Gamma detectors for molecular imaging with radionuclides: design and applications

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10th Topical Seminar on Innovative Particle and Radiation Detectors
1 - 5 October 2006 - Siena - Italy
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- Overview
  - Applications of single photon technique
- Detector Design
- Some preliminary results

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Molecular Imaging with radionuclides

- **Non invasive**, *in vivo* observation of biological processes at cellular and molecular level
- Probe molecular anomalies (basis of disease) rather than end effects of molecular alterations

Potentialities

- (disease development) Analysis and understanding of disease processes at molecular level (e.g. using small animals as human model)
- (early disease diagnosis) Earlier detection and characterization of disease (before its symptomatic manifestation)
- (therapeutic response) Earlier and direct molecular assessment of treatment effects

Rat and mouse host a large number of human disease

Opportunity to study disease:

- under controlled conditions, repetitively in same animal
- faster screening, smaller number of animals required
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# Molecular Imaging with radionuclides

- **Non invasive**, *in vivo* observation of biological processes at cellular and molecular level
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[CT images]
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Dual Modality (e.g. PET & CT)

### Nuclear Imaging: PET vs SPECT

- **PET**: higher sensitivity (for short time), intrinsic limit on spatial resolution, expensive
- **SPECT**: overall higher sensitivity, large set of radiotracers, ~5 time cheaper
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Dual Modality (e.g. PET & CT)

![Fused PET + CT](image)

 cisbani@iss.infn.it (ISS & INFN Roma)
**Single Photon Detector System**

Components

- Radioactive drug injected into patient/model emits $\gamma$
  - Collimator (Tungsten/Lead): projects the $\gamma$ on the scintillator plane
  - $\gamma$ converter (scintillator): converts $\gamma$ into optical photons

- Position Sensitive Photon Detector (PMT): converts light into electrical signal
- Readout Electronics: amplifies and digitizes electrical signals
- Software: back-reconstruct gamma image from digitized (raw) data

Example: cisbani@iss.infn.it (ISS & INFN Roma)  
03 Oct 06 - IPRD06 4 / 17
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\(\gamma\) for Mol.Ima.

03 Oct 06 - IPRD06
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Design and implement SPE(CT) detectors with
- submillimeter resolution
- adequate sensitivity

suitable for molecular imaging of biological processes (on small animal) related to:

- **Atherosclerotic plaques**: study the way to identify the vulnerable plaques that have high probability to cause atherosclerosis
- **Stem Cells**: investigate stem cells ability to regenerate injured tissue by monitoring in vivo migration and homing
- ... and more (early diagnosis of breast cancer, prostate tumor)
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Atherosclerosis causes most of the premature deaths in western countries

- Plaques develop slowly, silently and asymptotically since youth, as accumulation of lipids, inflammatory cells and connective tissue on the vascular walls
- Vulnerable plaques rupture manifests suddenly (and dramatically) as cardiac death, stroke, myocardial infarction
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Atherosclerotic Plaques / Model

- ApoE Mice (transgenic mice where atheromas are induced by fatty diet) used as model for the study of the atherosclerotic pathogeneses
- Increased apoptosis (programmed cells death) is expected to be a characteristic of vulnerable plaque
- Single Photon Imaging apoptosis by $^{99m}$Tc-HYNIC-Annexin-V (binds to apoptotic cells with high uptake 10-20 respect to tissue)

Facts:
- image plaque on $\sim 2$ mm diameter aorta of mouse
- plaque size: $0.5 \times 1 \times 4 \text{ mm}^3$
- when 2.5 mCi is injected into the mouse:
  - plaque activity: $\sim 200 \div 400$ nCi
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Stem Cell Study

Stem cells may be able to home toward sites of injury (e.g. myocardial) to participate in tissue regeneration

- Postmortem tissue analysis are presently the main tool to investigate such processes, but effectiveness is controversial
- Very promising technique for homing studies:
  - Labelling the stem cells with proper radiotracer (e.g. $^{111}$In-oxine in J. Gao et al. Cells Tissues Organs 2001; 169;12-20)
  - Molecular (Cellular) Imaging their dynamics over several days

Application Requirements

- image organs where the cell migrates: heart, liver, lung, spleen, spine
- typical activity concentration: $< 40 \mu\text{Ci}/\text{Mcells}$
- monitoring of the same cells infusion may extends over several days
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SPECT System Requirements

- Spatial Resolution: $\sim 500 \, \mu m$
  - $\sim$ plaque min. size

- System Sensitivity: $\sim 250 \, \text{cps/} \mu \text{Ci}$ (from plaque)
  - assuming $\sim 1000$ counts/view/resolution element for reasonable image
  - 1 view takes about 100 s
  - plaque consists of approx. 10 resolution elements
  - typical vulnerable plaque activity $\sim 0.3 \mu \text{Ci}$

- Active area (single module): $\sim 10 \times 10 \, \text{cm}^2$
  - Mouse longest size $\sim 4 \div 5 \, \text{cm}$
  - Reasonable Magnification: $\sim 3$

- Compactness (for large acceptance multiheads detector)
- Cost effectiveness (use of commercial components)
**Design Approach / Camera Detector Components**

Optimal combination of existing *conventional* components

- **Collimator**: (Multi) Pin Hole / Coded Aperture ⇒ Sensitivity
- **Scintillation Crystal**: Pixellated (NaI, CsI) / Continuous (LaBr$_3$)
- **Position Sensitive Photon Counting Detector**: Multi Anode PMT (3 and 1.5 mm)
- **Readout Electronic**: Individual Channel Readout, Selftriggering, Multiplexed digitization (and zero channel suppression) at $\sim 5$ kHz event rate
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Design / Collimators Geometry

Single Pin-Hole

High Res., border artefacts, low sensitivity $S_{ph} \sim \left[\frac{d}{4p}\right]^2$

$M = \frac{q}{p}$

$R \sim \sqrt{\left[\frac{d(1 + \frac{1}{M})}{2}\right]^2 + \left[\frac{R_i}{M}\right]^2}$ (d effective hole diameter)

$d \sim 0.3 \text{ mm, } M \sim 3 \Rightarrow R_i < 1 \text{ mm}$

Multi Pin-Holes

High res., low FoV ↔ artefact, good sensitivity $S_{mph} \sim N S_{ph}$

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- **M = q/p**
- **Detector**
- **Object**

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Multi Pin-Holes

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High res., low FoV ↔ artefact, good sensitivity \( S_{mph} \sim NS_{ph} \)

Coded Apertures

High resolution, low DoF ↔ artefact, high efficiency \( S_{ca} \sim \alpha S_{mph} \)
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- Readout Electronic: Individual Channel Readout, Selftriggering, Multiplexed digitization (and zero channel suppression) at ∼ 5 kHz event rate
GEANT4 simulators
Custom C++ code
ROOT analysis

(simple detector, but large number of

events and optical photons/event)

⇓

Quality parameters:

- Intrinsic Spatial Res.
- Useful Field of View
- Efficiency
- Energy Resolution
- Distorsion
- SNR (and contrast)
GEANT4/Root Optimization

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Quality parameters:
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CsI(Na) 0.8mm pitch H9500

CsI(Na) 0.8 pitch coupled to 3.0 anodes PMT w/o exit window
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Csl(Na) 0.8 pitch coupled to 1.5 anodes MCP w/o exit window

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Quality parameters:
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CsI(Na) 0.8 mm pitch, WW, Burle

CsI(Na) 0.8 pitch coupled to 1.5 anodes MCP w/ exit window
GEANT4/Root Optimization

GEANT4 simulator
Custom C++ code
ROOT analysis
(simple detector, but large number of events and optical photons/event)

Quality parameters:
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- Efficiency
- Energy Resolution
- Distorsion
- SNR (and contrast)

CsI(Na) 0.4 mm pitch, WoW, Burle

Csl(Na) 0.4 pitch coupled to 1.5 anodes MCP w/o exit window
Optimization: preliminary results

For Cont. LaBr₃:
- largest crack (5 vs 1.7 cm)
- “white” reduces useful FOV (∼ 70%)
- now available in tile ∼ 10 × 10 cm², but expensive

For Pix. CsI(Na):
- CsI(Na) interesting but hygroscopic
- not available below 0.8 mm

SNR estimation almost completed
Next step: multi pinhole (coded aperture)
Optimization: preliminary results

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First measurements at JHU/School of Medicine

- Scintillators: Pixellated NaI(Tl) 1.2 mm and CsI(Tl) 1.0 mm
- Photon Detector: MAPMT 2×2 H9500 (1024 chs)
- Electronics: Mutiplexed IDE.AS (no zero suppression) < 2 kHz rate
- ApoE (live) mouse + AnnexinV; test with MDP

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Spatial Resolution ~ 0.6 mm
Preliminary results from JHU measurements

- Set up has been tested on MDP (bone binding) injected mouse
- Protocol defined for (live) ApoE mouse (calibration point sources, 64 views 90 seconds each)

Lesson learned

- Reliable protocol defined for ApoE live mouse
- Spatial resolution is acceptable
- Sensitivity: a factor of \( \sim 10 \) needed (\( \Rightarrow \) multipin hole)
- Electronics: PMT anodes non-uniformity (up to 6:1) and selftriggering require better control on single channel thresholding
  \( \Rightarrow \) reduce ‘counting artefact’ in image (and increase sensitivity)
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Conclusion and Outlook

- Happy for the first results of the test trials
- Simulation: finalize analysis (and validation); implement multi pinhole reconstruction
- Detector: improve the tuning of the individual anode responses
- Electronics: re-design selftriggering and multiplexing (add zero suppression)
- ...

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