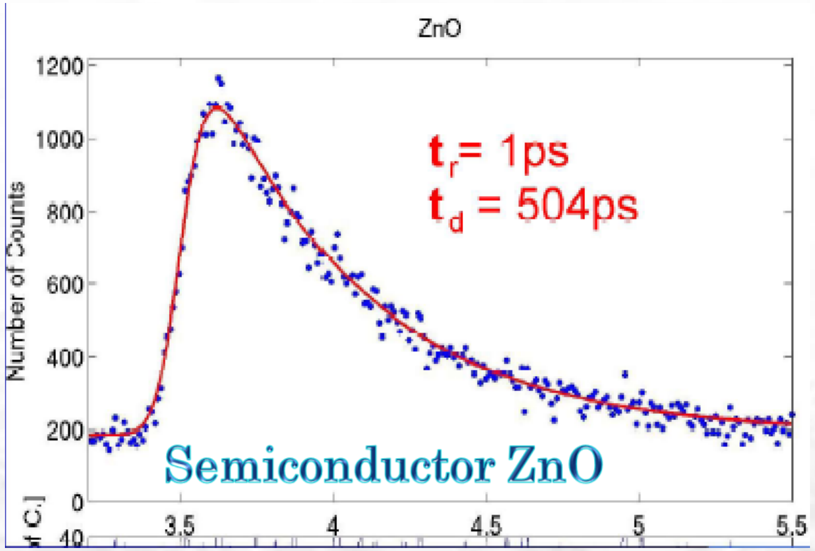
Scintillators 2018

Large development effort by the nuclear security community
- Good energy resolution (LaB3, SrI2)
- Neutron sensitivity



HEP needs material beyond PbWO
- Radiation hardness compensation

PET needs material beyond LSO
- ToF and energy resolution

Recent using nanotechnologies → photonic crystal (NASA, MIT,…)
- Increase light output
- Decrease photostatistic jitter
- Redistribute the light in the fastest propagation mode in the crystal

TOF areas to improve?

- Better scintillators?
  - Want fast and bright and dense
  - LaBr is fast, bright, not so dense
  - LSO could be brighter, but is able to deliver < 300ps
- Better light sensors
- Faster, stable electronics
- All major medical imaging vendors have TOF whole body PET systems with timing resolutions ~ ~~550~~ ps ~300ps

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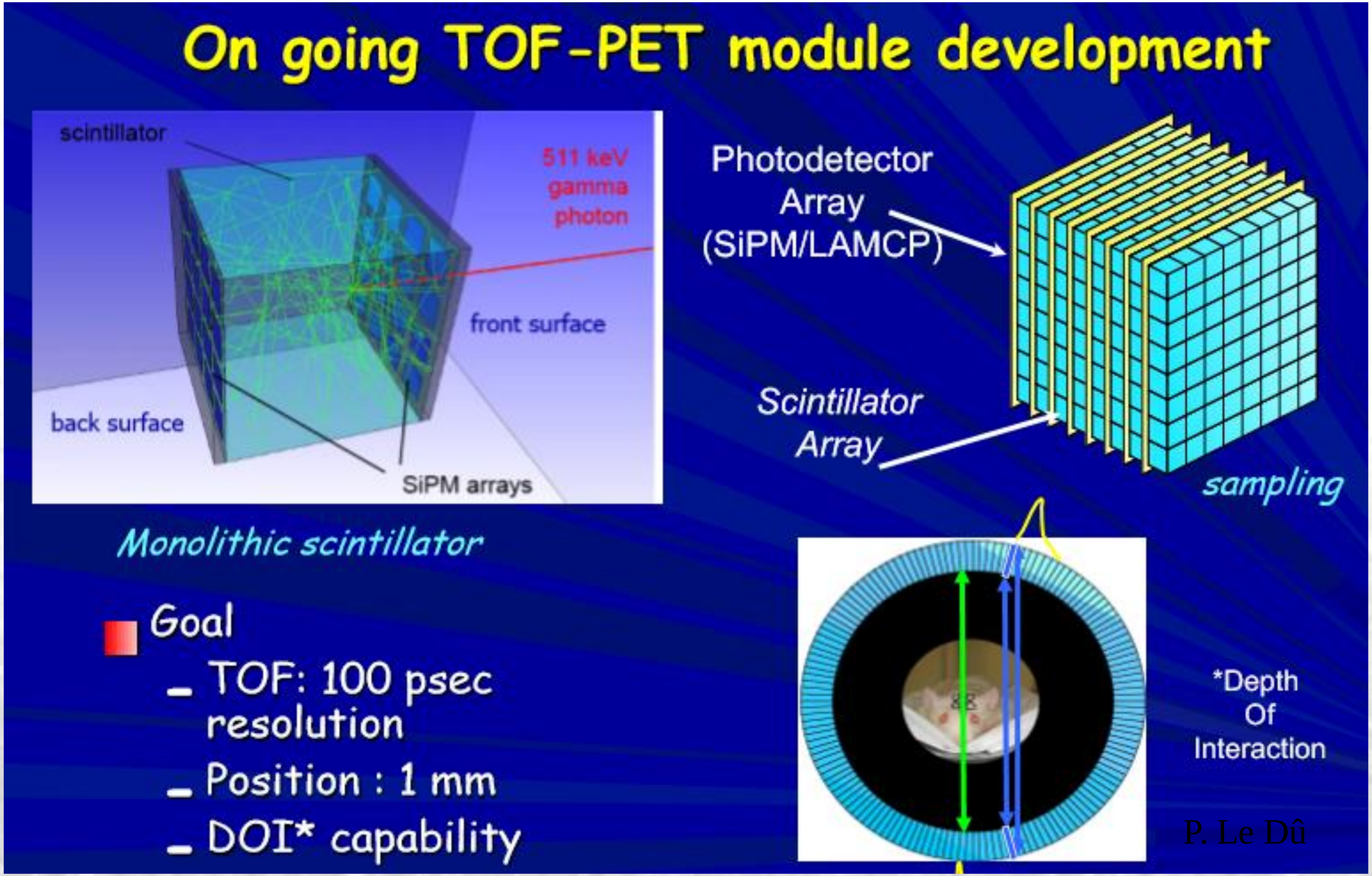

On going TOF-PET module development
scintillator
511 keV gamma photon
front surface
back surface
SiPM arrays
Monolithic scintillator
Photodetector Array (SiPM/LAMCP)
Scintillator Array
sampling
Goal
– TOF: 100 psec resolution
– Position : 1 mm
– DOI* capability
*Depth Of Interaction
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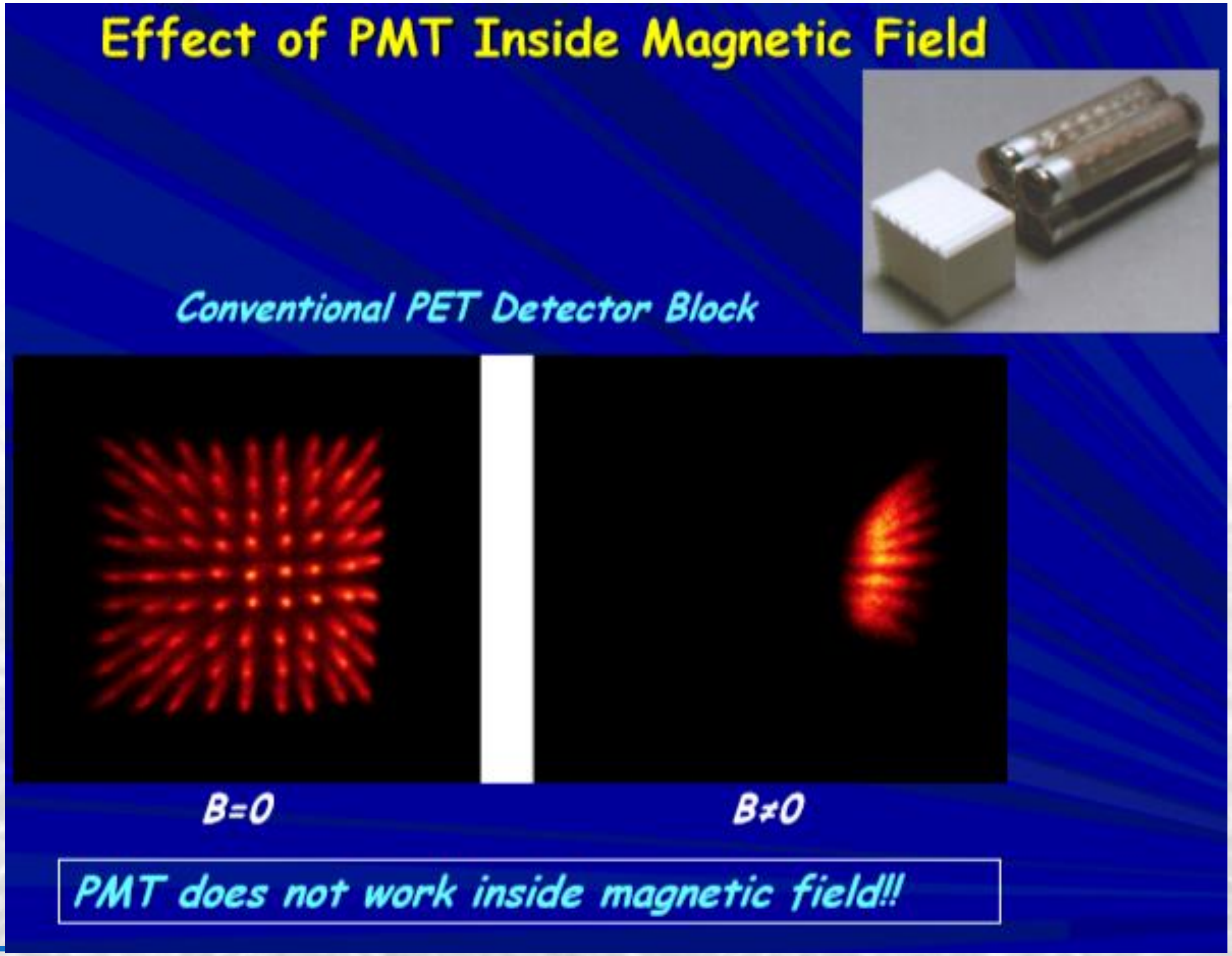
PET milestones as a foundation for the future…
What's next?

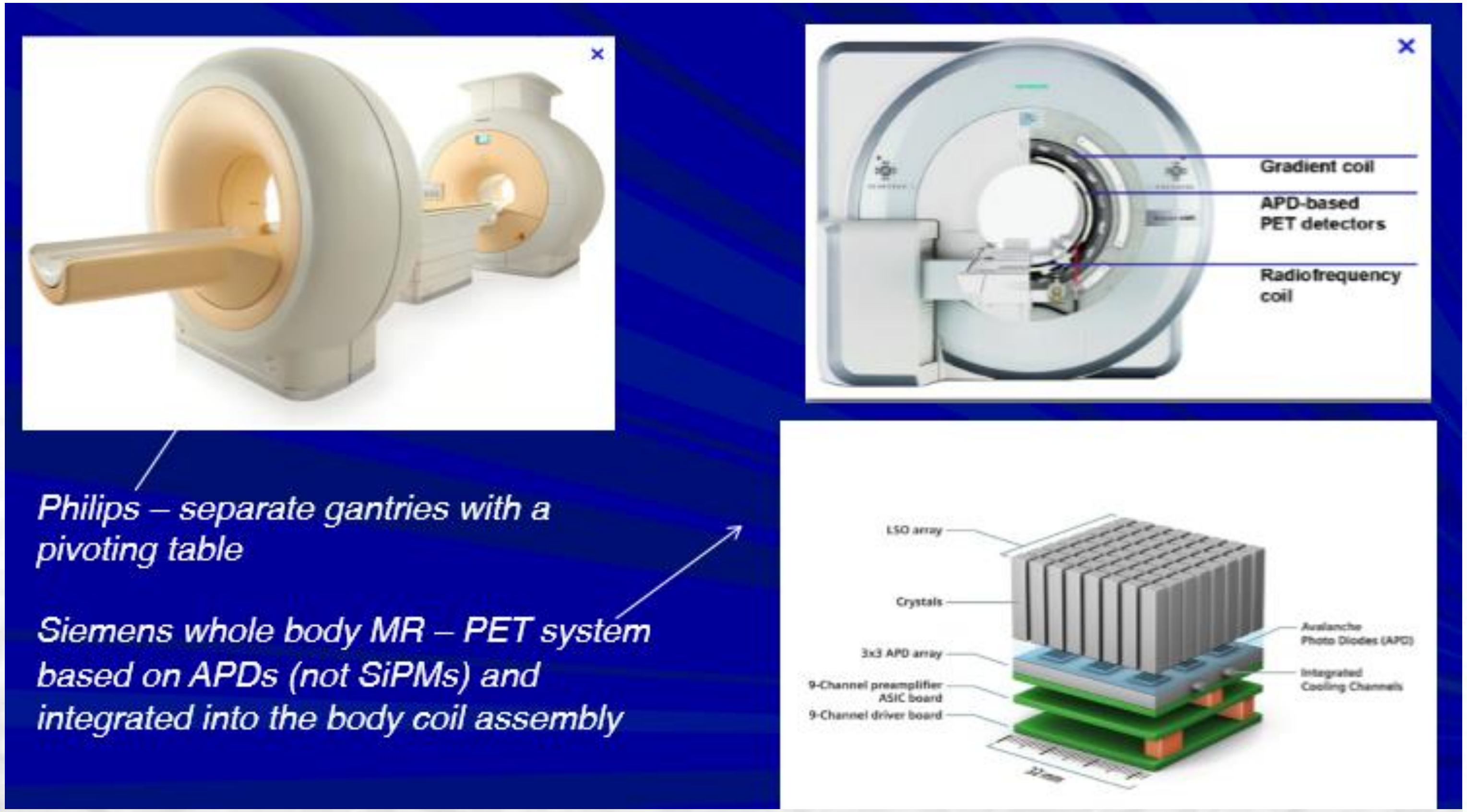
PET/MRI (still…)

Began at the same time as PET/CT, but slow

- Radiofrequency interference
- PET has always been put inside the MRI



Approaches to PET/ MRI



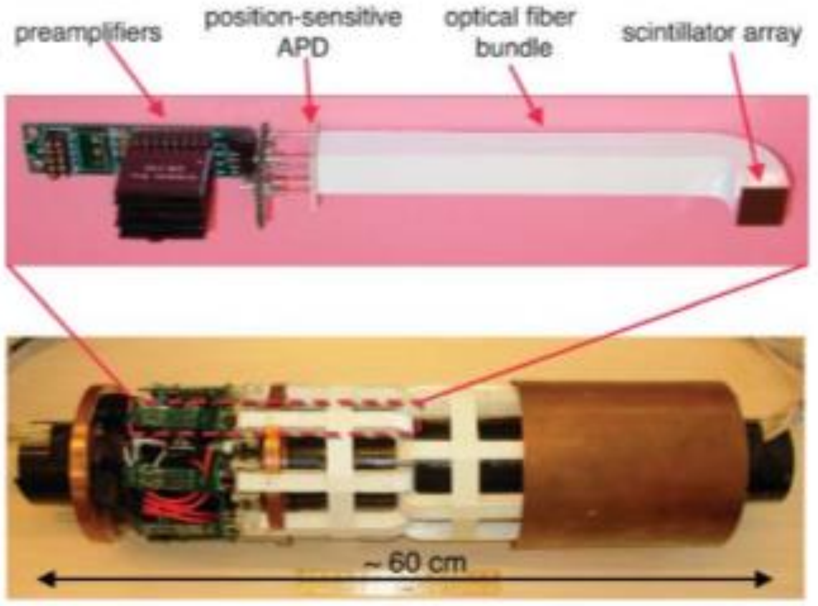
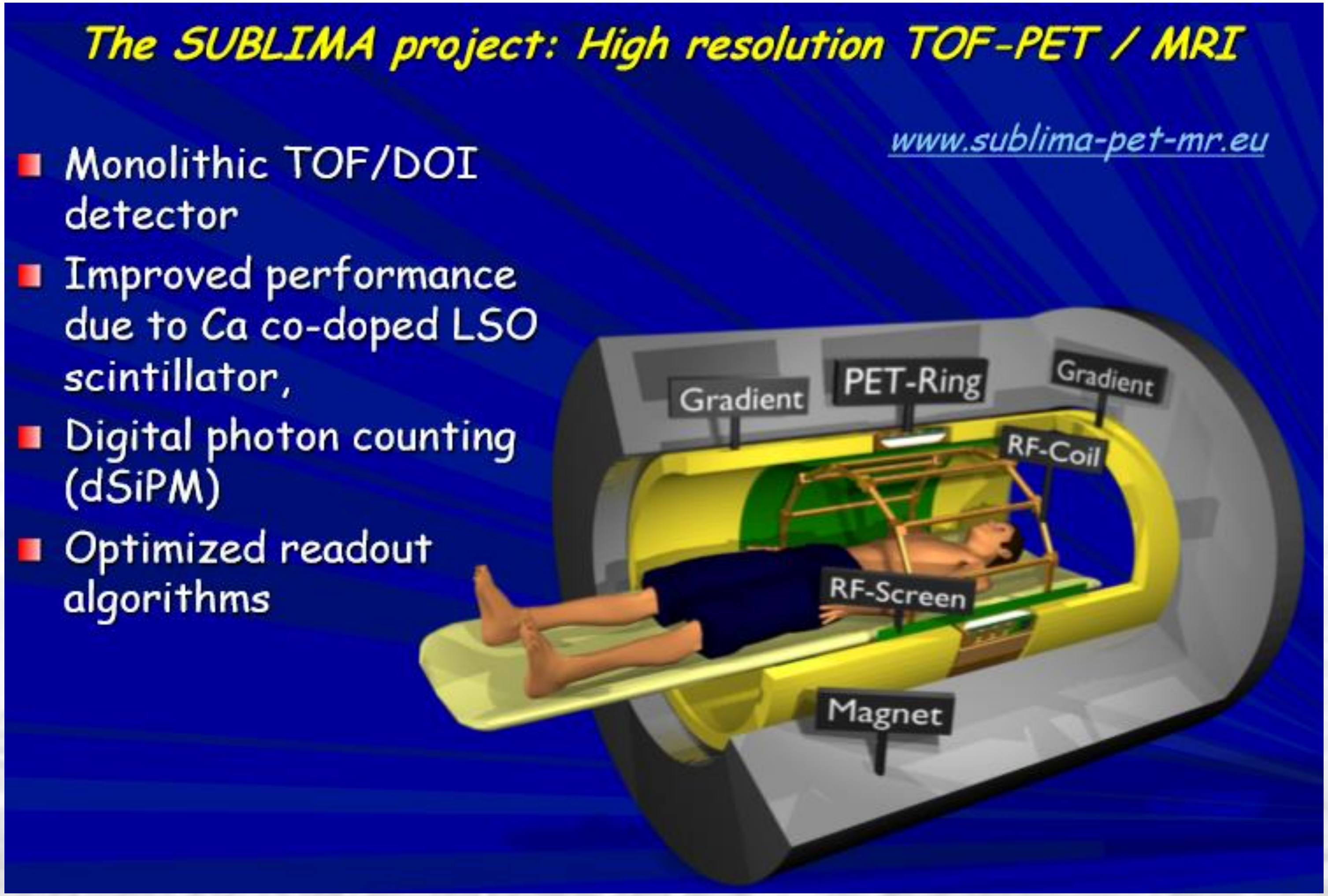


FIGURE 6. Photograph of MRI-compatible PET insert based on arrays of LSO scintillator coupled through short lengths of optical fibers to position-sensitive APDs and MRI-compatible electronics. This insert fits inside bore of 7-T animal MRI scanner, permitting simultaneous PET and MRI studies.

Much development since SiPM

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



SUBLIMA gave new PET detector technology that offers unprecedented imaging performance and is highly compact

PET milestones as a foundation for the future…
What's next?

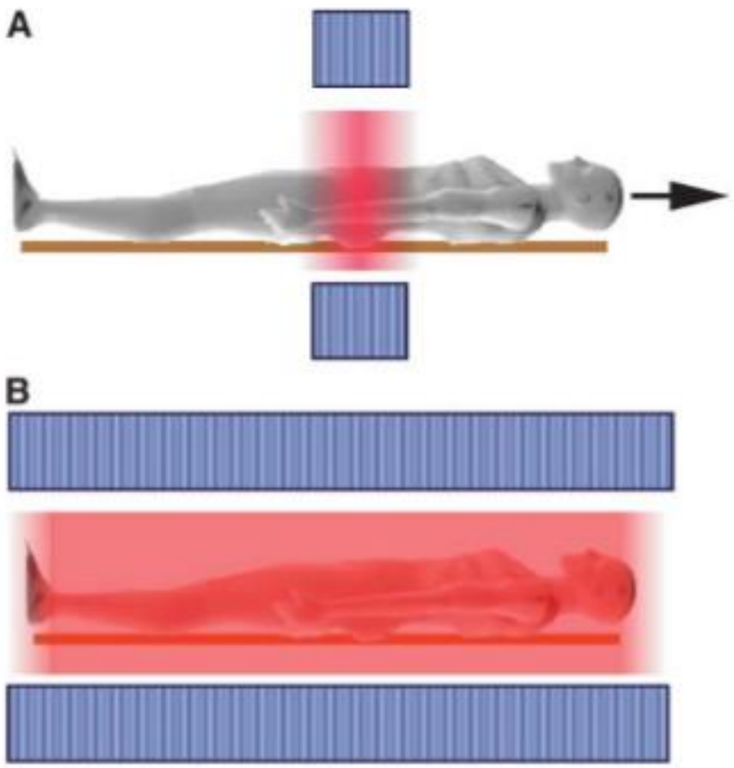
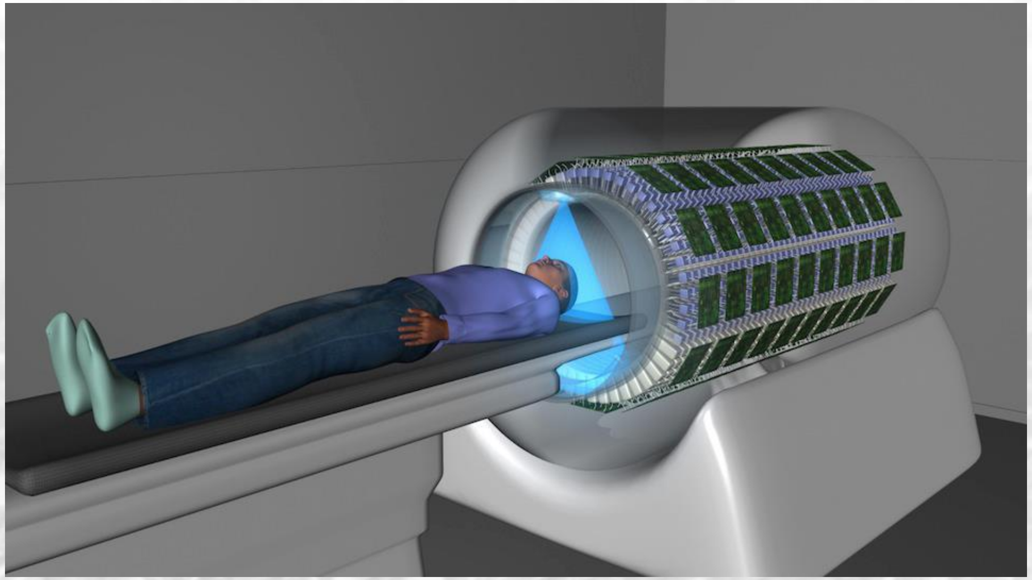


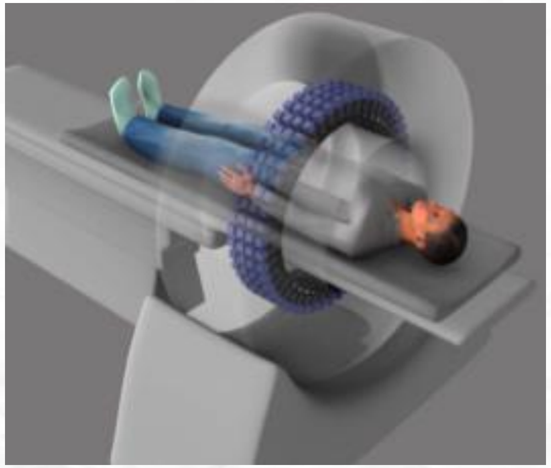
FIGURE 7. Schematic illustration of current configuration and sensitivity for 3D whole-body PET (A) compared with configuration in which whole body is within field of view (B). Axial extent of PET detectors is indicated by blue, and sensitivity is indicated by the intensity of red.

Total-body PET

The future is NOW!
PET EXPLORER Project



Whole-body ≠ Total-body

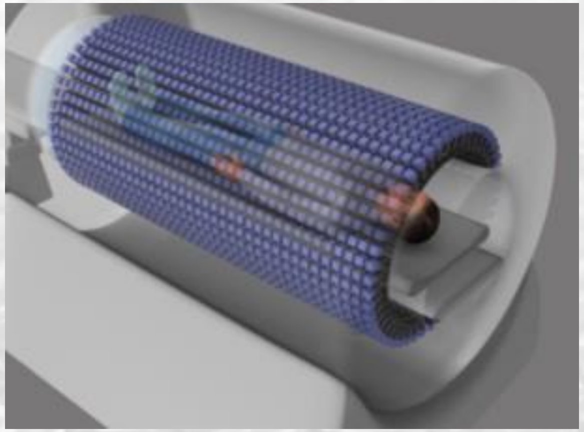


Whole-body PET

- Sensitivity <1%
- FOV ~20cm
- 85-95% of the body is outside FOV → no signal collected
- Radiation is isotropically emitted → 3-5% of signal inside FOV can be collected

Simulations of total-body PET

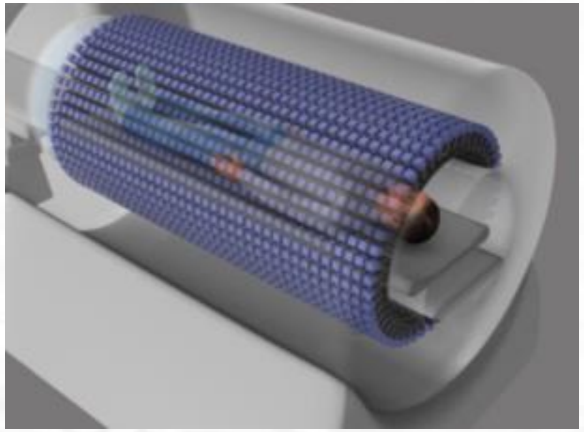
- FOV from 20cm → 200cm
- Effective sensitivity (NECR) → 40-fold increase
- Predicted sensitivity eyes-to-thighs → 24-fold increase



Workshop Day 5… What about the brain?

Organ inside FOV, but isotropic radiation collected
→ 4-5 fold increase in effective sensitivity

Predictions for Total-body PET



$$SNR \approx k\sqrt{SxAxT}$$

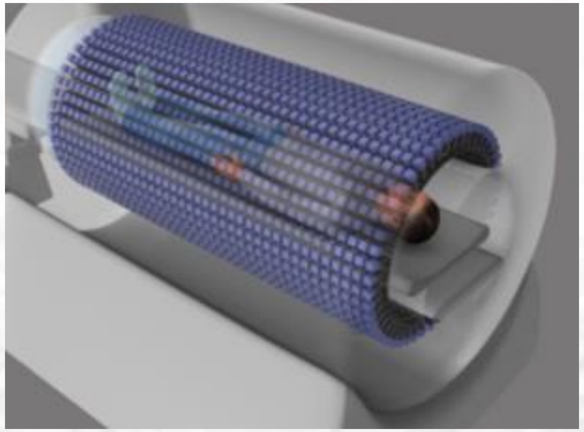
- S=effective sensitivity of the scanner
- A=injected activity
- T=imaging time

What can we do with 40-fold greater effective sensitivity?

- reconstruct at higher spatial resolution
- detect smaller lesions
- low-constrast structures
- improve quantification

Predictions of Total-body PET

$$\text{SNR} \propto \sqrt{\textit{number detected events}}$$



What more can we do with 40-fold greater effective sensitivity?

- Keep the SNR and reduce imaging time
  - Less patient motion, single-breath PET?

- Keep the SNR and reduce injected activity
  - Cost effective, PET for sensitive populations

- Repeated scans later after injection
- Multi-tracer stuies?
- Total-body kinetic modeling, parametric imaging

The PET total-body EXPLORER project

- Consortium formed 2011: University of California Davis, LBL, Upenn
- Research award 2015 to build the first scanner

explorer.ucdavis.edu

FIGURE 2. Photograph of EXPLORER mock-up installed at University of California Davis Medical Center.

Begin without radiation: EXPLORER Prototype (December 2016)

- Investigate patient tolerance
- claustophobia
- Air flow through the bore
- Motion-tracking strategies
- Patient couch deflection
- How to inject tracers deep inside the bore
- How to perform arterial blood sampling
- Clinical work flow
- Simulator for training patients and staff

The PET total-body EXPLORER project

Total-body PET requires 4-5m x 8-9m room → not much bigger than standard PET/CT, PET/MRI rooms

Largest sensitivity gain comes from geometry → detectors cover the entire body and efficiently detect almost all the photons that leave the body, regardless of the direction in which they are emitted

Total-body PET Challenges

Event rates and system electronics

- Rate of singles detection same as whole-body PET for same injected activity
- Coincidence electronics must process data from more detectors
- Higher rates of singles and coincidence events
- …or…Collect all single events and label with a precise time stamp, sort coincidence events between modules later

Move, process, reconstruct the data

- Reconstruct 40-fold more events for a standard injected activity
- Large image matrix, large axial FOV

Detector modules must be tightly packed tightly axially and transaxially

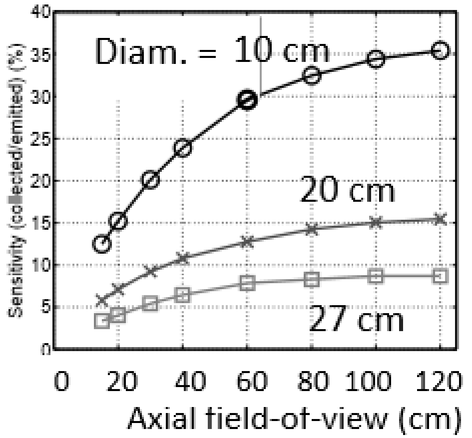
- Modules need excellent temperature stability, cooling of electronics
- Modules accessible for servicing or replacement

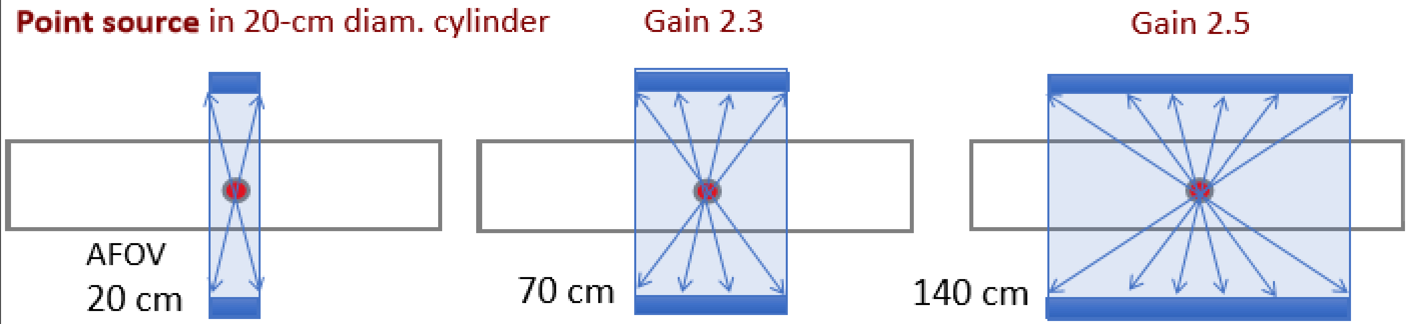
Long cantilever of the bed

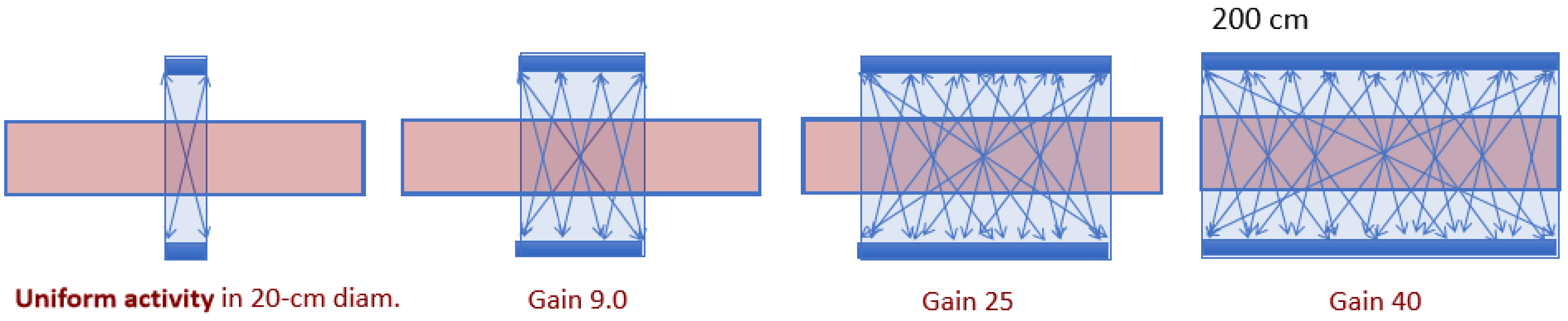
Internal bore covers must be strong, low-attenuation, liquid-impermeable, easily cleaned or sterilized

Total Body PET Design: *Performance considerations*

- Scanner length
  - Longer axial FOV increases sensitivity – increased solid angle in 3D
  - Gain in point source (per slice) sensitivity limited due to attenuation



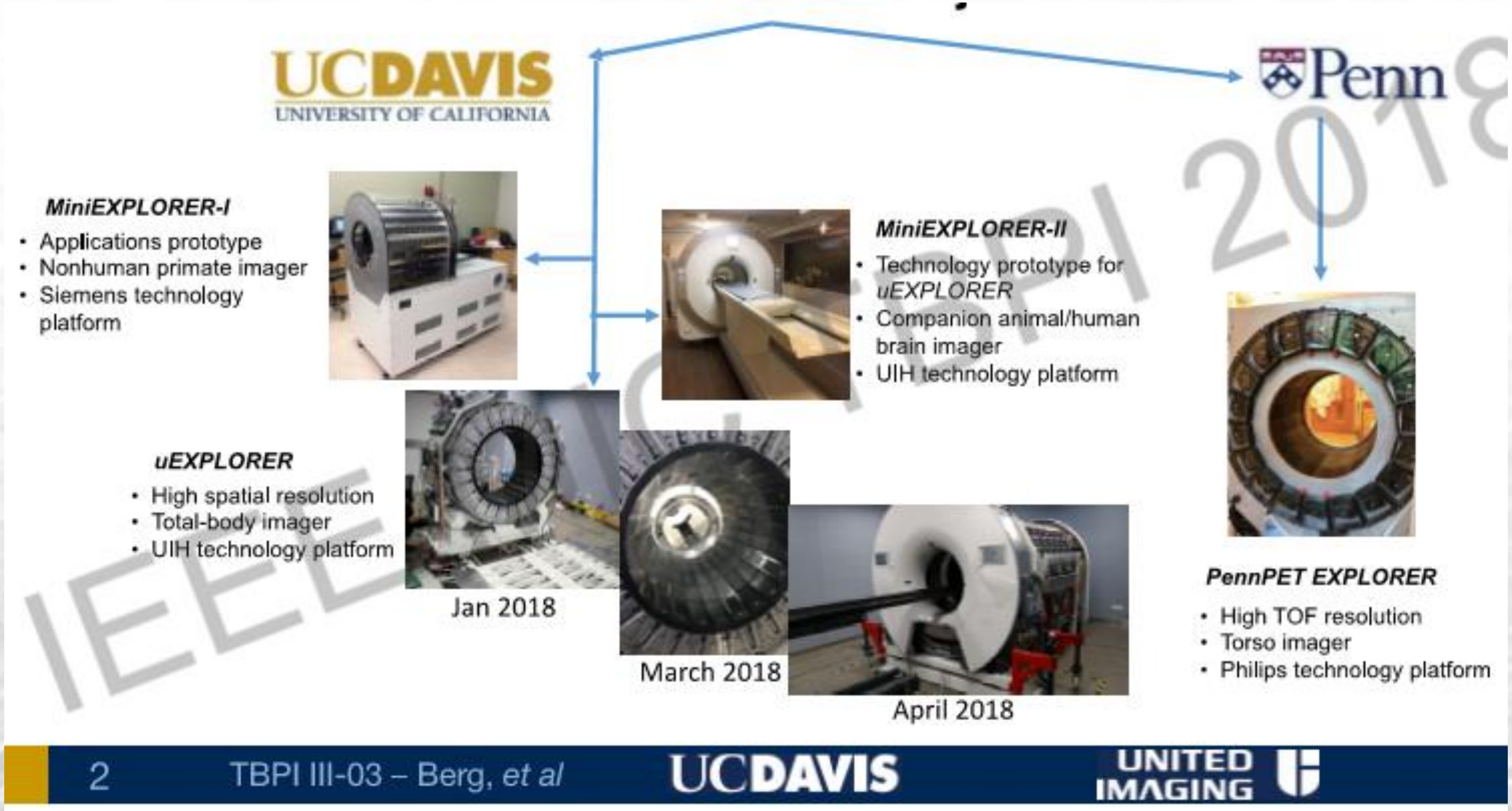




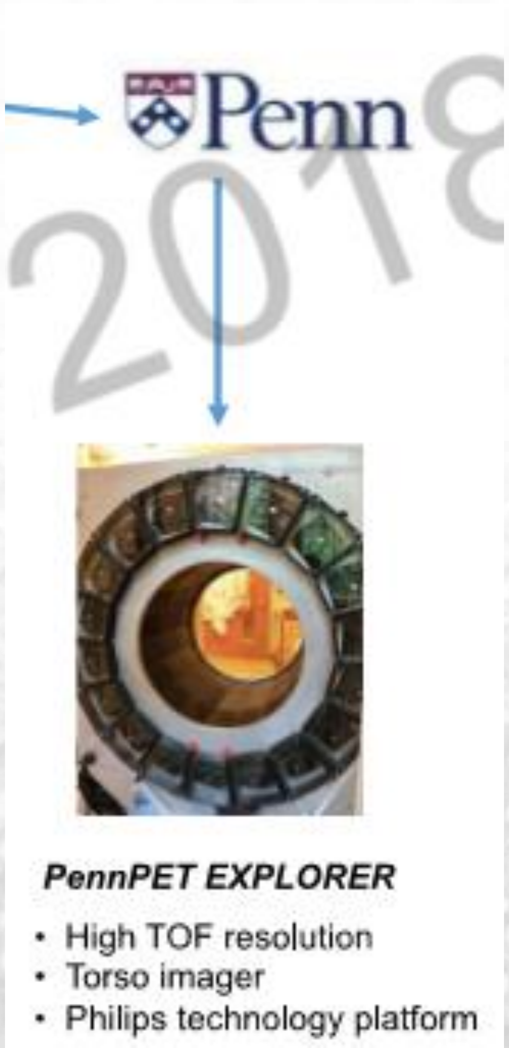
JS Karp et al. IEEE MIC Atlanta, GA, October 26, 2017

The PET total-body EXPLORER project

- EXPLORER is many total-body scanners!



The PET total-body EXPLORER project



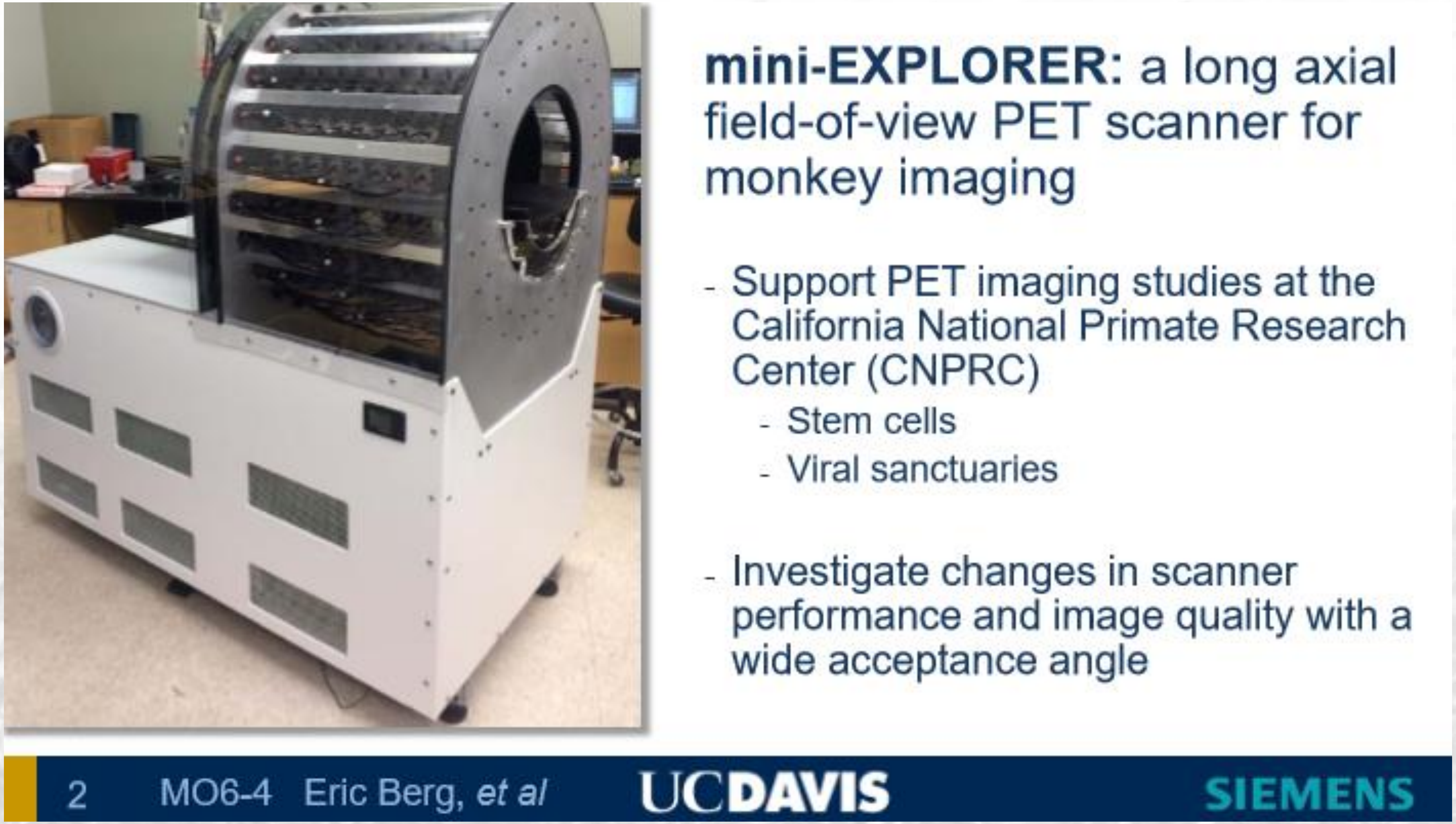
UPenn EXPLORER

- Digital silicon photomultipliers
- Study the effects of better timing resolution (250ps)
- Based on Philips Vereos (1:1 crystal to PM-sensor)

Mini-EXPLORER II

Test environment before human uEXPLORER

mini-Explorer I



mini-EXPLORER I

Nov 2016 experiments: evaluation of a long axial field-of-view PET scanner for non-human primates

Experiment aims

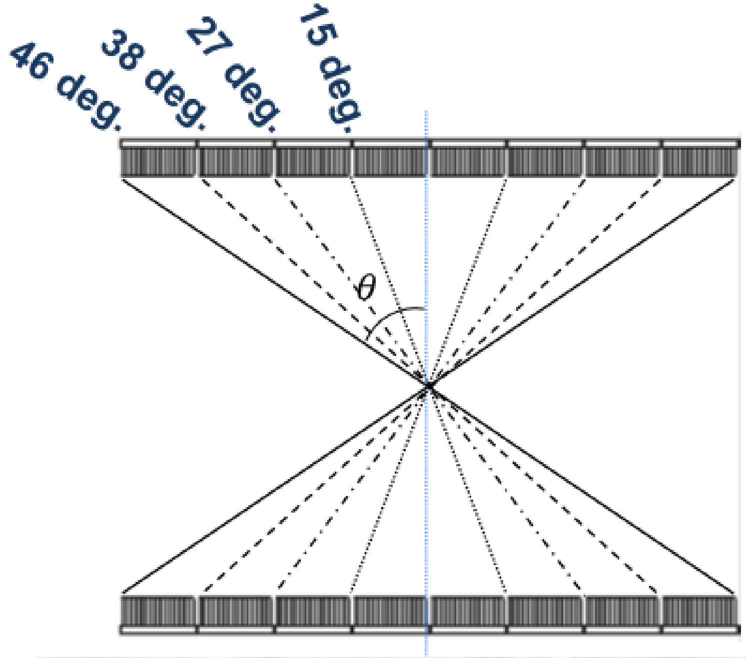
1. Benchmark the scanner performance for monkey imaging.
2. What are the benefits / trade-offs of a wide acceptance angle?

Physical performance

- Sensitivity
- Noise equivalent count rate (NECR)
- Scatter fraction (SF)

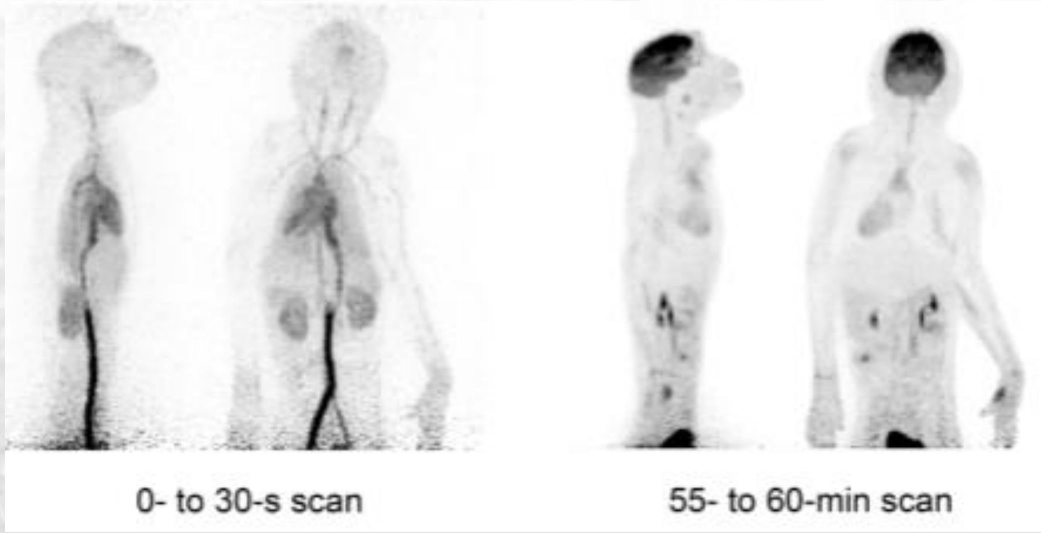
Phantom imaging studies

- Image uniformity
- Transaxial spatial resolution
- Axial spatial resolution

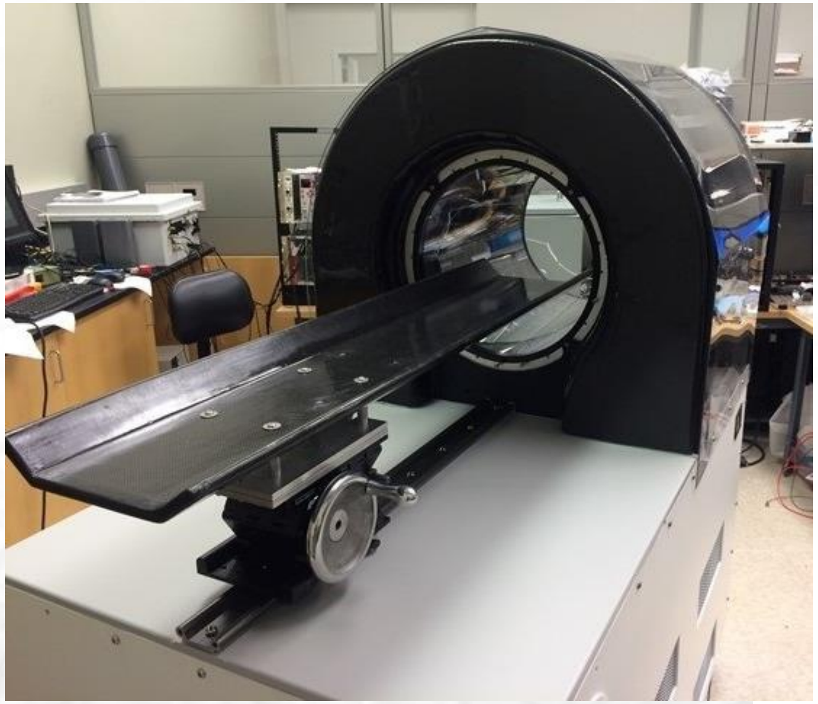


mini-Explorer I

- 192 PMT block detectors
- 45cm FOV
- 13x13 array of LSO crystals
- Timing resolution 609ps
- No Depth of Interaction enoding



1/10 stanard injected activity 18FDG



mini-Explorer I

Sensitivity: 5% total NU-2 sensitivity (5-fold higher than mCT), 15% peak

Count rate performance: up to 1741 kcps peak NECR, 16.5% SF

Spatial resolution: Resolve 3 mm structures transaxially and axially

Image quality: Highly uniform image quality achieved with 46 deg.

Long axial FOV + wide acceptance angle provides high sensitivity with acceptable trade-offs for monkey imaging

21 MO6-4 Eric Berg, *et al* UCDAVIS SIEMENS

Image longer:

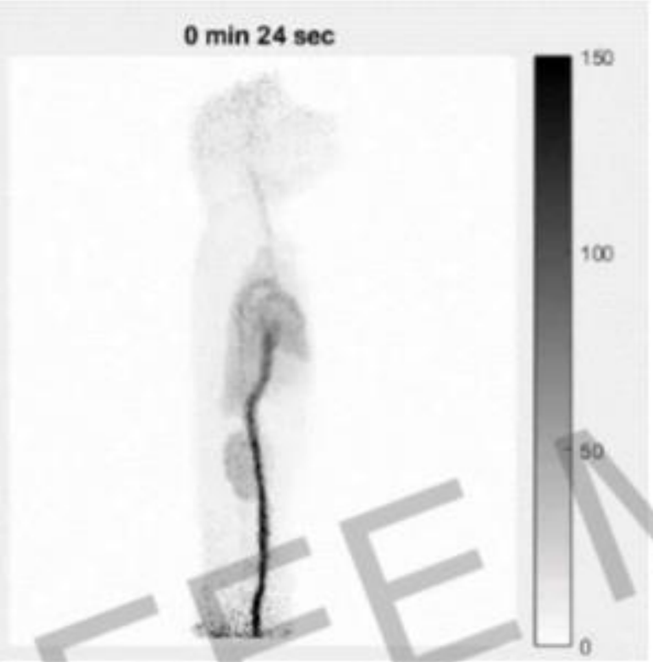
30-day ^{89}Zr-antibody imaging with miniEXPLORER I

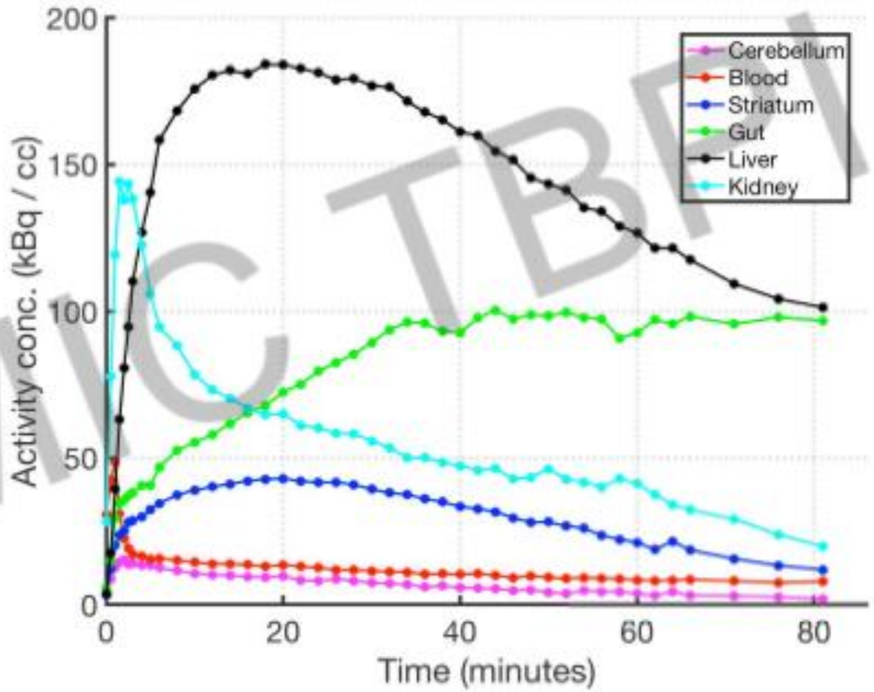
Rhesus monkey (2 yr, 2.1 kg)
1.1 mCi ^{89}Zr-antibody injection + cold antibody on Day 0

UCDAVIS Genentech UCDAVIS CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

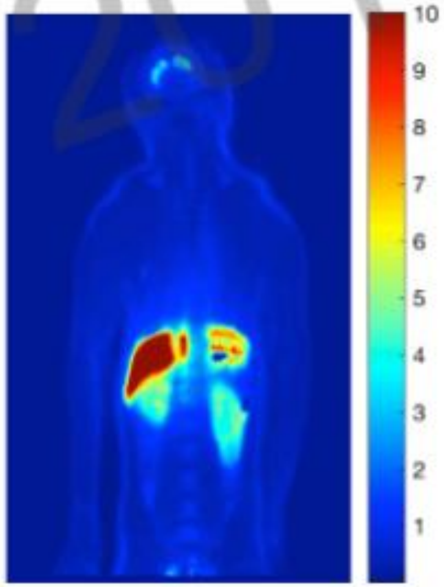
Dynamic imaging of the whole body

Total body kinetic modeling of ^{11}C-raclopride in monkeys using miniEXPLORER I



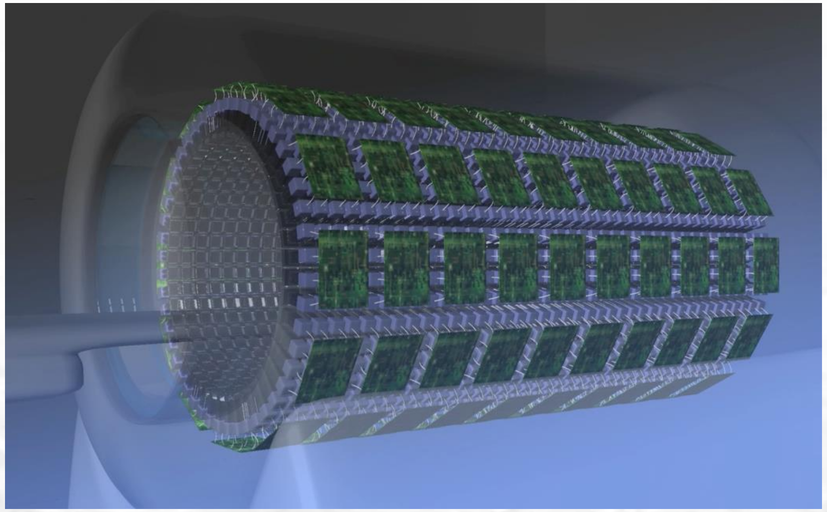


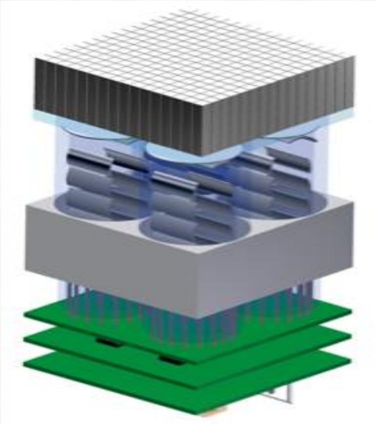
Distribution Volume by Logan Plot



Liz Li Guobao Wang

The PET total body EXPLORER project
UC Davis Construction 2018

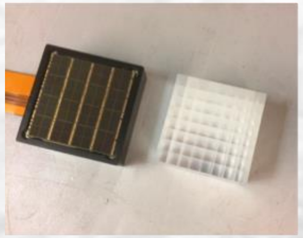


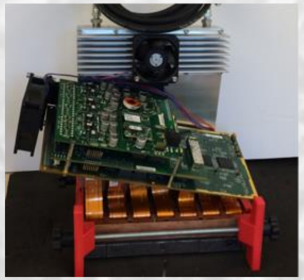


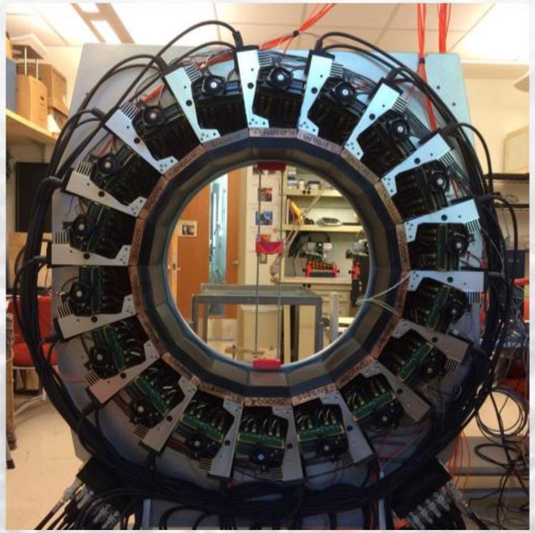
- Modular "Block" Detectors
- ~3.1 x 3.1 x 20 mm L(Y)SO
  - 880 kg of L(Y)SO!
- PMT (SiPM) readout
- 430ps TOF and 1-bit DOI
- 40 rings, 48 detectors/ring
- 78.6 cm ring diameter, 76cm patient bore
- 194 cm axial FOV
- 80-row, 160-slice CT scanner

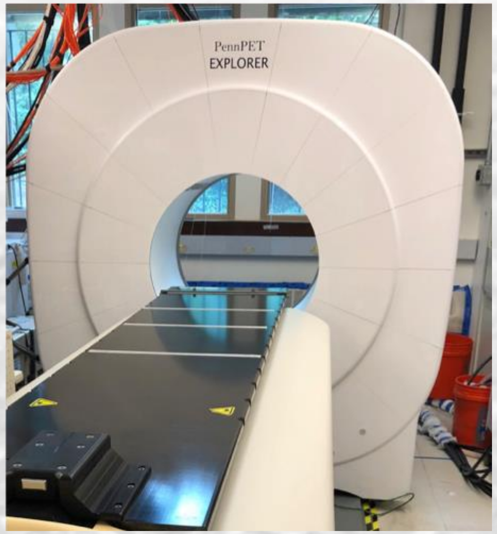
uEXPLORER
May 2018

The first medical imaging scanner capable of capturing 3-dimensional images of the entire human body at the same time









Does uEXPLORER reality live up to total-body PET theory?

First studies have been performed!

JNM The Journal of NUCLEAR MEDICINE

First Human Imaging Studies with the EXPLORER Total-Body PET Scanner*

Ramsey D. Badawi, Hongcheng Shi, Pengcheng Hu, Shuguang Chen, Tianyi Xu, Patricia M. Price, Yu Ding, Benjamin A. Spencer, Lorenzo Nardo, Weiping Liu, Jun Bao, Terry Jones, Hongdi Li and Simon R. Cherry

J Nucl Med. 2019;60:299-303.
Published online: February 7, 2019.
Doi: 10.2967/jnumed.119.226498

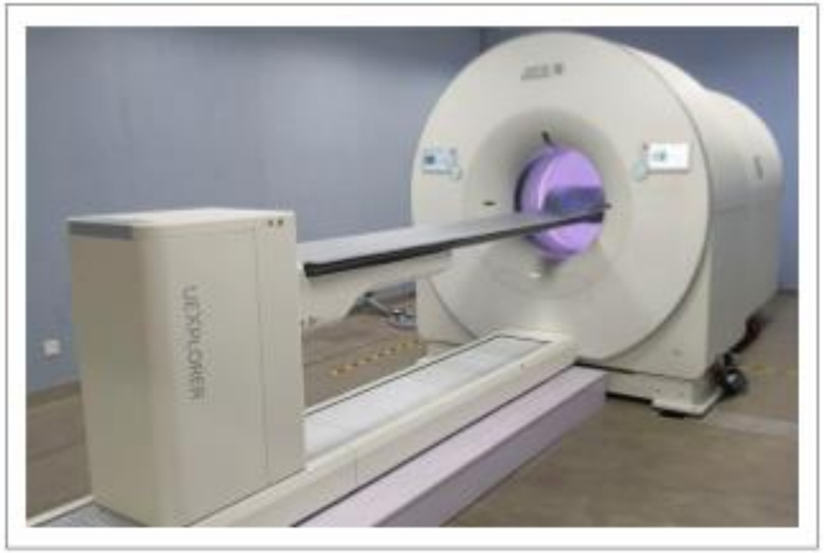


FIGURE 1. Photograph of completed EXPLORER total-body PET/CT scanner.

Normal volunteer stuies with 18F FDG

Does uEXPLORER reality live up to total-body PET theory?

The claims:

- Improve image quality
- Fast scanning
- Delayed sanning after many half-lives
- Low-dose scanning
- Total-body pharmacokinteic imaging

Subject Demographics and Injected Activity

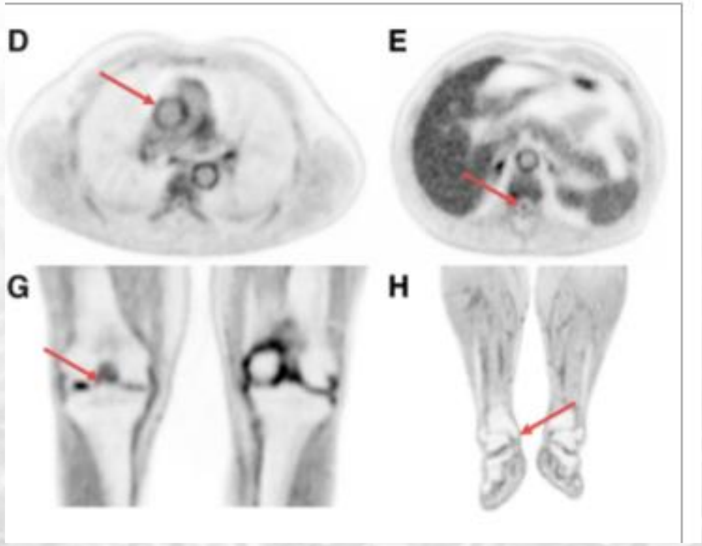
Subject	Sex	Age (y)	Weight (kg)	Height (cm)	Blood glucose level (mmol/L)	Injected activity (MBq)
1	Male	61	65	163.5	4.9	290 (7.8)
2	Female	61	56	156.0	4.8	256 (6.9)
3	Female	63	55	150.0	4.3	81 (2.2)
4	Female	45	43.5	152.0	5.1	25 (0.68)

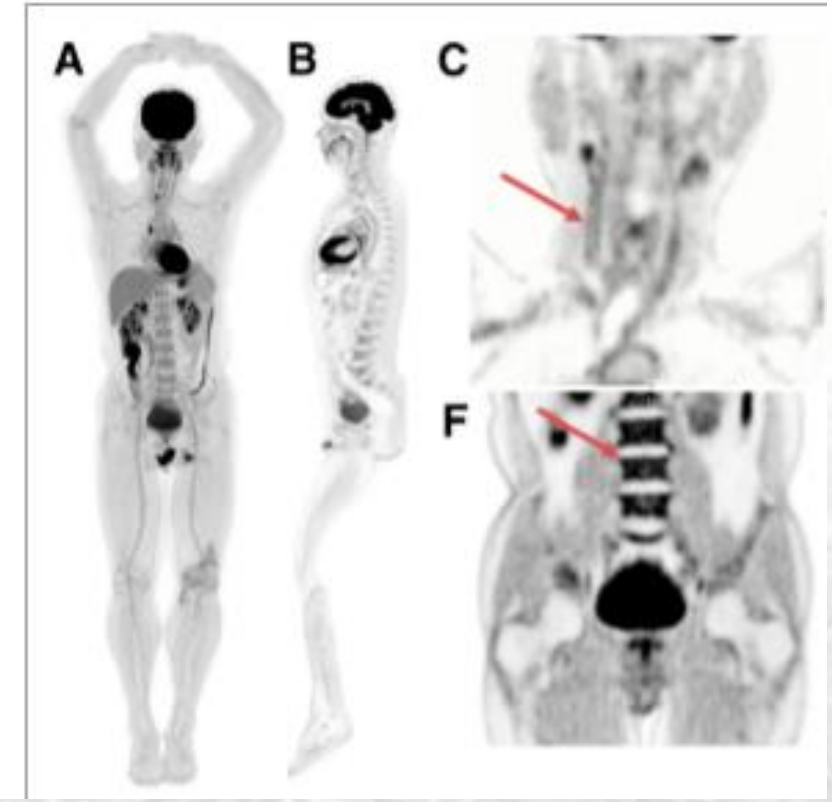
Data in parentheses are mCi.

J Nucl Med 2019; 60:299–303

Does uEXPLORER reality live up to total-body PET theory: Improved image quality

290MBq 18F-FDG injected activity
Data acquired 82min after injection
20-min scan duration





- Uniformity of uptake in liver
- High count density gives small anatomical features without high image noise

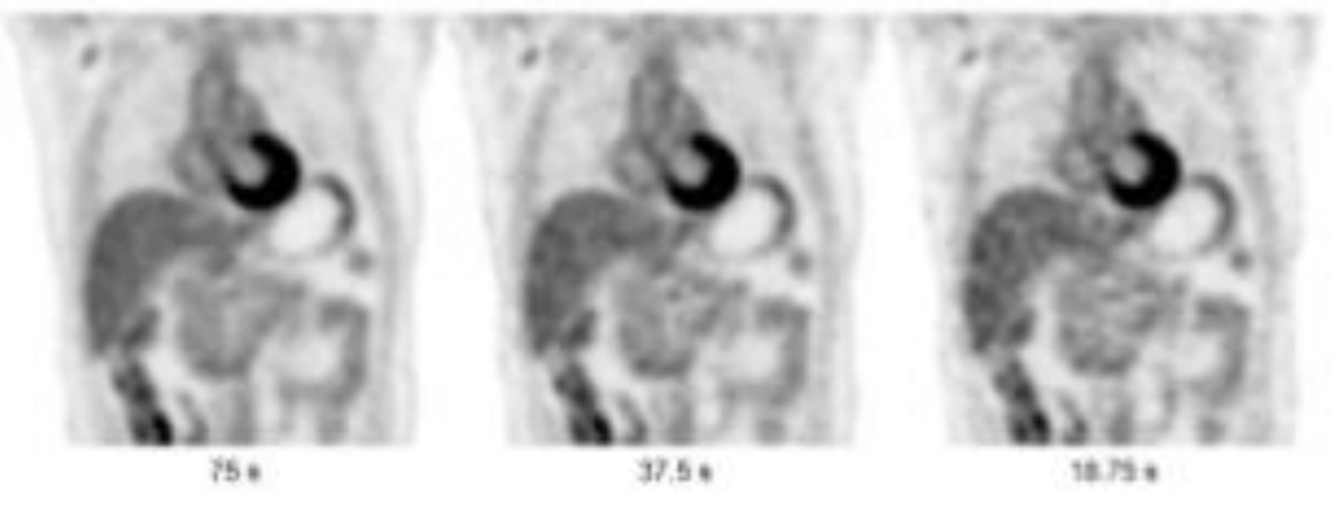
Does uEXPLORER reality live up to total-body PET theory: Fast scanning

290MBq 18F-FDG injected activity
Data acquired 82min after injection
20-min scan duration

Data organized into list-mode datasets of varying duration:
20 min,
10 min
5 min
2.5 min
75 s
37.5 s
18.75 s
OSEM-PSF-TOF reconstruction

Noise as scan time

Diagnostic quality images at 37.5s, maybe 18.75s



Julie Haglund, haglundj@aol.com, september 2019

Does uEXPLORER reality live up to total-body PET theory: Scan after many $t_{1/2}$

256MBq 18F-FDG
Time after injection:
- One hour
- 2 hours
- 8 hours
- 10 hours

Scan duration: 14min
OSEMPSF-TOF reconstruction

Images appear to be of diagnostic quality even after 10h

Scan after many $t_{1/2}$: Play with the math!

256MBq 18F-FDG injected dose

Activity after 10hours = 5.7MBq

Obs! Even less in the field of view due to urinary excretion

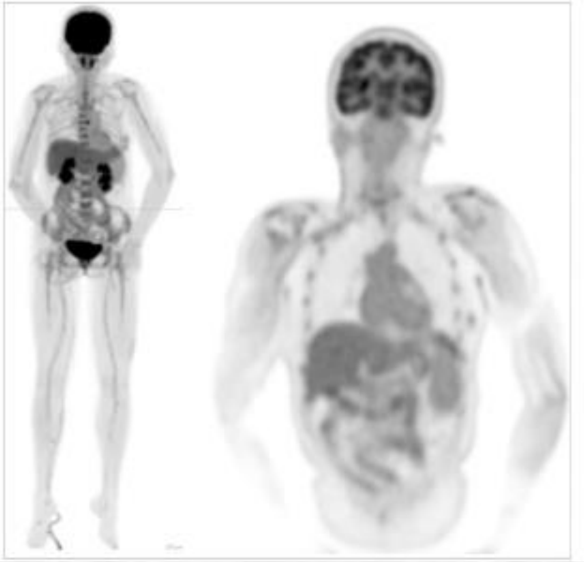
Thought experiment:

8.3MBq injected dose
Activity after one hour = 5.7MBq

Ignoring excretion, the total body PET scan yields diagnostic quality images for an effective dose of 0.16mSv

Does uEXPLORER reality live up to total-body PET theory: Low-dose scanning

25MBq injected activity
10min scan time
50min uptake time
OSEM-PSF-TOF reconstruction



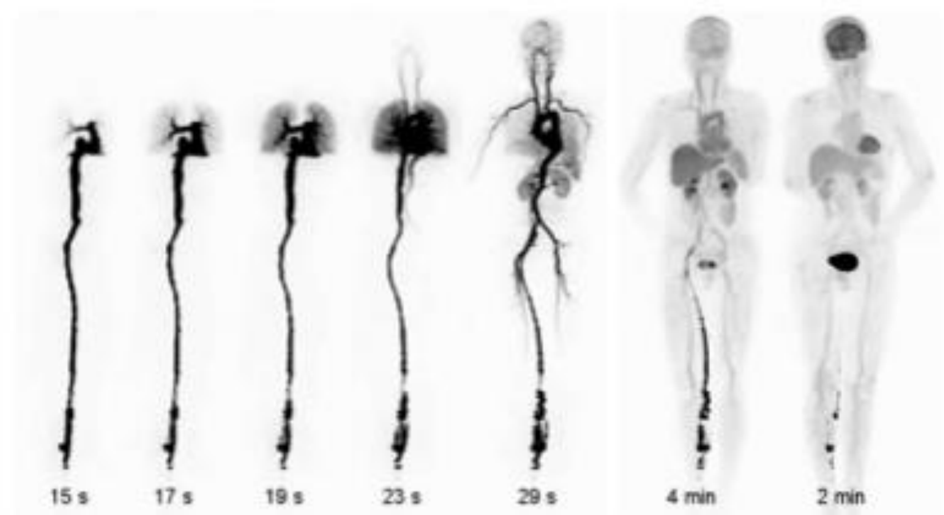
Dedicated low-dose brain scan
25MBq injected activity
30 cm from end of the axial FoV

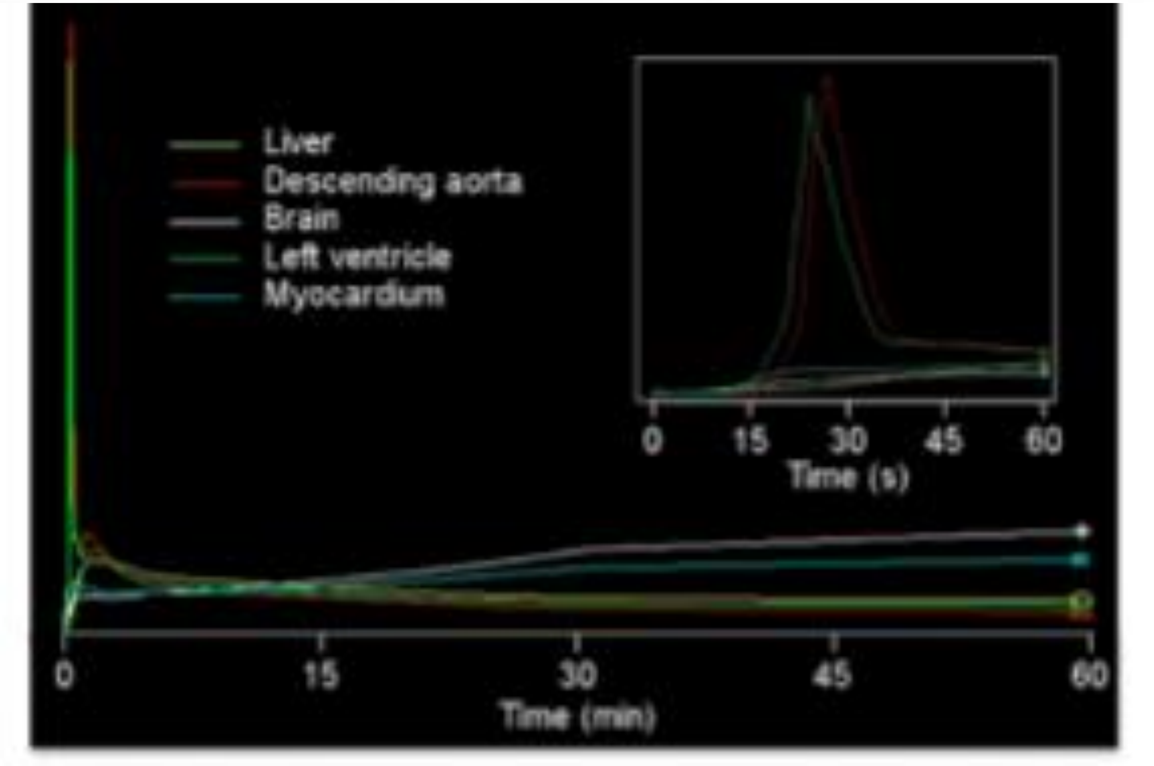
High sensitivity supports very-high-resolution reconstruction (10 iterations) without high noise penalty

For this qualitative study, the images appear to be of diagnostic quality

Does uEXPLORER reality live up to total-body PET theory: Total-body pharmacokinetic imaging

Data acquired in list-mode during injection and for one hour after injection
Data binning in 1s frames





Time activity curves

Julie Haglund, haglundj@aol.com, september 2019

uEXPLORER and total-body PET: What' next?

The future is quantitative and practical (clinical utility)!

Image better

- **> 6-fold increase in SNR**
- Reconstruct at higher resolution
- Detect smaller lesions
- Detect low-grade disease
- Better statistics for kinetic modeling

Image faster

- **Total-body PET in 15-30 secs**
- Image in a single breath hold
- Reduce respiratory motion
- Higher resolution
- Total-body kinetic imaging with good temporal resolution

Image longer

- **40-fold increase in dynamic range**
- Image for 5 more half lives
- ^{11}C > 3 hours
- ^{18}F > 18 hours
- ^{89}Zr > 30 days

Image gently

- **40-fold reduction in dose**
- Whole-body PET at 150 μSv
- PET in new populations (adolescents, pediatrics)
- Many repeat scans in an individual (follow disease trajectory)

References and Thanks

Thanks to IFMP for the opportunity and help to study a topic in Hybrid Imaging and to give a lecture at this Plovdiv workshop 2019!

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