Time-of-flight: The last frontier in Positron Emission Tomography

Georgios Konstantinou

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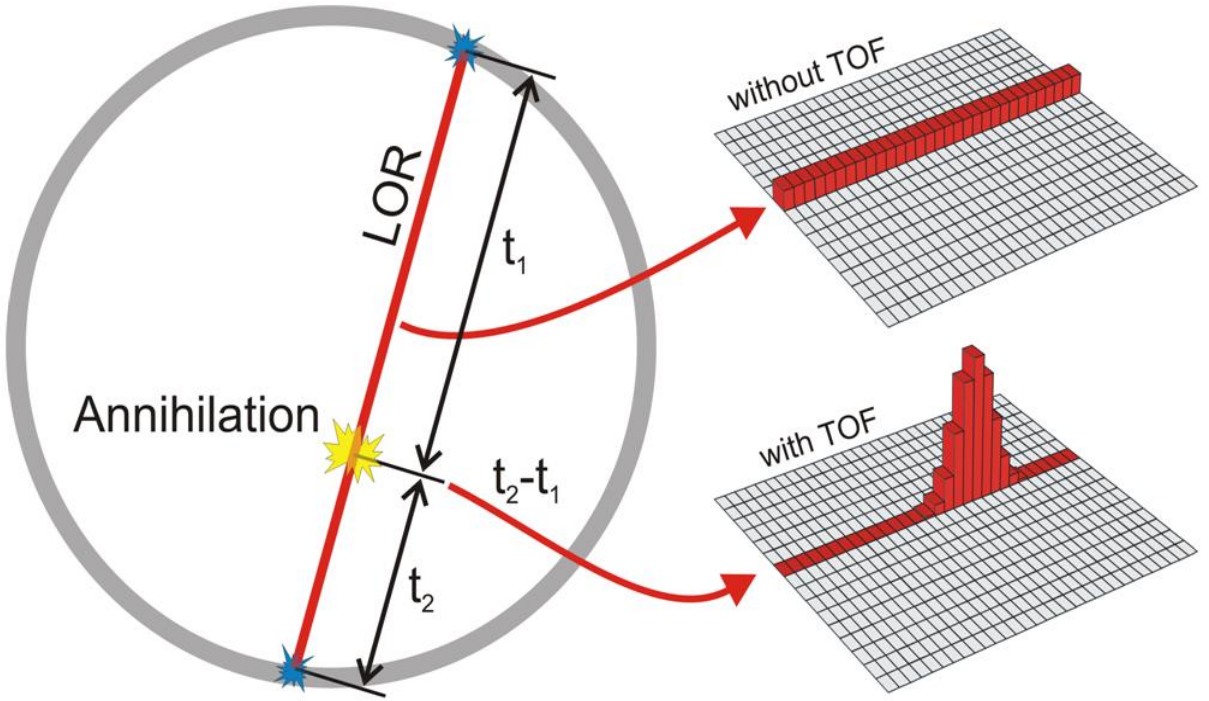
- Basics of TOF PET
- Clinical Advantages
- Why the last frontier?
- State of the art in instrumentation
- The 10 ps PET: A possible future

Basics of TOF PET



https://the10ps-challenge.org/

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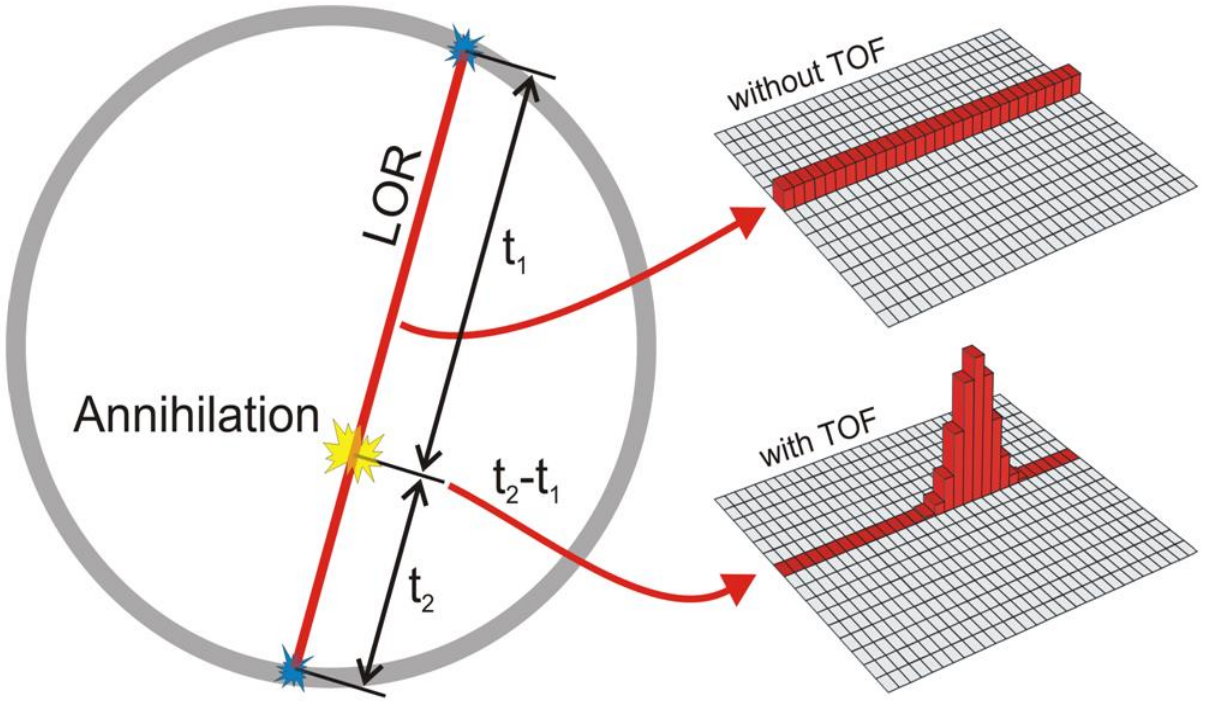

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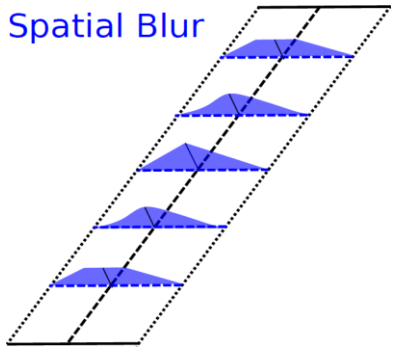
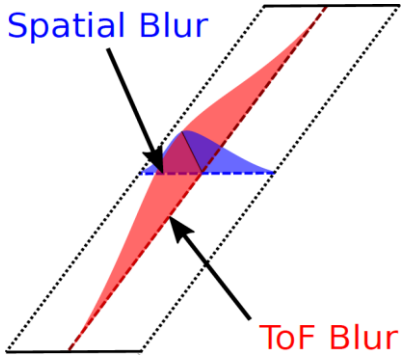
Complementary information: Transverse and longitudinal

Courtesy of R. Lecomte, Sherbrooke



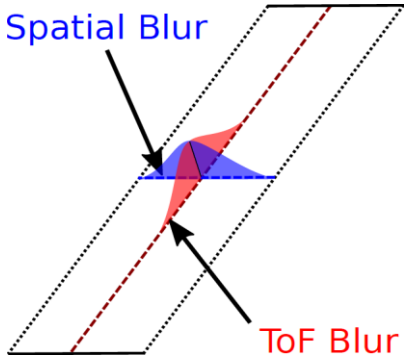
No ToF

Classical tomographic reconstruction



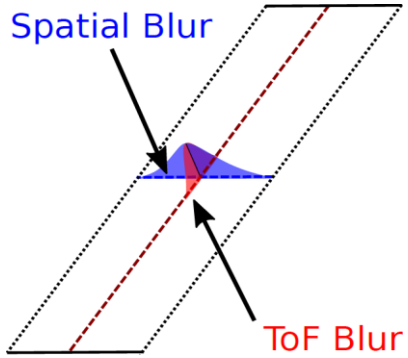
Current

CTR ~200 ps
ToF-weighted reconstruction



Near future

CTR ~ 30 ps
$R_{ToF} \approx R_{det}$
No more reconstruction*!*



Far future?

CTR ~ 10 ps
$R_{ToF} < R_{det}$
ToF-enhanced reconstruction*!*

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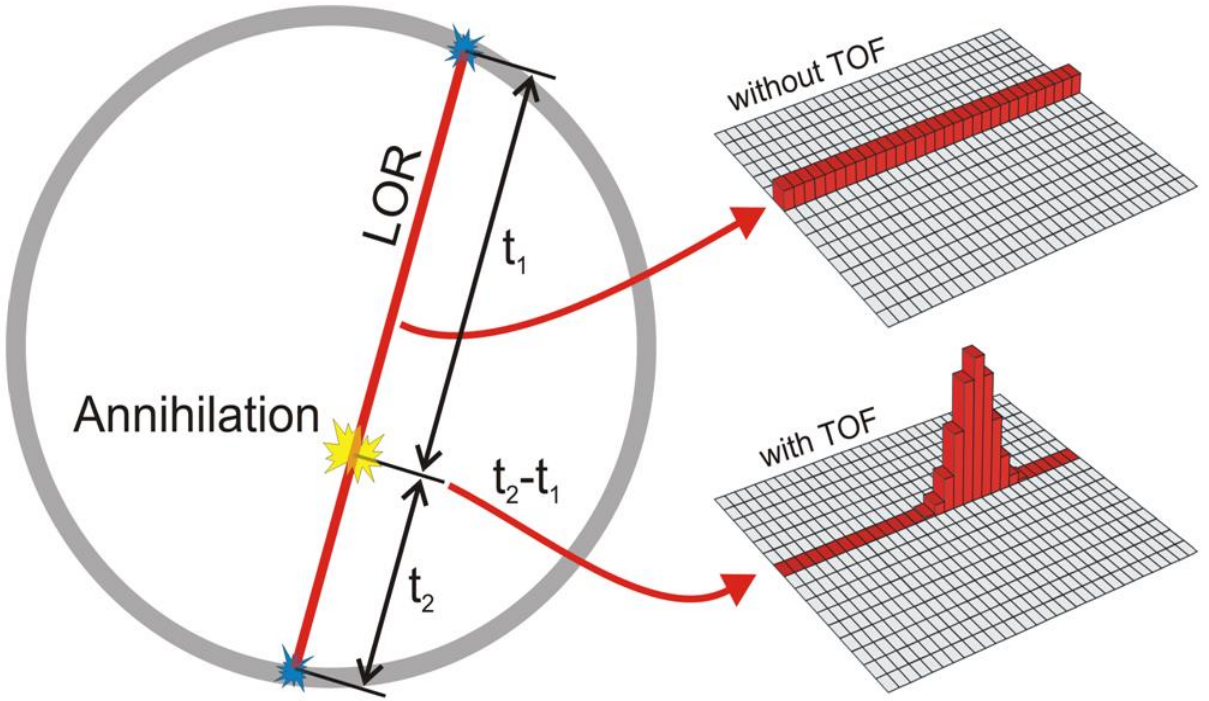

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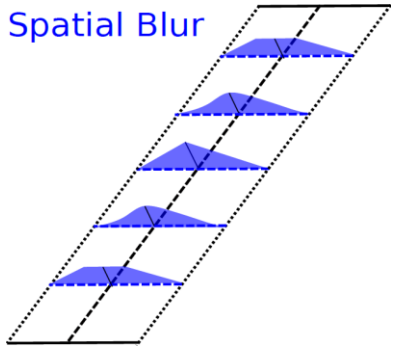

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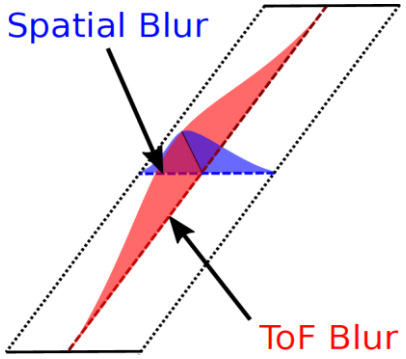

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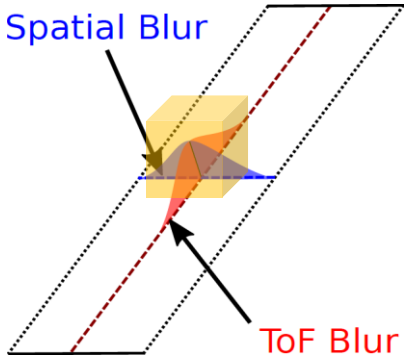

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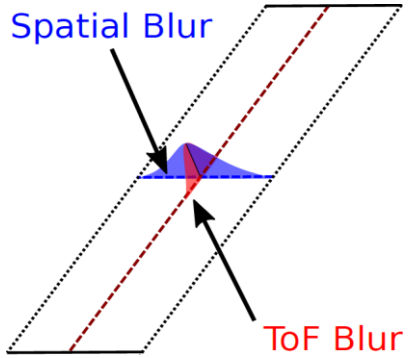

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$$\Delta x = \frac{c\Delta t}{2}$$

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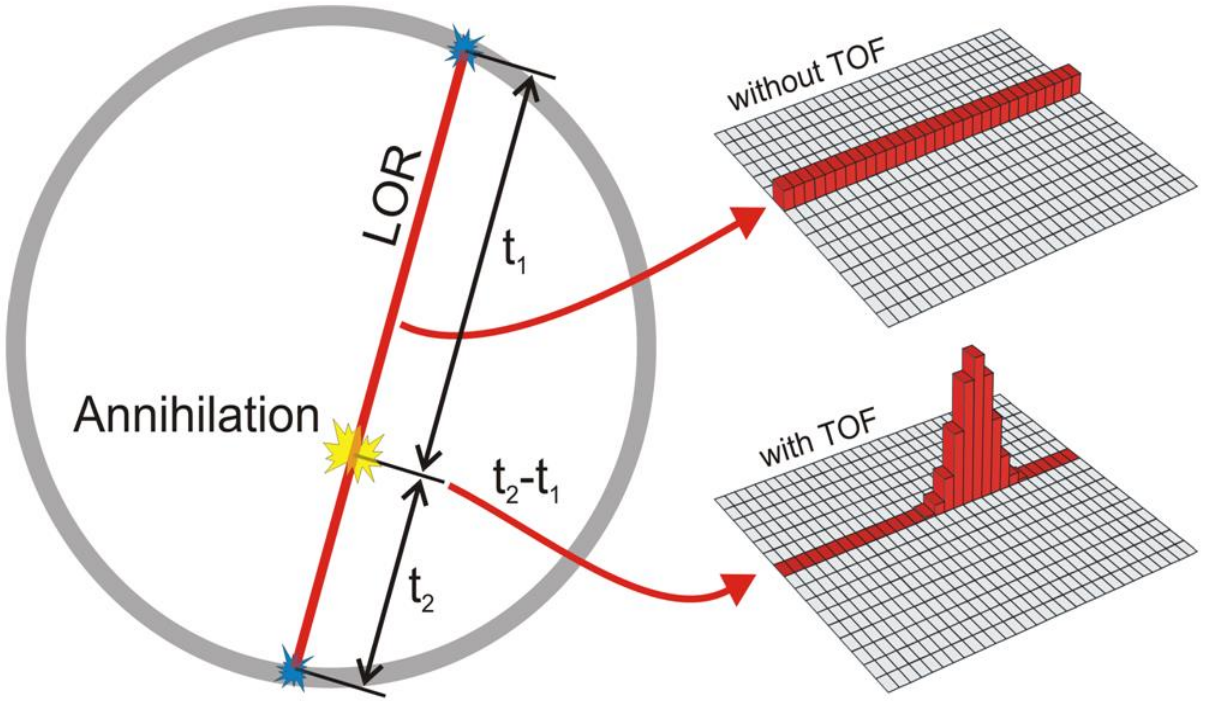
Budinger, 1983



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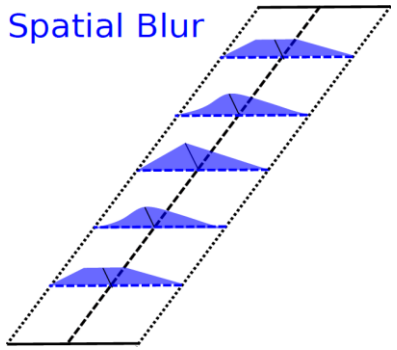

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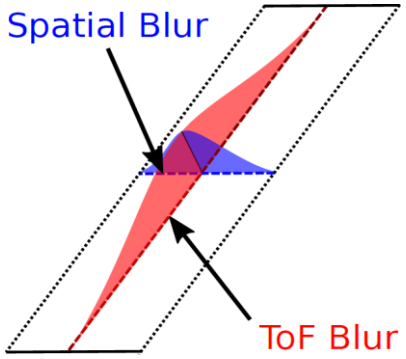

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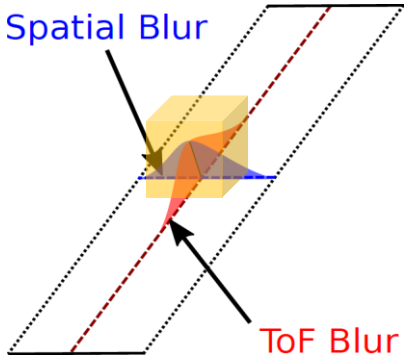

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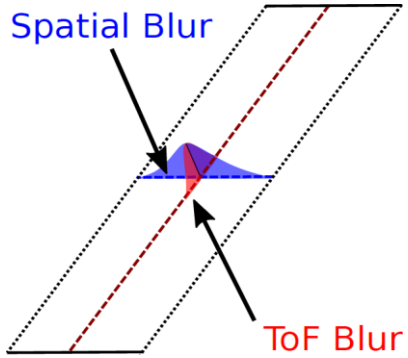

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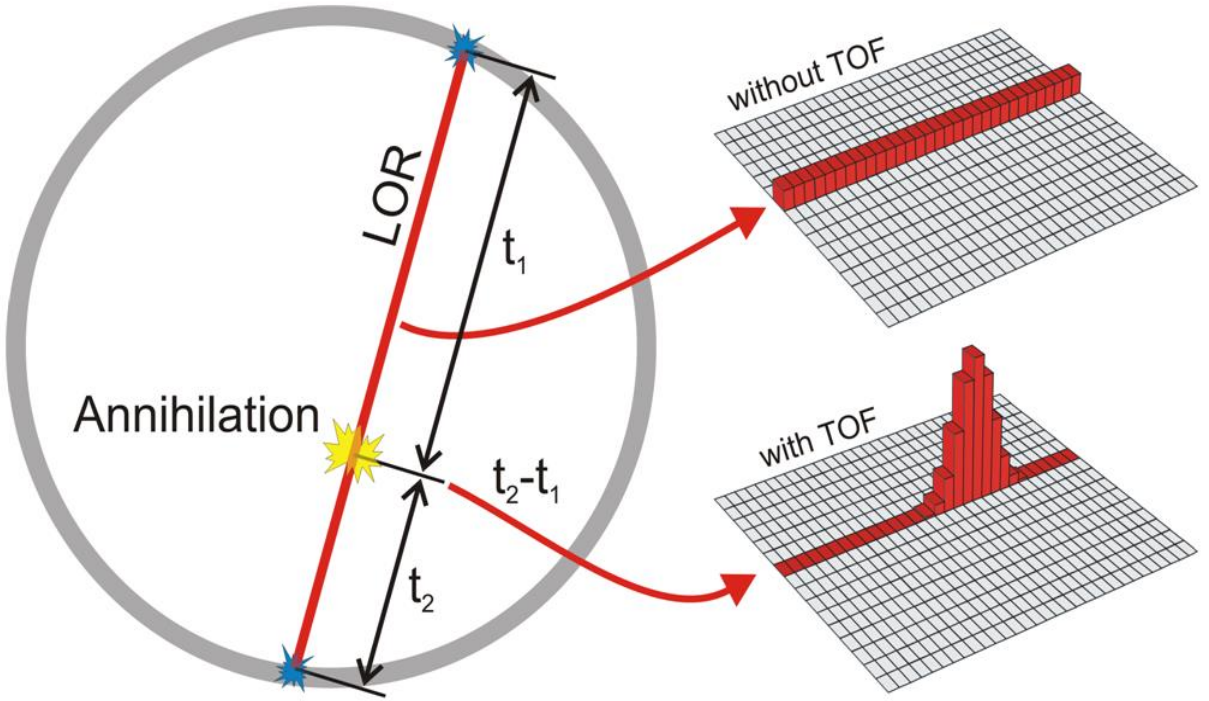

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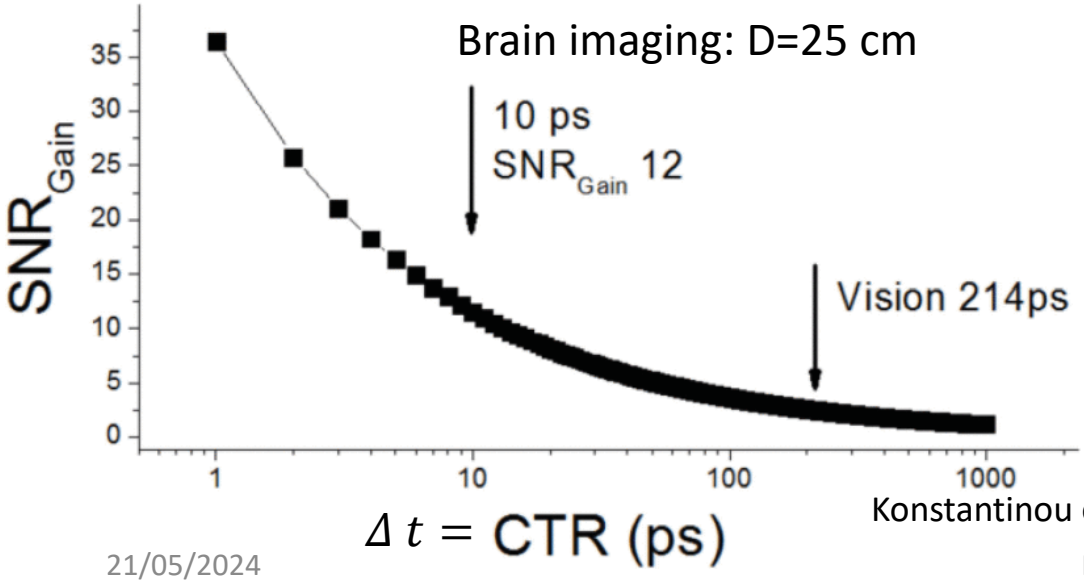

Konstantinou et al., 2021

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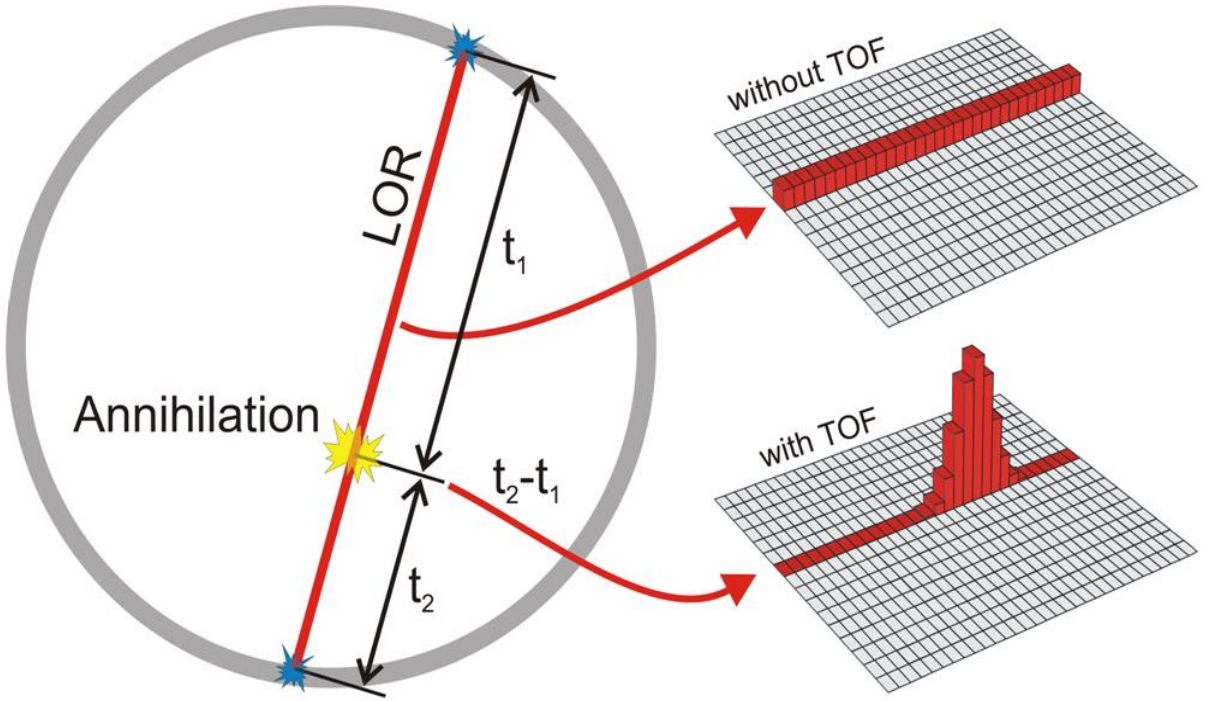

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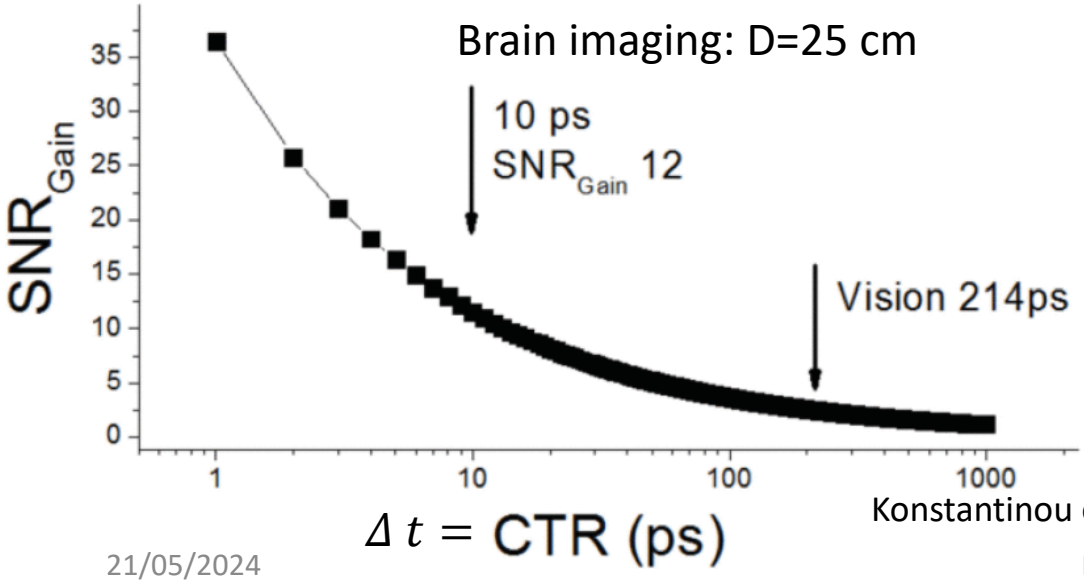
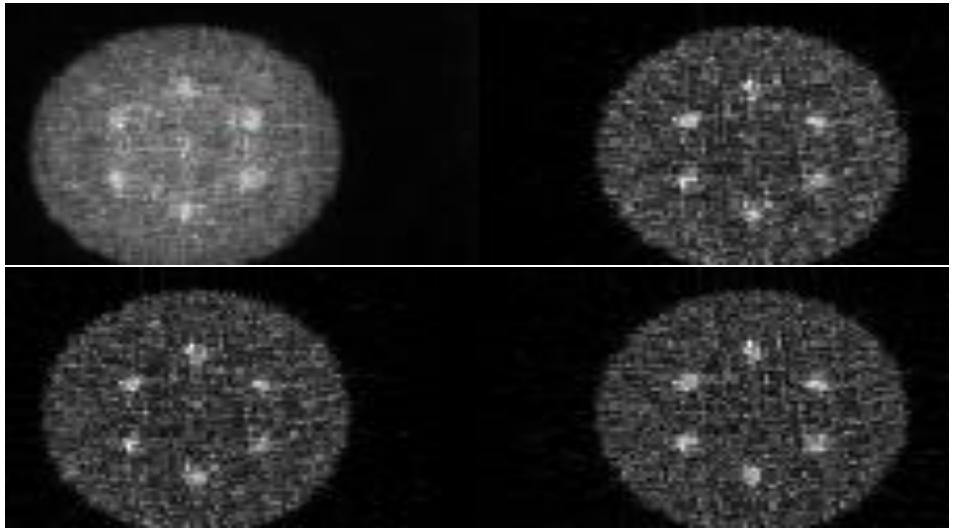


Konstantinou et al., 2021



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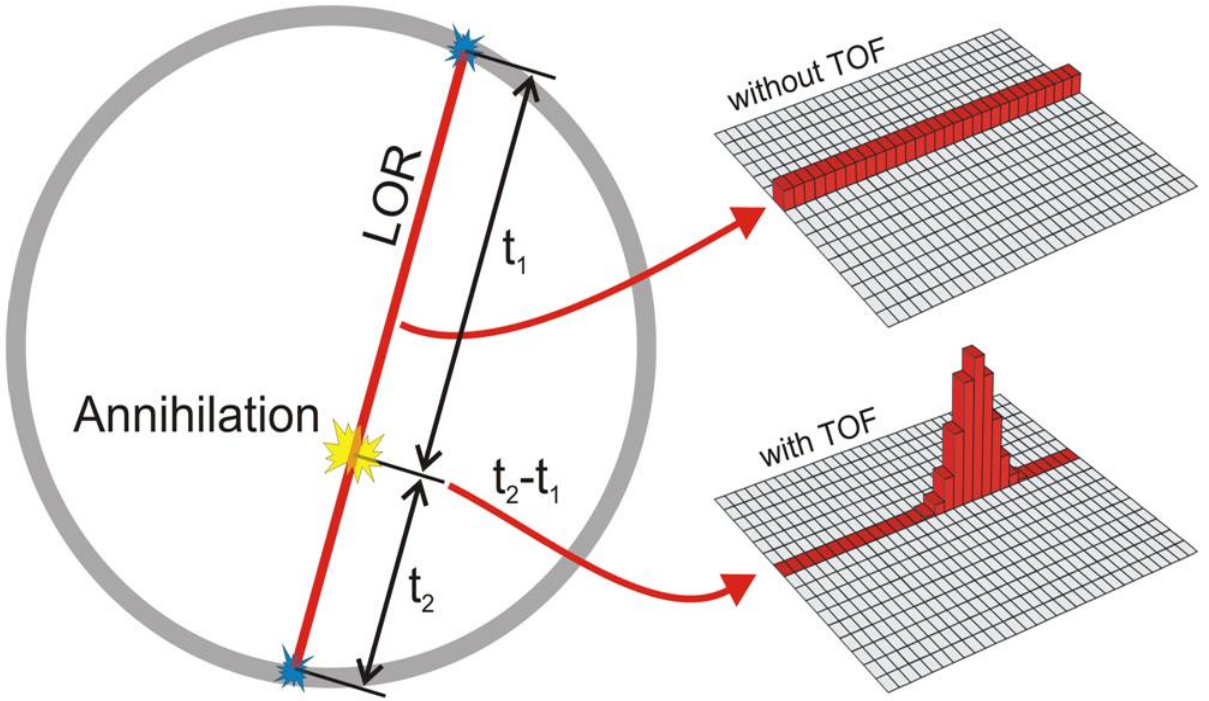

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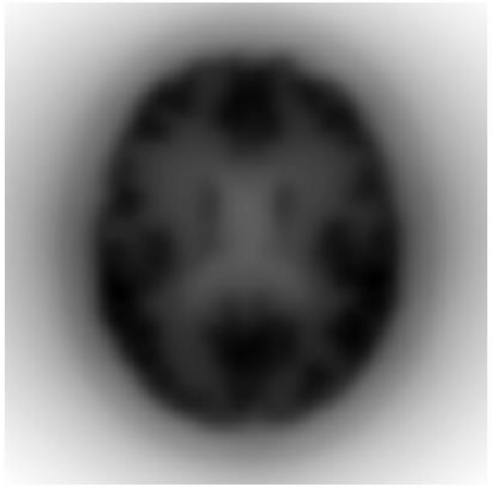
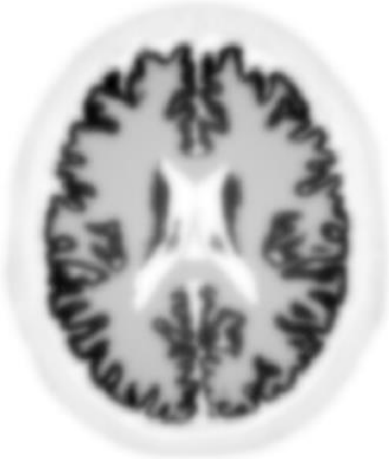
Hoffman brain phantom

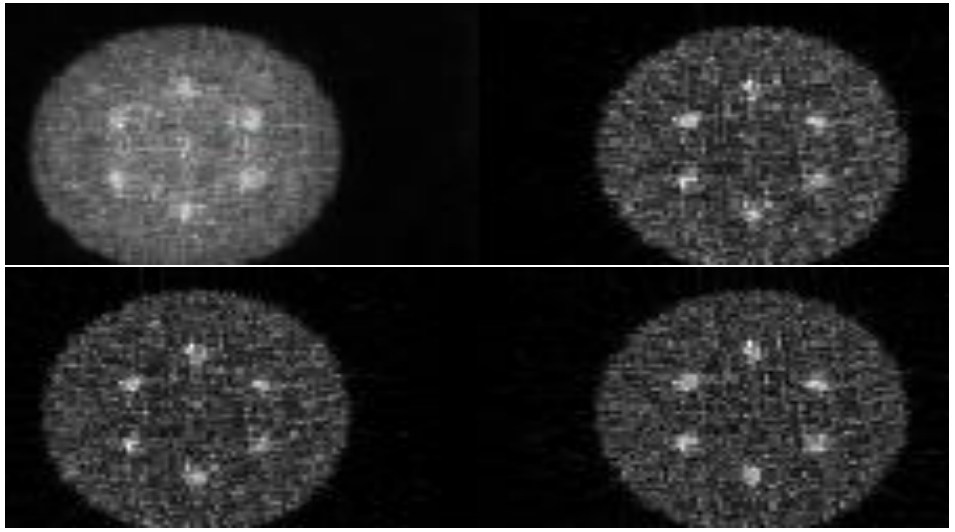


Non-TOF back-projection



TOF back-projection with 10ps CTR

No TOF 700 ps



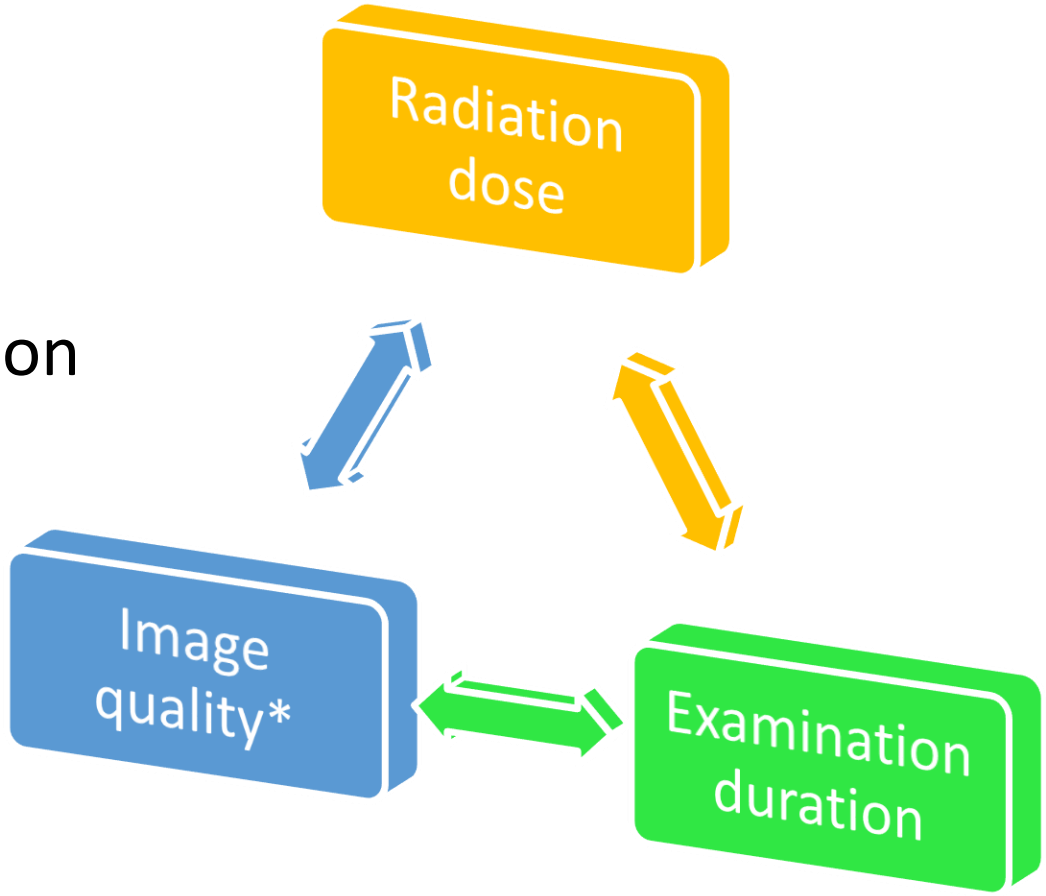
500 ps 300 ps

Courtesy of Johan Nuyts

Clinical advantages

Improved SNR:

- Lower noise, Improved lesion detection
- Better patient throughput
- Less radiation necessary



Examination duration

Vertex to thigh (halfbody) scan times:

- Biograph mCT TrueV (with TOF)
  - Median: 16:00
  - IQR: 14:00 to 17:30

TOF: 530 ps

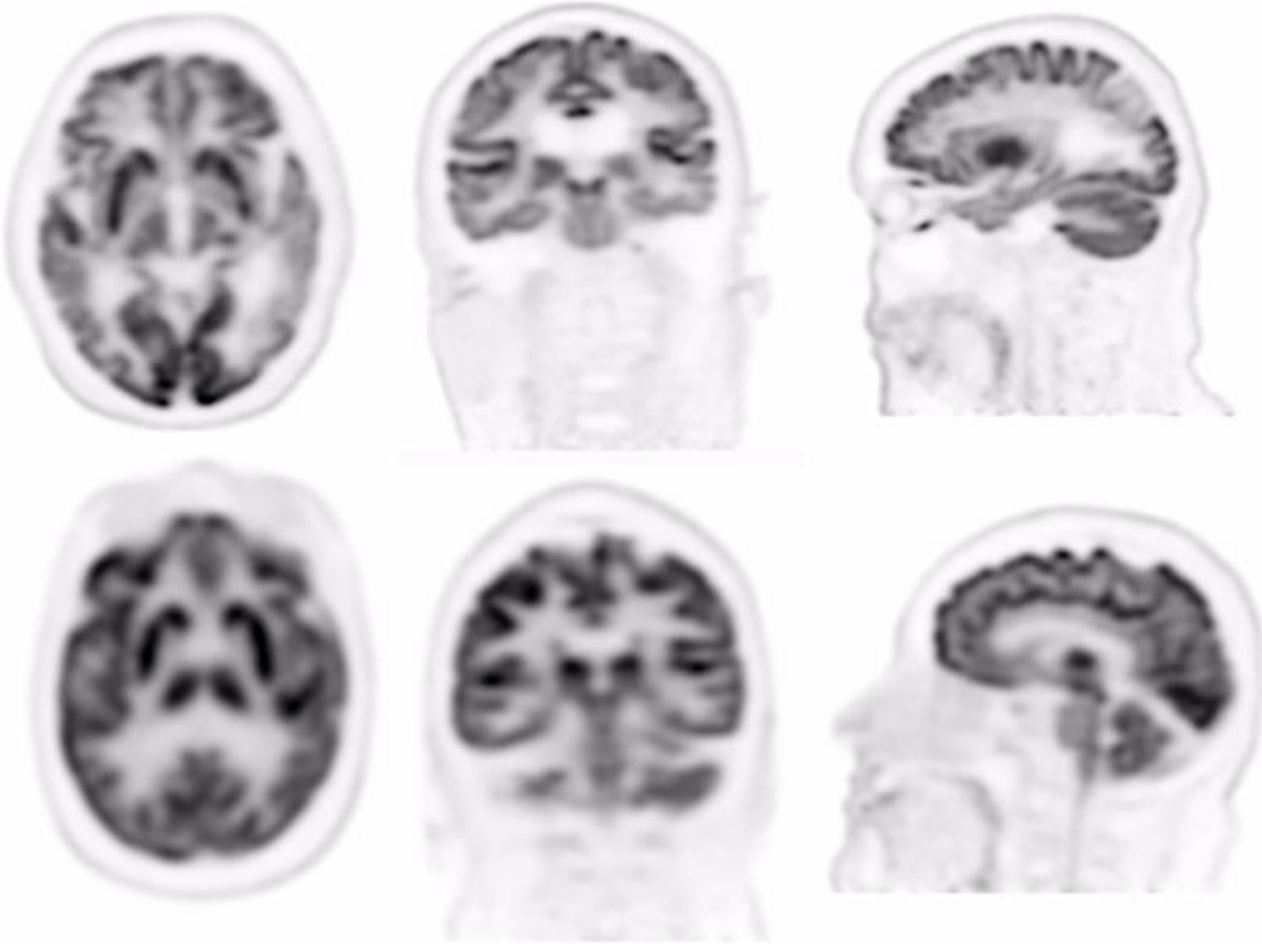
- Biograph Vision 600 (with TOF)
  - Median: 8:44
  - IQR: 7:46 to 9:55

TOF: 214 ps

Administered activity at 3.5 MBq/kg, max 280 MBq at 80 kg

Manchester Hospital, NHS trust, courtesy Ian Armstrong & Siemens Healthineers

Image quality*



Biograph Vision (SiPM TOF)

250 MBq FDG

15 minute

0.8 × 0.8 × 1.6 mm^3 voxels

TOF: 214 ps

Biograph mCT (PMT TOF)

250 MBq FDG

20 minute

2.0 × 2.0 × 2.0 mm^3 voxels

TOF: 530 ps

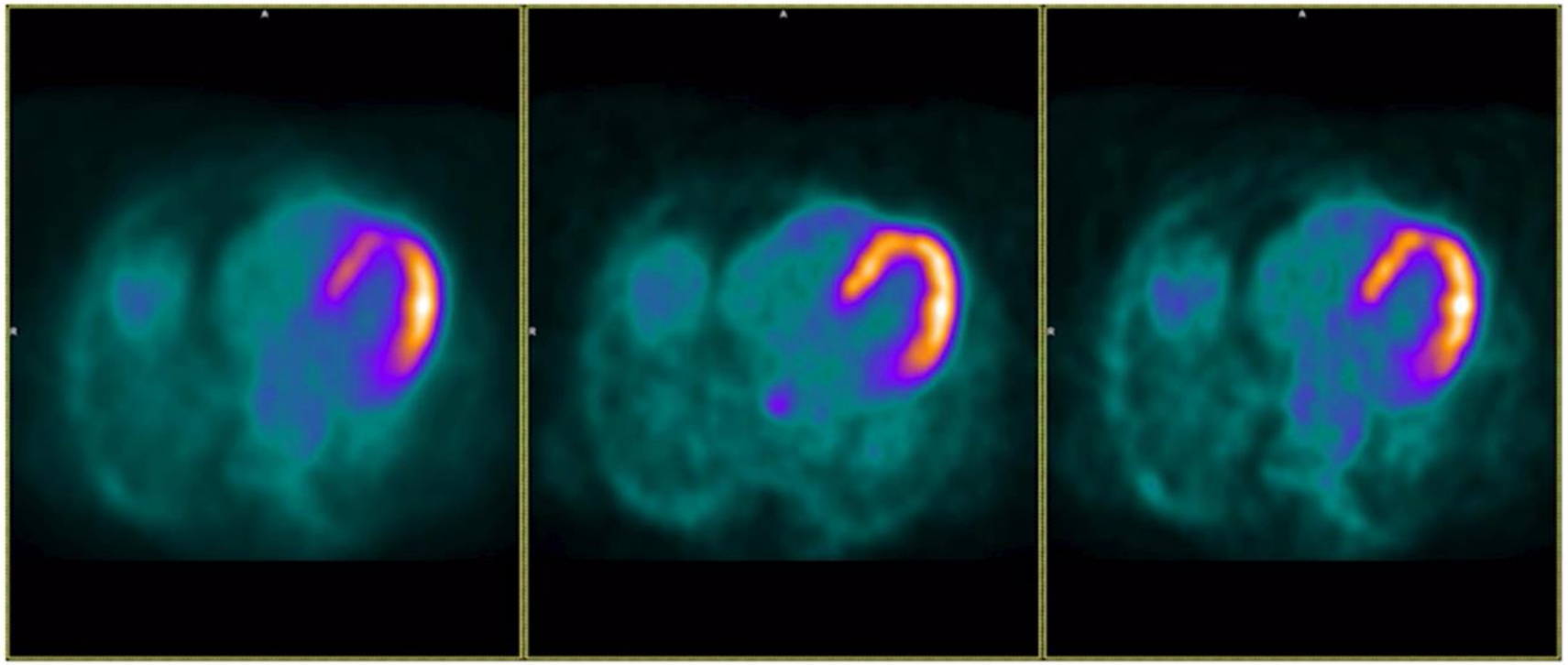
Manchester Hospital, NHS trust, courtesy Ian Armstrong & Siemens Healthineers

Clinical advantages

- Availability of **smaller voxels**
- Less reliance on post-reconstruction techniques to control image noise, **faster convergence**
- Improves visualization and quantification of **smaller lesions** and fine detail
- Reduces **artifacts** caused by misregistration or open architectures (streaks, bluring)

Faster convergence

Rubidium Cardiac Scan, 214 ps TOF resolution

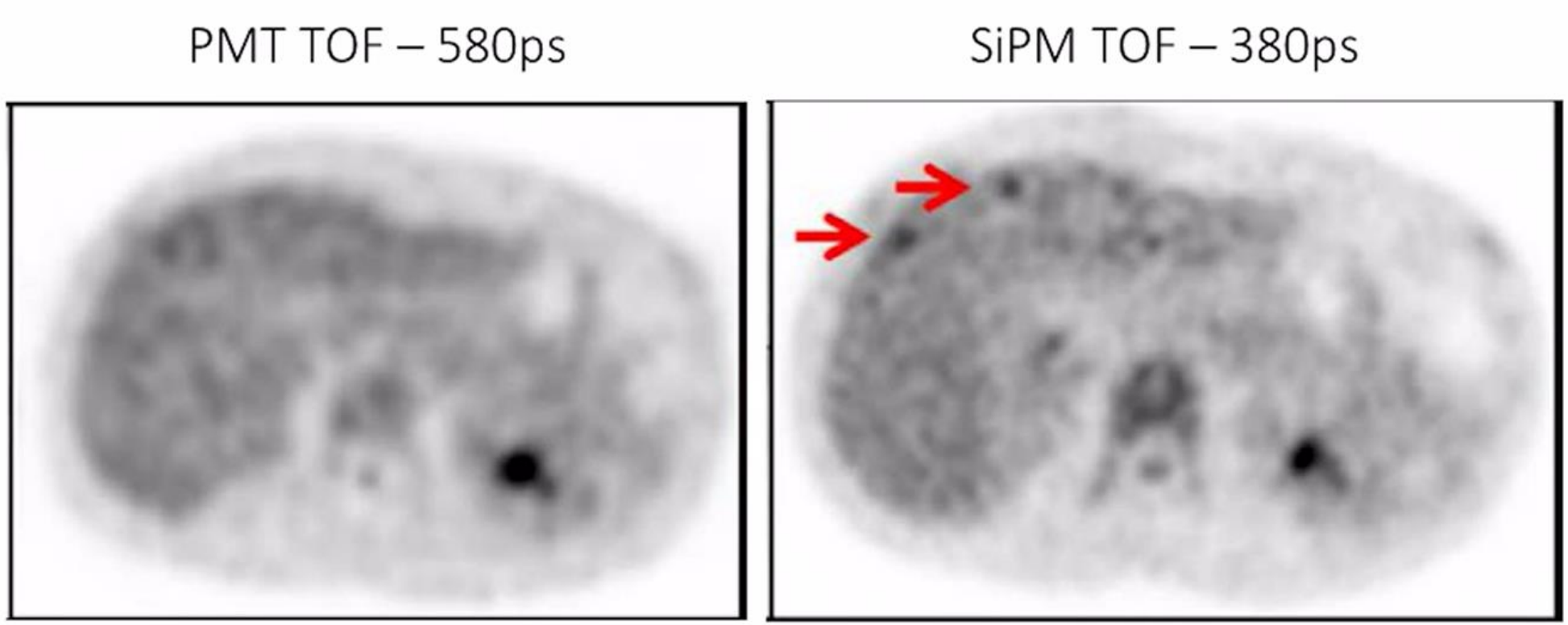


No TOF 4i | TOF 4i | No TOF 10i

Faster convergence → Fewer iterations → Less noise

Manchester Hospital, NHS trust, courtesy Ian Armstrong & Siemens Healthineers

Small lesion detection



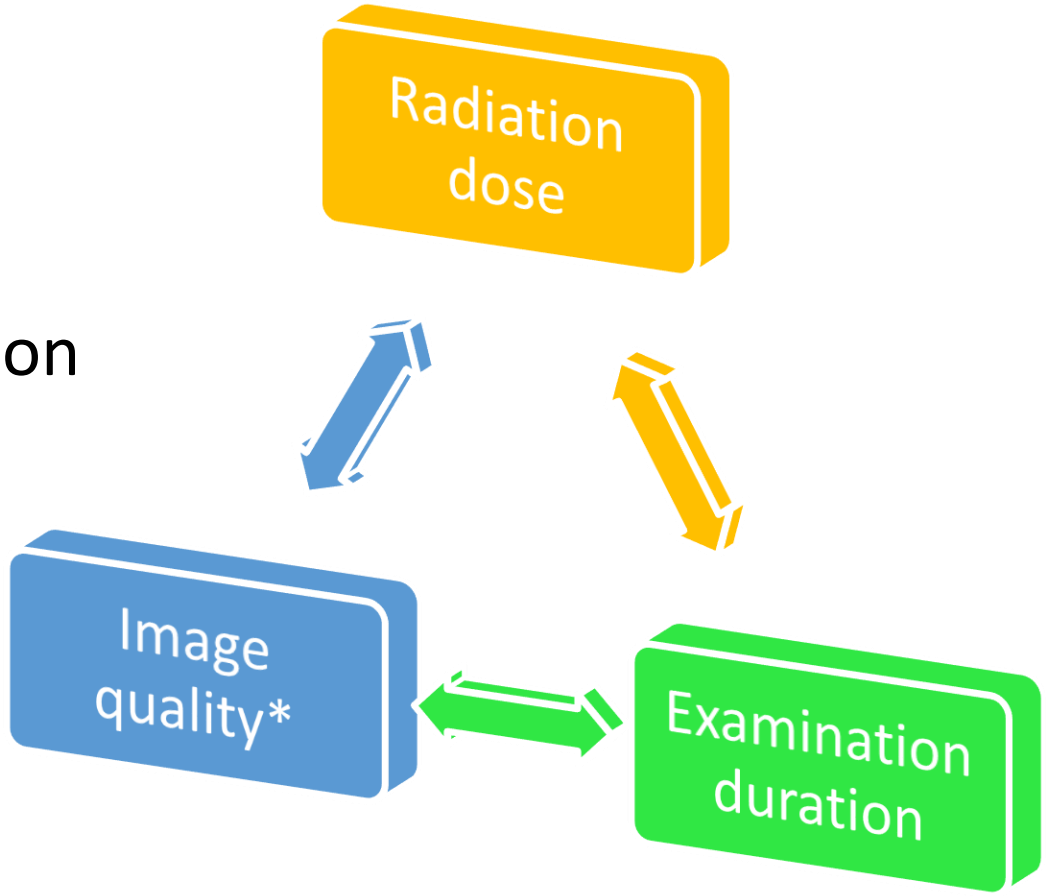
Liver metastasis FDG examination

Fuentes-Ocampo et al., 2021

Clinical advantages

Improved SNR:

- Lower noise, Improved lesion detection
- Better patient throughput
- Less radiation necessary

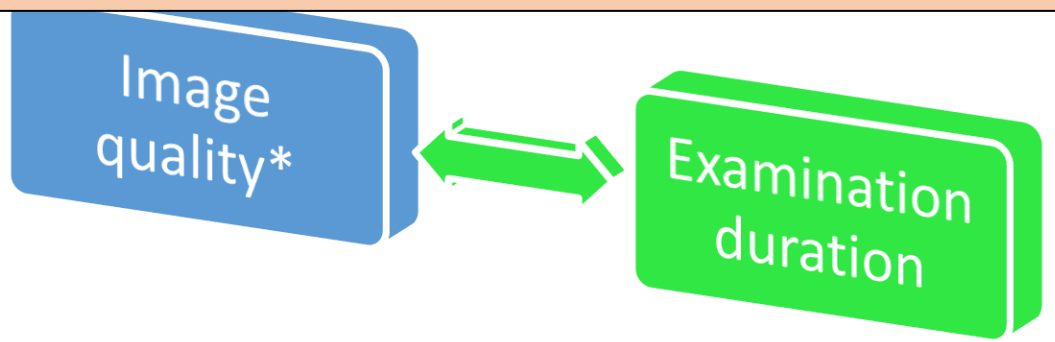


Clinical advantages

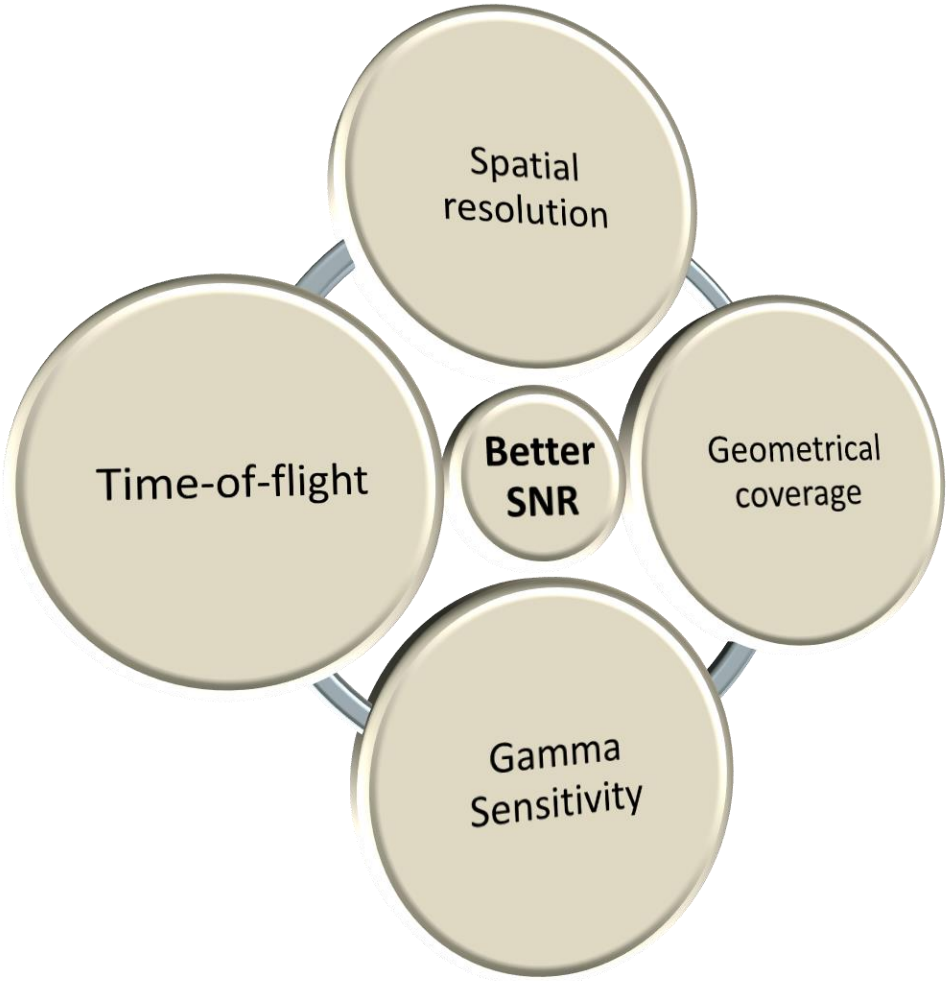
Improved SNR:

- Lowe
- Bette
- Less radiation necessary

Is this not what every instrumentation, data processing or reconstruction upgrade aims for?

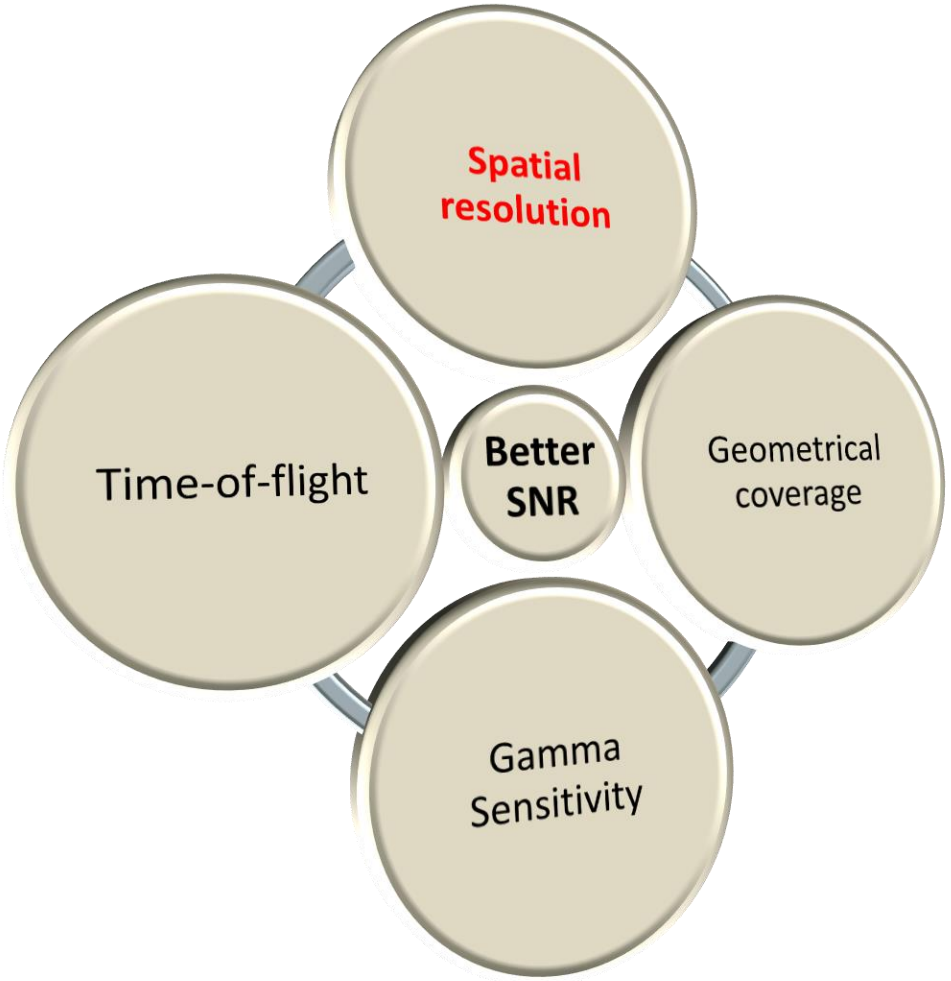


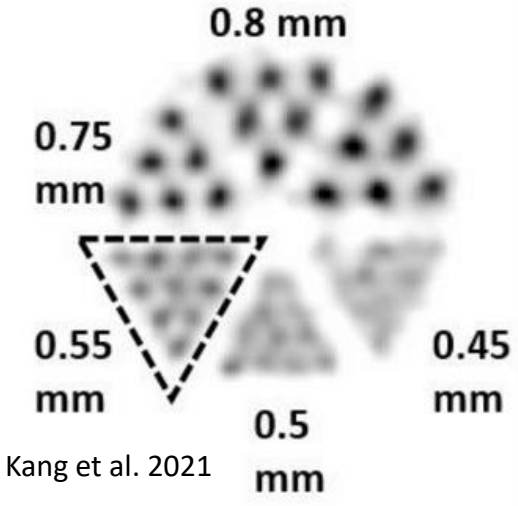
The SNR equation



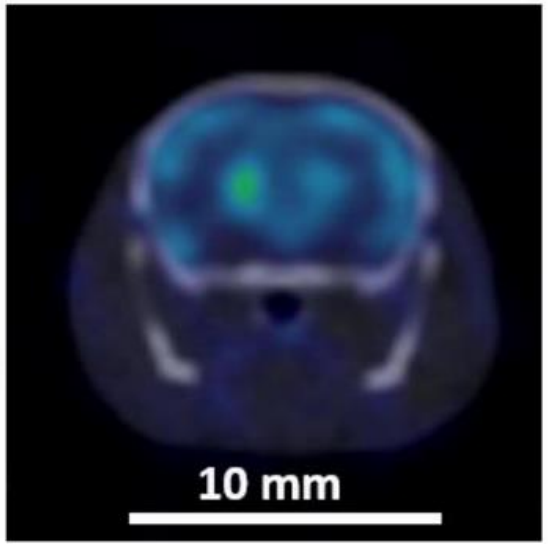
Spatial resolution

$$SNR \propto \frac{1}{R}$$





Kang et al. 2021



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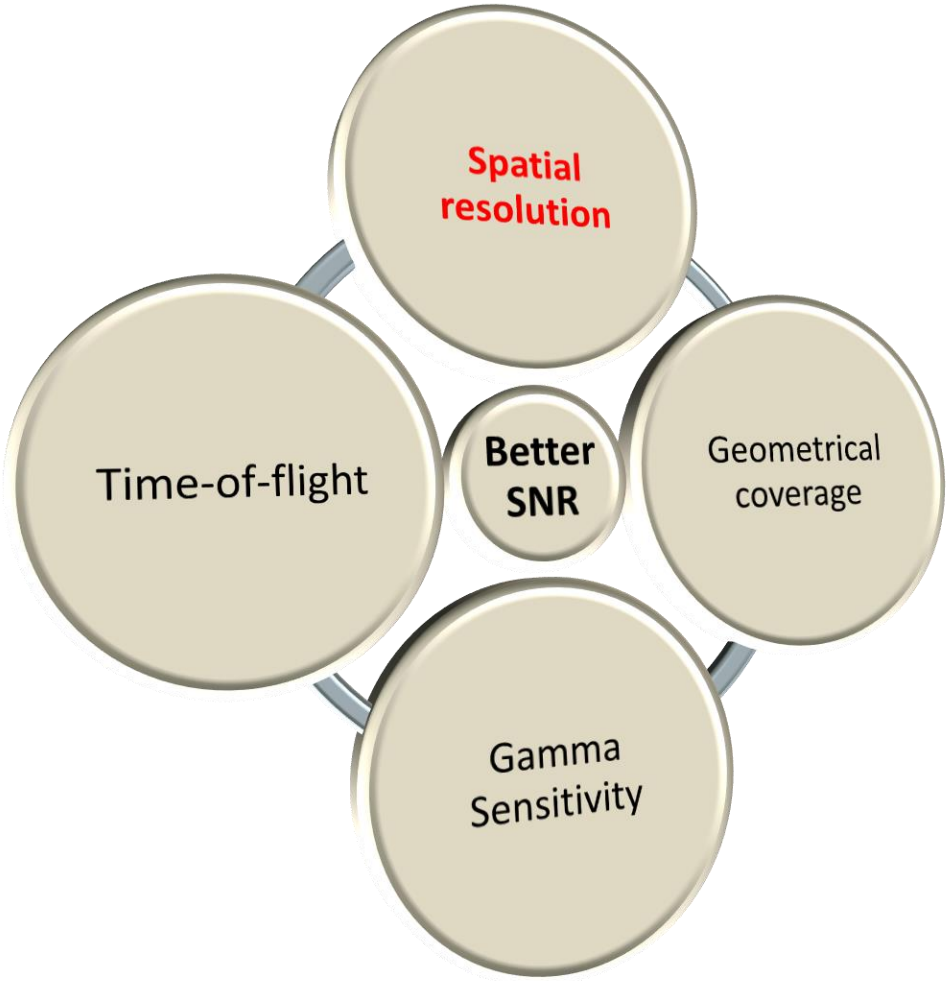
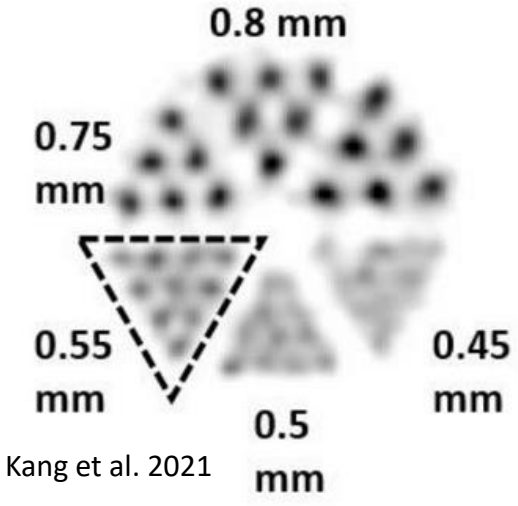
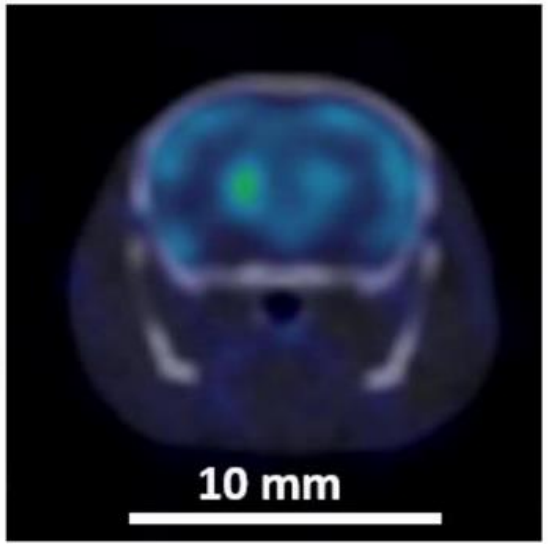
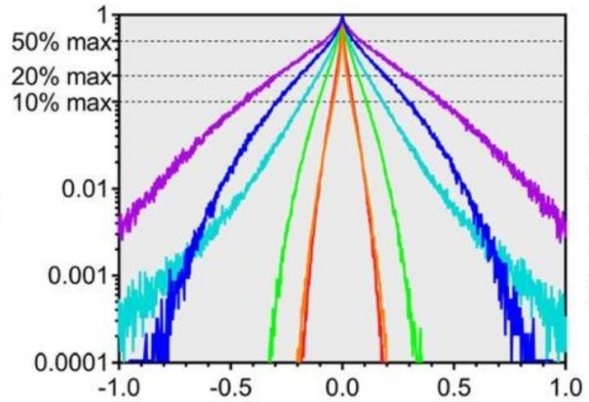




Kang et al. 2021



- Positron range



Carter et al. 2020

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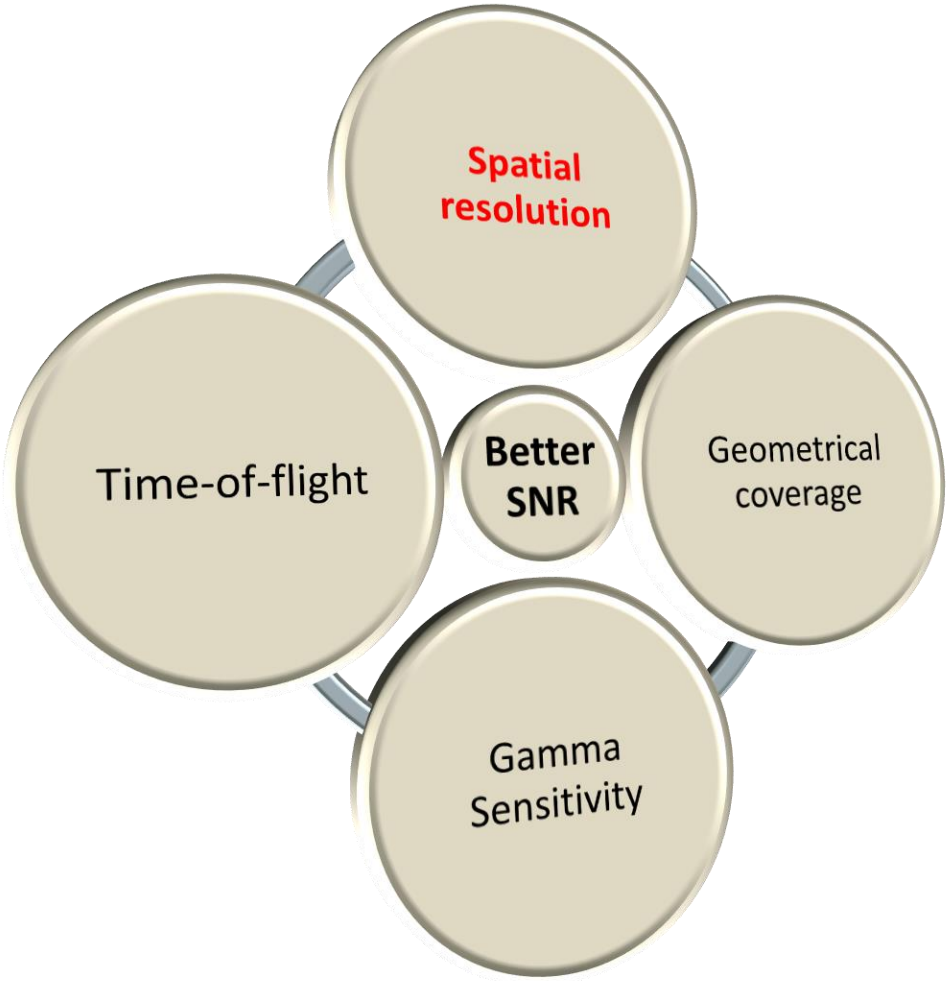

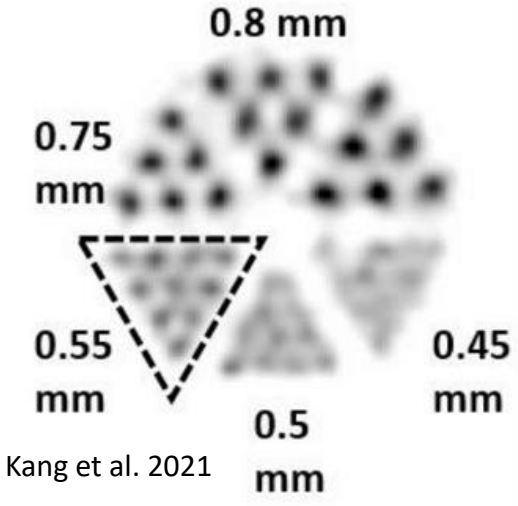

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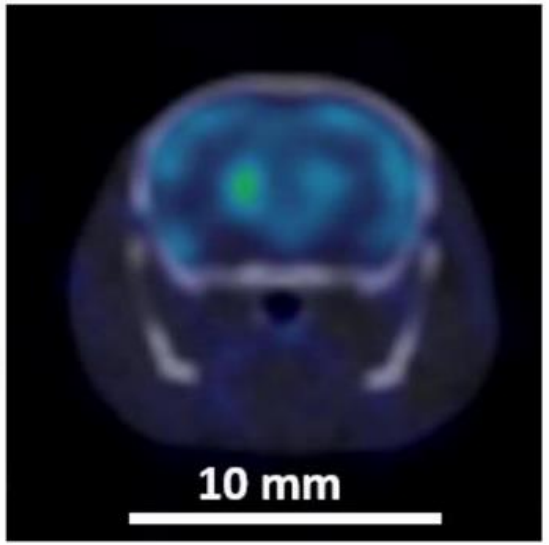

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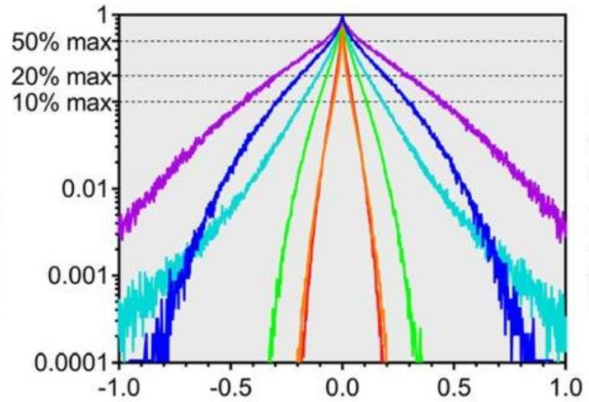
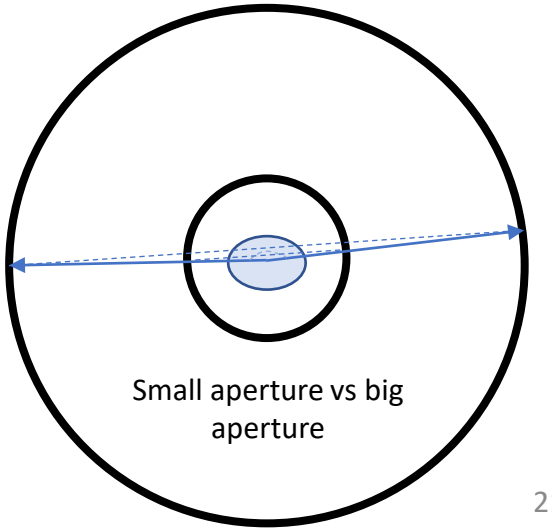


Carter et al. 2020

- Acolinearity



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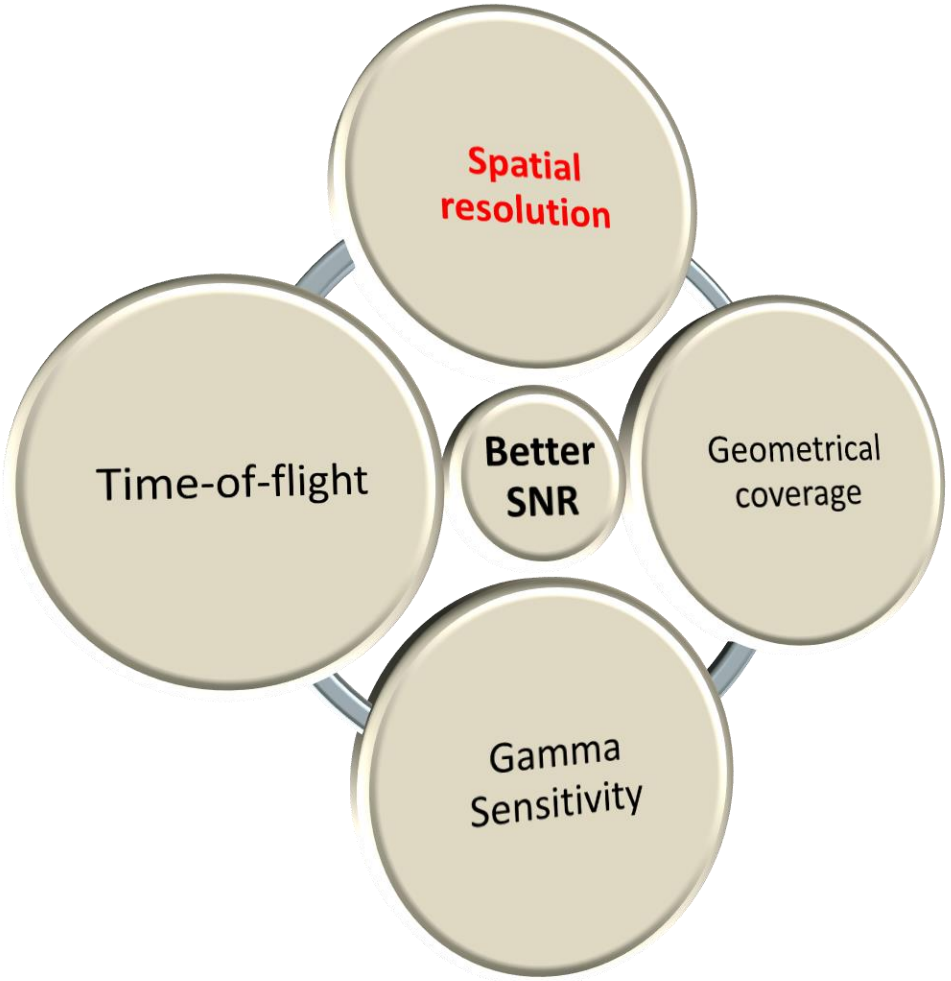

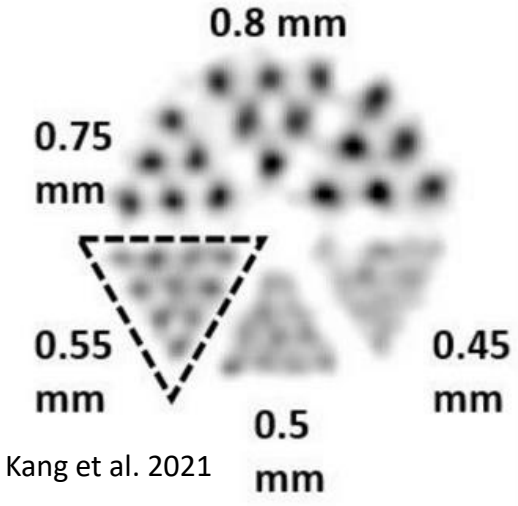

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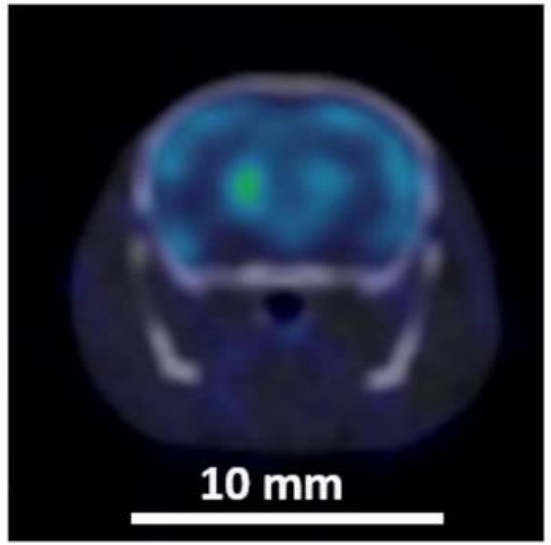

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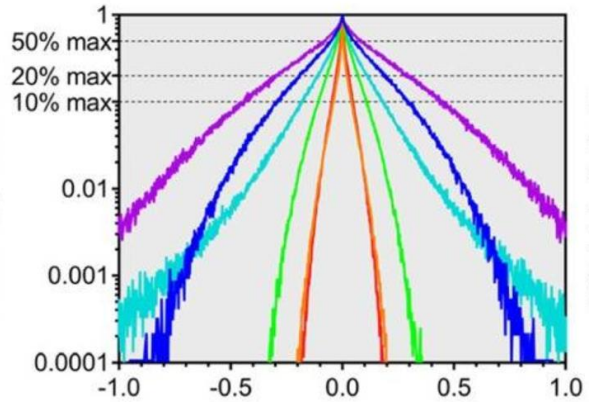

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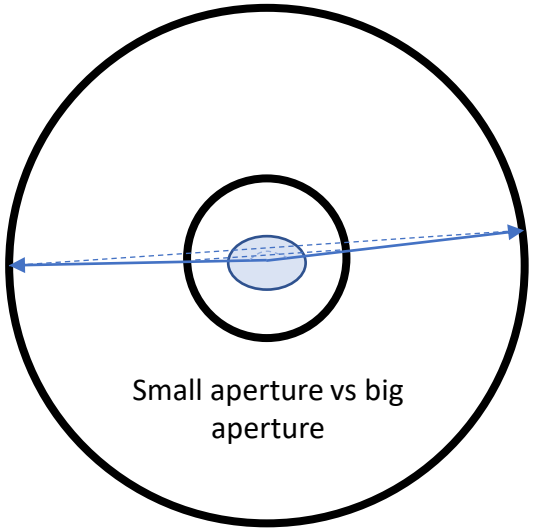
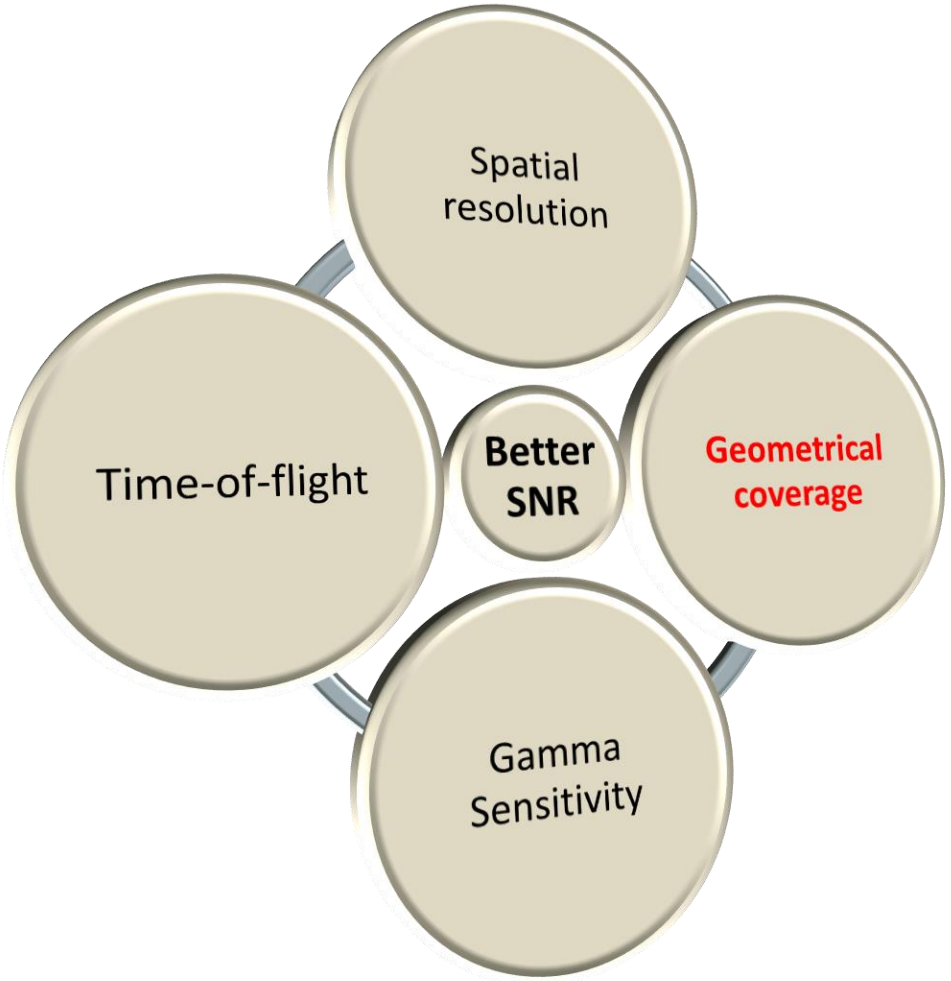
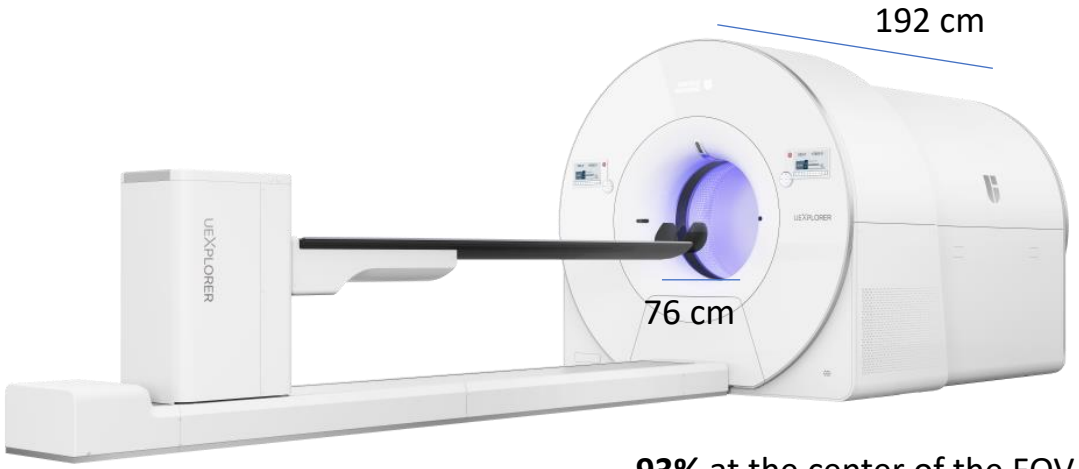


Physical limit: up to 2 mm

Geometry

$$SNR \propto \sqrt{C}$$

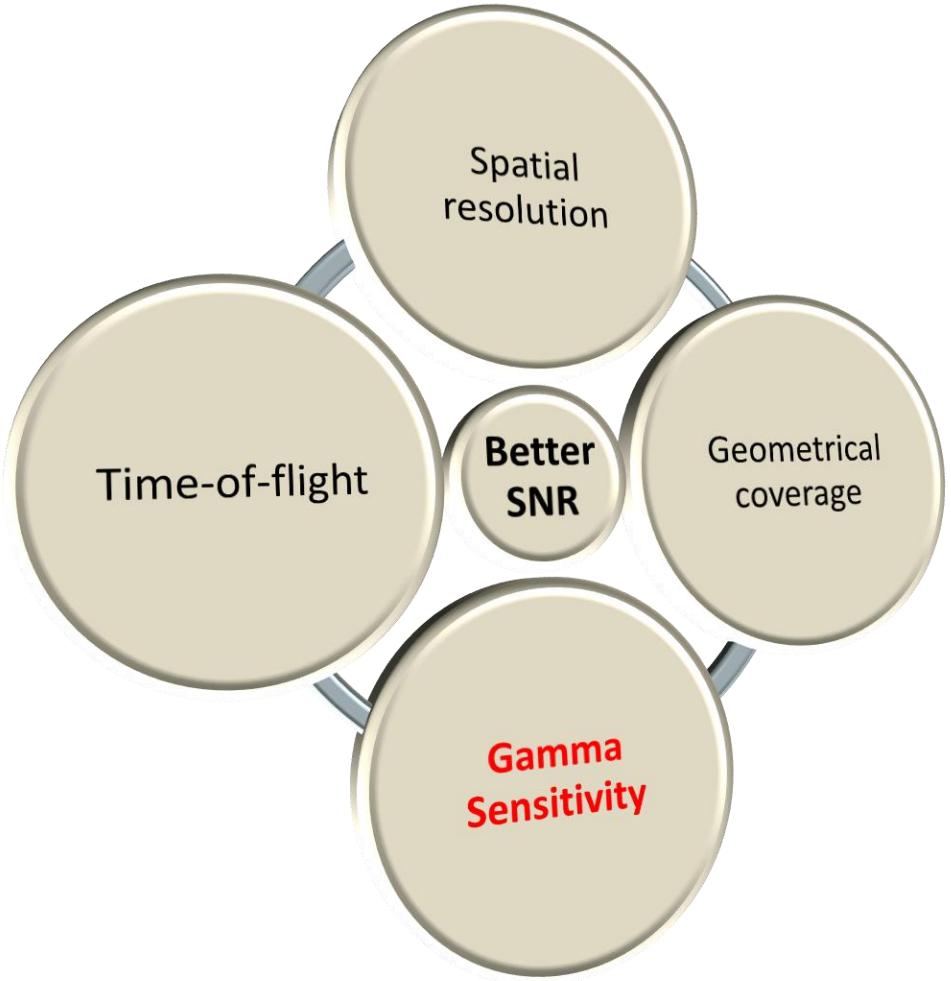


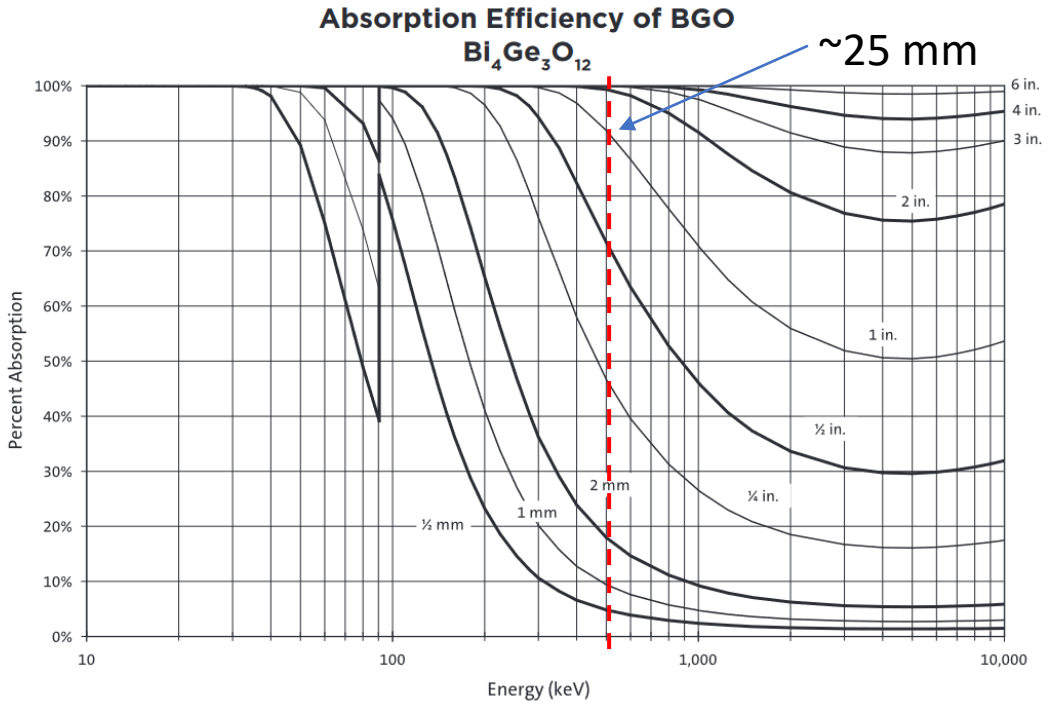


93% at the center of the FOV
206.5 cm maximum length of LOR

Efficiency

$$SNR \propto \sqrt{E}$$

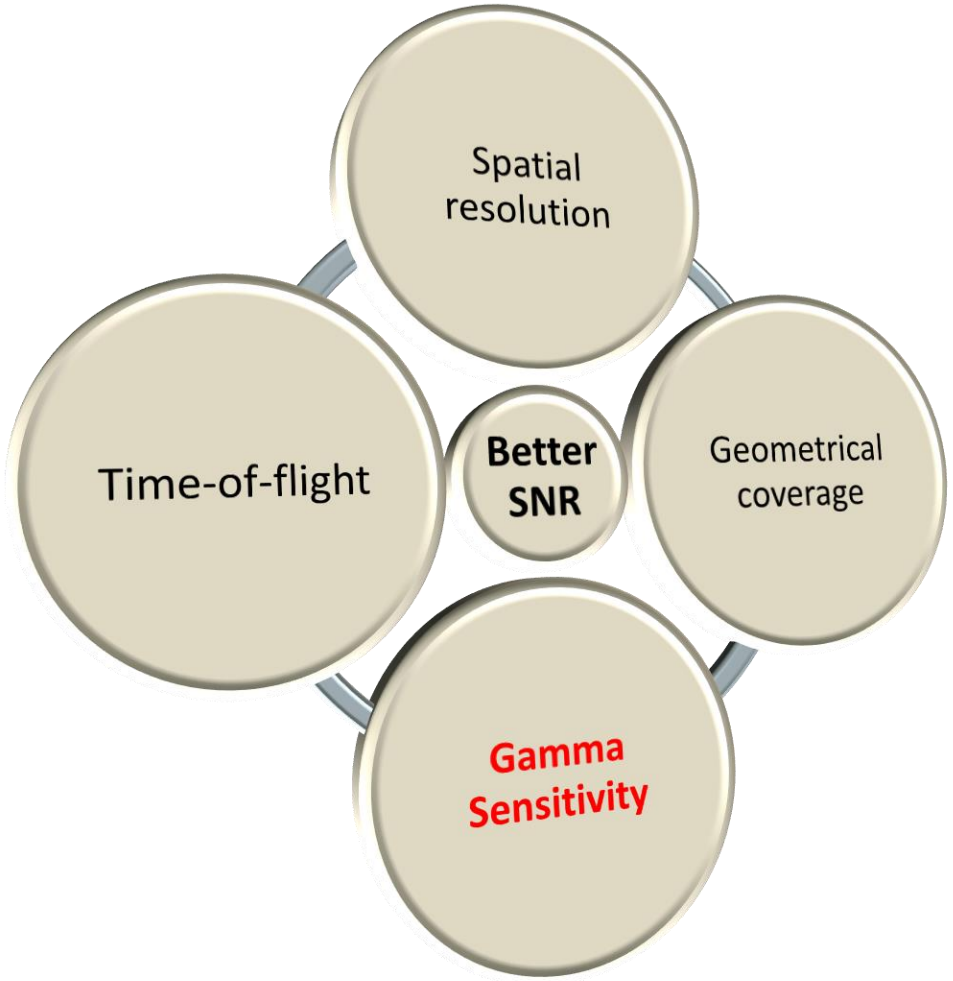


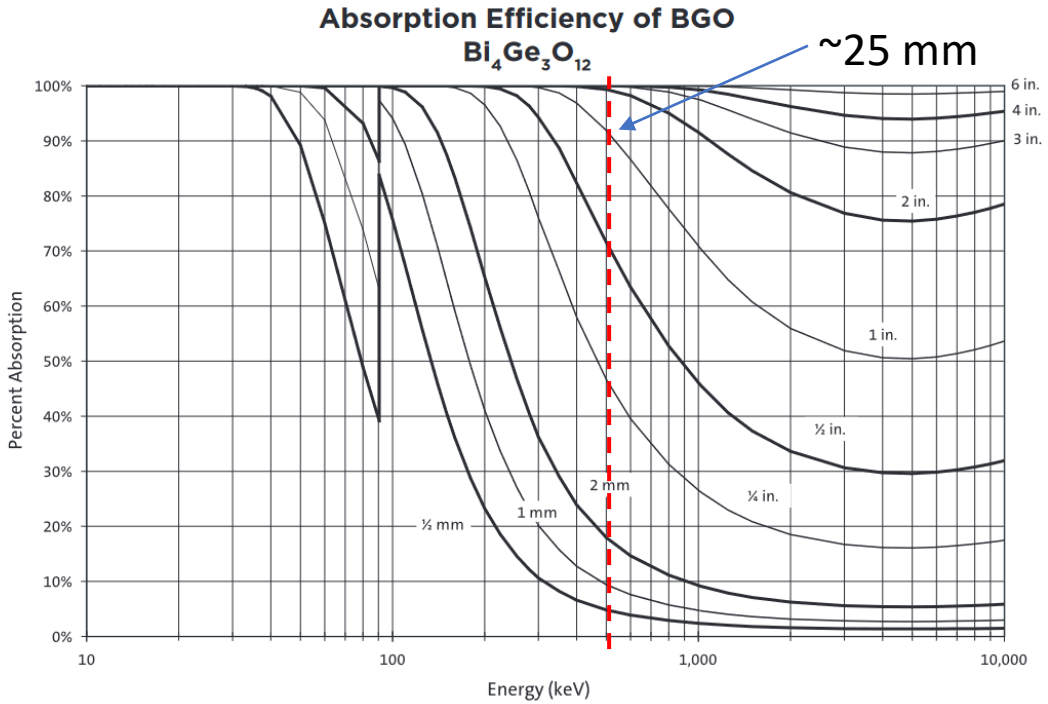


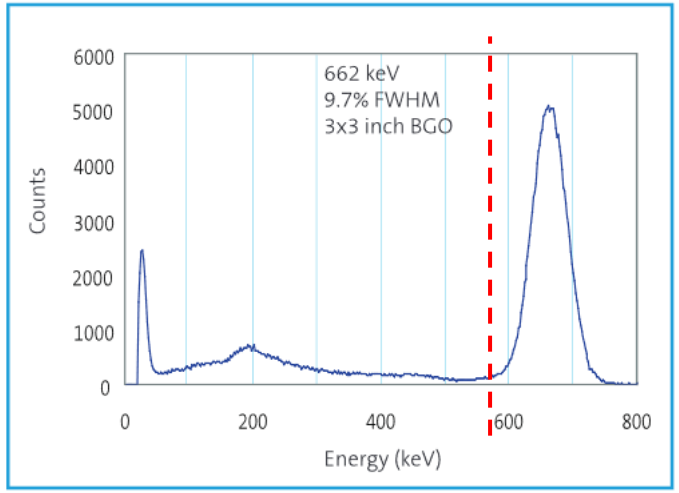
30 mm BGO:
90% singles

Efficiency

$$SNR \propto \sqrt{E}$$



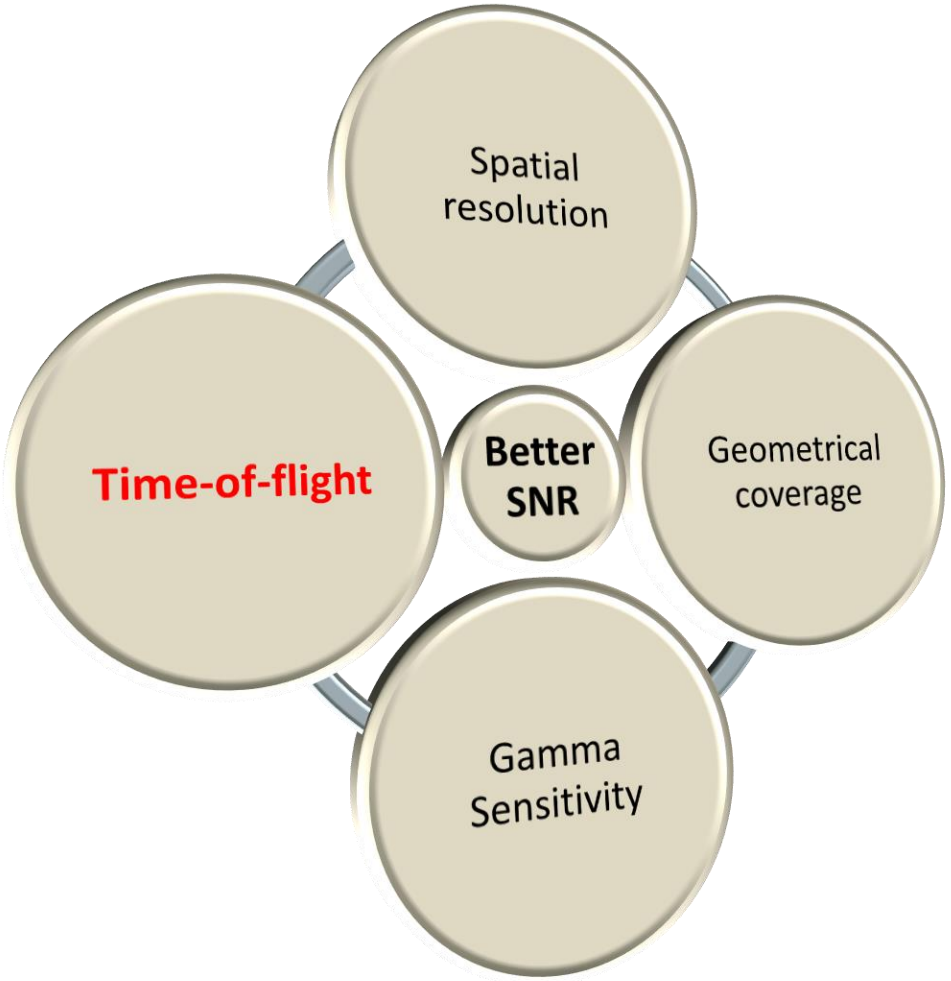


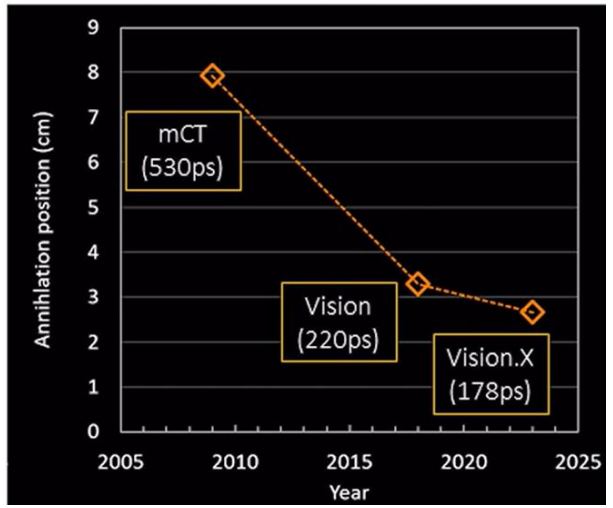


30 mm BGO:
90% singles
~60% photopeak

Why TOF is the last frontier?

$$SNR \propto \frac{1}{\sqrt{\Delta t}}$$





Courtesy of I. Armstrong

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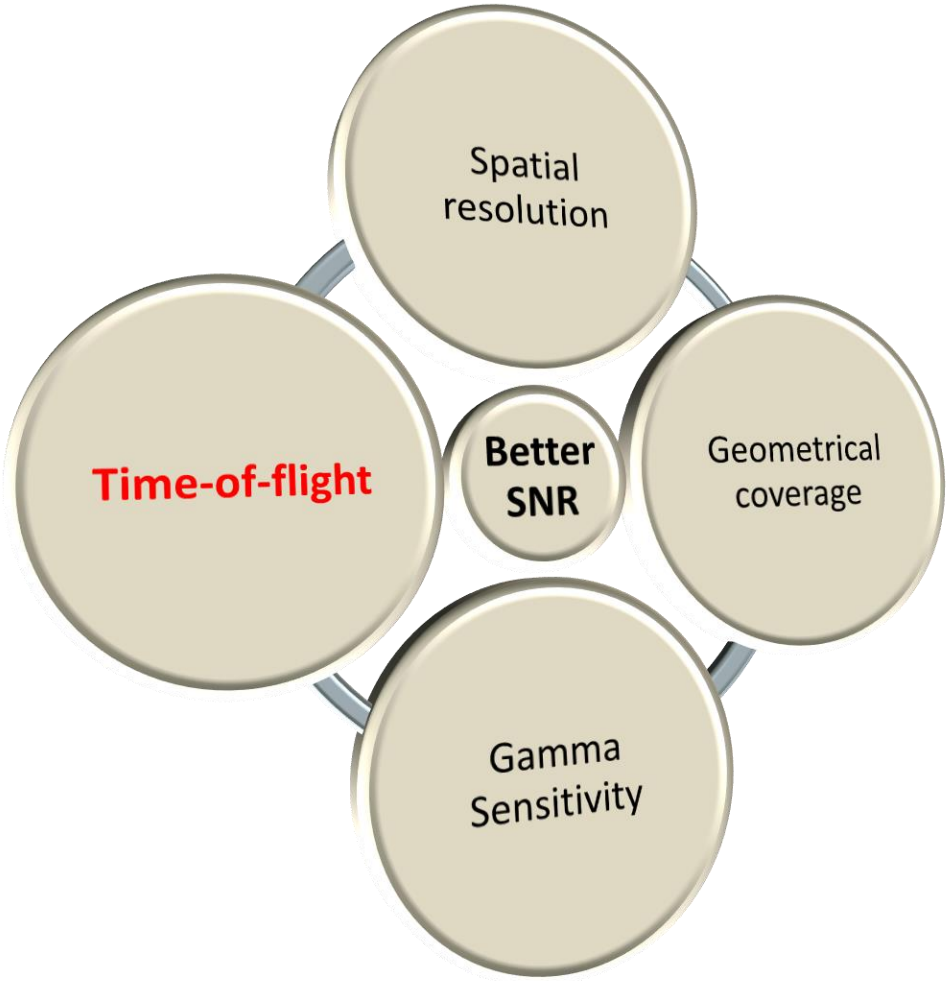
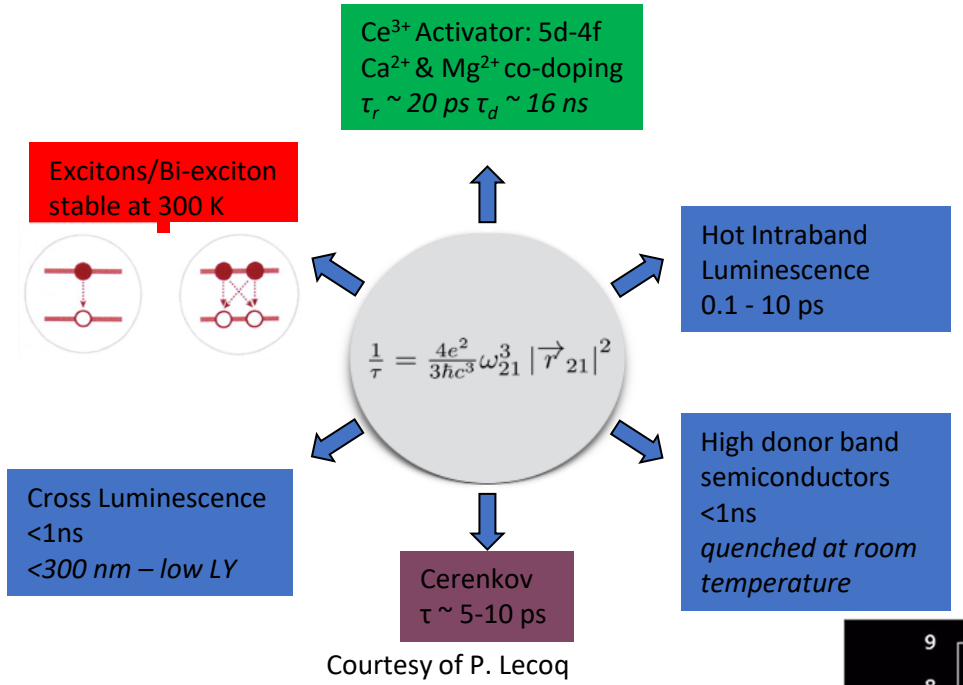


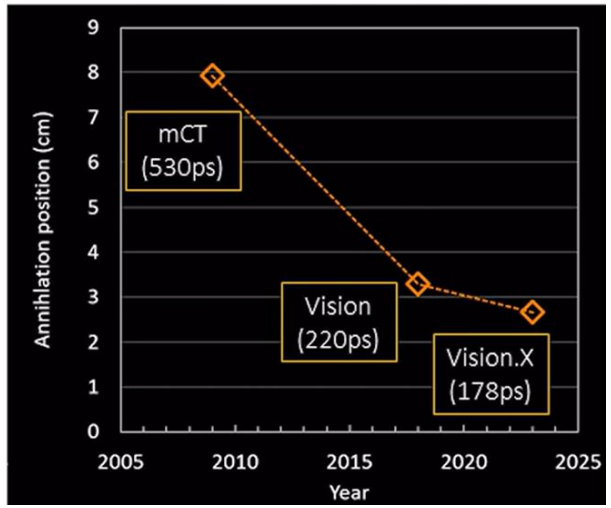


Courtesy of P. Lecoq

Physical limit

VS

Clinical application



Courtesy of I. Armstrong

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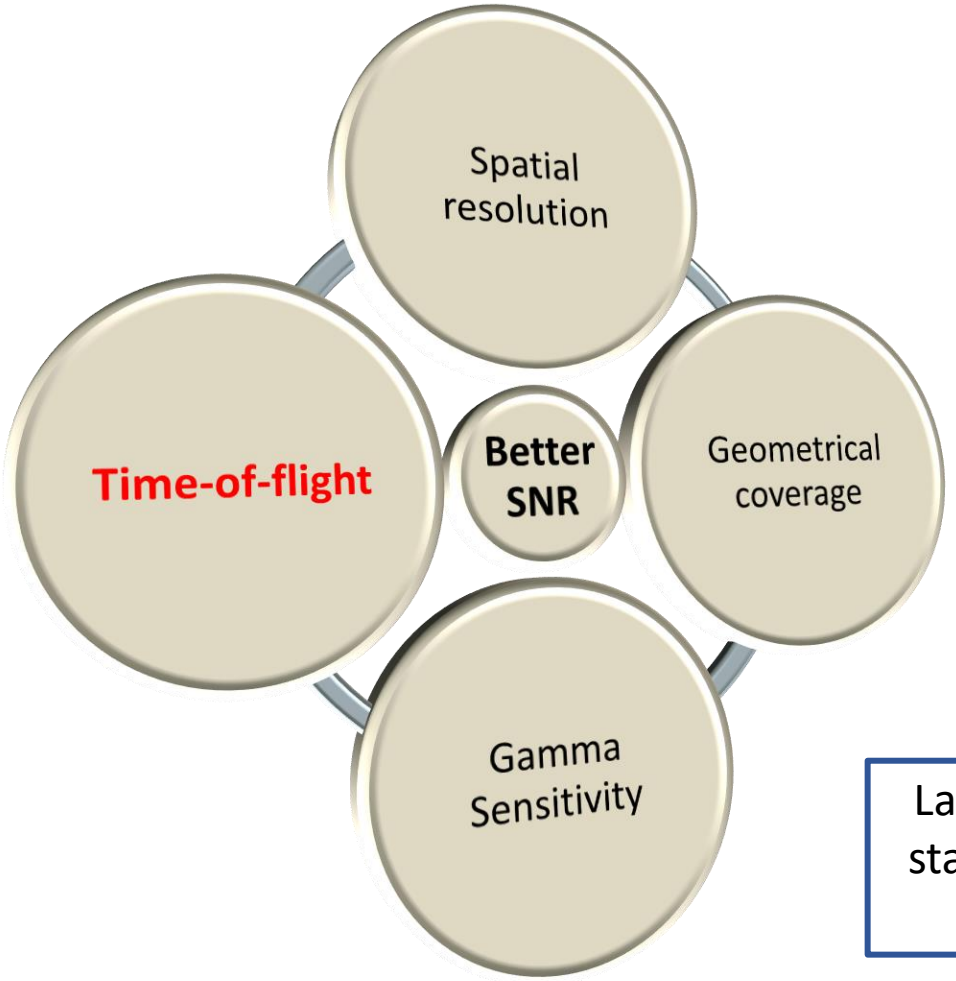
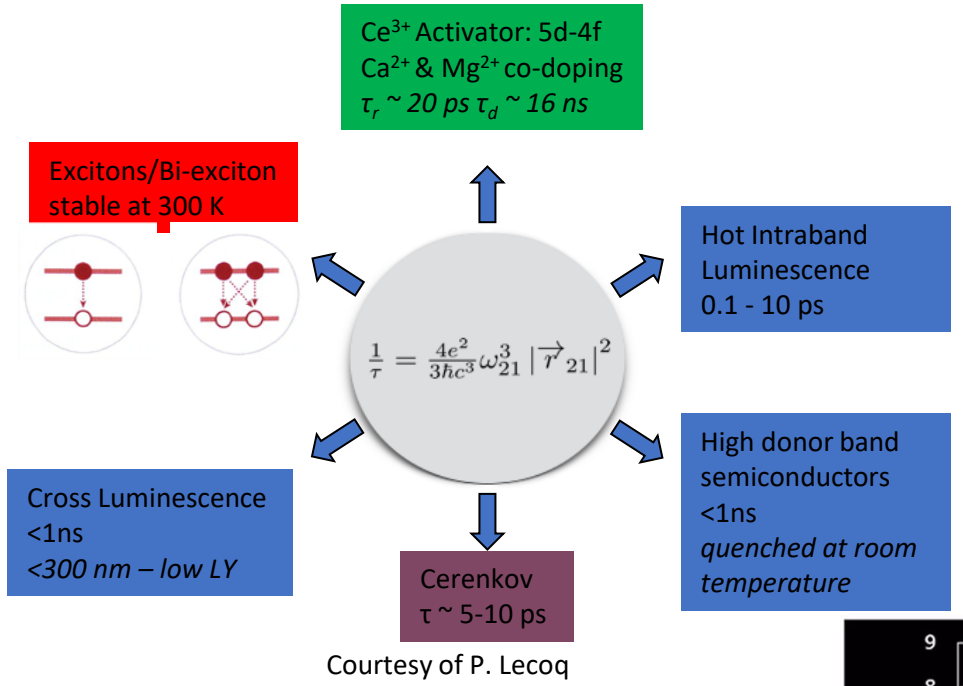




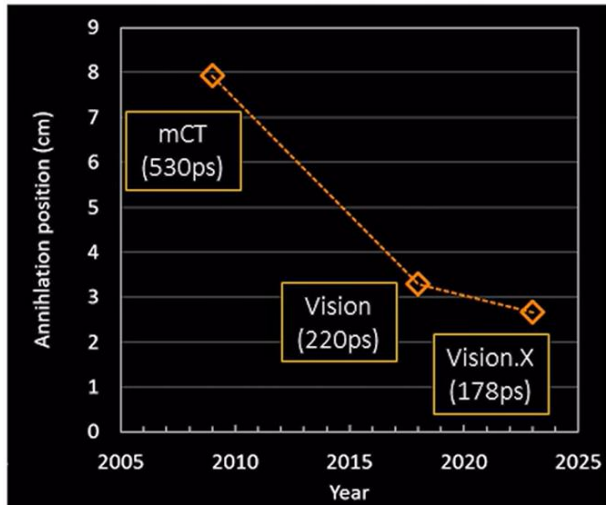
Courtesy of P. Lecoq

Laboratory state of the art

Physical limit

VS

Clinical application



Courtesy of I. Armstrong

Scintillator

Photodetector

Data acquisition

Data management

State-of-the-art in the laboratory

Article | Published: 14 October 2021

Ultrafast timing enables reconstruction-free positron emission imaging

Sun Il Kwon, Ryosuke Ota, Eric Berg, Fumio Hashimoto, Kyohei Nakajima, Izumi Ogawa, Yoichi Tamagawa, Tomohide Omura, Tomoyuki Hasegawa & Simon R. Cherry

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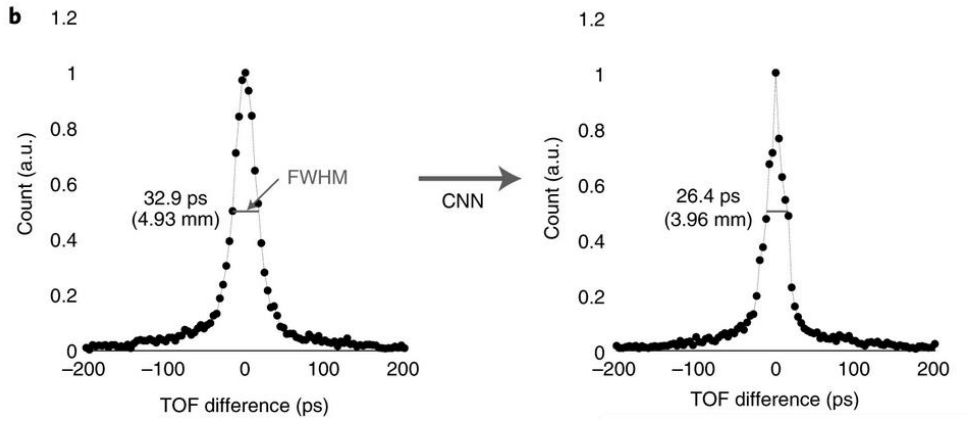

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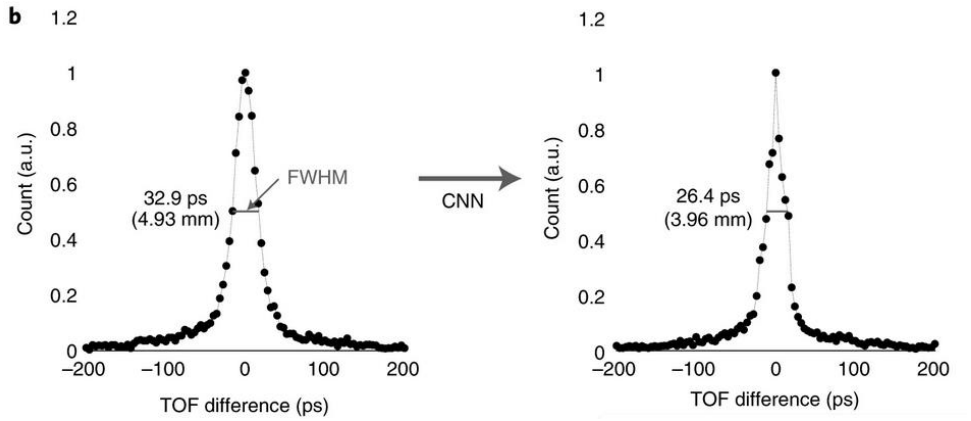

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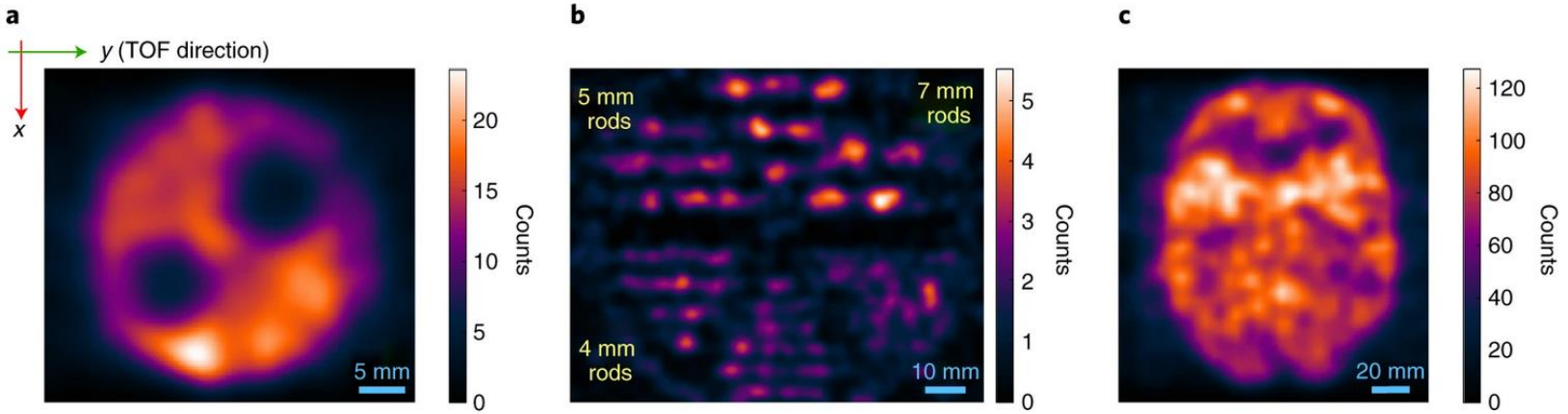
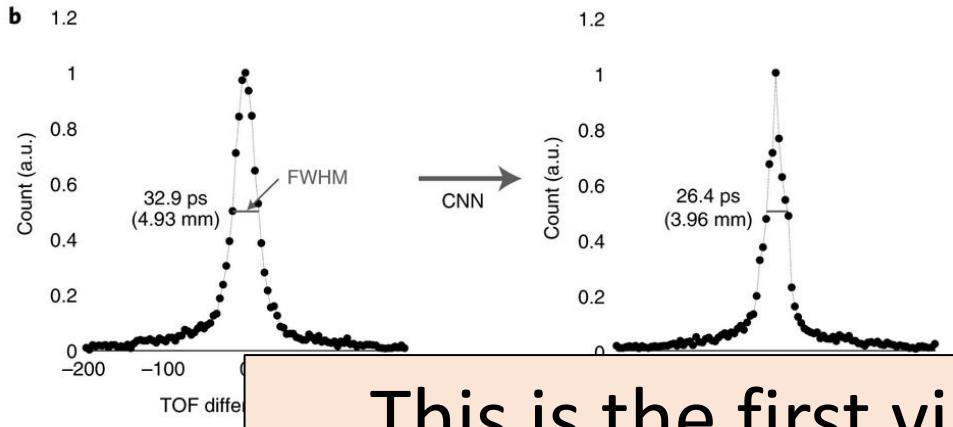


- 4 mm spatial TOF resolution, BUT:
- Detection efficiency of 12.9% (1.65% in coincidence)

State-of-the-art in the laboratory



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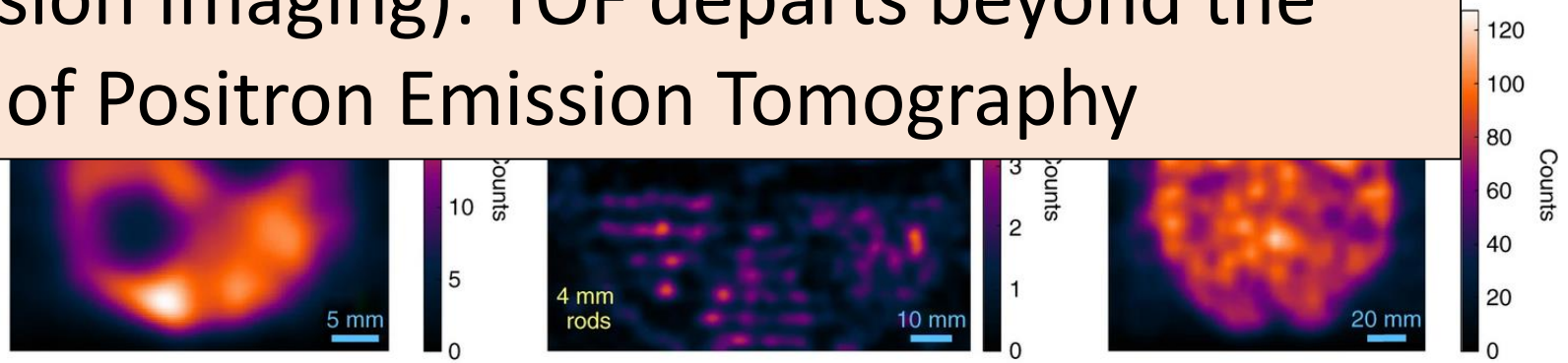
This is the first viable proof-of-concept of dPEI (Direct Positron Emission Imaging): TOF departs beyond the concept of Positron Emission Tomography

- Cheren
- Micro-Channel Plate PMT
- Convolutional neural networks



- 4 mm spatial TOF resolution, BUT:
- Detection efficiency of 12.9% (1.65% in coincidence)

Prompt emission vs γ Sensitivity vs LY

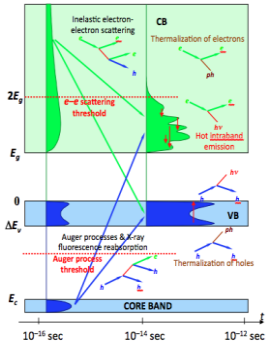
Scintillator

Photodetector

Data acquisition

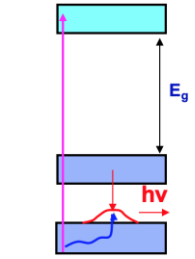
Data management

Courtesy of Paul Lecoq

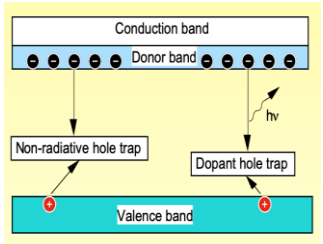


Hot Intraband
High density
≤50ph
Large spectrum

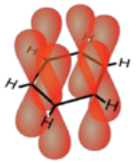
Cerenkov
High density
≤20ph
Large spectrum



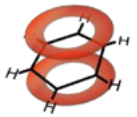
C – Crossluminescence



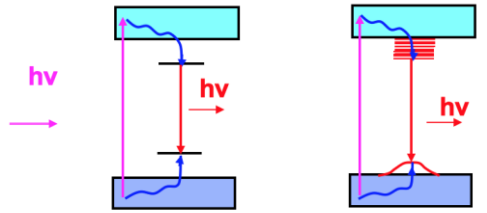
Sigma Bonds
sp^2 Hybridized orbitals



6 p_z orbitals



delocalized pi system



A – Doped ion, or intrinsic defect

B – Self- trapped exciton

Quantum confined Excitons/Bi-excitons

X-luminescent
High density
≤2000ph/MeV
UV

Nanocrystals
High density
High LY through high QE
Tunable WL

High Donnor band Semiconductors
High density
≤4000ph/MeV low T, quenched at RT

Organic scintillators
Low density
≤20000ph/MeV
Blue, Near UV

Inorganic scintillators Intrinsic or activated
High density
Up to 150000ph/MeV
Near UV and visible

10ps 100ps 1ns 10ns 100ns

Prompt emission vs γ Sensitivity vs LY

vs cost, self absorption, surface treatability, ease of use, availability, industrial processing, scale-up …

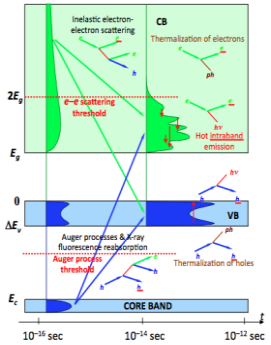
Scintillator

Photodetector

Data acquisition

Data management

Courtesy of Paul Lecoq



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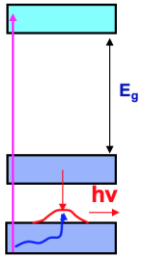

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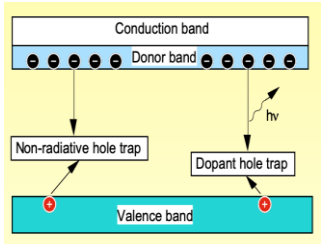

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High density
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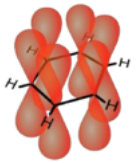
sp^2 Hybridized orbitals



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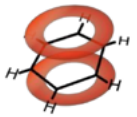
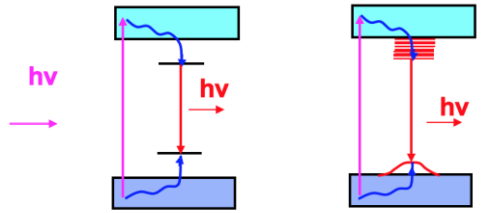


delocalized pi system

Organic scintillators
Low density
≤20000ph/MeV
Blue, Near UV



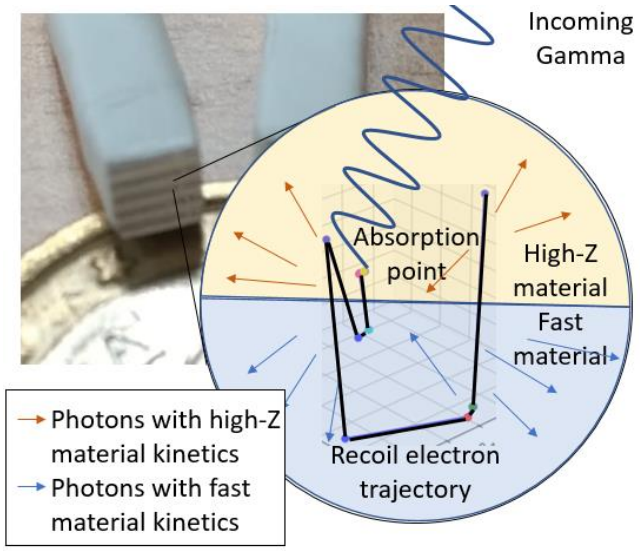
A – Doped ion, or intrinsic defect

B – Self- trapped exciton

Inorganic scintillators Intrinsic or activated
High density
Up to 150000ph/MeV
Near UV and visible

10ps 100ps 1ns 10ns 100ns

Combining different materials



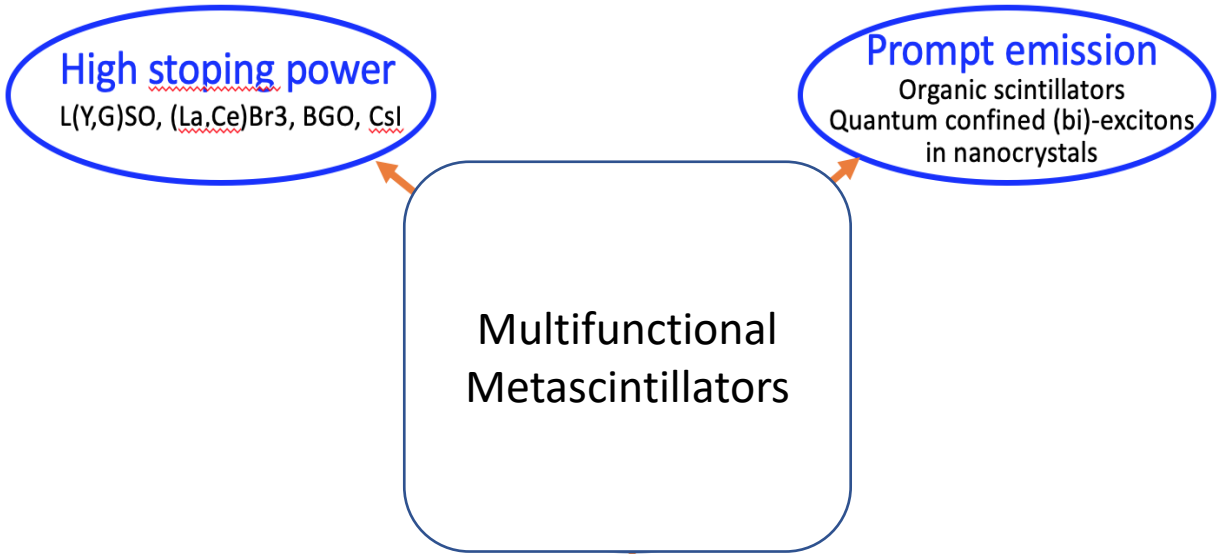
Latella et al., 2023

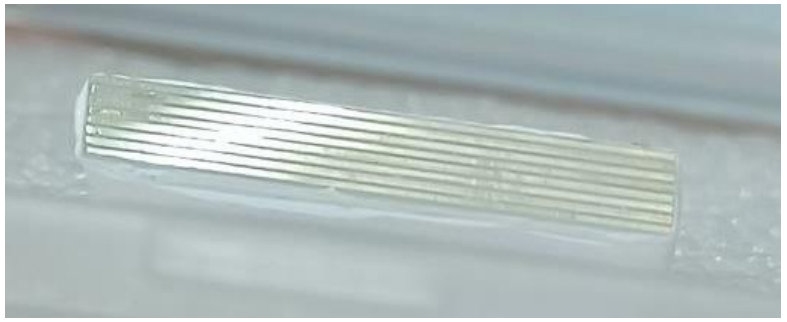
Metascintillators

Composite topologies of scintillating and light-guiding materials, arranged to produce a synergistic effect at some step of the scintillation process, from gamma absorption to light detection, combining thus the favorable physical characteristics of their constituting components

Konstantinou et al., 2021

Metascintillators



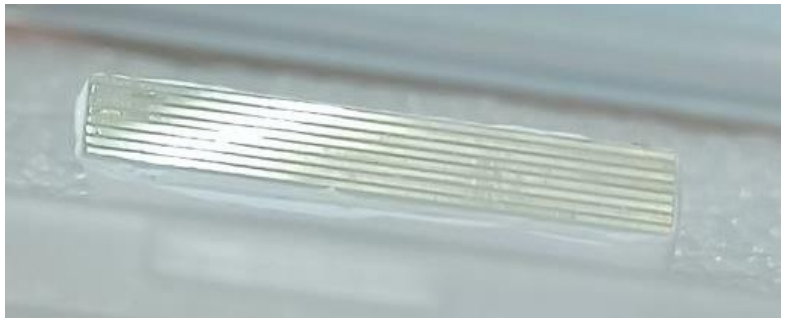


BGO-EJ232
Semi-monolithic
Metascintillator

1st generation: Metascintillator heterostructures

- 200ps CTR at system level,
- BGO/BaF_2
- BGO/EJ232

Metascintillators



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Metascintillator

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- BGO/BaF_2
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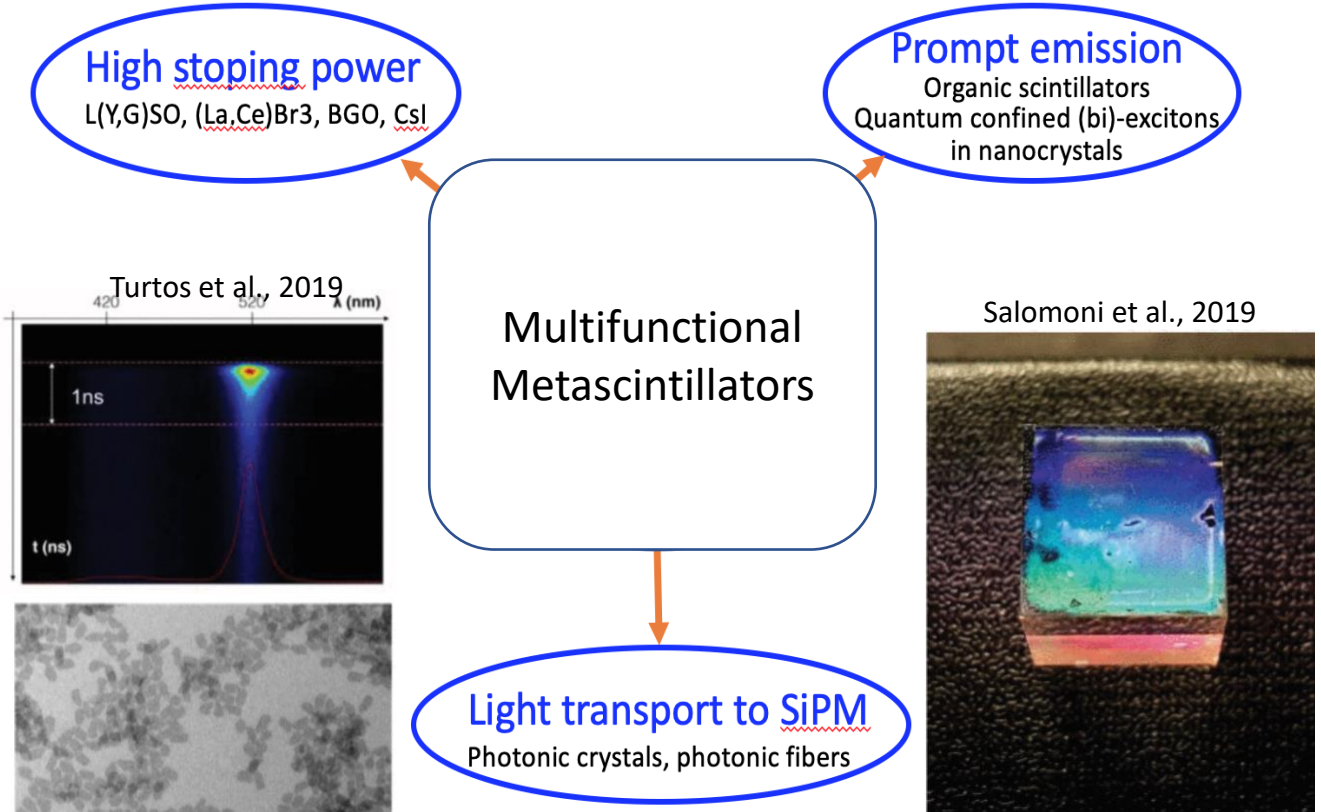
2nd generation metascintillators

- 80 ps CTR at system level
- LYSO/PEA_2PbBr_4
- CdSe nanoplatelets
- Photonic crystal slabs



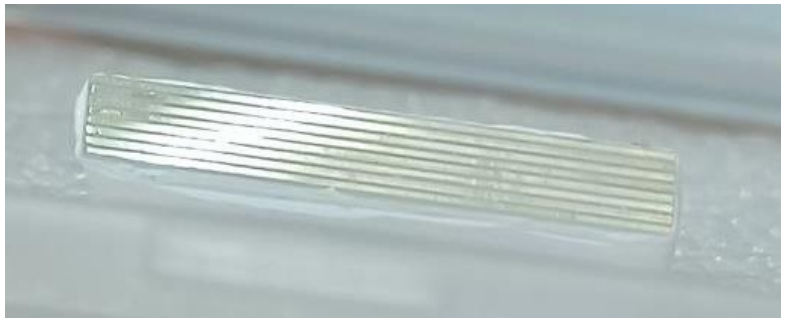
Turtos et al., 2019

CdSe nanoplatelets

Salomoni et al., 2019

Extraction facilitating PhC

Metascintillators



BGO-EJ232
Semi-monolithic
Metascintillator

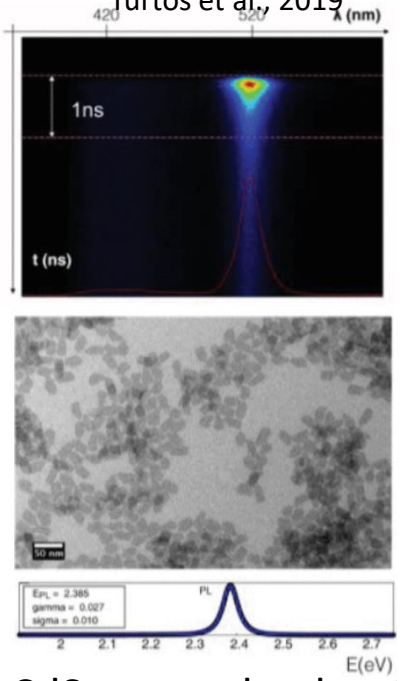
High stoping power
L(Y,G)SO, (La,Ce)Br3, BGO, CsI

Prompt emission
Organic scintillators
Quantum confined (bi)-excitons
in nanocrystals

Multifunctional
Metascintillators

Light transport to SiPM
Photonic crystals, photonic fibers

Turtos et al., 2019



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- LYSO/PEA_2PbBr_4
- CdSe nanoplatelets
- Photonic crystal slabs

3rd generation metascintillators

- 10-30ps CTR at system level
- New nanoscintillators
- New nanophotonic features
- Purcell effect, hyperbolic metamaterials

Beyond the scintillator: Photodetector

Scintillator

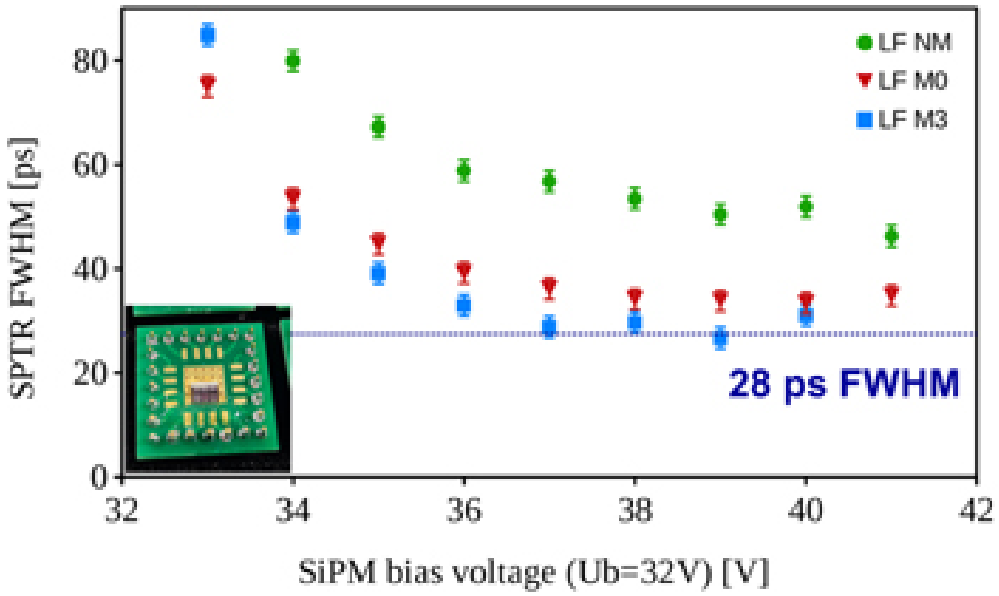
Photodetector

Data acquisition

Data management

- NUV MT SiPM

Gundacker, Kwon et al., 2023: 28 ps SPTR



Beyond the scintillator: Photodetector

Scintillator

Photodetector

Data acquisition

Data management

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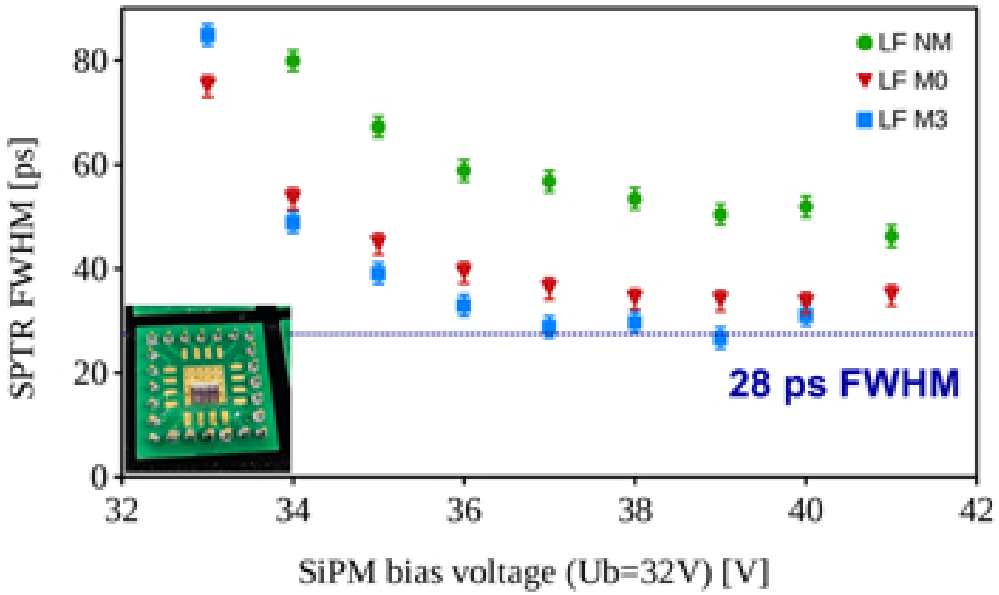
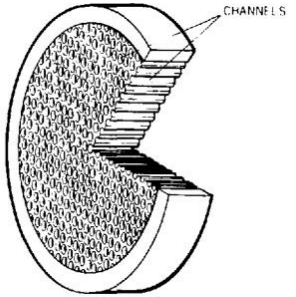
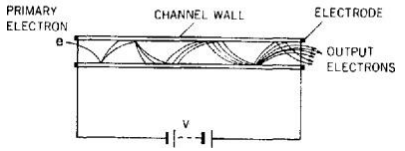


- MCPs

MCP-PMT: Kwon, Ota et al. 2021, 20 ps SPTR





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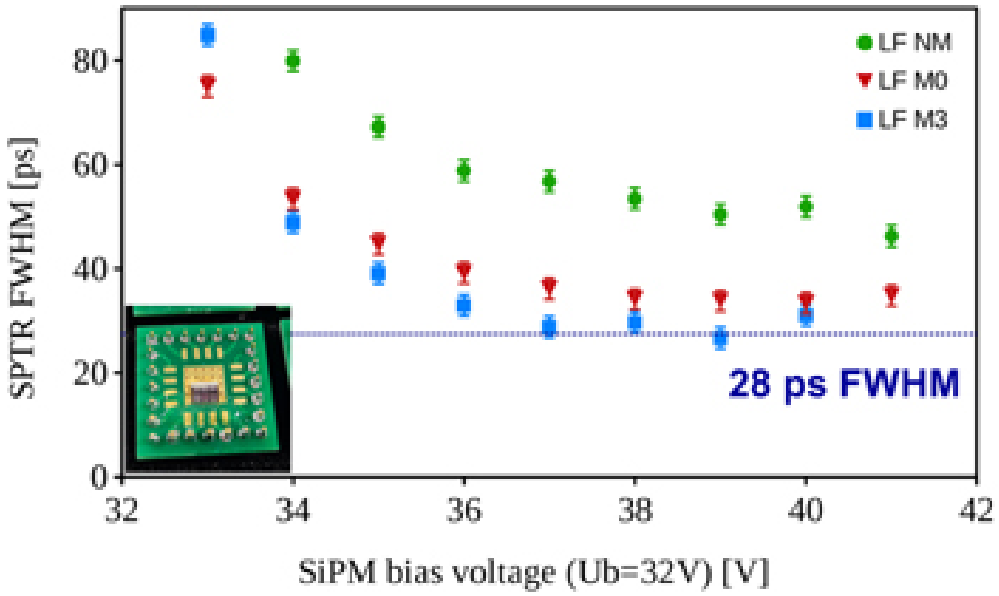
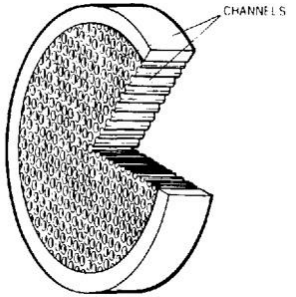
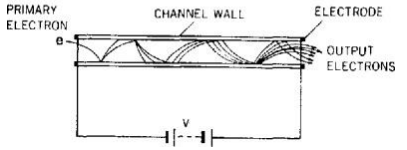


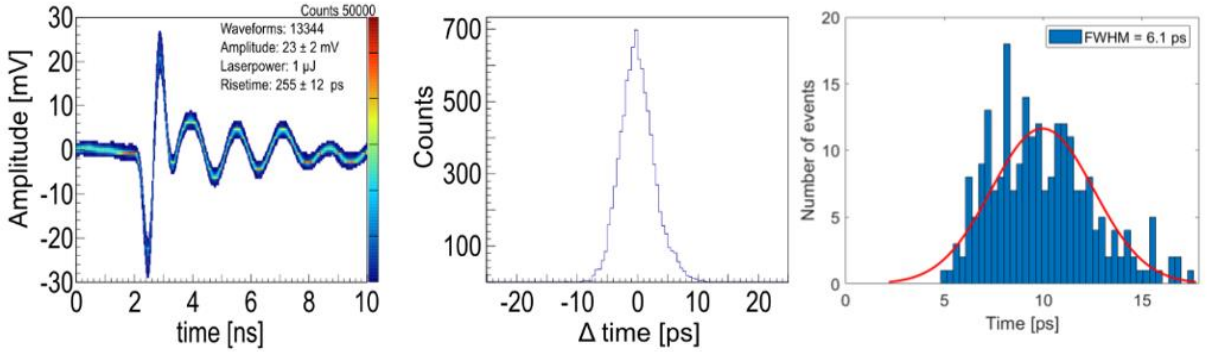
- MCPs

MCP-PMT: Kwon, Ota et al. 2021, 20 ps SPTR





Amorphous silicon MCPs: Frey, Konstantinou et al, 2024. 6.1 ps SPTR



Scaling up: Data acquisition

Scintillator

Photodetector

Data acquisition

Data management

- It is easy to perform measurements with high end oscilloscopes or dedicated single channel electronics

Scaling up: Data acquisition

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- It is easy to perform measurements with high end oscilloscopes or dedicated single channel electronics
- Scalability is, in contrast, not as easy as it sounds

Scaling up: Data acquisition

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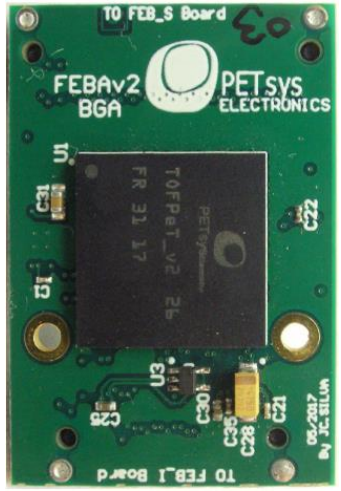
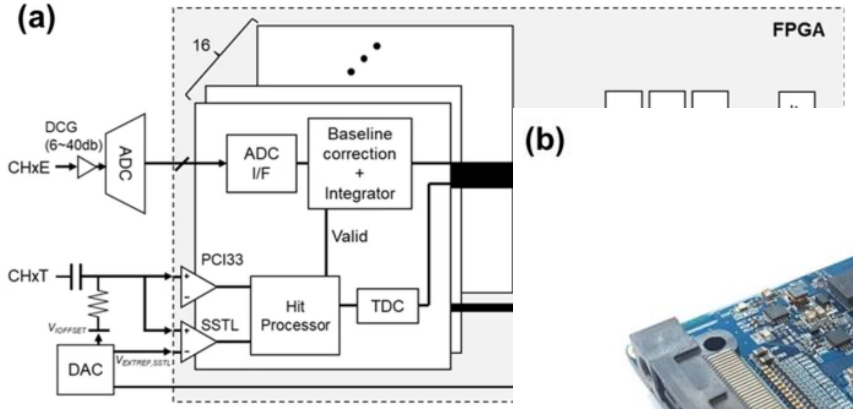


PETSYS TOFPET2 brochure, 2019



Ko et al. 2024

- It is easy to perform measurements with high end oscilloscopes or dedicated single channel electronics
- Scalability is, in contrast, not as easy as it sounds
- TOFPET3: 26 ps jitter
- FPGA solutions take advantage of superior, readily available, high-end CMOS manufacturing

The machine learning magic: Data processing

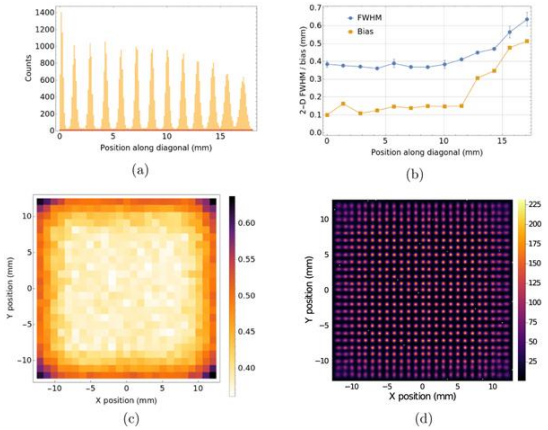
Scintillator

Photodetector

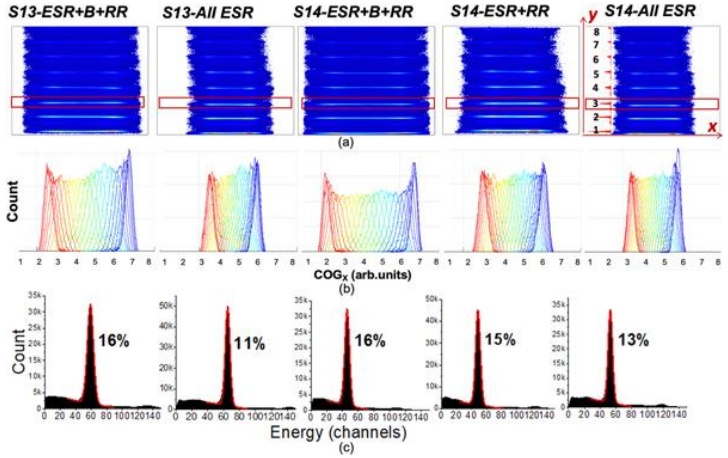
Data acquisition

Data management

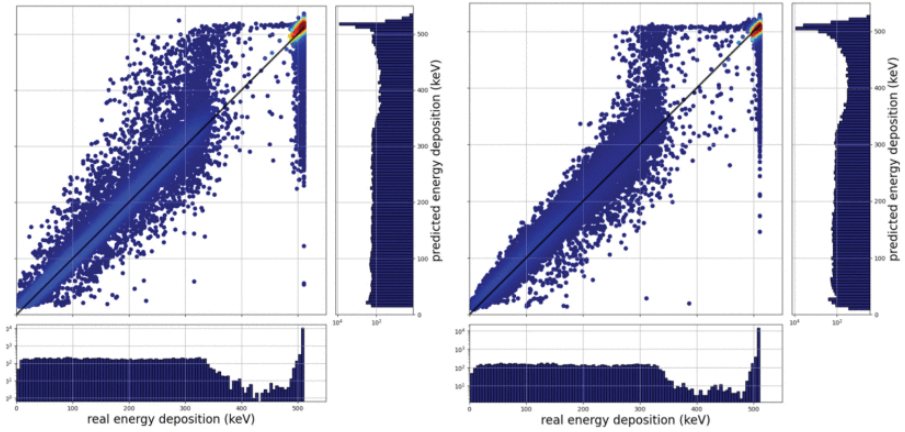
- Numerous works utilize **NN** for different aspects of detector improvement (DOI, spatial resolution, TOF) or a combination thereof, with impressive results (in both **simulation** and **experimental** data)



P. Carra et al, 2022



M. Freire et al, 2022



G. Konstantinou, L. Zhang et al, 2024

The machine learning magic: Data processing

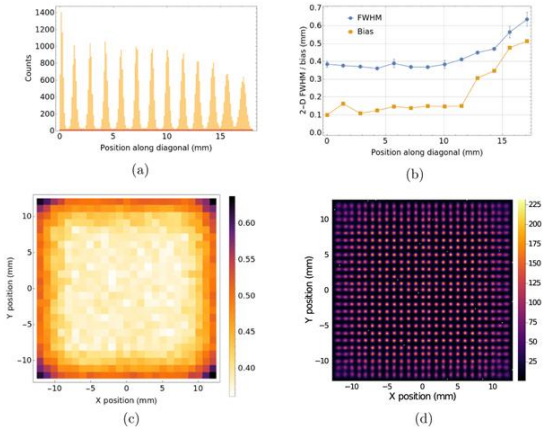
Scintillator

Photodetector

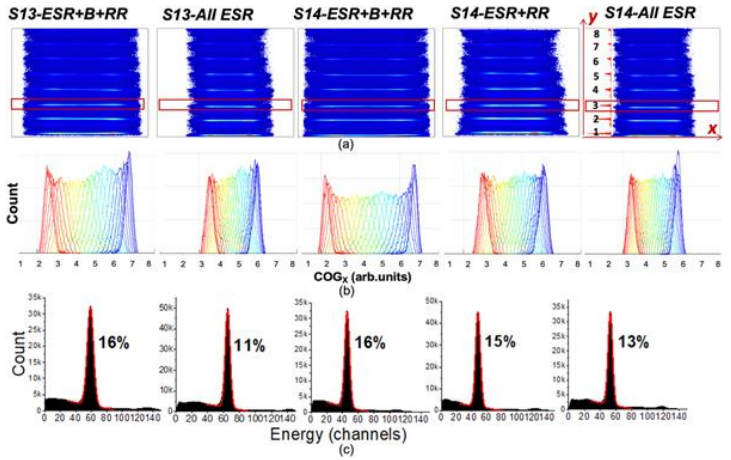
Data acquisition

Data management

- Numerous works utilize **NN** for different aspects of detector improvement (DOI, spatial resolution, TOF) or a combination thereof, with impressive results (in both **simulation** and **experimental** data)
- Streamlining machine learning in the **DaQ** chain is possible and can facilitate different aspects of **scaling up** (data throughput, on-the-fly data corrections, combinatory timewalks and more)



P. Carra et al, 2022



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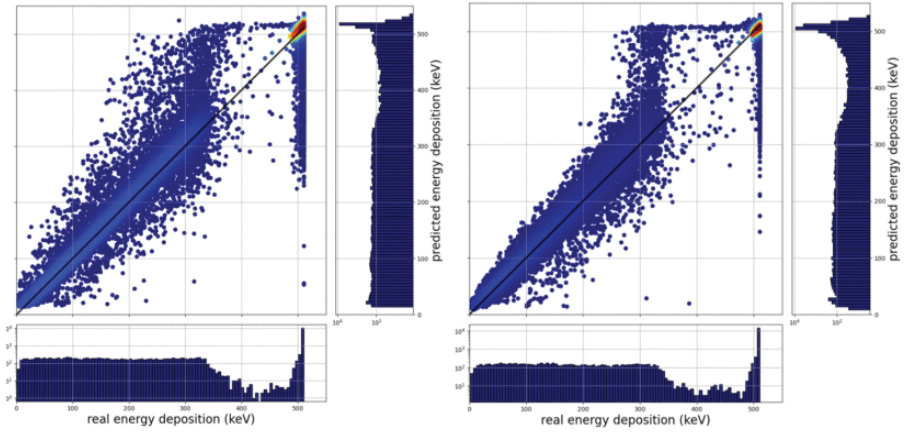


G. Konstantinou, L. Zhang et al, 2024

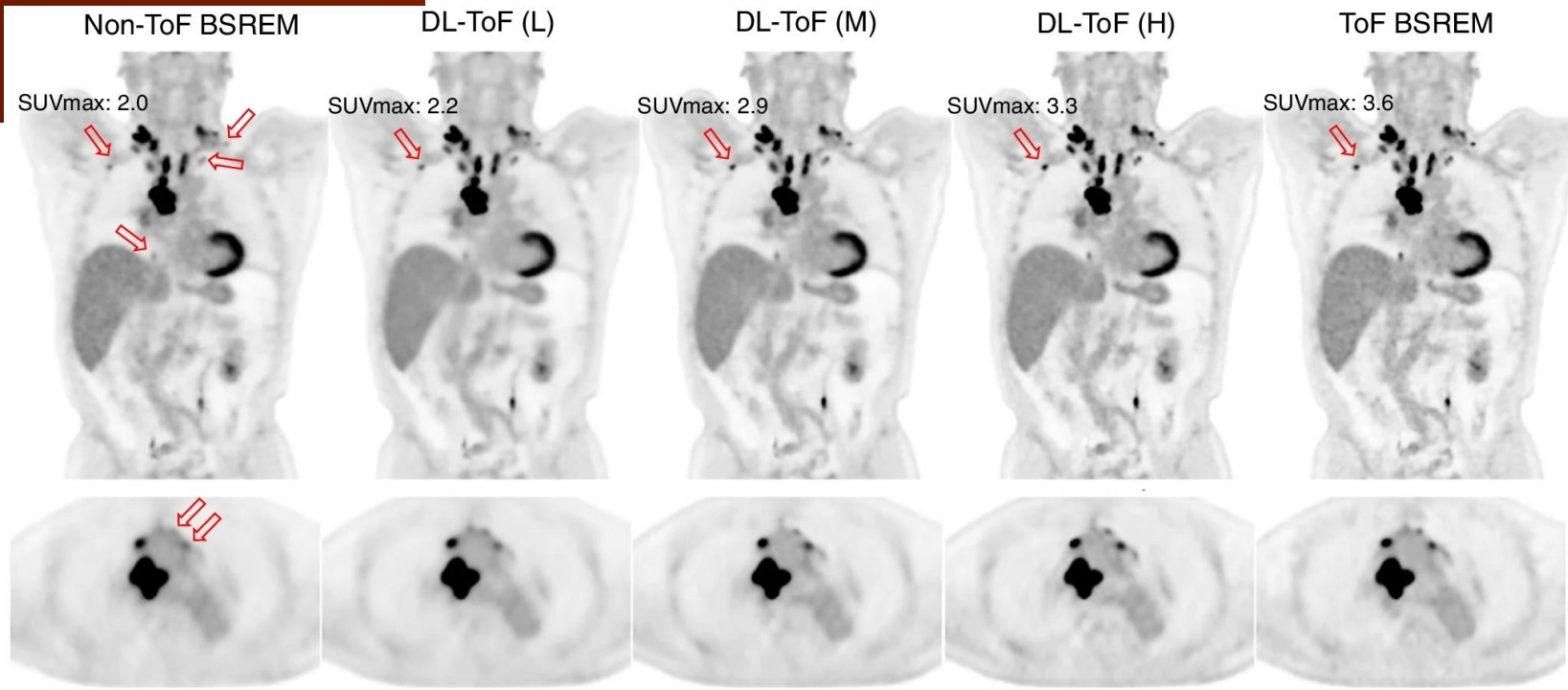
The Deep learning magic: Reconstruction

Home › European Journal of Nuclear Medicine and Molecular Imaging › Article

Deep learning–based time-of-flight (ToF) image enhancement of non-ToF PET scans

Original Article | Open access | Published: 04 May 2022
Volume 49, pages 3740–3749, (2022) Cite this article

515 MBq scanned on GE Discovery MI (5-ring) PET/CT scanner (slice thickness 2.8 mm). Arrows point to lesions with lower detectability in non-ToF BSREM as well as the SUV_{max} of an example lesion



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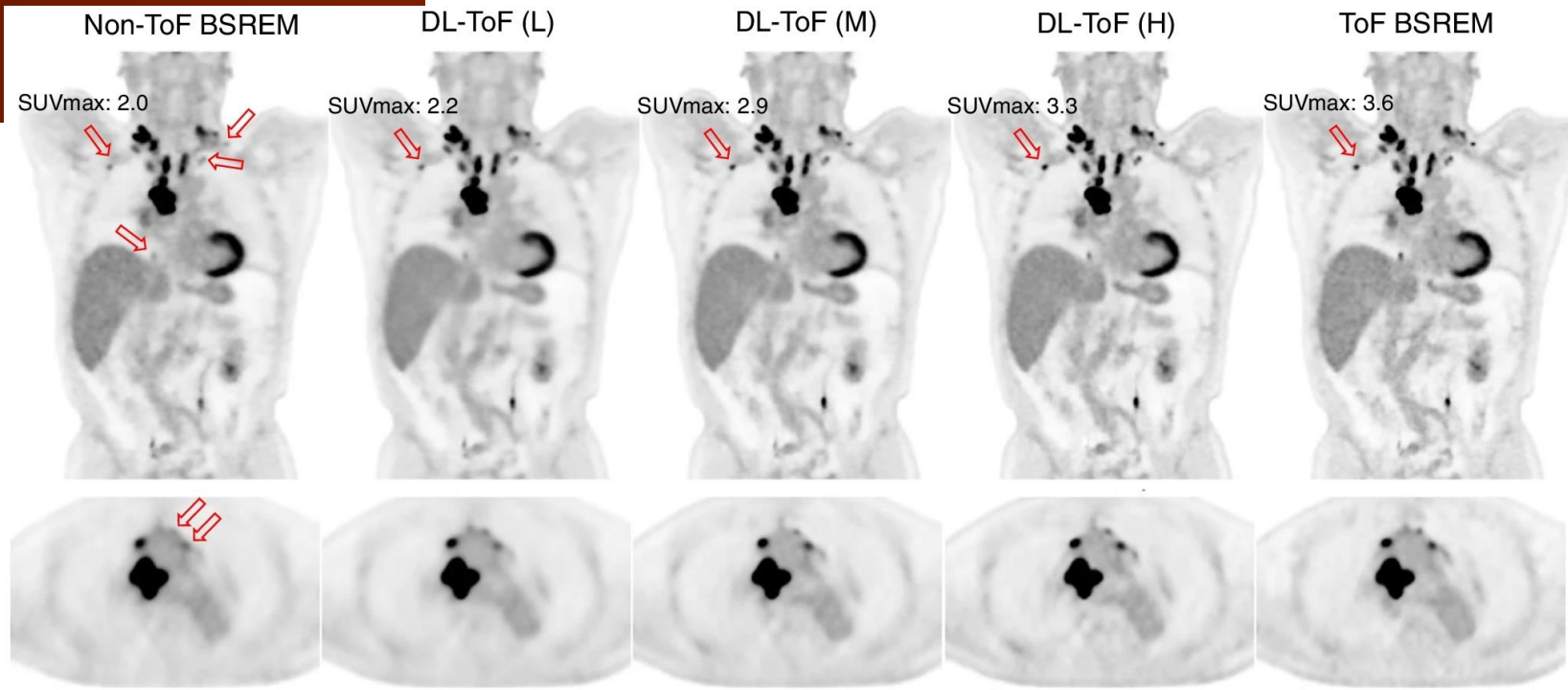


Following the reverse RIRO principle, superior quality TOF input data leads to ever improving results

What if 10 ps was possible today (or tomorrow)?

Sun il Kwon @ Duisburg Sept 2023:

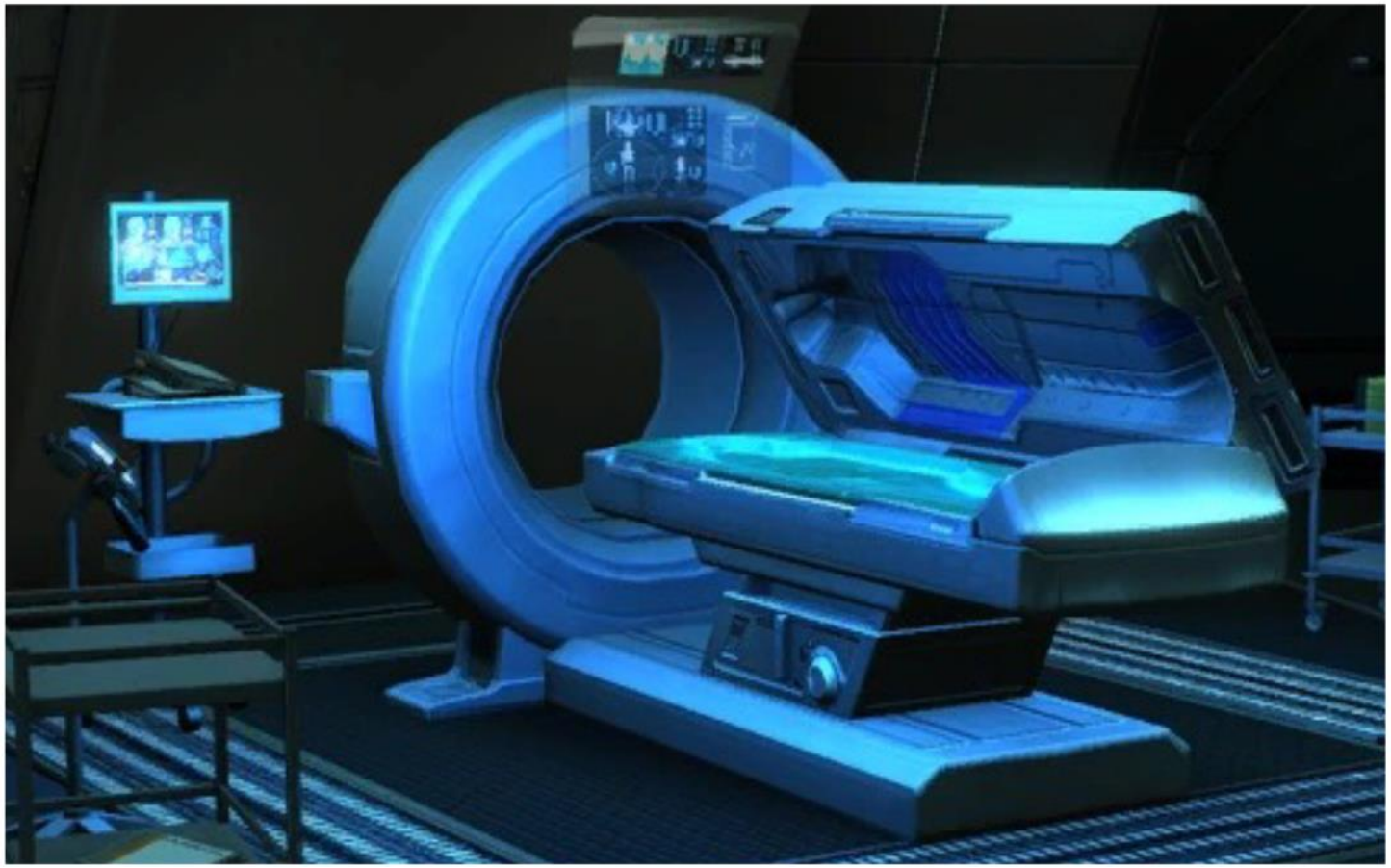
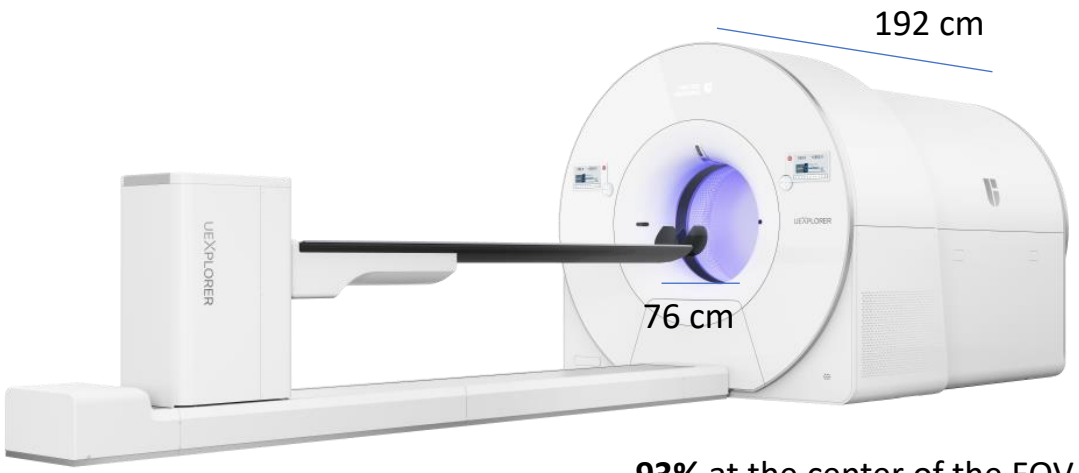
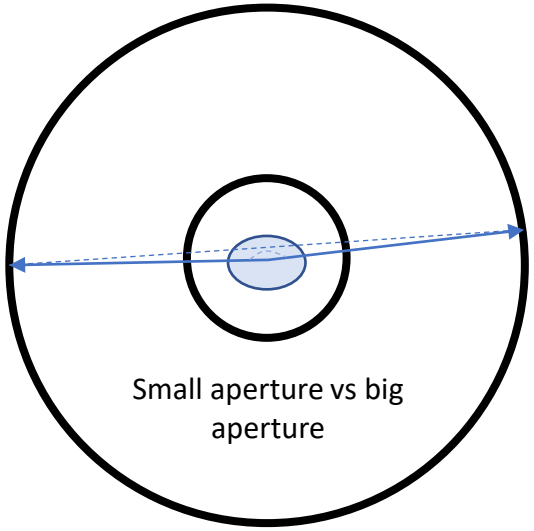


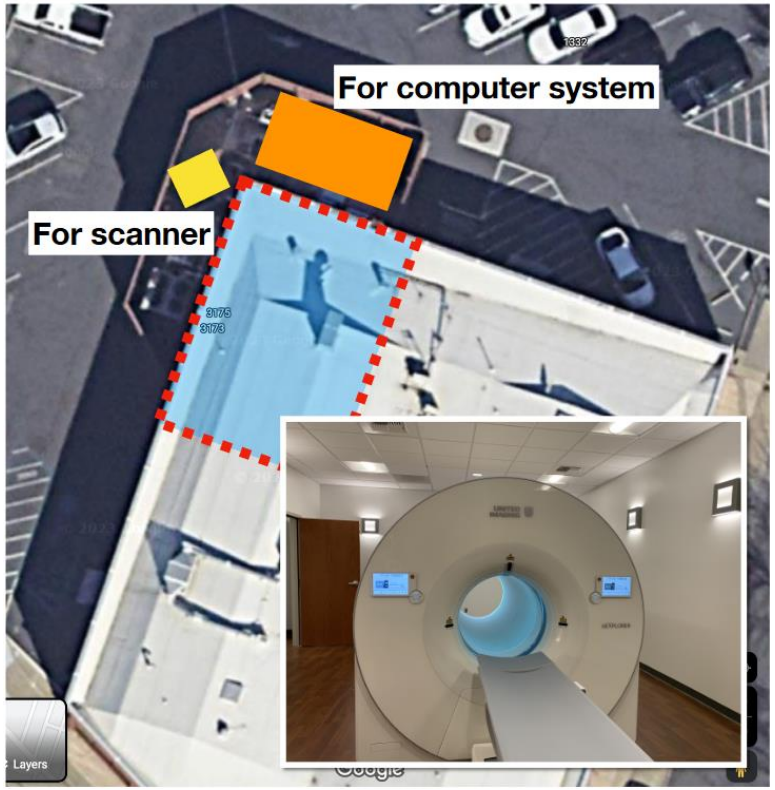
Image from movie Avatar

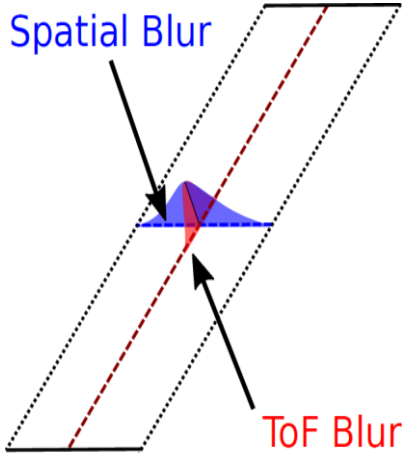
What if 10 ps was possible today (or tomorrow)?



93% at the center of the FOV
206.5 cm maximum length of LOR



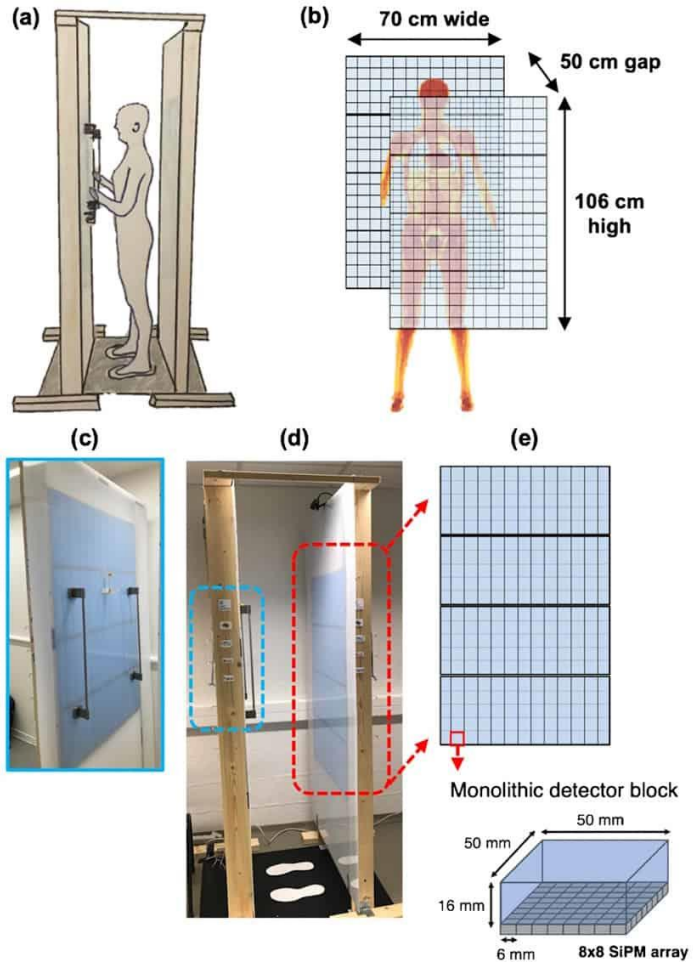




- Direct voxel reconstruction → Minimization of computational resources
- Prediction of acolinearity →pushing the spatial resolution limit
- Imaging of a large (D) target: Significant TOF gain

EXPLORER Molecular Imaging Center (EMIC) @Sacramento, CA 95616

What if 10 ps was possible today (or tomorrow)?



Vandenberghe et al. 2023

- No open geometry artifacts
- Improved sensitivity
- Superior throughput

What if 10 ps was possible today (or tomorrow)?

Conventional PET

10ps TOFPET

- Access to all patients (infants, pregnancy), potential for PET screening, not only diagnosis
- Access to ALL patients
- Reduced radiation AND reduced examination duration

What if 10 ps was possible today (or tomorrow)?

Conventional PET

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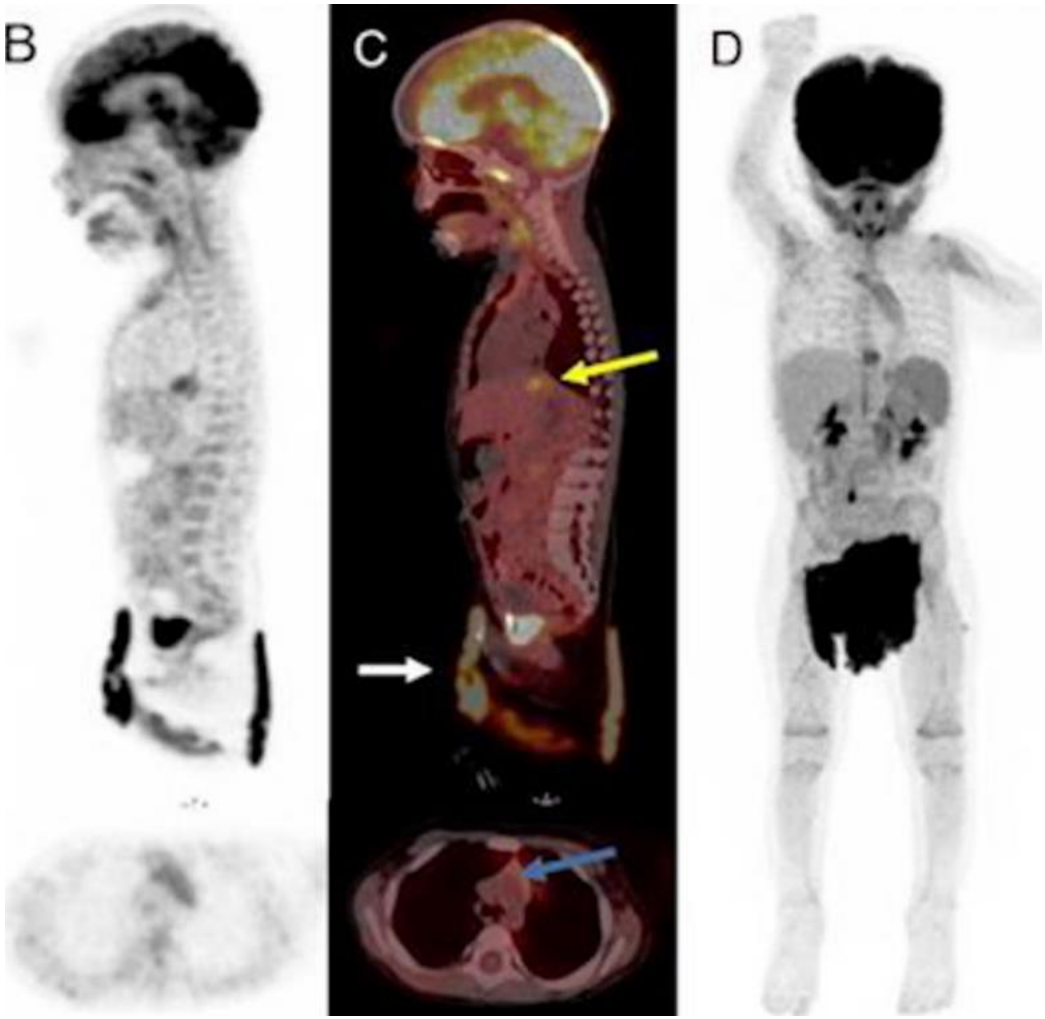


- Access to all patients (infants, pregnancy), potential for PET screening, not only diagnosis
- Access to ALL patients
- Reduced radiation AND reduced examination duration

Reichkendler et al. 2022

17-mo-old girl suspected of having incomplete Kawasaki disease after 12 days of fever despite broad-spectrum antibiotics. 5 min acquisition, no sedation

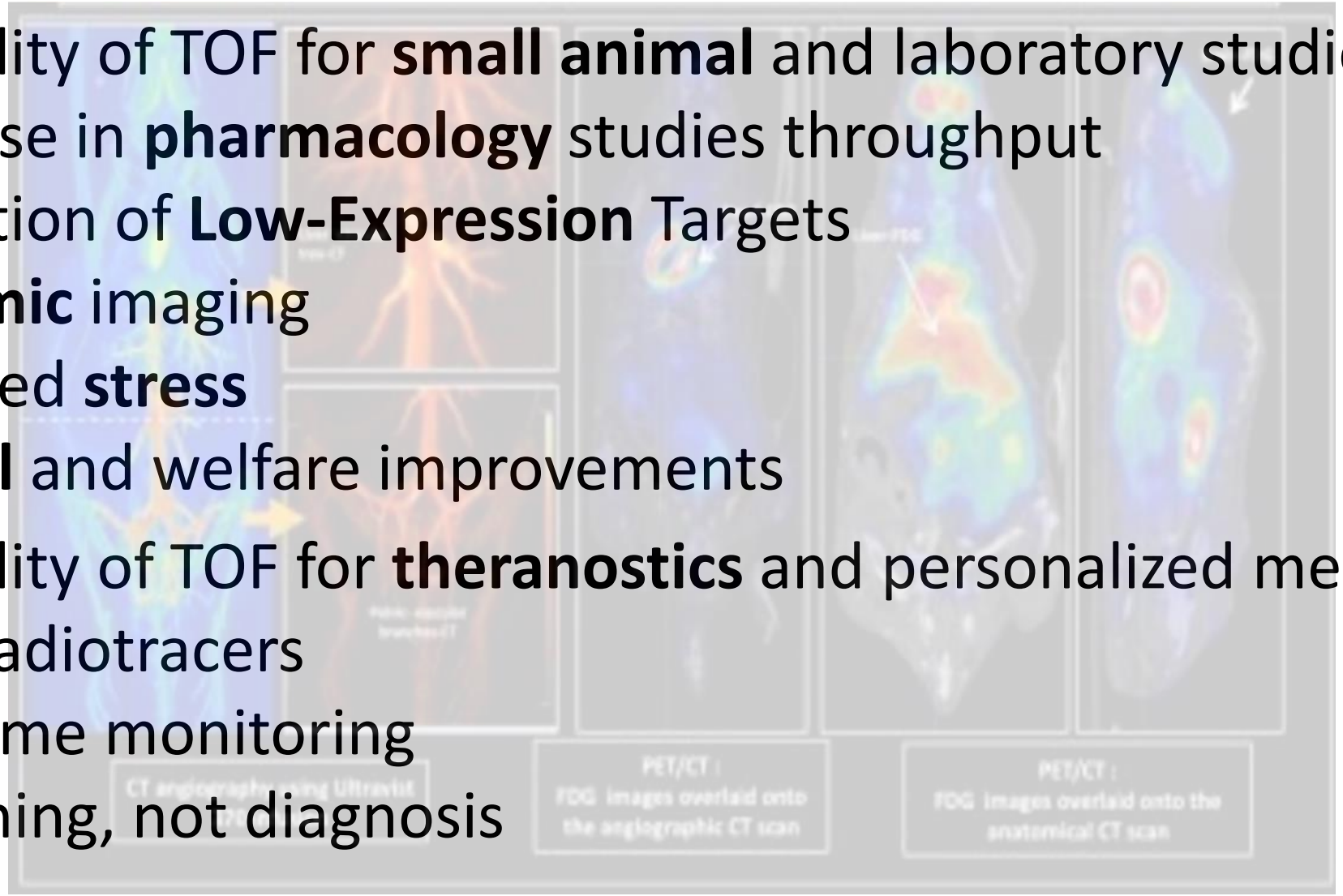
What if 10 ps was possible today (or tomorrow)?

Availability of TOF for **small animal** and laboratory studies

- Increase in **pharmacology** studies throughput
- Detection of **Low-Expression** Targets
- **Dynamic** imaging
- Reduced **stress**
- **Ethical** and welfare improvements

Availability of TOF for **theranostics** and personalized medicine

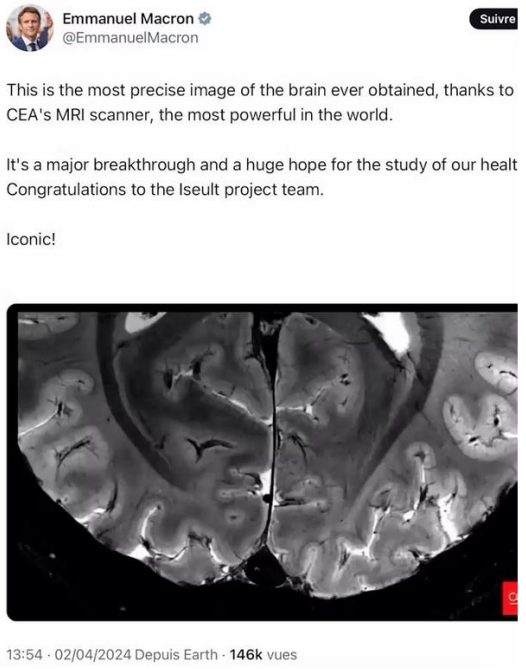
- New radiotracers
- Real time monitoring
- Screening, not diagnosis



Khalil, 2017

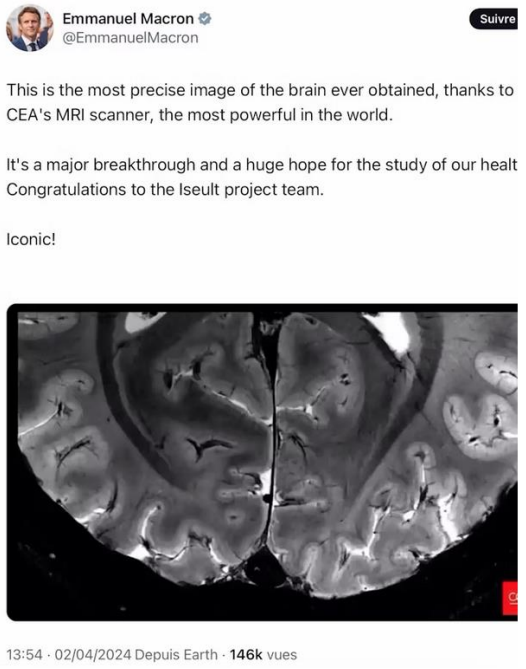
Thinking big

- Dr. S. Cherry, in the previous version of FTMI (2022, Valencia): “We should think bigger”



Thinking big

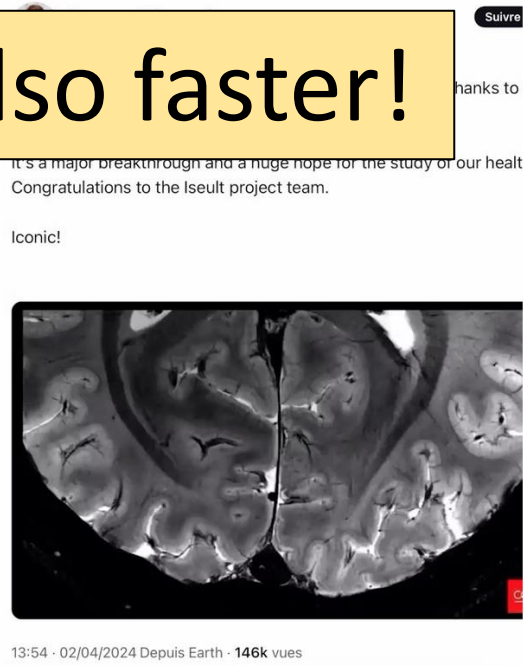
- Dr. S. Cherry, in the previous version of FTMI (2022, Valencia): “We should think bigger”
- Synergy on the fundamental mission of improving life on earth
- Current developments demonstrate the impact of this mission
- A piece is still missing, where the physical limit is an order of magnitude (at least!) beyond the clinical application



Thinking big

- Dr. S. Cherry, in the previous version of FTMI (2022, Valencia): “We should think bigger”
- Synergy on the fundamental mission of improving life on earth
- Curr
of this mission
- A piece is still missing, where the physical limit is an order of magnitude (at least!) beyond the clinical application

We should not only think bigger, but also faster!



PV-lab
IEM NEUCHATEL
EPFL

Acknowledgements

i3M
Instituto de Instrumentación para Imagen Molecular

TOF: The last frontier in PET

Thank you for your attention

Looking forward to the rest of a fascinating series of sessions and exchanges