DETECTOR REQUIREMENT FOR PRE-CLINICAL IMAGING

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WHAT CAN SMALL ANIMAL IMAGING DO?

Why small animals?

- The traslational paradigm from small animals to humans is today well accepted.
  - Rats and mice show genetic likelihood with humans
  - Transgenic animals showing particular anomalies are now available

Study of mechanism and possible cure of human diseases (e.g. cancer..)

Oncology

  - Study of tumor development and evaluation of the adopted treatment

New drug development

Drug development

  - Speeding up of test procedures ↣ Distribution, specificity, metabolism, toxicity
  - In vivo imaging repeatability on the same animal
  - Reduction of animals to be sacrificed - Less expensive procedures

Study and validation of gene therapies

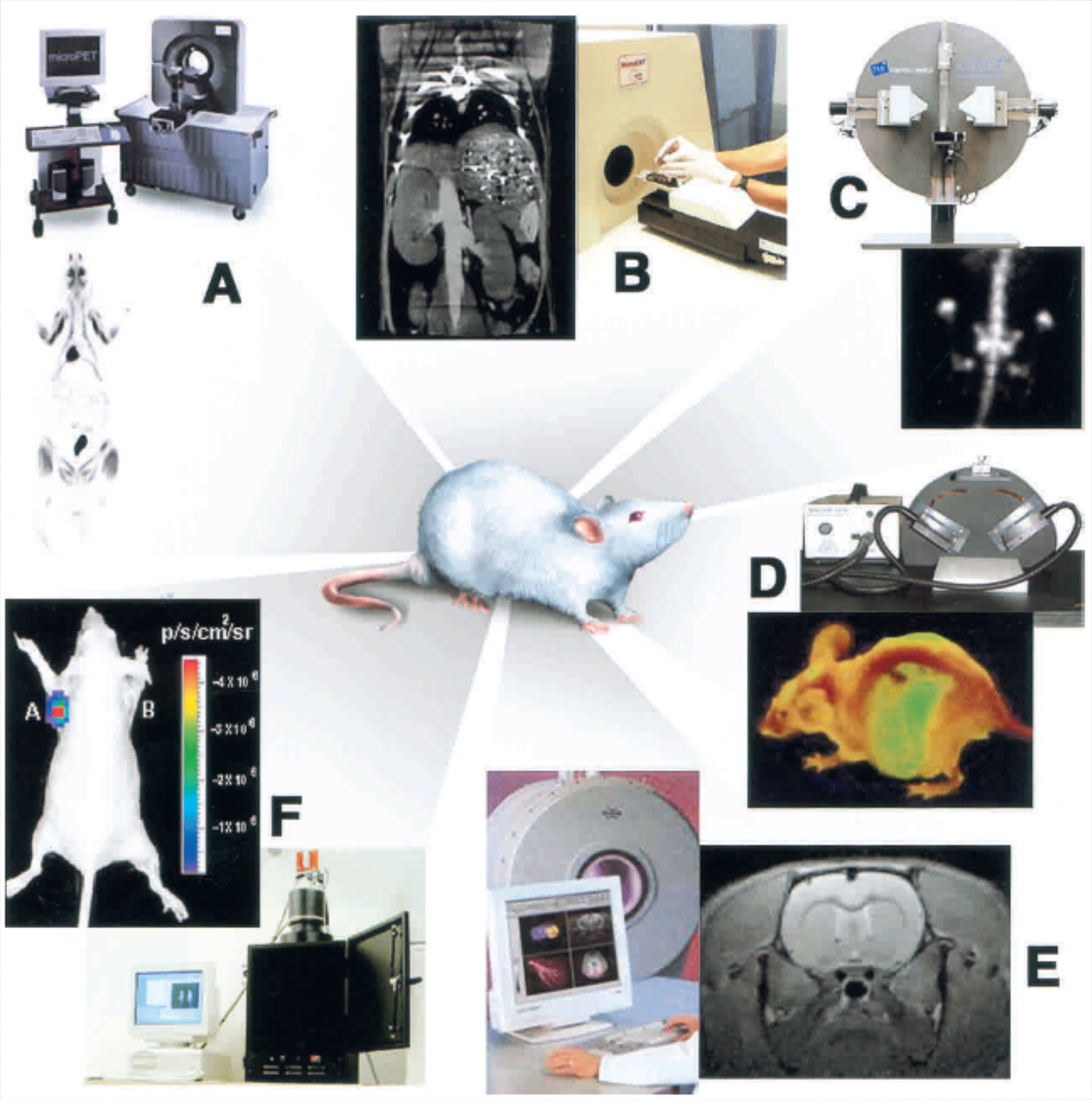
Gene research

  - Molecular targets, receptors and drug binding sites
  - Relationship between genes & phenotype
  - Gene expression & gene therapy assessment

Molecular Imaging

MOLECULAR IMAGING ON SMALL ANIMALS

- A. PET Imaging on rats using ^{18}F-FDG showing glucose metabolism
- B. CT Imaging of a mouse abdomen after the injection of a contrast agent
- C. SPECT Imaging of a mouse abdomen after the injection of ^{99m}Tc "methylene diphosphonate" showing the accumulation of the tracer in bones.
- D. Optical Imaging of a mouse showing the fluorescence of GFP from liver, abdomen, spinal chord and brain due to the presence of cancer cells.
- E. MRI image T2-weighted of a mouse brain.
- F. Bioluminescence optical imaging of a mouse superimposed to the picture of the animal.



Molecular imaging in living subjects: seeing fundamental biological processes in a new light
T. Massoud and S.S.Gambhir
GENES & DEVELOPMENT 17:545–580, 2003

PRELIMINARY ISSUES FOR SMALL ANIMAL MOLECULAR IMAGING

Sensitivity:

- what concentration of a tracer, probe or contrast agent must I have to be able to detect an object?

Spatial resolution:

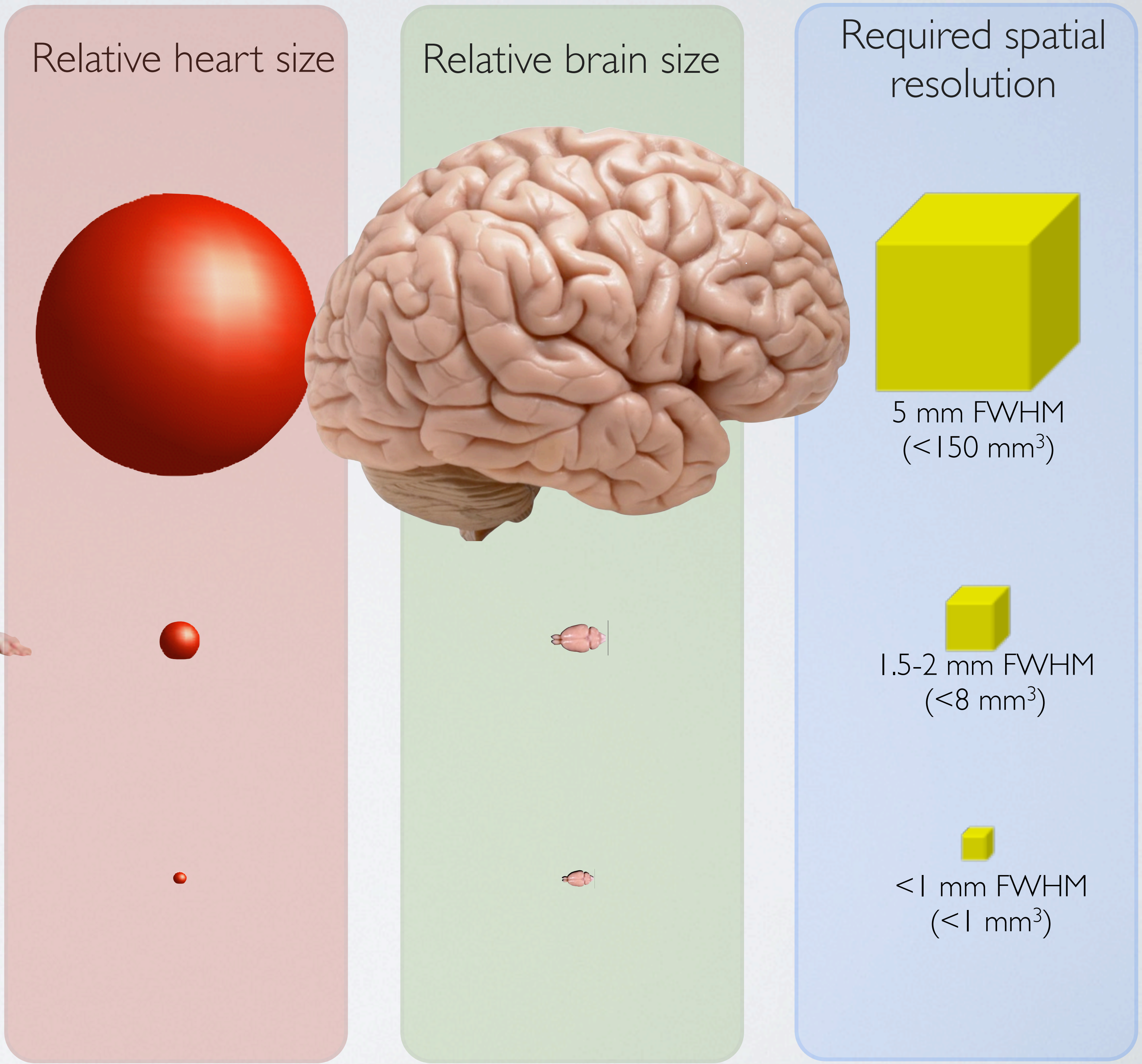
- what is the smallest object I can visualize?

SPATIAL RESOLUTION REQUIREMENTS

Human body: ~70 kg
Heart mass: ~300 g
Aorthic cannula Ø: ~30 mm
Brain cortex apex – temporal lobe: ~105 mm

Rat body: ~200 g
Heart mass: ~1 g
Aorthic cannula Ø: 1.5 - 2.2 mm
Brain cortex apex – temporal lobe: ~10 mm

Mouse body: ~20 g
Heart mass: ~0.1 g
Aorthic cannula Ø: 0.9 - 1.3 mm
Brain cortex apex – temporal lobe: ~6 mm



Relative heart size	Relative brain size	Required spatial resolution
		5 mm FWHM (<150 mm^3)
		1.5-2 mm FWHM (<8 mm^3)
		<1 mm FWHM (<1 mm^3)

It is clear that dedicated imaging systems are necessary!

LIMITS AND POSSIBILITIES

Imaging technique	*Source of signal*	*Spatial resolution*	*Sensitivity (mol/l)*	*Quantitative information*	*Morphological information*
PET	γ-rays (511 keV)	1-2 mm	10^{-11}-10^{-12}	★★★	★
SPECT	γ-rays (<300 keV)	300 μm-1 mm	10^{-10}-10^{-11}	★★	★
Optical bioluminescence	visible light	3-5 mm	Theoretical limit 10^{-15}-10^{-17}	★☆	n.a.
Optical fluorescence	visible light and NIR	2-3 mm	Probable limit 10^{-9}-10^{-12}	★☆	n.a.
MRI	Radio waves	25-100 μm	10^{-3}-10^{-5}	★★	★★★
CT	X-rays (30-120 keV)	10-100 μm	n.a.	n.a.	★★★

Spatial resolution and sensitivity may be limited by both the physics of the involved processes and the detector technology.

SPATIAL RESOLUTION LIMITATIONS IN PET

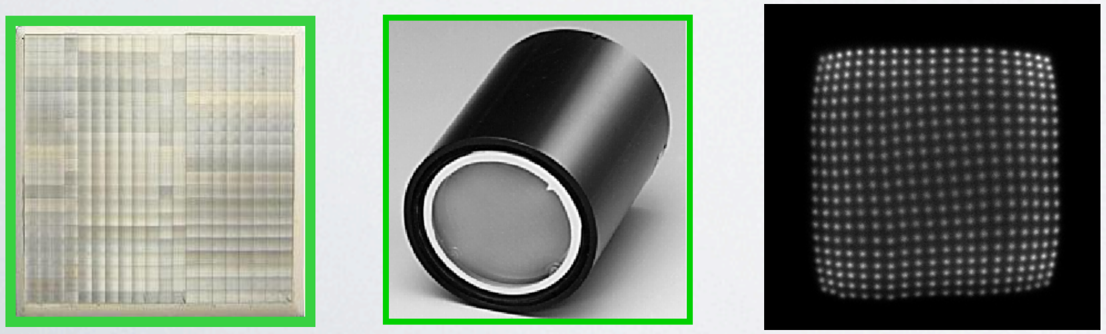
$$FWHM = \underbrace{1.2}_{\text{Reconstruction}}\sqrt{\underbrace{\left(\frac{d}{2}\right)^2}_{\text{Crystal pitch}} + \underbrace{b^2}_{\text{Coding}} + \overbrace{\underbrace{(0.0022D)^2}_{\text{Non-collinearity}} + \underbrace{r^2}_{\text{Positron range}}}^{\text{Physics}} + \underbrace{p^2}_{\text{Parallax}}}$$

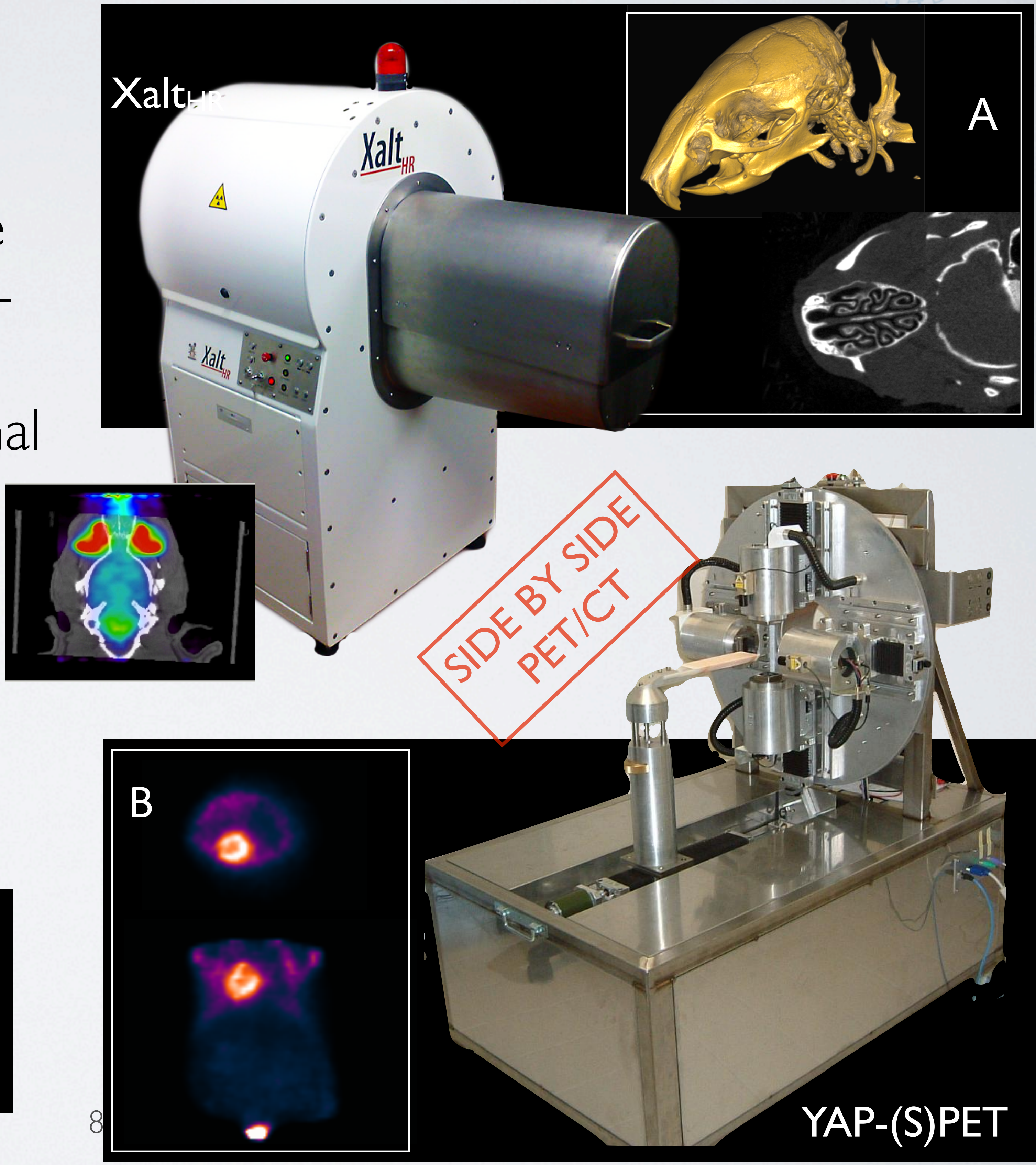
Due to the available technology, present small animal systems have a typical spatial resolution of about 1.3-1.6 mm FWHM at the center of the field-of-view (FOV).

This is good enough for most cases (especially for rats).

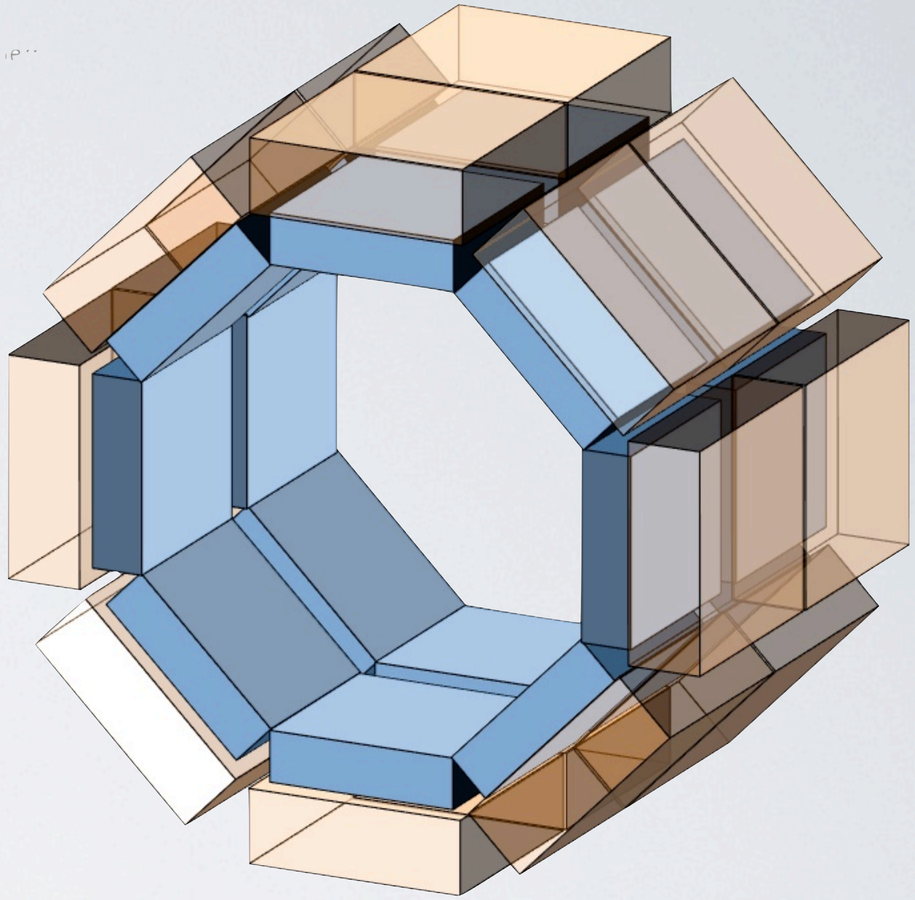
Latest systems, incorporating the high granularity detectors and in some cases DOI capability, offer a volumetric spatial resolution of close to 1 mm^3 that is very close to the theoretical one.

SIDE BY SIDE PET & CT SYSTEMS

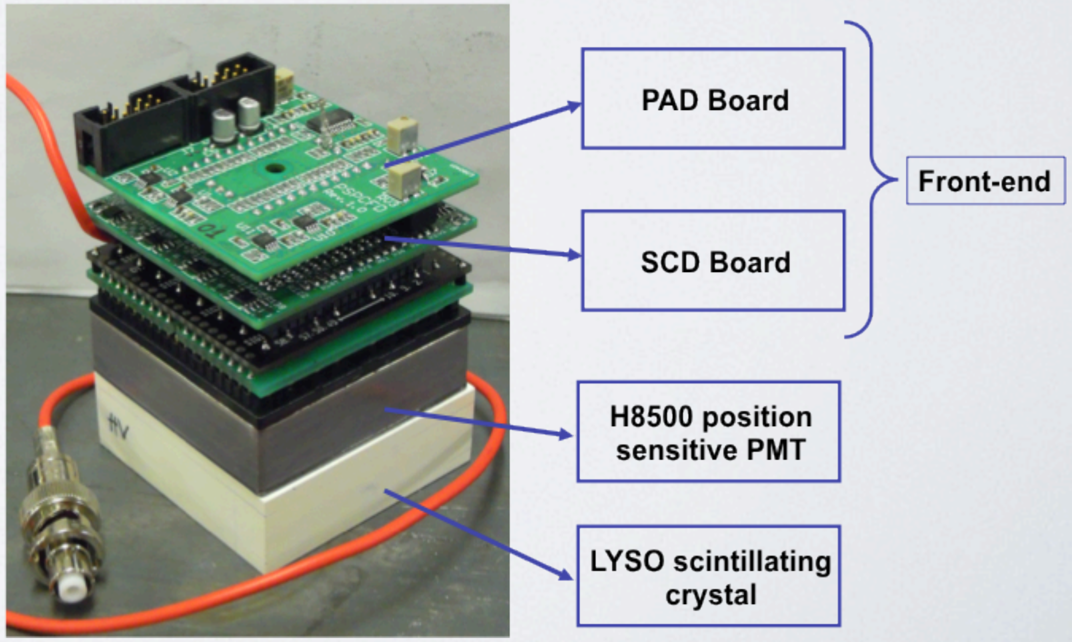
- For example at the IFC-CNR we are using a stand-alone / custom-made animal CT system (Xalt$_{HR}$) in combination with a small animal PET scanner (YAP-(S)PET)
- YAP-(S)PET is based on YAP:Ce crystals coupled to PS-PMTs (Hamamatsu R2486)
- 



FURTHER DEVELOPMENTS AT PISA UNIVERSITY

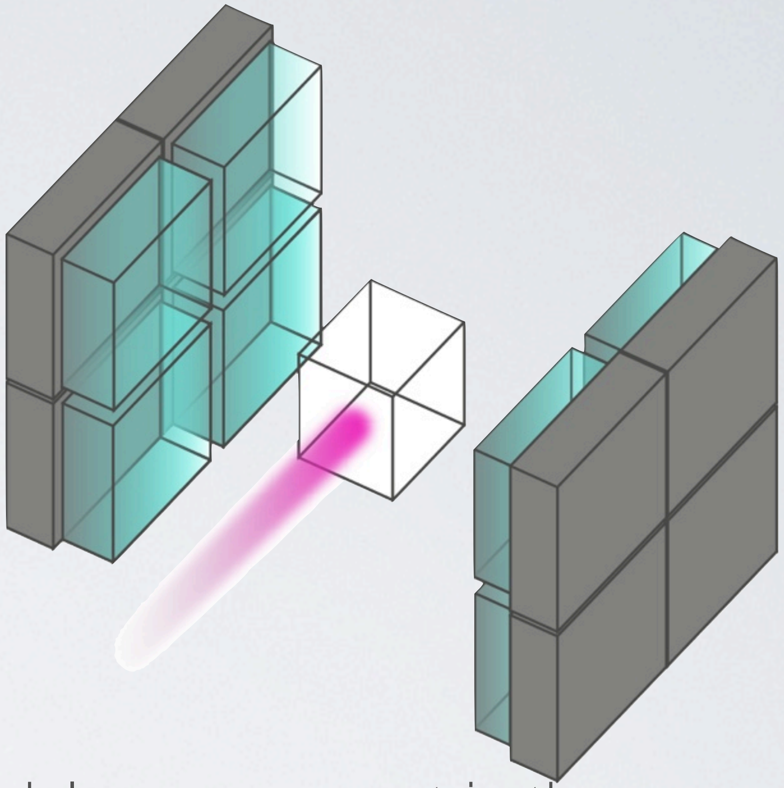


- Along this line we are developing a docked small animal PET/CT system.
- The CT part is based on a commercial flat panel CMOS detector and a microfocus x-ray tube
- The PET part is based on a modular detector approach featuring well established detector technology

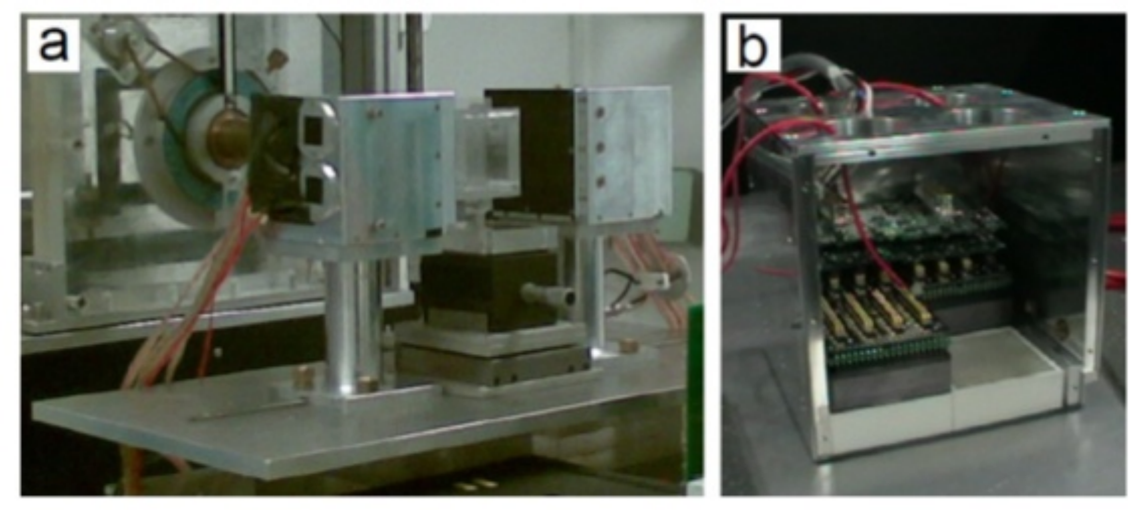


MODULARITY = MULTIPURPOSE

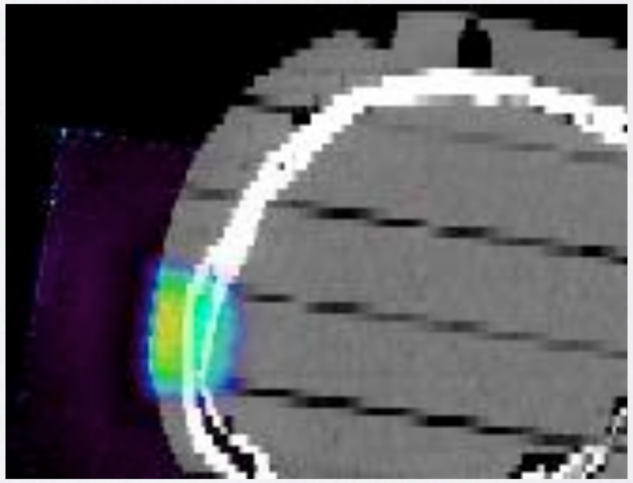
- Thanks to the modular approach also present in the DAQ the same detectors can be used also for other purposes.
- For example we have developed an in-beam PET system for range monitoring in hadrontherapy



Module arrangement in the present 4 vs 4 configuration (10 cm x 10 cm). The system will be extended to 9 vs 9 modules



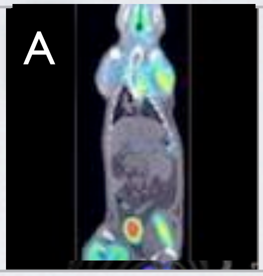
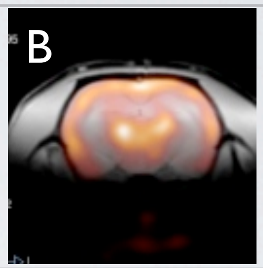
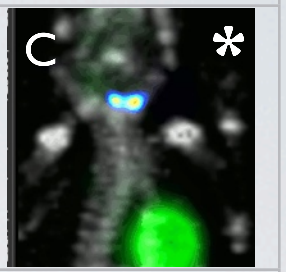
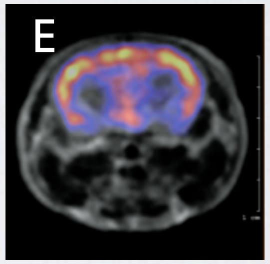
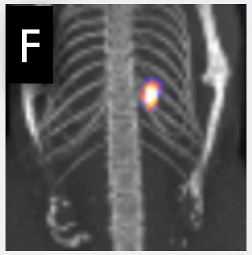
Inside of the modules and heads arrangement at the CATANA beamline



Example of the measured activity distribution (p, 62 MeV) in a section of a RANDO phantom

WHAT IT IS AVAILABLE IN 3D HYBRID SYSTEMS

- Today, many combinations of hybrid imaging technique for small animals are available in commercial systems.
- The most common is the docked solution where it is not possible to perform simultaneous hybrid imaging.
- Challenges are:
    - Detector for simultaneous imaging
    - New detectors to overcome the present limitation

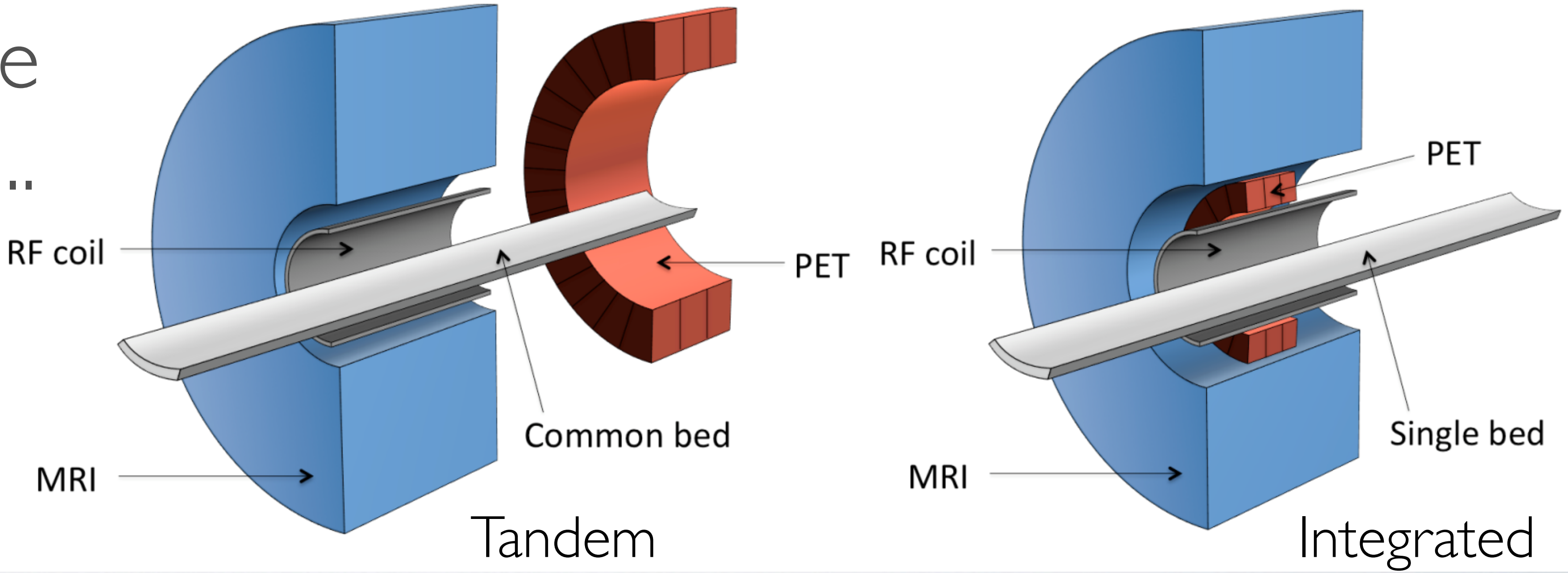
Imaging technique	CT	MR	SPECT
PET			
SPECT			
Optical			

- A. Triumph PET/CT by Gammamedica
- B. SuperArgus PET/MR by Sedecal
- C. VECTor PET/SPECT by MI Labs. (***simultaneous)
- D. Inveon SPECT/CT by Siemens
- E. NanoSPECT/MR by Mediso
- F. BioFLECT/CT by Bioscan

PET/MR TECHNOLOGICAL STRATEGIES

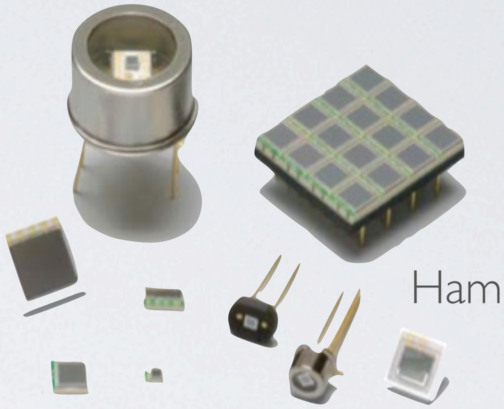
- Like in the clinical environment the next step is the integration of PET/MR
- Even in small animal systems the technical challenges in integrating PET and SPECT with MRI relate primarily to the various ways in which the systems can interfere with each other.
- System integration and technological strategies to solve this problem are similar to those used in clinical systems

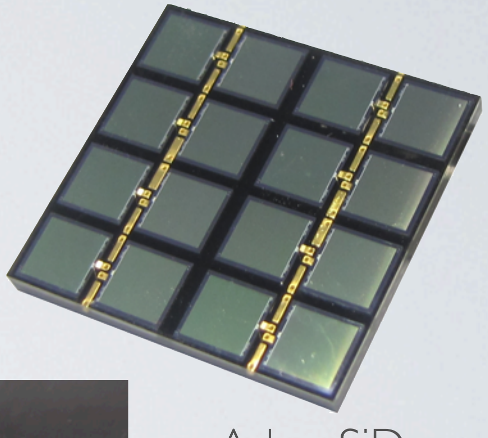
From the docked to the integrated solution ....

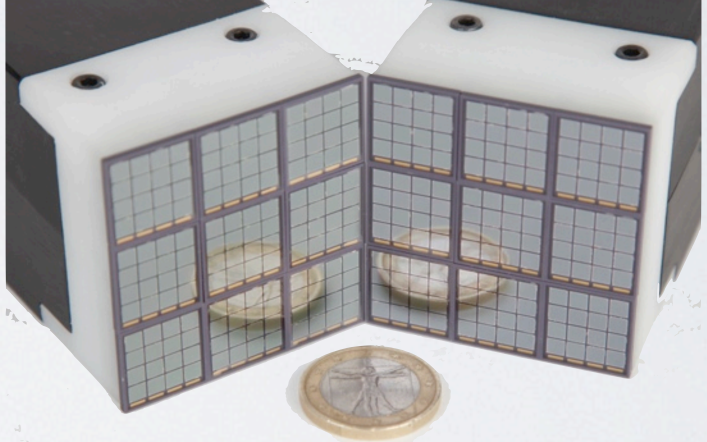


TOWARD THE INTEGRATED SOLUTION: SOLID STATE PHOTO DETECTORS FOR PET/MR

- Scintillator based solution are always the preferred one for PET
- Solid state detectors used as photodetectors
  - APD = Avalanche Photodiode
  - SiPM = Silicon Photomultiplier
    - Insensitive to magnetic field
    - Higher gain than APD
    - Single photon resolution
    - Superior timing performance compared to other solid-state photodetectors
    - Criticity: high dark count rate (not an issue for PET)
    - Difficult to handle a lot of DAQ Channels to exploit full features
  - Digital SiPM


Hamamatsu


AdvanSiD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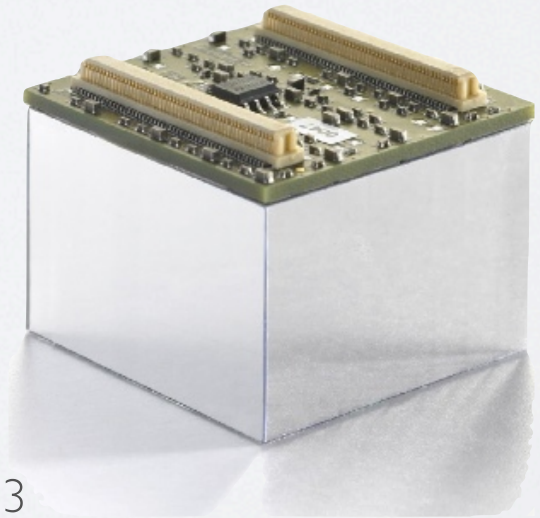
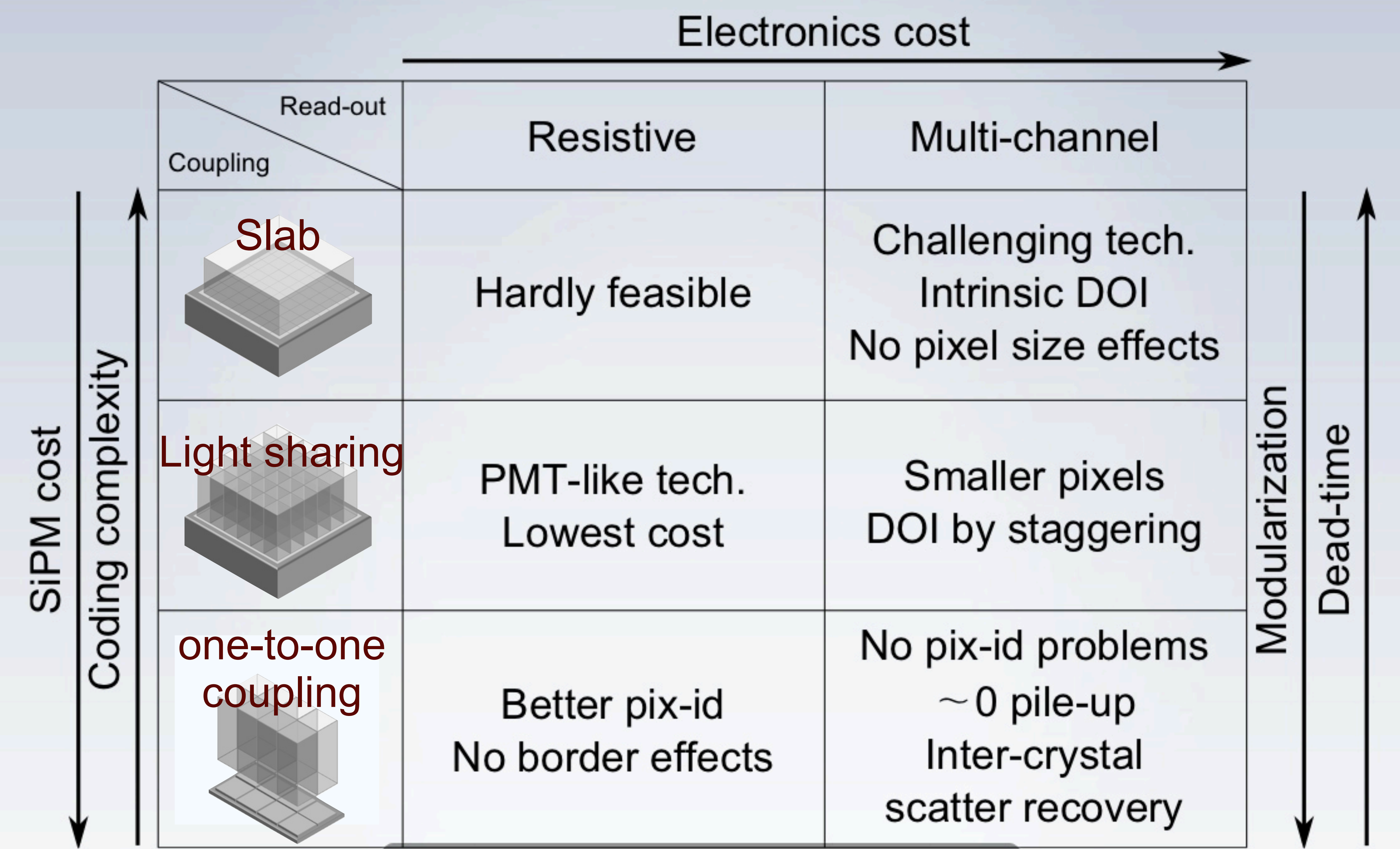

Philips

Example of single SiPM in various packages or SiPM arrays either build as matrix of single elements or build on a common substrate.

Digital SIPMs are also available

COUPLING AND READ-OUT SOLUTIONS FOR SIPM+SCINTILLATOR



Electronics cost

Read-out Coupling	Resistive	Multi-channel
Slab	Hardly feasible	Challenging tech. Intrinsic DOI No pixel size effects
Light sharing	PMT-like tech. Lowest cost	Smaller pixels DOI by staggering
one-to-one coupling	Better pix-id No border effects	No pix-id problems ~0 pile-up Inter-crystal scatter recovery

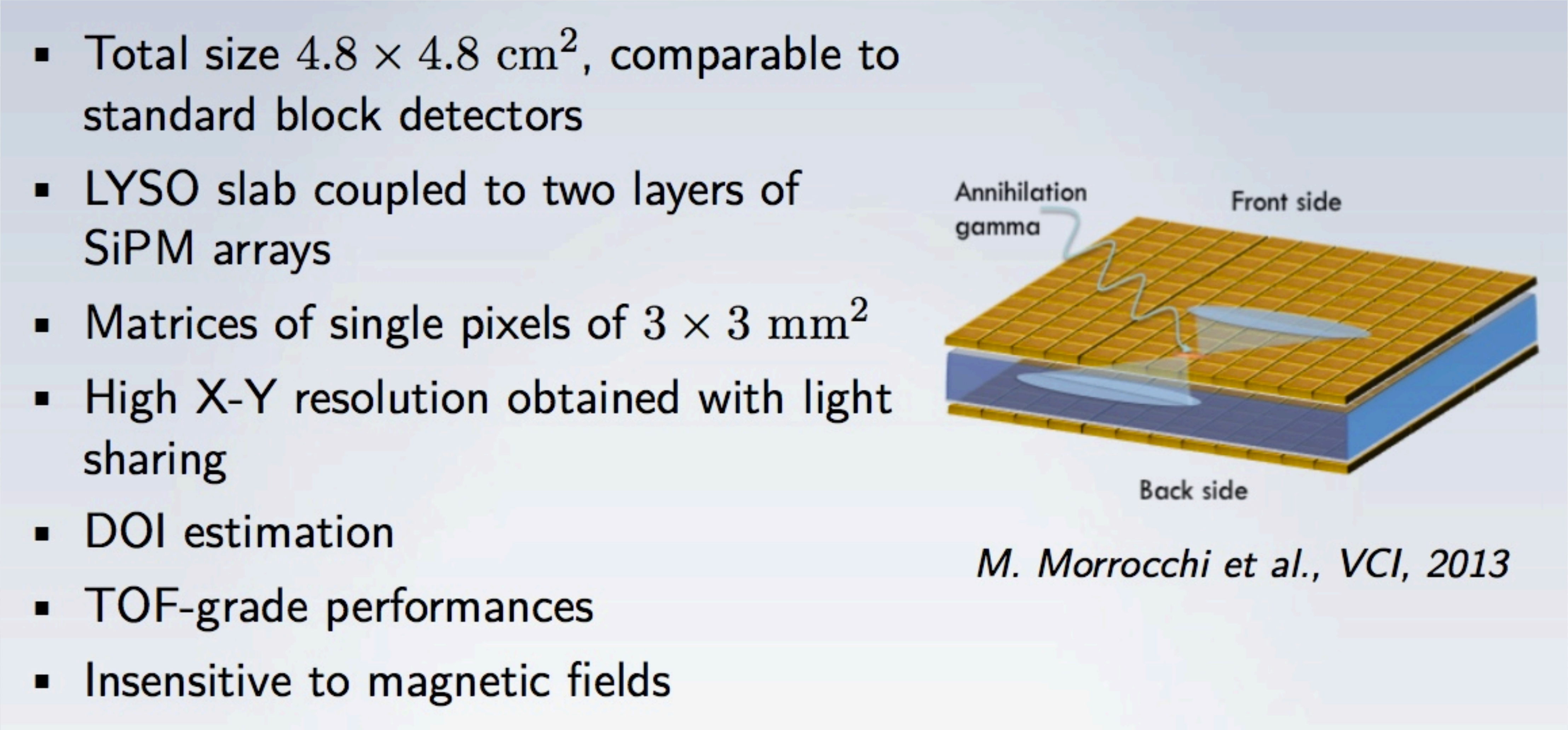
SiPM cost

Coding complexity

Modularization

Dead-time

EXAMPLE OF SIPM + SCINT. SLAB CONCEPT

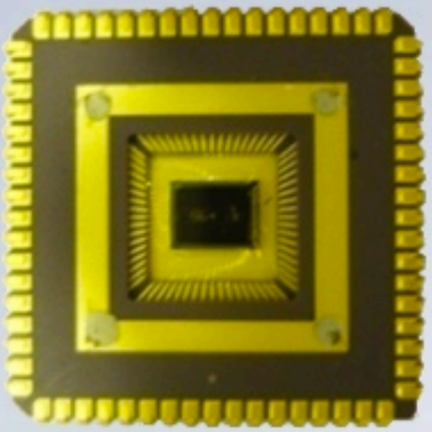


- Total size $4.8 \times 4.8 \ \mathrm{cm}^2$, comparable to standard block detectors
- LYSO slab coupled to two layers of SiPM arrays
- Matrices of single pixels of $3 \times 3 \ \mathrm{mm}^2$
- High X-Y resolution obtained with light sharing
- DOI estimation
- TOF-grade performances
- Insensitive to magnetic fields

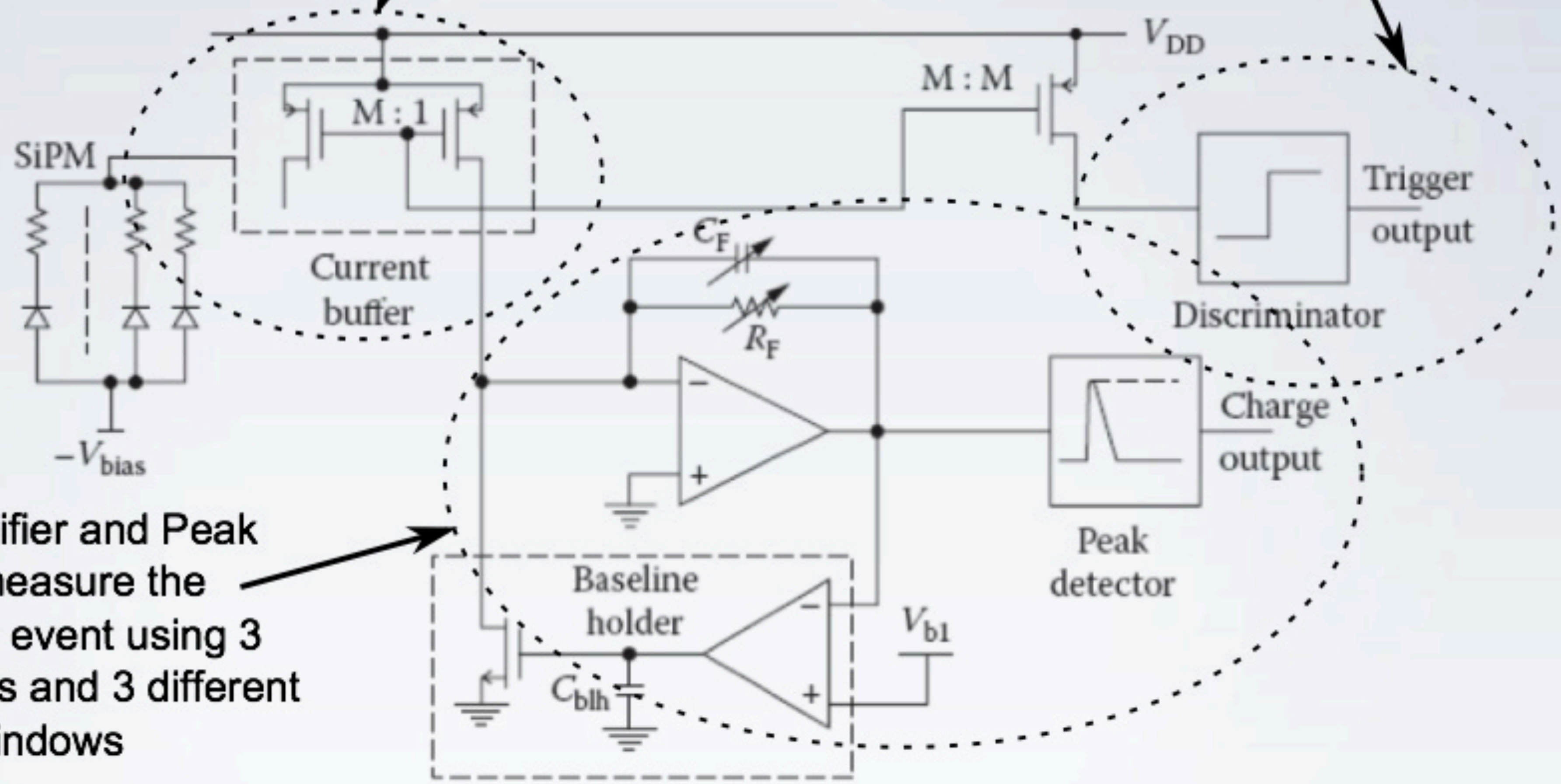
M. Morrocchi et al., VCI, 2013

We are also investigating direct coupling between SiPM and Scintillators solutions

NEEDS OF DEDICATED ASICS



32-Channels Front-End chip developed at the Politecnico of Bari
(C. Marzocca et al., 8th Int. Meeting on Front-End Electronics, 2011 Bergamo)



SiPM signal is replicated by a Front-End buffer and splitted in two branches

Fast discriminator for timing information: external trigger is obtained by the OR logic of the 32 triggers

Charge Amplifier and Peak Detector to measure the energy of the event using 3 different gains and 3 different integration windows

CONCLUSIONS

- Requirements for pre-clinical imaging are now clear.
- Nuclear techiques are well established but there is still room for improvement
  - New photodetectors and scintillators to be fully explored (e.g. SiPM + LaBr for SPECT)
  - Direct conversion photodetectors (also for PET)
- A lot is yet to be done in the field of multimodality integration
  - Simultaneous PET/MR detectors
  - Simultaneous SPECT/MR detectors
- Detector modularity is a critical requirement to extend the technology also to other fields