Proposal and demonstration of a novel SPECT for high-precision gamma-ray imaging

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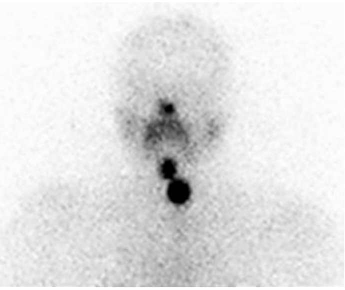
Introduction Imaging of therapeutic drugs

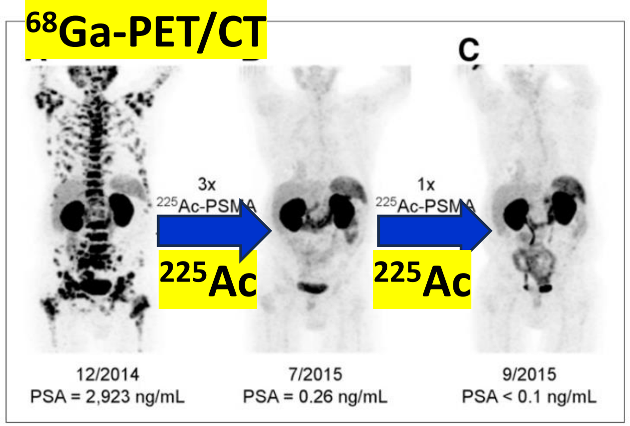
- Imaging of therapeutic drugs is essential for effective treatment

^{131}I
- Thyroid cancer
- β particles
- Gamma ray: **364 keV**



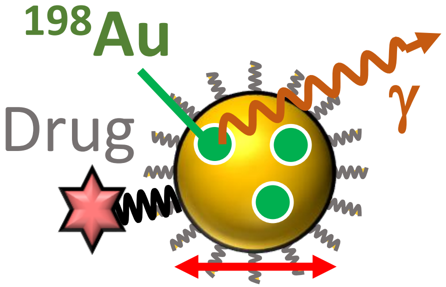
Szumowski et al. *Sci. Rep.*, 2021

^{225}Ac
- Prostate cancer
- α particles
- Gamma ray: **440 keV**



Kratochwil et al. *J. Nucl. Med.*, 2016

[^{198}Au]AuNP
- Drug carrier
- Gamma ray: **412 keV**



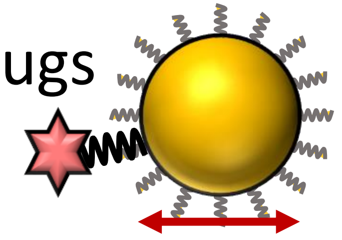
Gold nanoparticles (AuNPs)

Koshikawa et al., Appl. Phys. Lett., 2022

High-quality imaging with gamma rays in the range of several hundred keV is needed

Introduction Activation Imaging of Gold nanoparticles

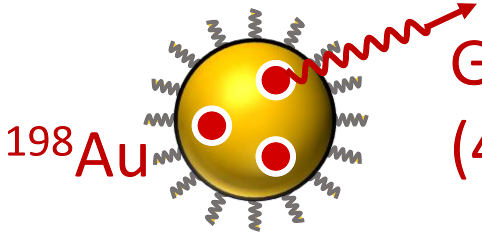
- Gold nanoparticles (AuNPs)
  ...Promising **drug carrier**



✓ Accumulation in tumors
✓ High biocompatibility
✓ Easy surface modification

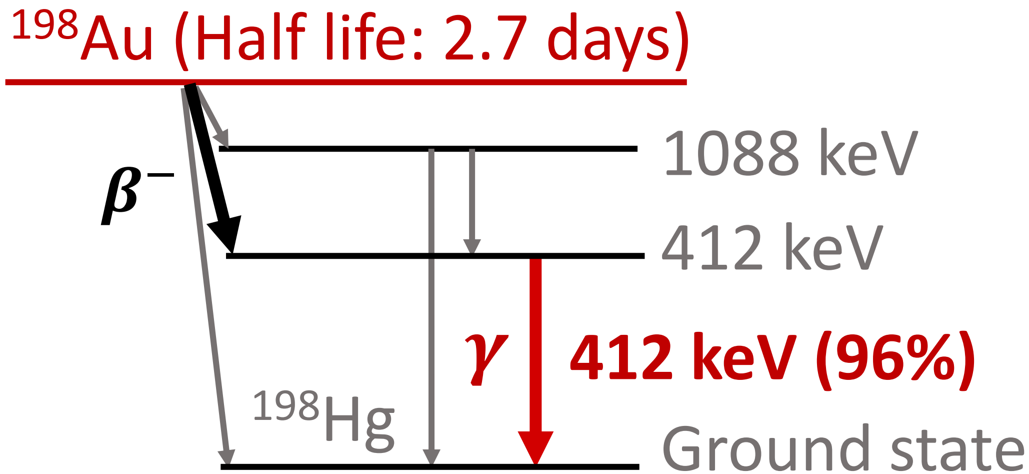
Distribution varies with size, shape, etc.
→ **Visualization of AuNPs** is important

- **[^{198}Au]AuNPs**



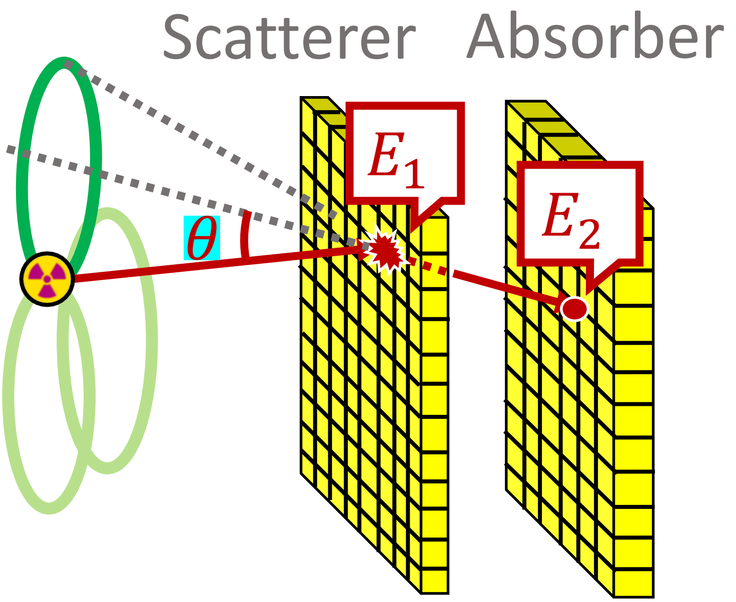
Koshikawa et al., *Appl. Phys. Lett.*, 2022

Neutron + ^{197}Au → ^{198}Au
Stable Radioactive



Introduction Imaging devices

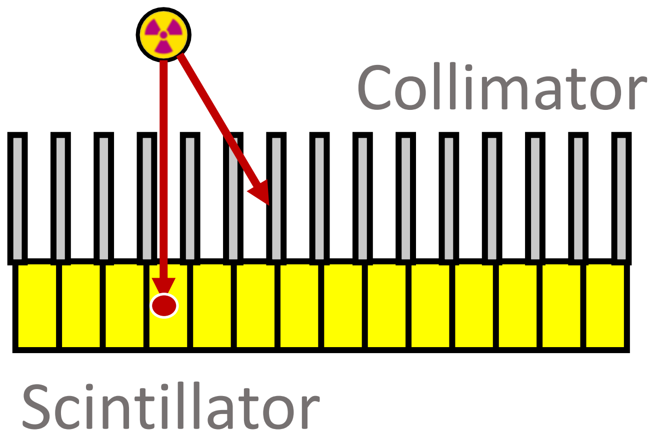
■ Compton camera



$$\cos\theta = 1 - m_e c^2 \left(\frac{1}{E_2} - \frac{1}{E_1+E_2}\right)$$

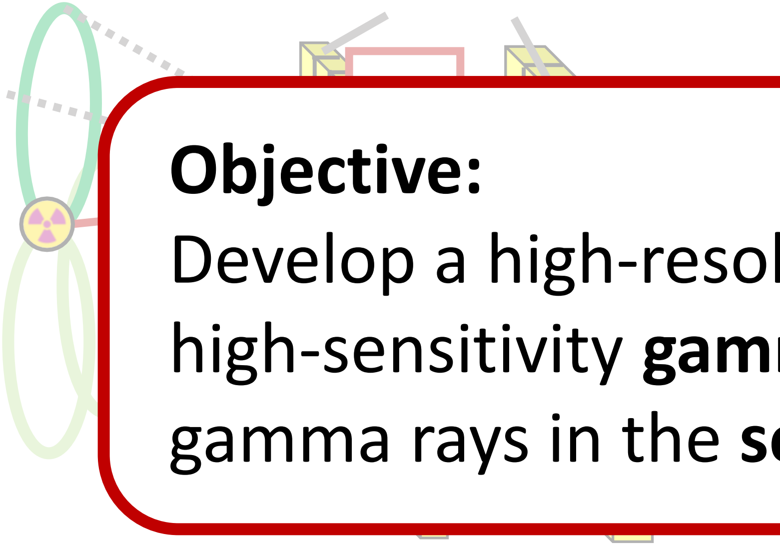
- ✔ Imaging in the hundreds of keV range
- ✔ No collimator required → Wide FOV
- ✘ Limited spatial resolution

■ SPECT (Single-photon emission computed tomography)



- ✔ High spatial resolution
- ✔ Widely used in clinical settings
- ✘ **Imaging in high-energy region**
  - → Thick collimator required
  - → Sensitivity decreases

- Compton camera



$$\cos\theta = 1 - m_e c^2\left(\frac{1}{E_2} - \frac{1}{E_1+E_2}\right)$$

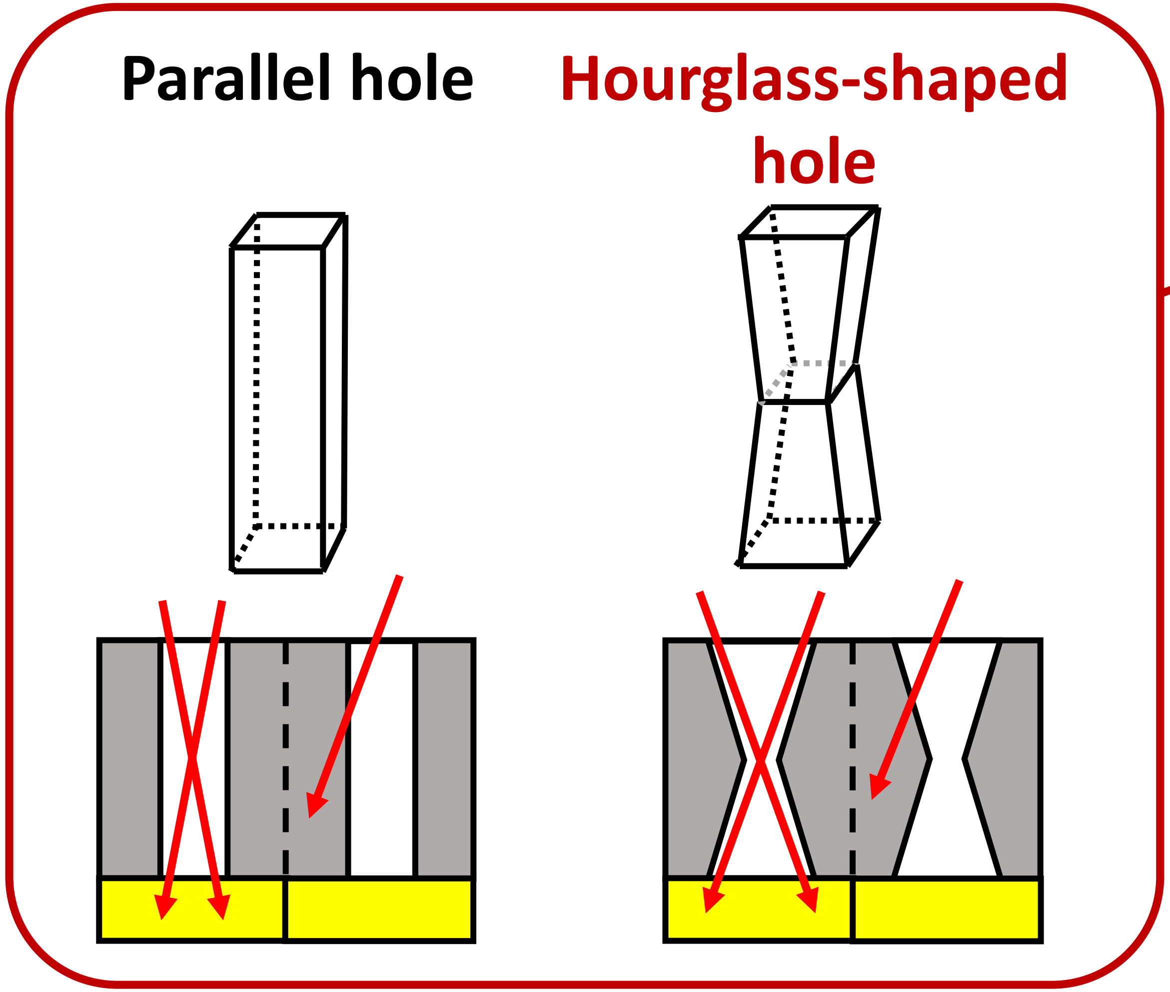
✓ Imaging in the hundreds of keV range
✓ No collimator required → Wide FOV
✗ Limited spatial resolution

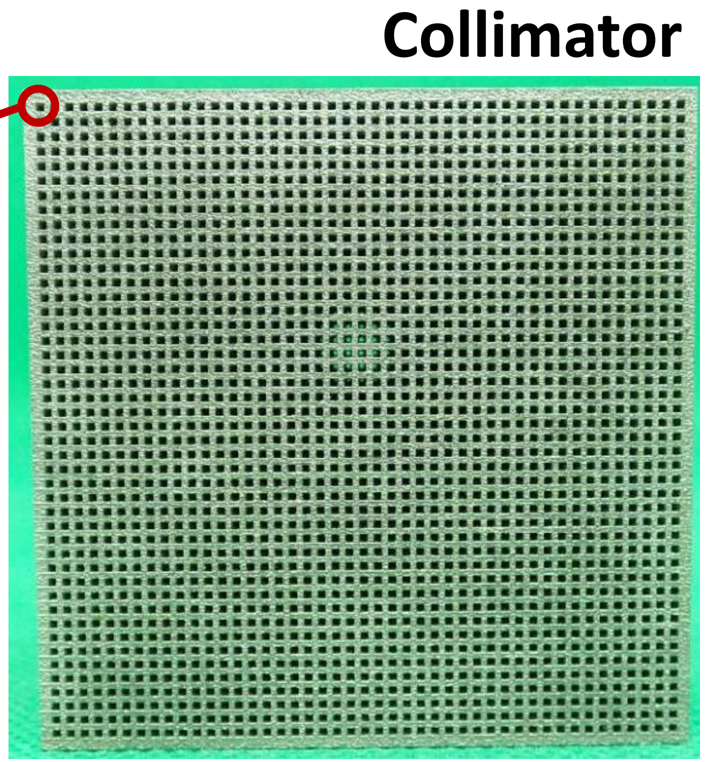
- SPECT (Single-photon emission computed tomography)

✓ High spatial resolution
✓ Widely used in clinical settings
✗ **Imaging in high-energy region**
→ Thick collimator required
→ Sensitivity decreases

Objective:
Develop a high-resolution (a few mm), high-sensitivity **gamma camera** for imaging gamma rays in the **several-hundred keV range**.

Hourglass hole collimator

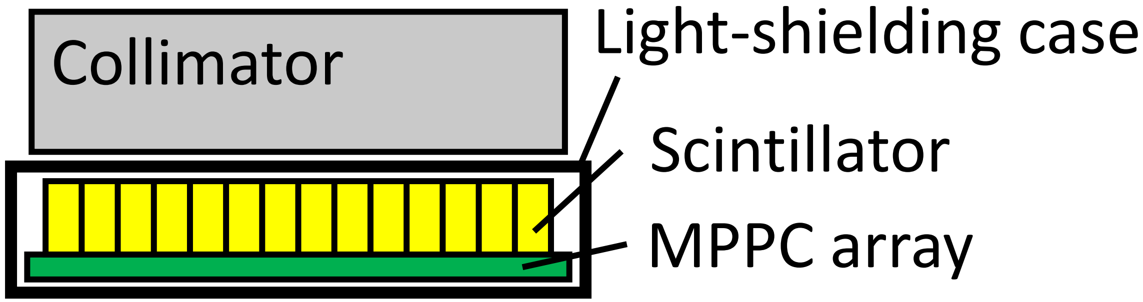




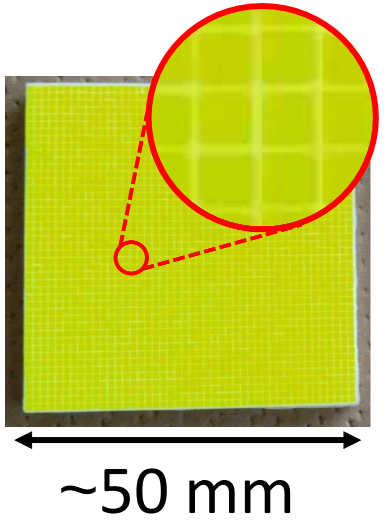
✓ Achieve high sensitivity while keeping spatial resolution

Configuration

Gamma camera

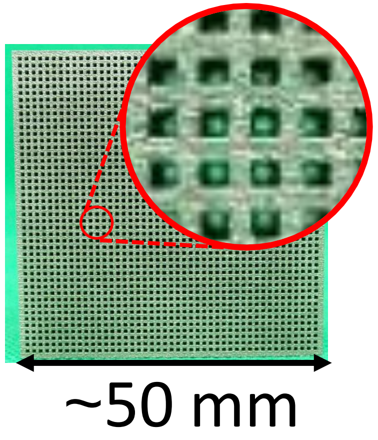


Scintillator



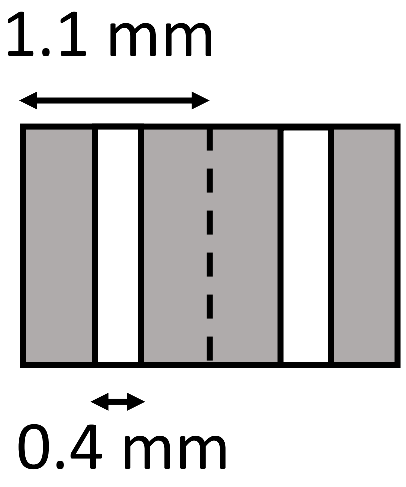
- GAGG ($Gd_3(Ga,Al)_5O_{12}(Ce)$)
- Pixel pitch: 1×1 mm^2
- 45×45 array
- Thickness: 5 mm
- Energy resolution: 7.5%(FWHM)@662 keV

Collimator (Toray Precision Co., Ltd)

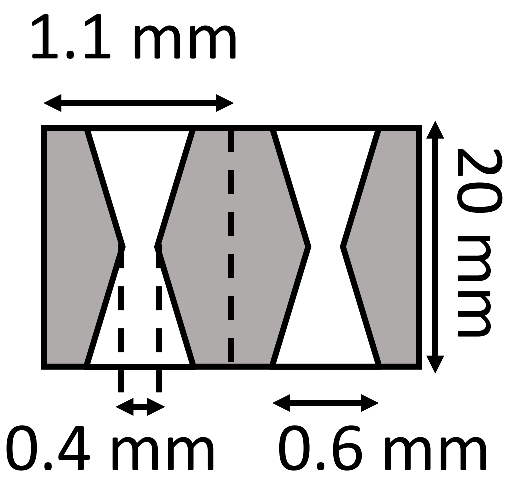


- Tungsten
- Pixel pitch: 1×1 mm^2
- 45×45 holes
- Height: 20 mm

Parallel hole

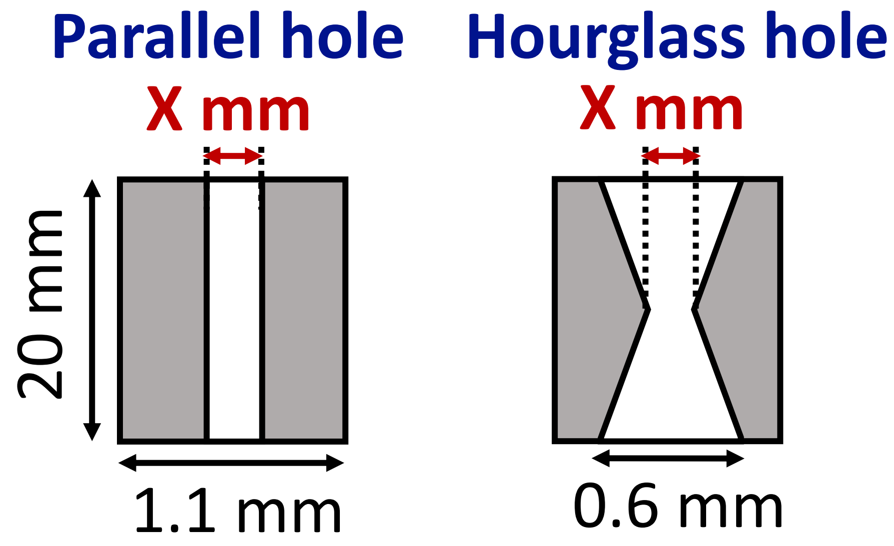


Hourglass hole

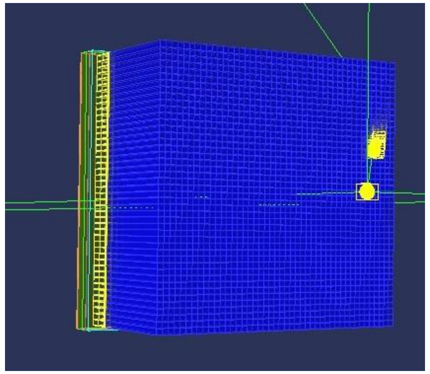


Configuration

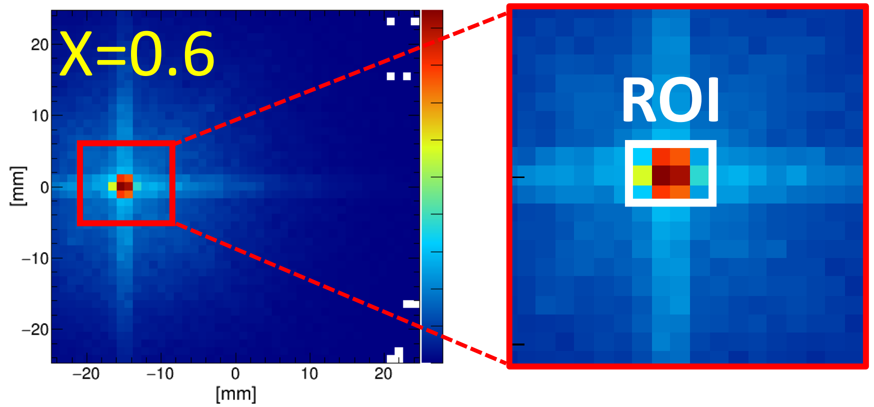
■ **Geant4 simulation**



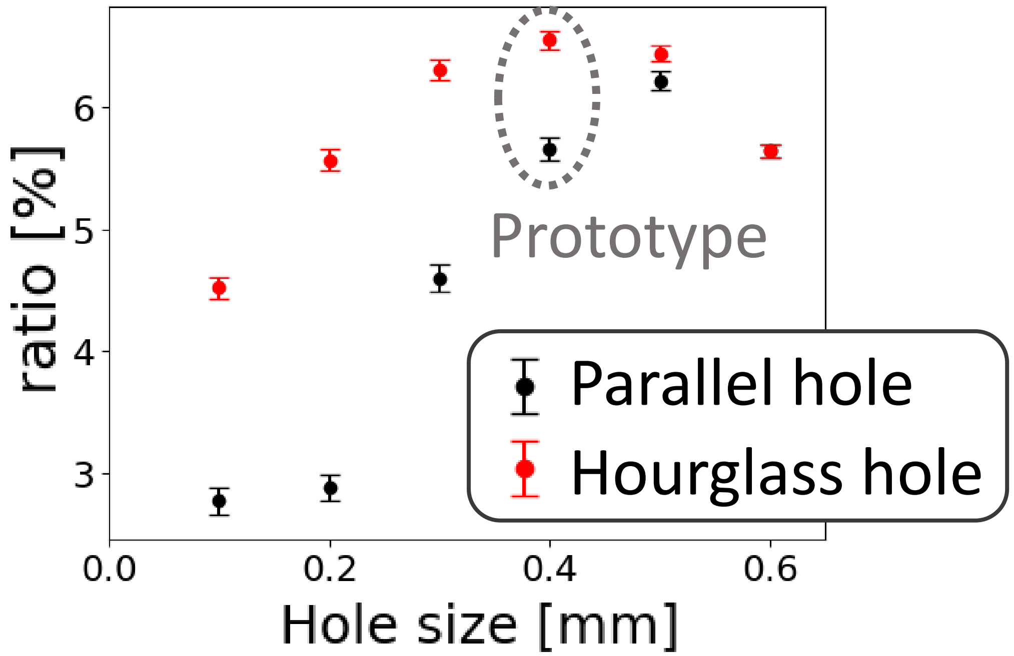
X = 0.1, 0.2, 0.3, 0.4, 0.5, 0.6



Source
Energy: 412 keV
Position: (-15, 0) mm
Size: ϕ3 mm



Pixel value inside ROI / All pixel value

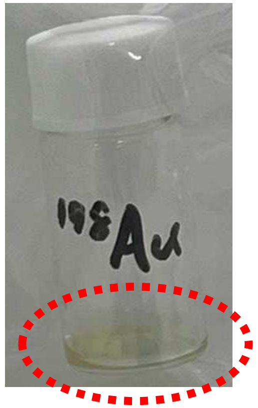


Imaging of activated gold

■ **Methods**

1. Prepare ^{198}Au

- Neutron irradiation to $HAuCl_4$ (precursor for AuNPs) @Kyoto university research reactor (KUR)

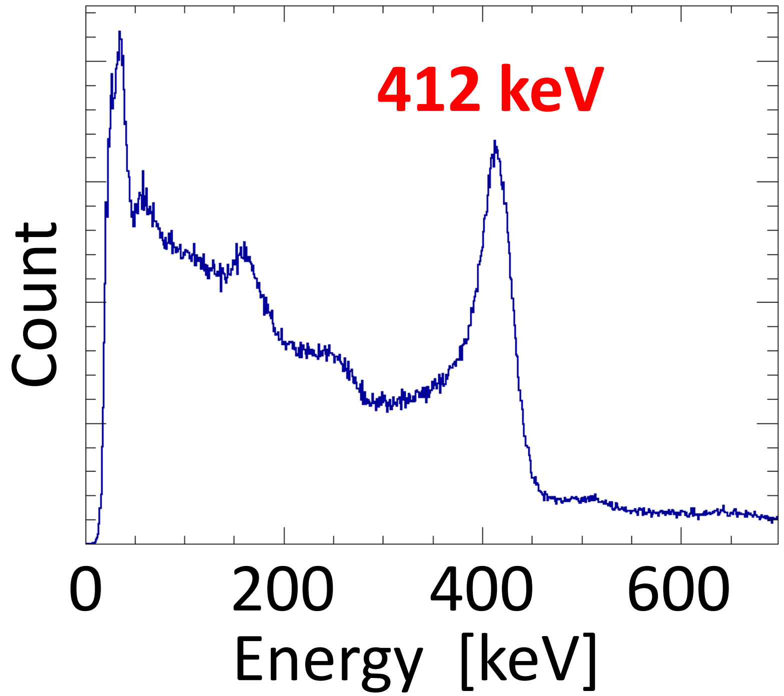


$HAuCl_4$ aq.

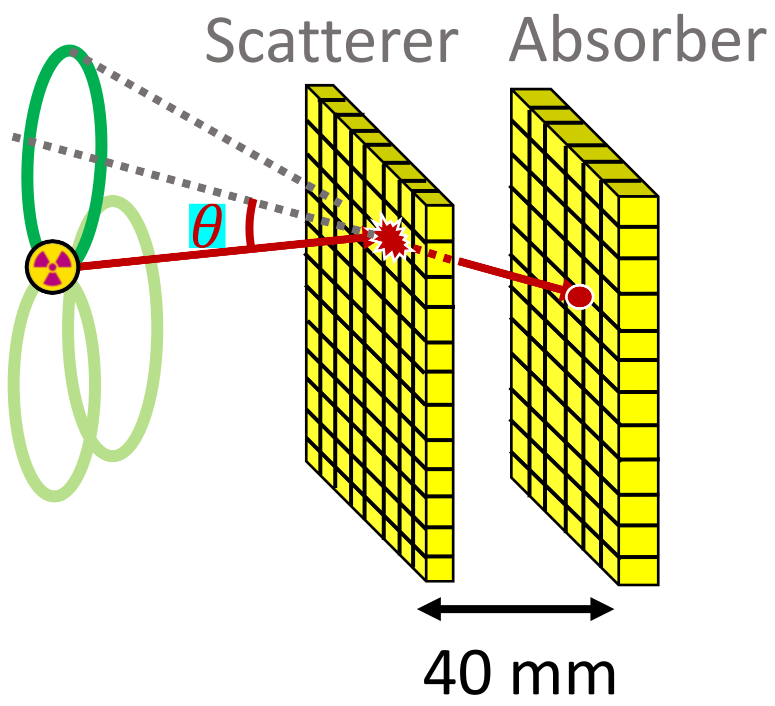
2. Inject into phantoms

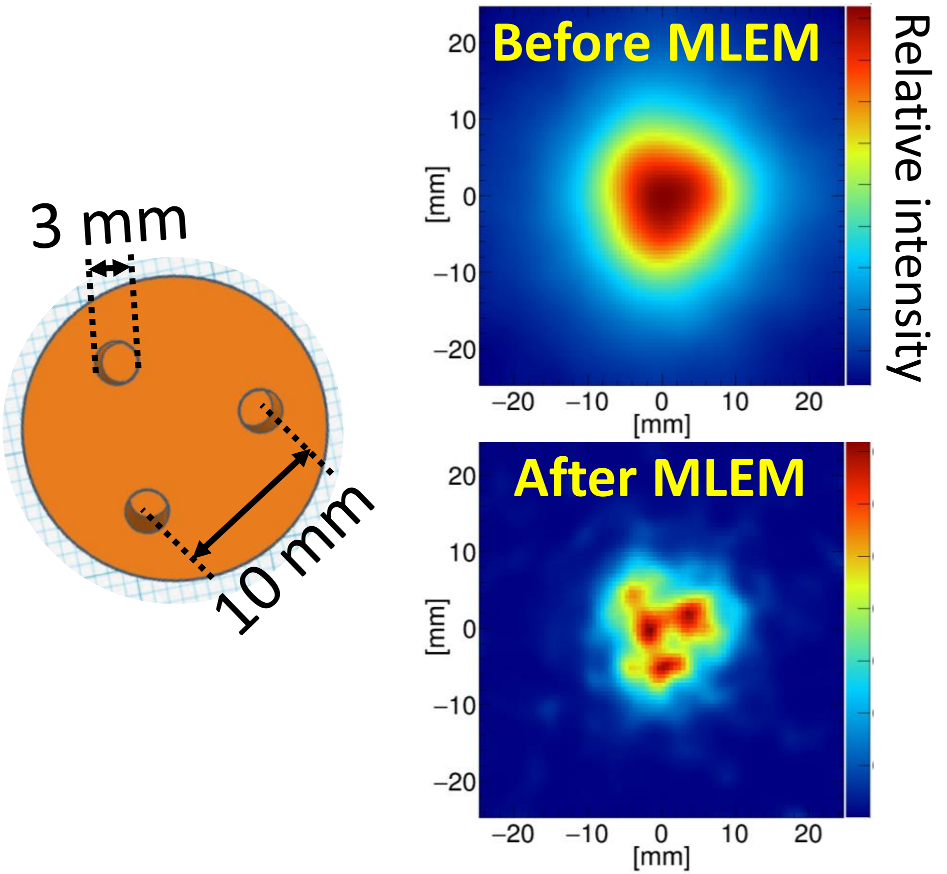
3. Perform imaging

- Compare b/w imaging devices
  Compton camera,
  Parallel hole / hourglass hole collimator
- Evaluate performance of
  hourglass hole collimator



Previous method: Compton camera

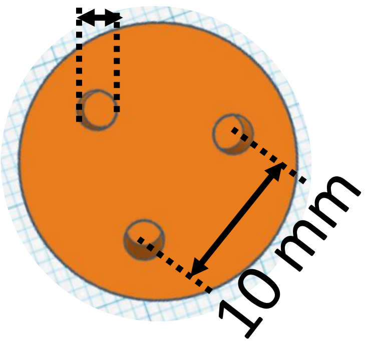


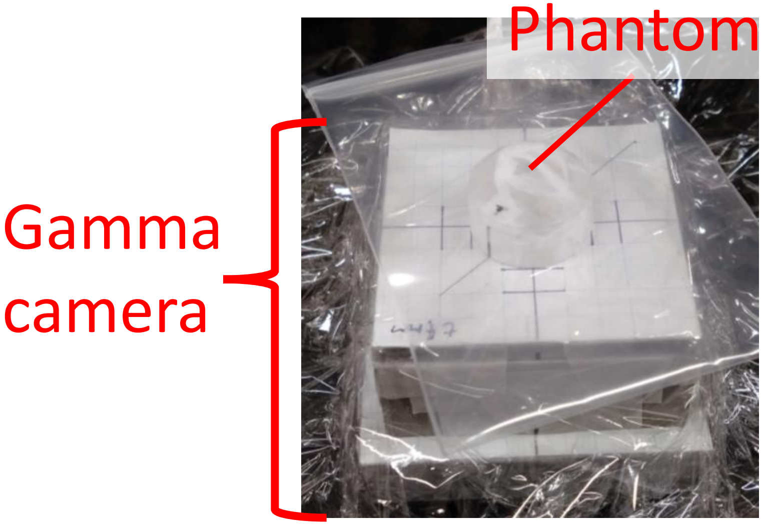


- GAGG scintillator
- Pixel pitch: 1×1 mm^2
- 45×45 array
- Thickness:
  Scatterer: 3 mm, Absorber: 5 mm

- ^{198}Au 70 kBq / hole
- Measurement time: 1 h
- Energy window: 412±30 keV
- Accumulation in incorrect position

Parallel hole vs. hourglass hole

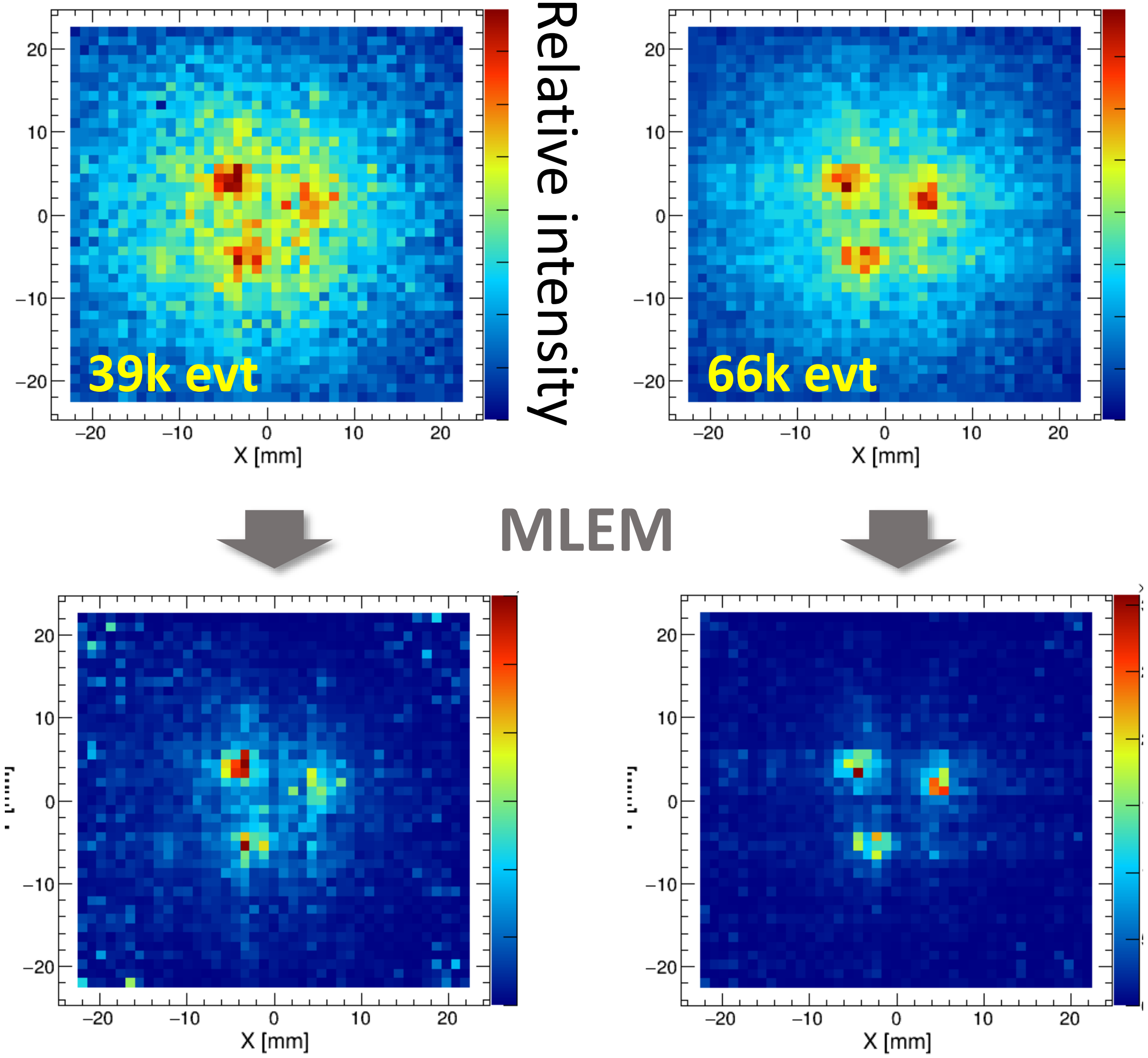




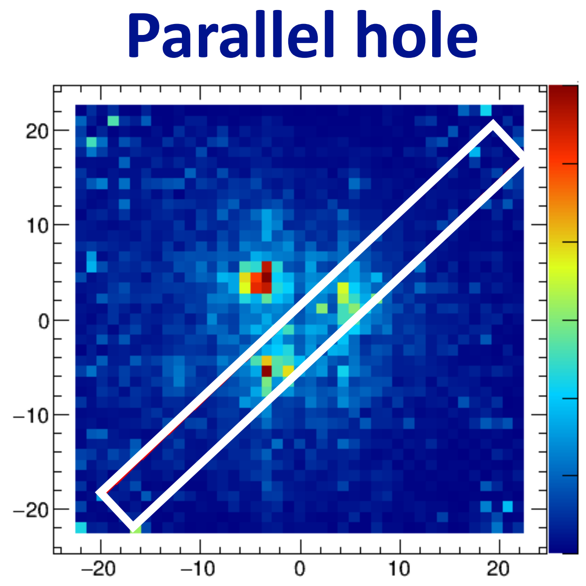
- ^{198}Au 70 kBq / hole
- Measurement time: 1 h
- Energy window: 402-442 keV

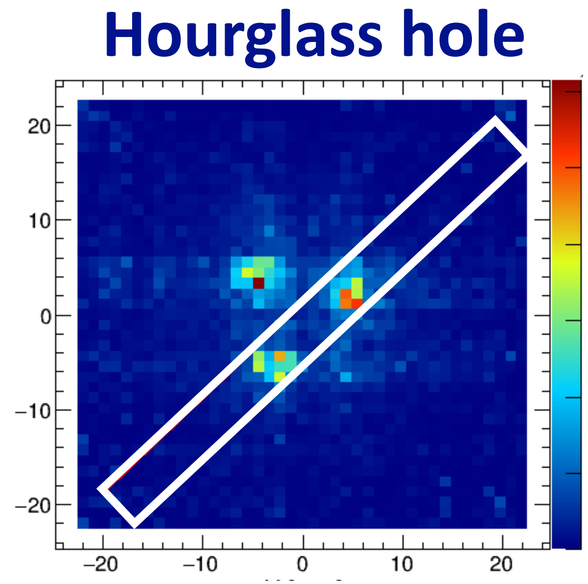
Parallel hole

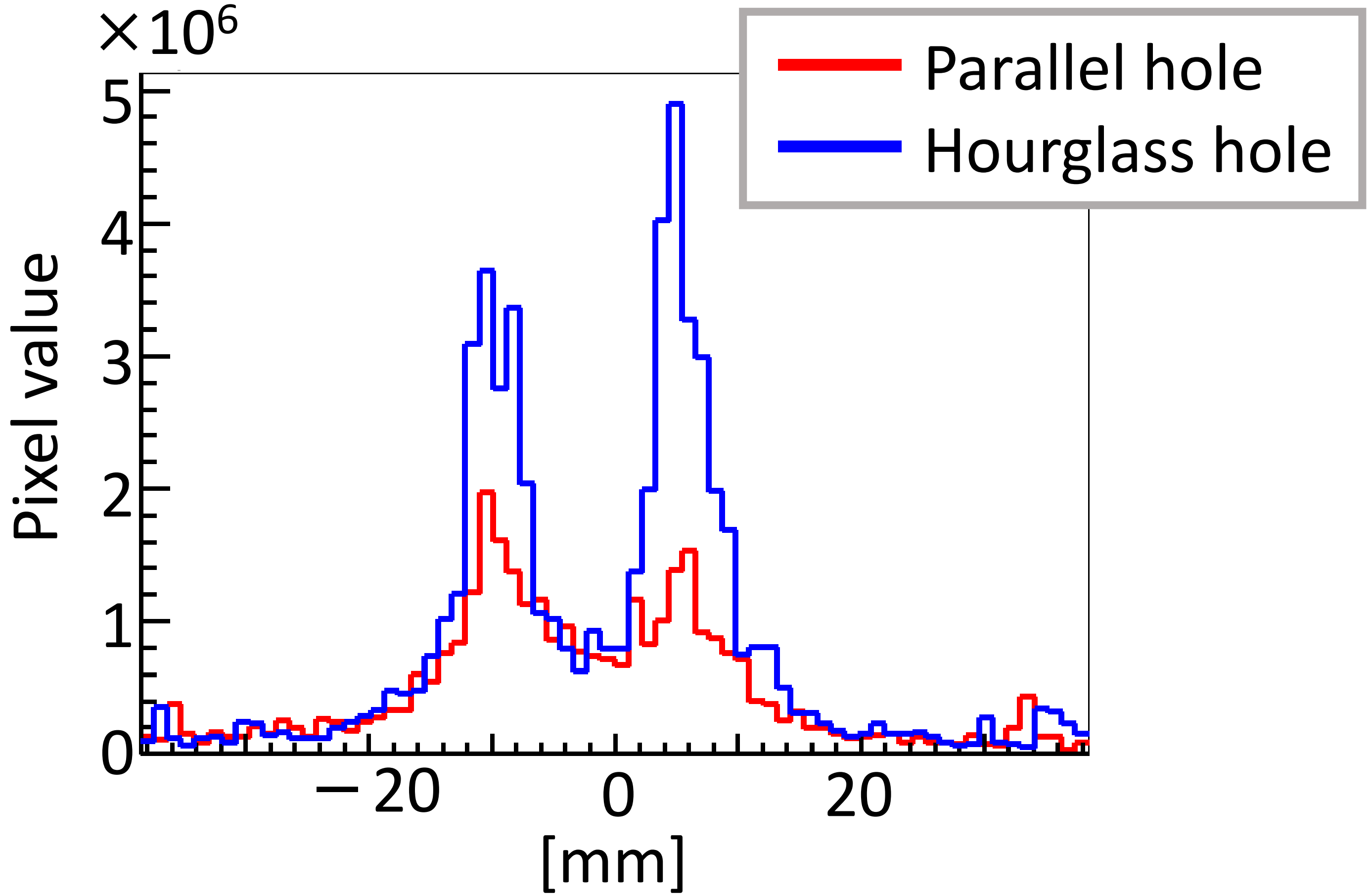
Hourglass hole



Parallel hole vs. hourglass hole



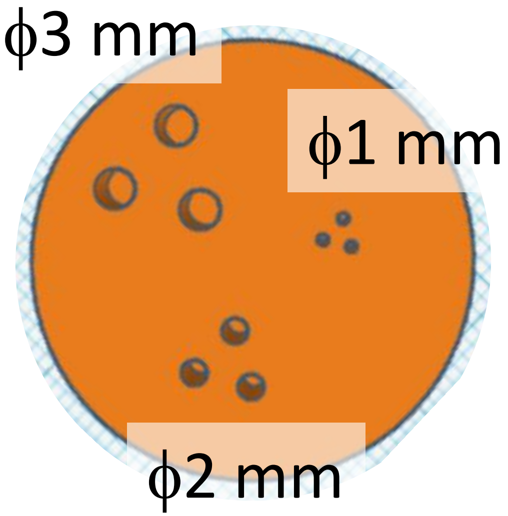




Peak / Valley
Parallel hole: 2.6
Hourglass hole: 6.9
×2.7

Performance of hourglass hole collimator

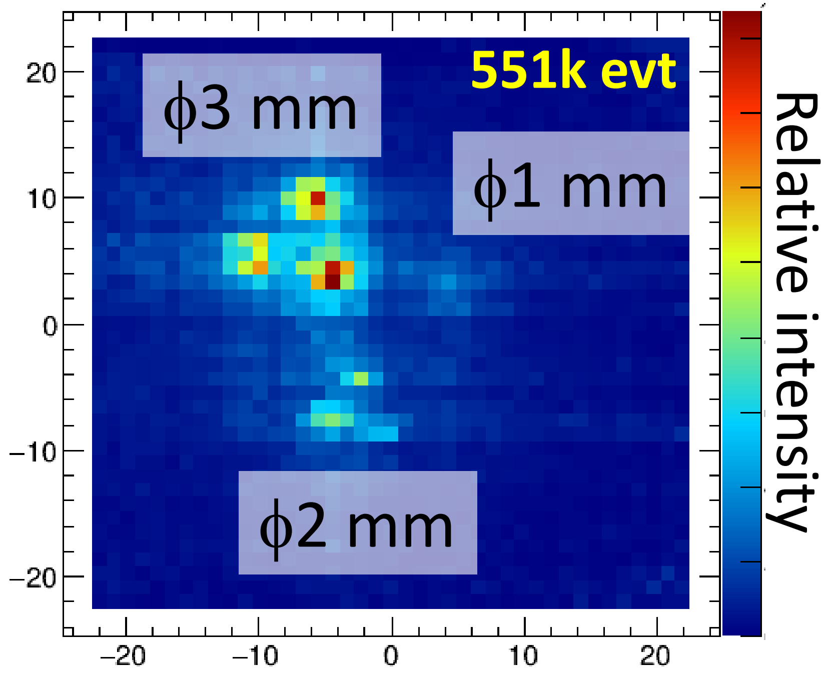
■ **Derenzo phantom**

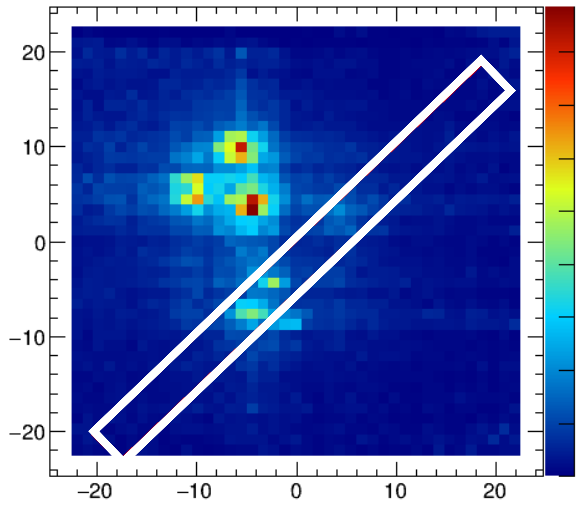


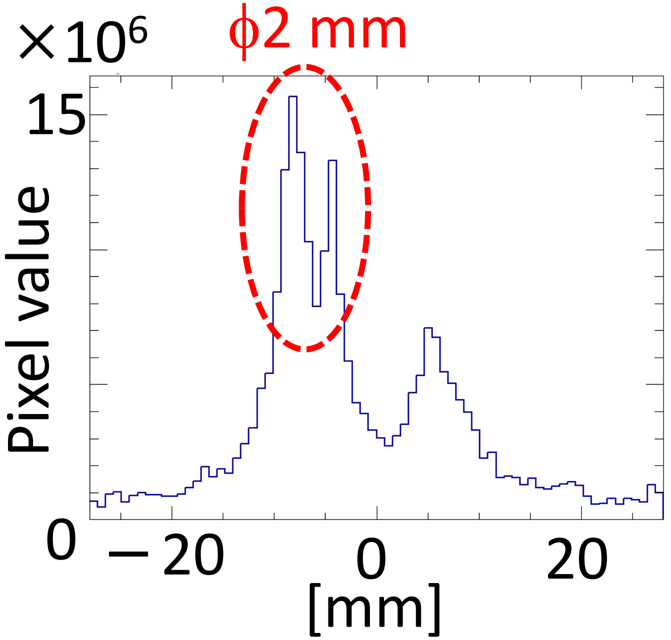
*Distance b/w holes is diameter×2

- ^{198}Au 210 kBq (total)
- Measurement time: 10 h
- Energy window: 402-442 keV

Hourglass hole

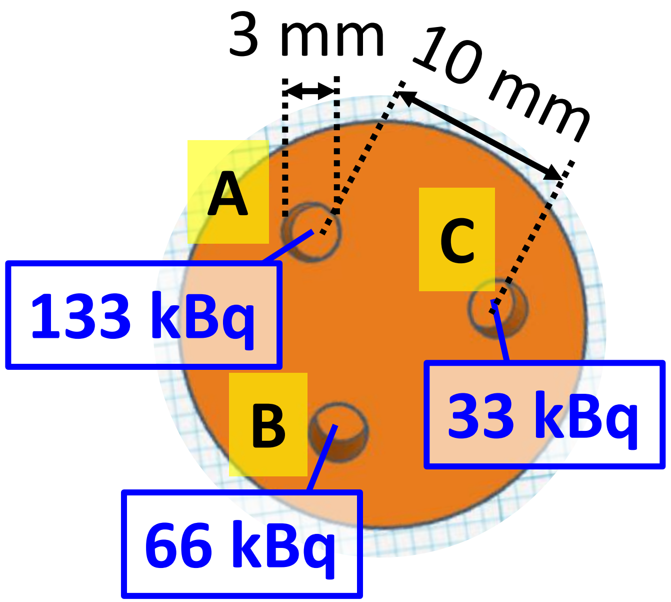


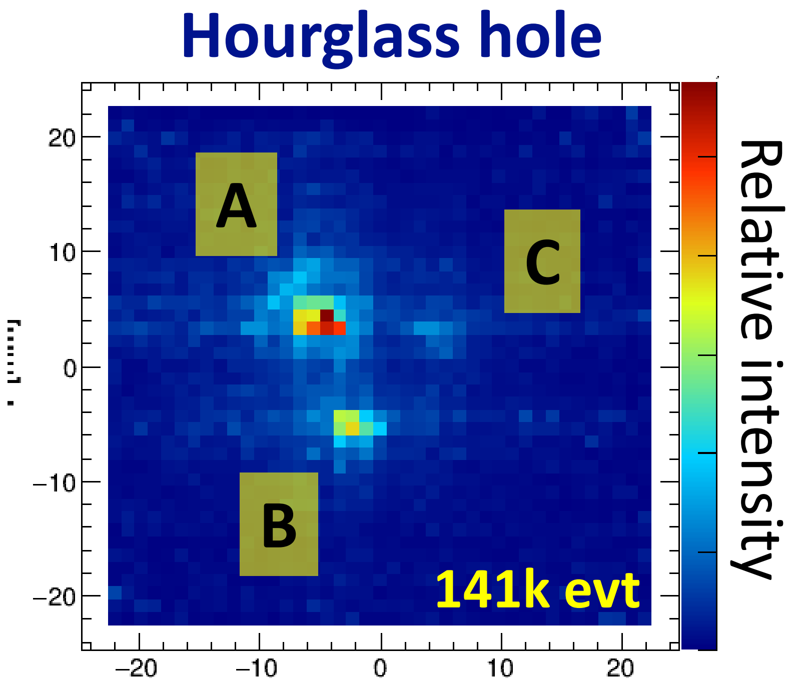




Performance of hourglass hole collimator

■ Phantom with different concentrations





- Concentration ratio
  A:B:C=4:2:1
- ^{198}Au 232 kBq (total)
- Measurement time: 2.4 h

Concentration ratio
A/B = 1.88±0.09
B/C = 2.52±0.22
Sample adsorption onto the pipette?

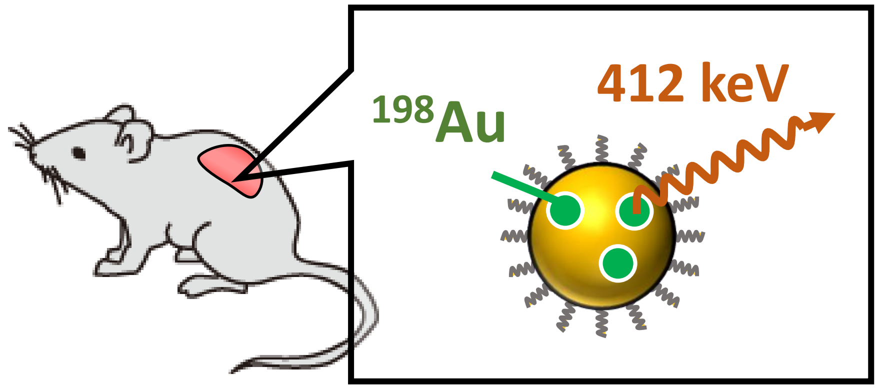
Summary and future work

Summary

- A high-resolution, high-sensitivity imaging device for gamma rays in the several-hundred keV range is needed
- We proposed hourglass hole collimator to achieve high sensitivity while keeping high resolution
- Hourglass hole collimator showed higher signal-to-noise ratio than parallel hole collimator

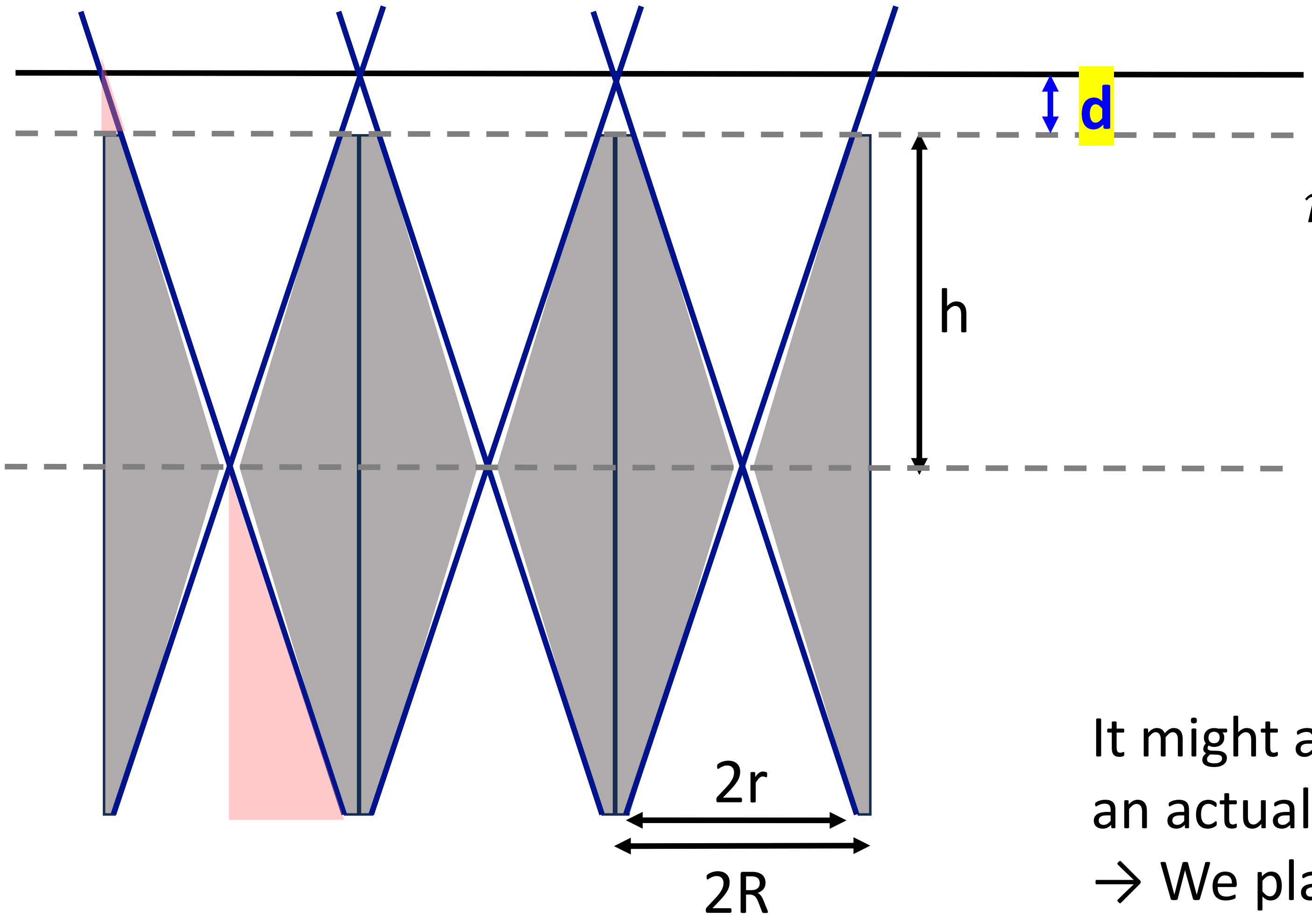
Future work

- Scale up the device ($10 \times 10\ cm^2$)
- In-vivo imaging of [^{198}Au]AuNPs for high-precision investigation of the dynamics of AuNPs



Appendix

Overlapping



$$r : h = (R - r) : d \Rightarrow d = \frac{h(R - r)}{r}$$

$$2h = 20\ \text{mm} \quad h = 10\ \text{mm}$$
$$2r = 0.6\ \text{mm} \quad r = 0.3\ \text{mm}$$
$$2R = 1.1\ \text{mm} \quad R = 0.55\ \text{mm}$$

$$\boldsymbol{d = 8.33\ \text{mm}}$$

It might affect spatial resolution when imaging an actual mouse…?

→ We plan optimization

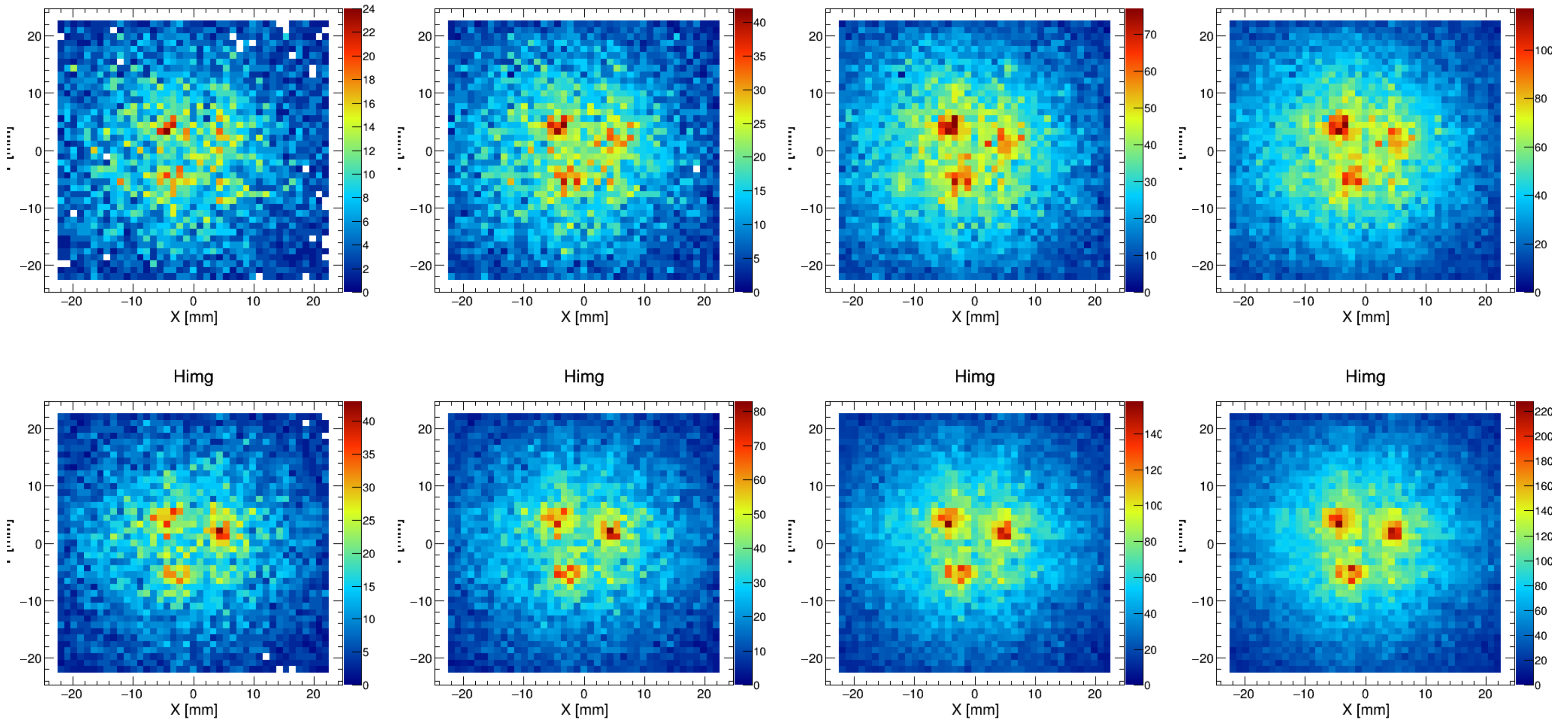
(more than 10 mm would be certain?)

Measurement time

15 min | **30 min** | **60 min** | **90 min**

Parallel hole (evt: 18 Hz)

Hourglass hole (evt: 11 Hz)



- 15 min may be sufficient to obtain a rough visualization of the sources using an hourglass-hole collimator.

MLEM (Maximum likelihood-expectation maximization)

- At each iteration, the current image estimate is used to calculate what the detector should have measured (based on the detection probability).
- Calculated response is then compared to the actual measured data, and the difference is used to adjust the image.

$$\lambda_j^{(k+1)} = \frac{\lambda_j^{(k)}}{\sum_{i=0}^{N-1} C_{ij}} \sum_{i=0}^{N-1} \frac{y_i C_{ij}}{\sum_{j'=0}^{M-1} C_{ij'} \lambda_{j'}^{(k)}}$$

k: Iteration number

i: Detector number

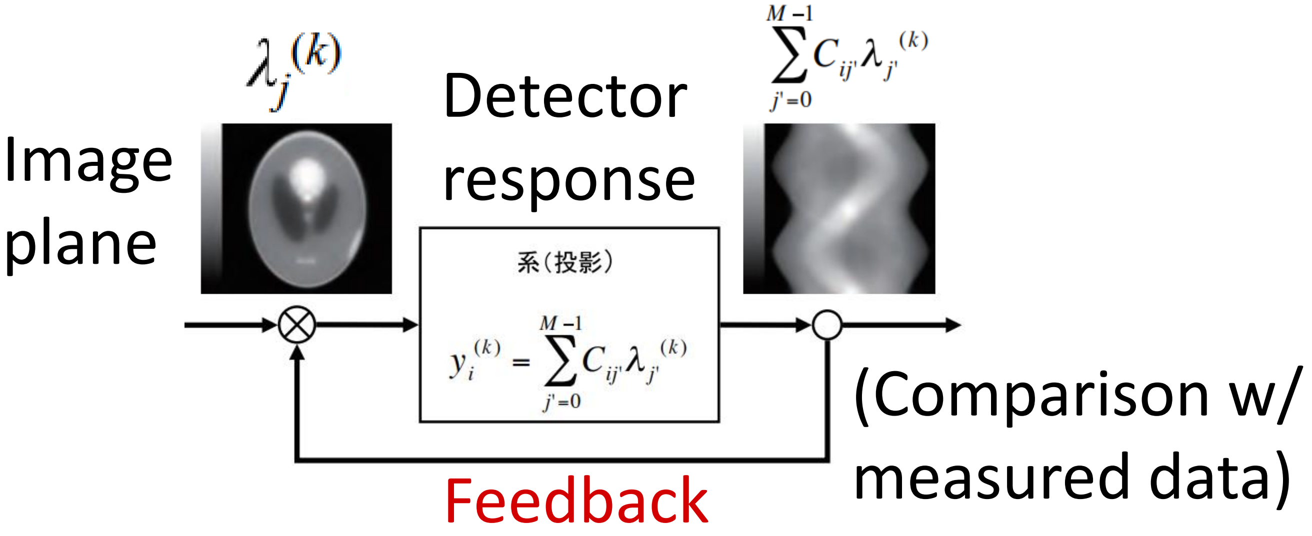
j: Pixel index of the image

C_{ij}: Detection probability

y_i: Measured data

λ_j: Pixel value of the image (at the k-th iteration)

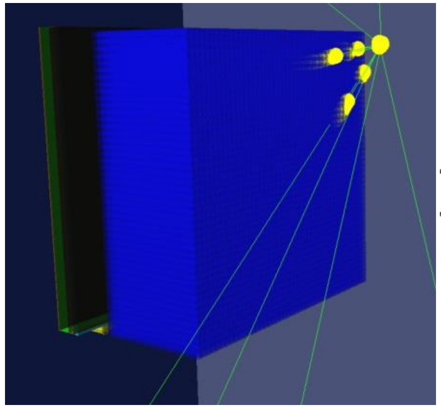
$\lambda_j^{(0)} = 1$ for all j

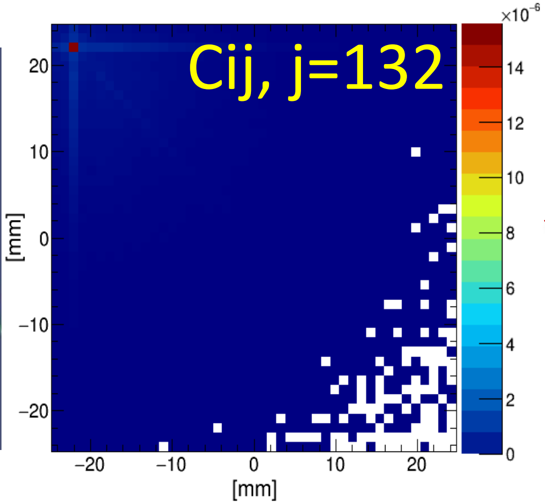


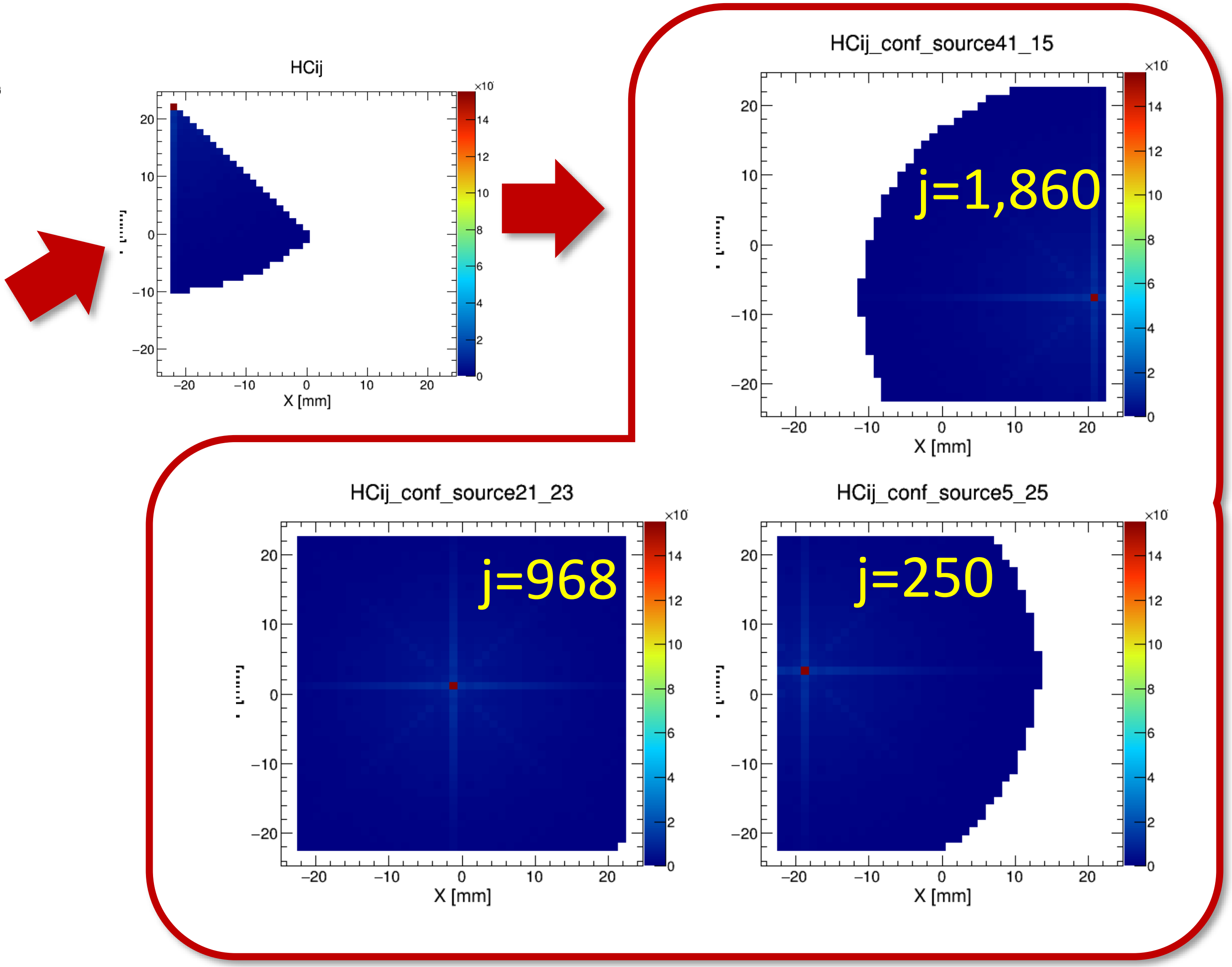
MLEM

45×45 scintillator pixels (i), image pixels (j) → $C_{ij}[45 * 45][45 * 45]$

- Geant4 simulation



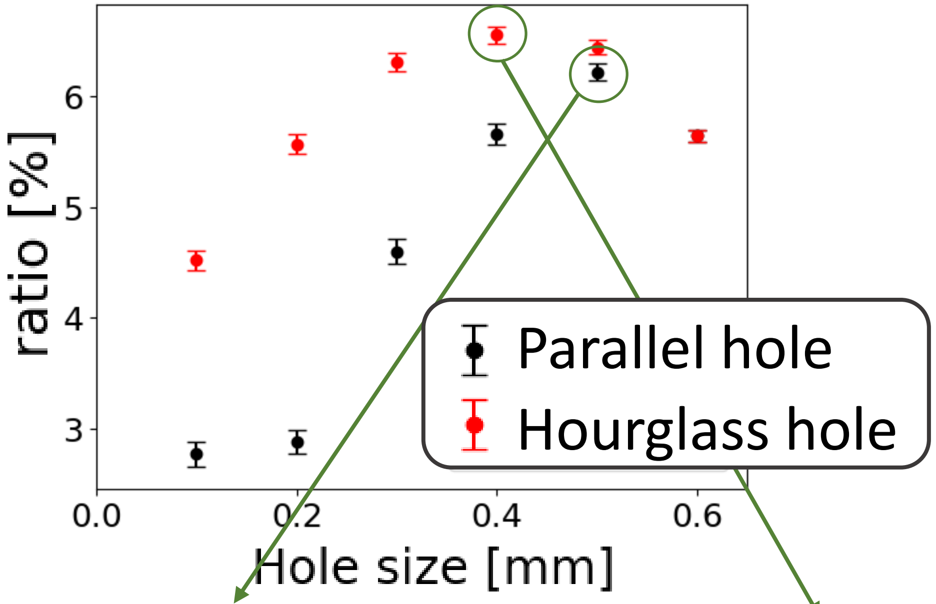




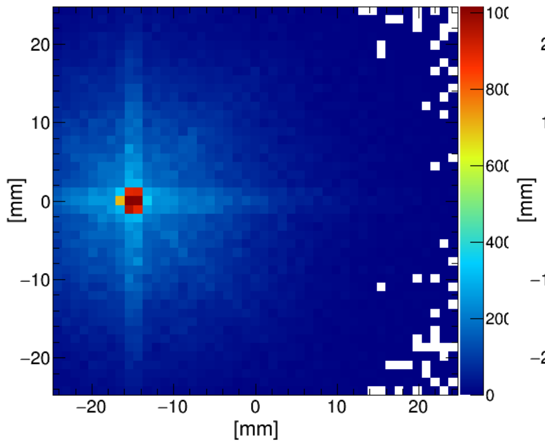
- 412 keV @pixel(2, 42)
- 1e10 injection

Parallel 0.5 mm vs. hourglass 0.4 mm

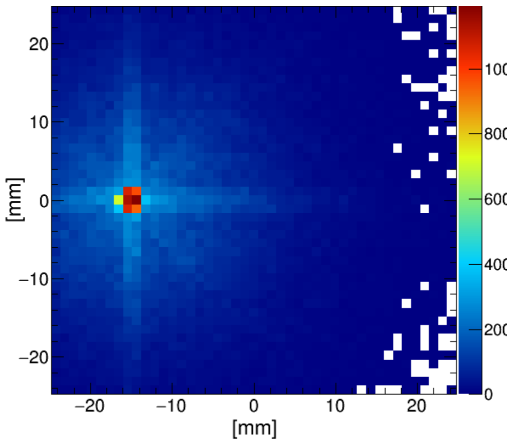
Pixel value inside ROI / All pixel value

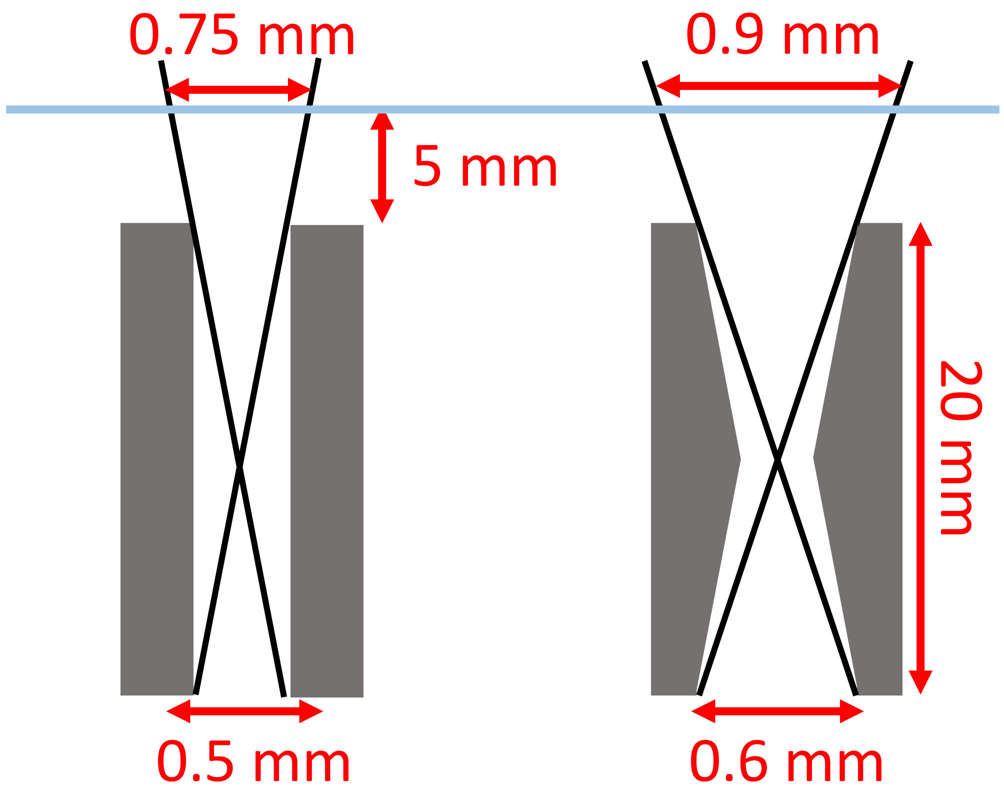


Parallel hole



Hourglass hole





Parallel hole **Hourglass hole**

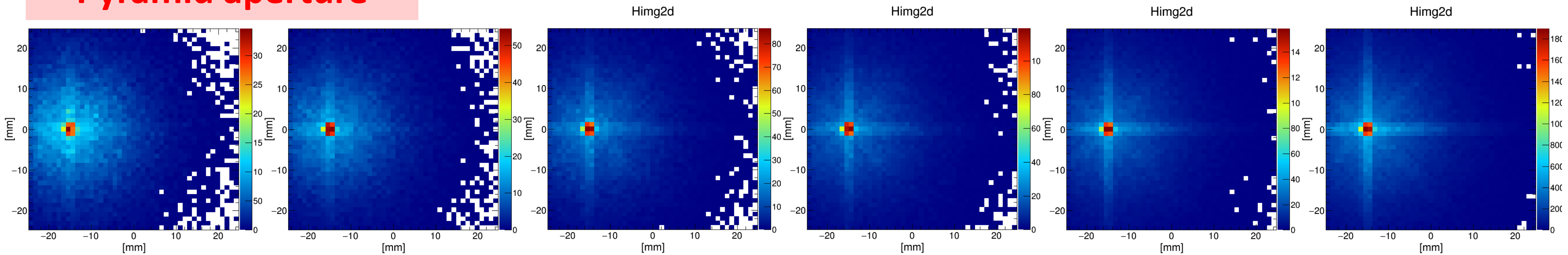
- Hourglass hole offers wider FOV compared to parallel hole
  → Less likely to miss small structure

Geant4 simulation: images

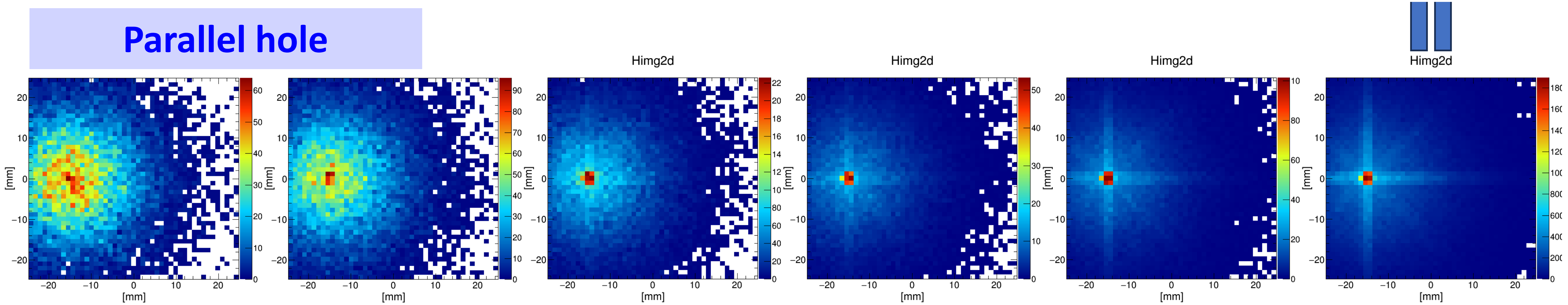
Injection: 1e9 (412 keV)

X=0.1 X=0.2 X=0.3 X=0.4 X=0.5 X=0.6

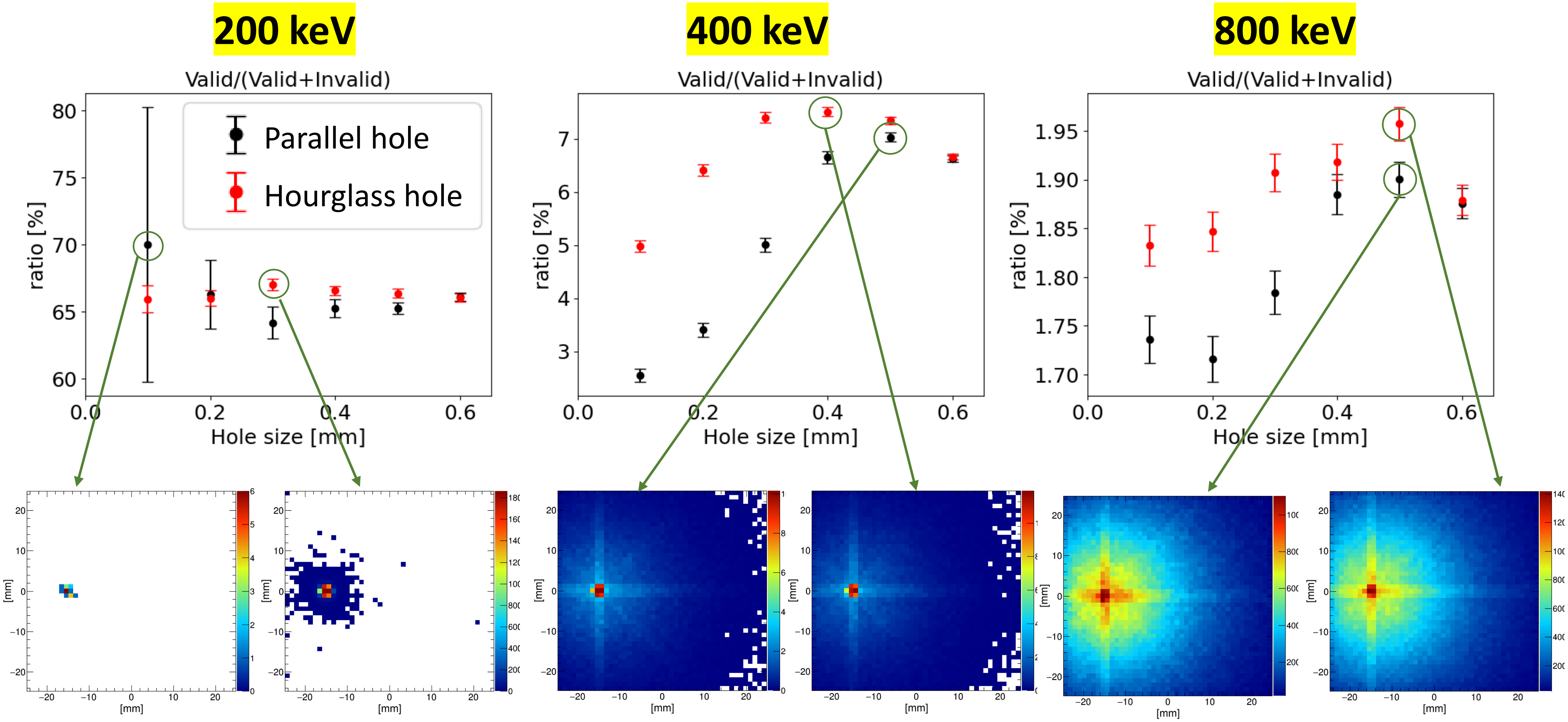
Pyramid aperture



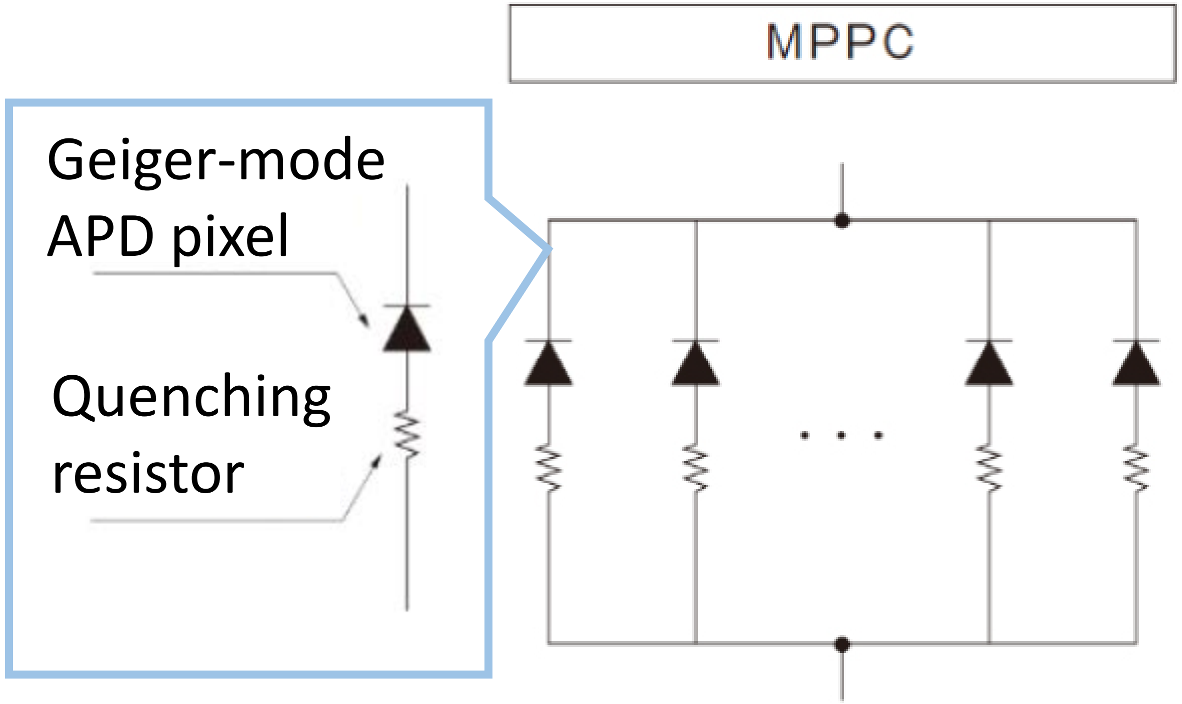
Parallel hole

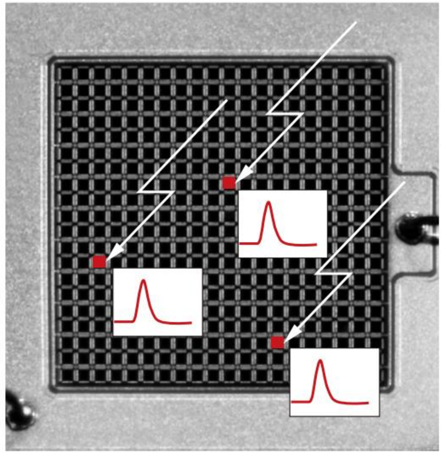


S/N at various energies



Multi-pixel photon counter （MPPC）

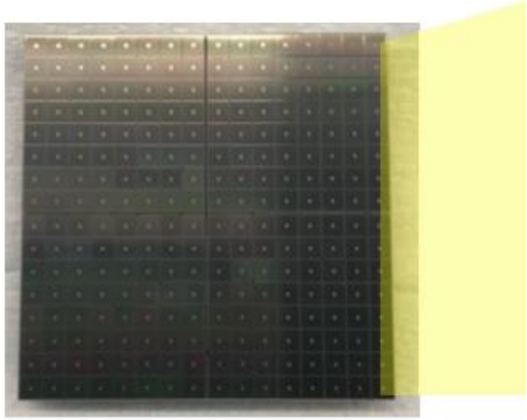


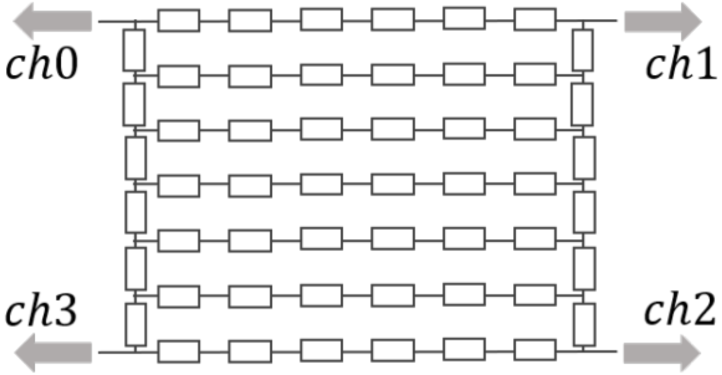


- Each APD detect **whether a photon came or not**
- Output: number of the photons
- Multiple photons in a APD -> worse linearity

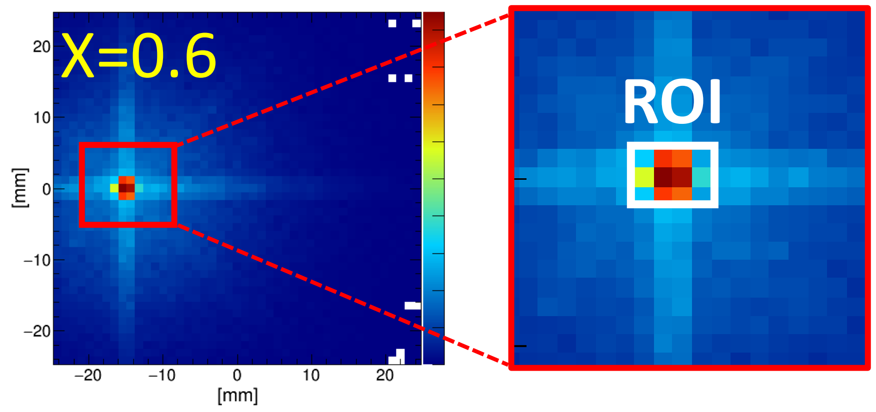
A resistor-divider circuit determine the interaction position through centroid calculation

- 50 µm pitch MPPC 16×16 array （Pixel number: 3,531）





Valid events vs. invalid events

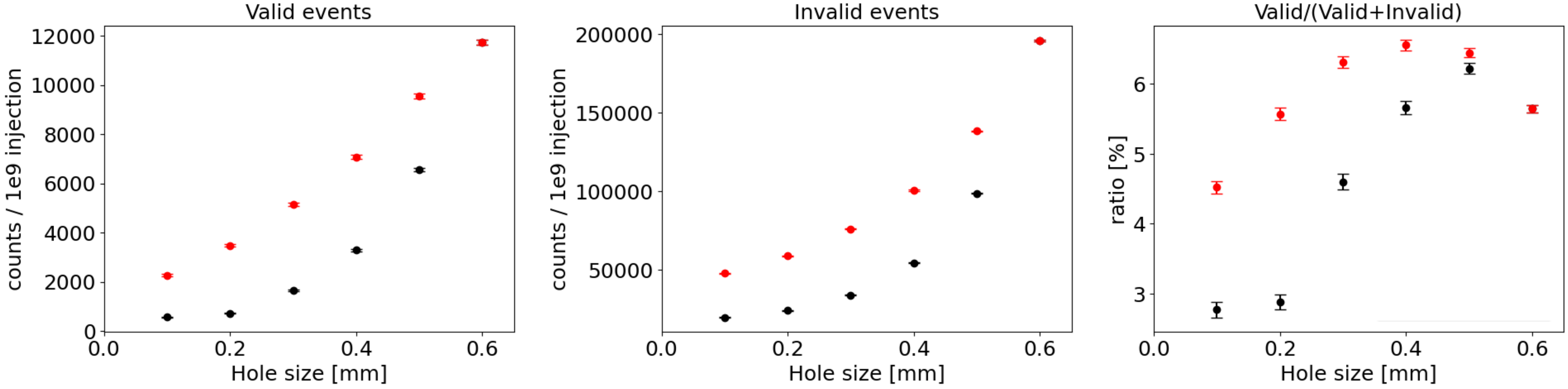


Within the ROI: valid events

Outside the ROI: invalid events

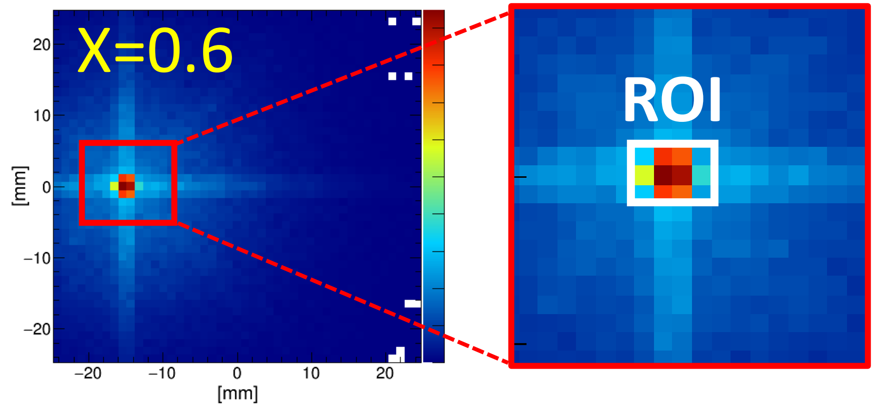
Parallel hole

Hourglass hole

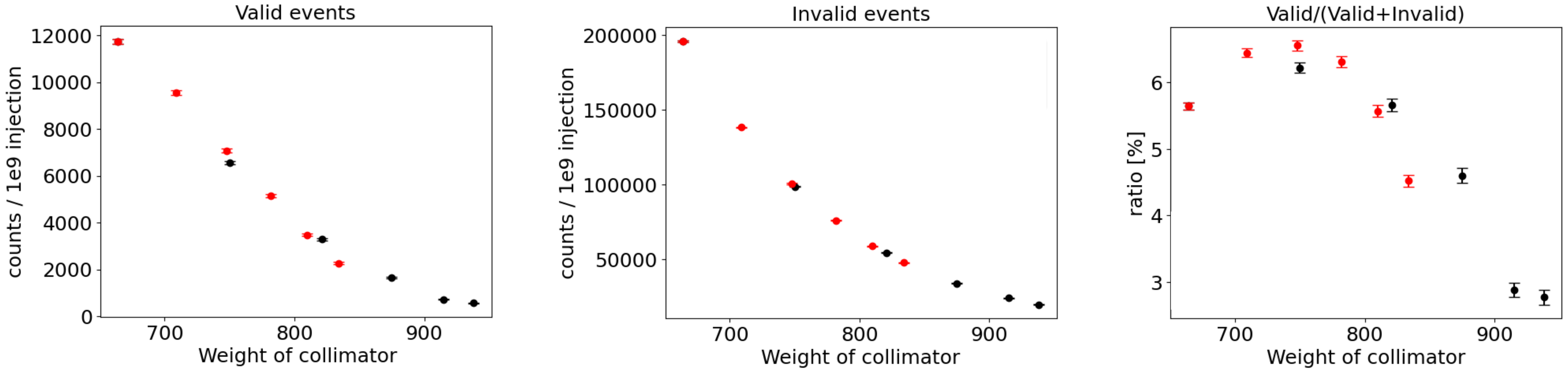


- Both valid and invalid events increase as the hole size increases
- In terms of valid-to-all ratio, hourglass-hole collimator offered highest value

Axis: collimator weight



Within the ROI: valid events
Outside the ROI: invalid events



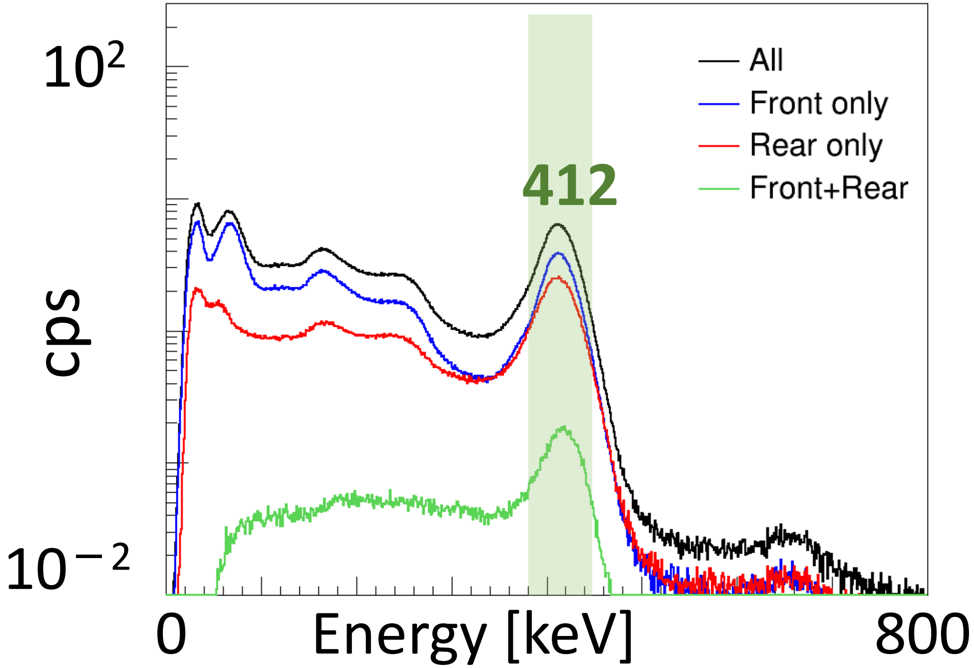
- Number of invalid events depends on the collimator weight
- Number of valid events depend on the geometry of the holes

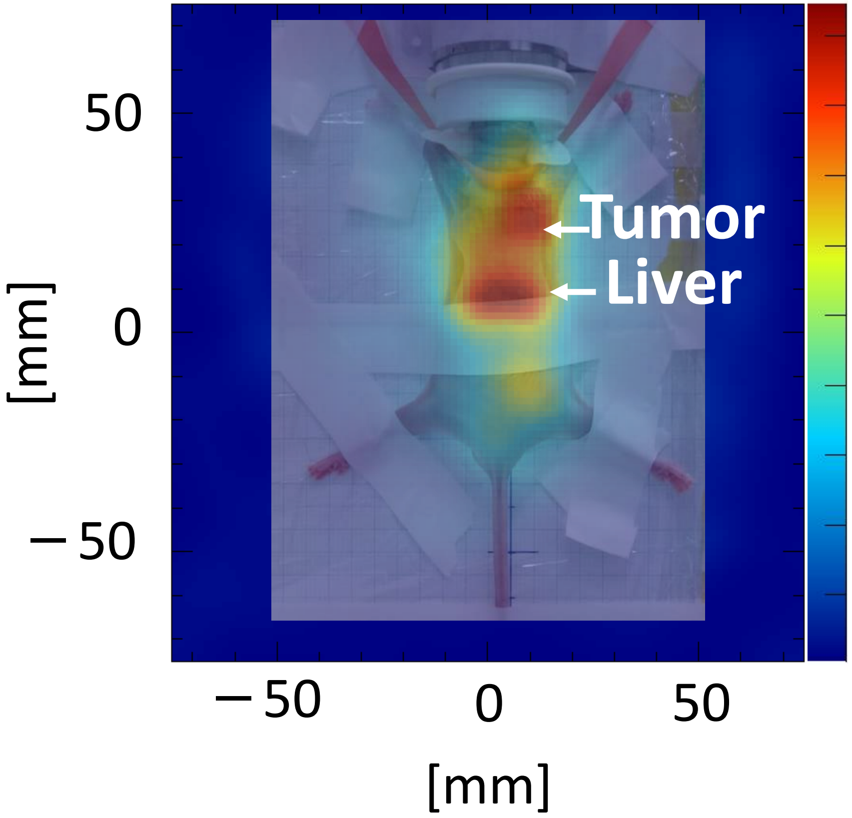
Intake of ^{198}Hg?

- In 2003, a study conducted by the Ministry of Health, Labour and Welfare of Japan reported that the total **daily mercury intake from food** for Japanese people was **8.1 μg/day**.
- Question:
  If 200 MBq of ^{198}Au is administered to the human body, how much mercury (Hg) would be produced?
  200 MBq = $\frac{\ln 2}{\tau} N \Rightarrow N = 6.73 \times 10^{13}$ = 1.1×10^{-10} mol
  1.1×10^{-10} mol × 198 = 2.2×10^{-8} g = 2.2×10^{-2} μg
- The amount of mercury generated is <u>negligible</u>.

In-vivo imaging of [^{198}Au]AuNPs using Compton camera

2 days after injection

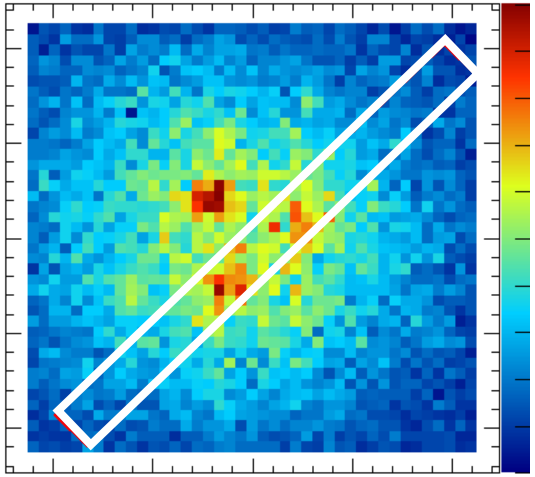




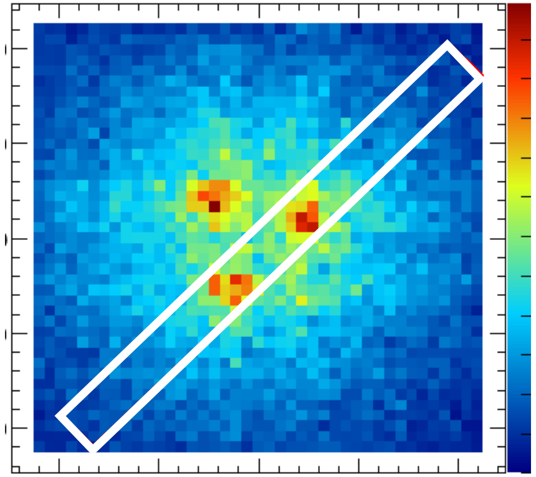
Hourglass-hole collimator would provide better spatial resolution

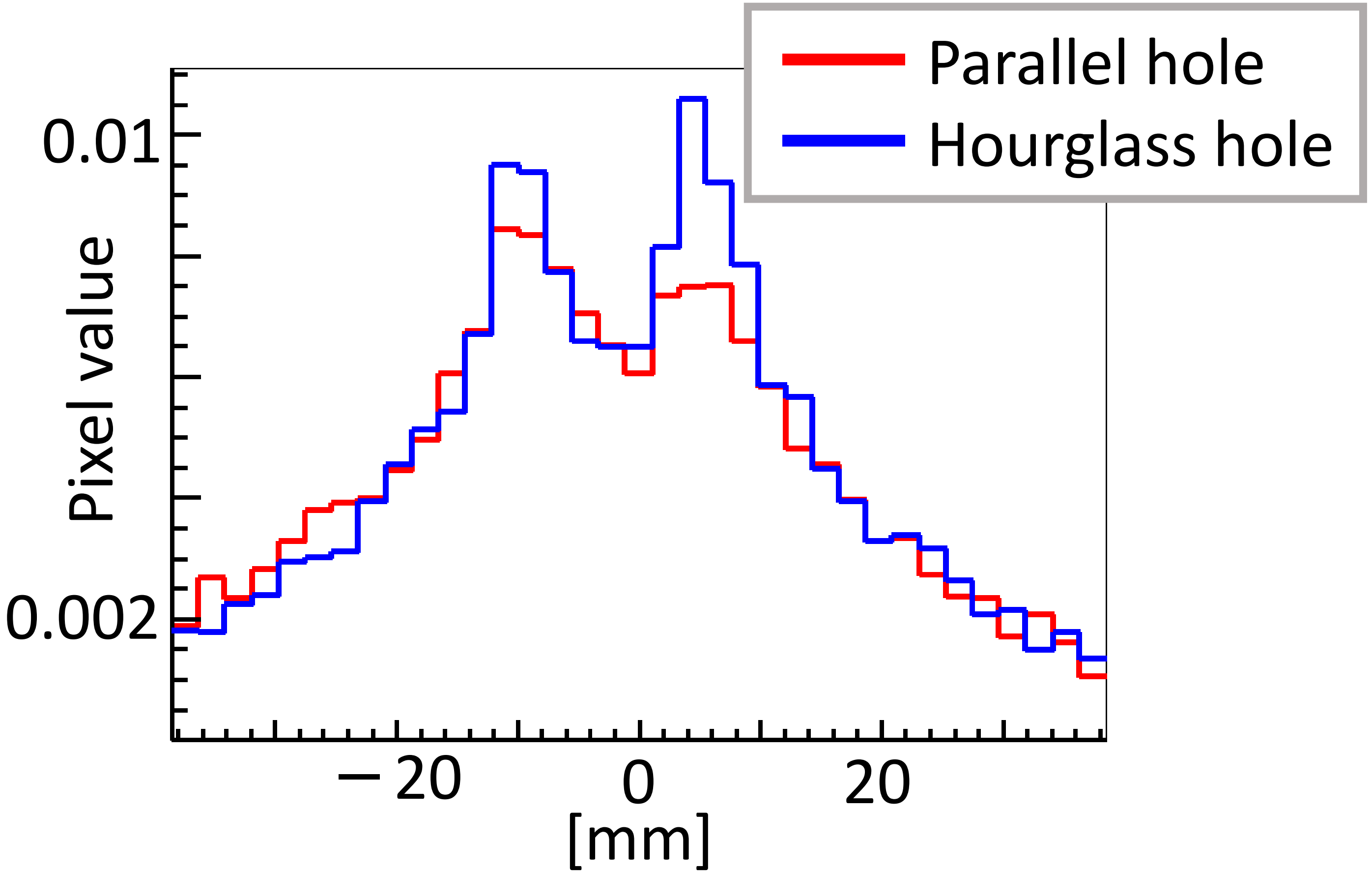
Parallel hole vs. hourglass hole (before MLEM)

Parallel hole



Hourglass hole



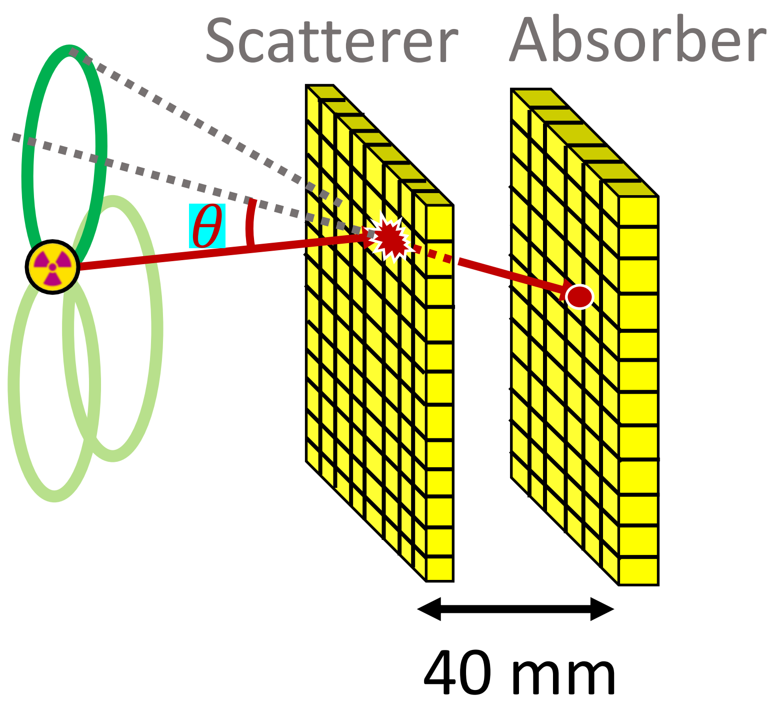


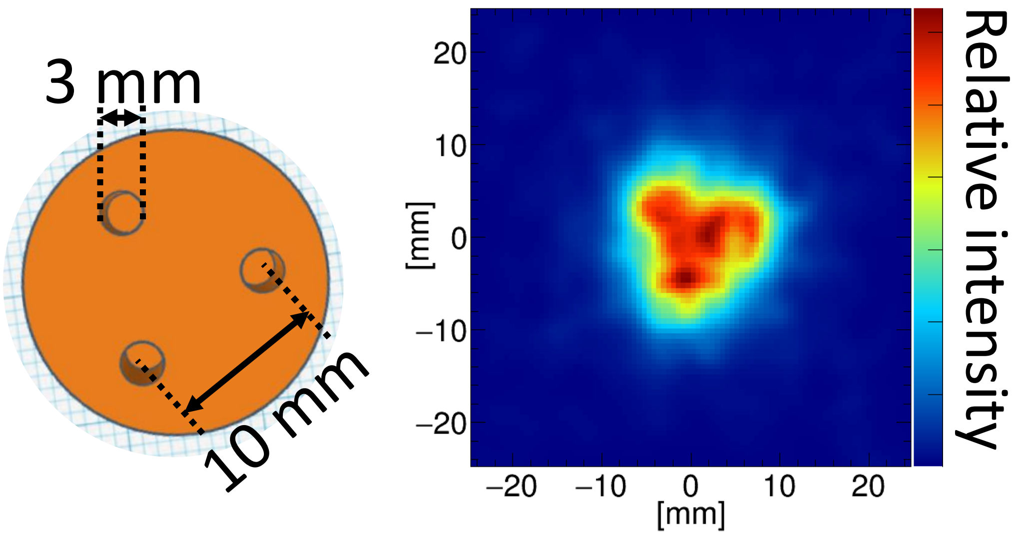
<u>Peak / Valley</u>

Parallel hole: 1.33

Hourglass hole: 1.55

Compton camera: 10-hr measurement



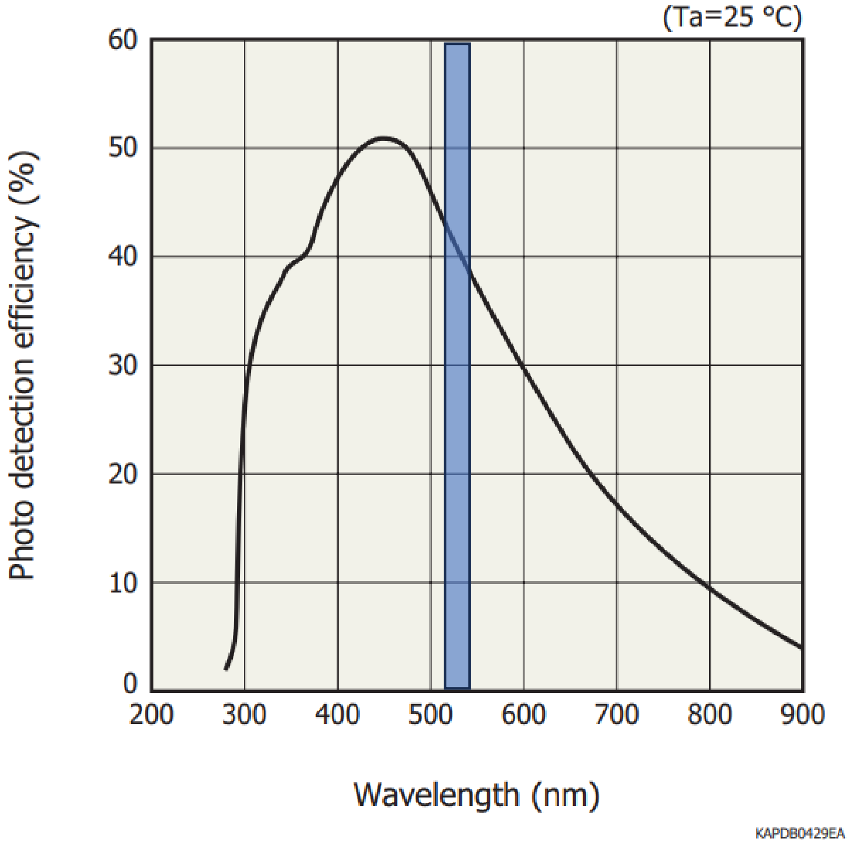


- GAGG scintillator
- Pixel pitch: 1×1 mm^2
- 45×45 array
- Thickness:
  Scatterer: 3 mm, Absorber: 5 mm

- ^{198}Au 70 kBq / hole
- Measurement time: 10 h
- Energy window: 412±30 keV
- Cannot divide three holes

Photon detection efficiency of MPPC

Photon detection efficiency vs. wavelength (typical example)



Photon detection efficiency does not include crosstalk and afterpulses.

- GAGG: 520-540 nm
  Detection efficiency: ~40%

MPPC property

$(T_a = 25°C,\ V_{over} = 2.7V)$.

項目		Unit
Photosensitive area	3×3	mm/ch
Pixel pitch	50	μm
Number of pixels	3531	μm
Sensitive wavelength range	$270 \sim 900$	nm
Peak sensitivity wavelength	450	nm
Detection efficiency @450 nm	50	%
Inter-terminal capacitance	500	pF/ch
Gain	2.5×10^6	-
Breakdown voltage	38	V
Recommended operating voltage	$V_{br} + 2.7$	V
Temperature coefficient @Vop	34	mV/°C
Temperature sensor	LM94021	(Texas Instruments)

MPPC property

Electrical and optical characteristics (Typ. Ta=25 °C, Vover=2.7 V, unless otherwise noted)

Parameter		Symbol	S14160/S14161 -3050HS-04, -08	S14160/S14161 -4050HS-06	S14160/S14161 -6050HS-04	unit
Spectral response range		λ	270 to 900			nm
Peak sensitivity wavelength		λp	450			nm
Photon detection efficiency at λp*3		PDE	50			%
Breakdown voltage		V_{BR}	38			V
Recommended operating voltage*4		Vop	V_{BR} + 2.7			V
Vop variation between channels in one product*5	Typ.	-	0.1			V
	Max.		0.2			
Dark current	Typ.	I_D	0.6	1.1	2.5	μA
	Max.		1.8	3.3	7.5	
Crosstalk probability		-	7			%
Terminal capacitance		Ct	500	900	2000	pF
Gain		M	2.5×10^6			-
Temperature coefficient of recommended reverse voltage		ΔTVop	34			mV/°C

*3: Photon detection efficiency does not include crosstalk and afterpulses.
*4: Refer to the data attached for each product.
*5: The parameter is for the S14161 series (multichannel type)