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Development of an instrument for time–activity curve measurements during PET imaging of rodents

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Abstract

Molecular imaging using PET in small rodents requires commonly the knowledge of the input function of the tracer (quantitative and kinetic studies of the metabolism, development of new drugs or new tracers, etc.). In this paper, we report the status and the performances of the prototype of a counting system that is under development at DAPNIA[a] in collaboration with SHFJ[b]. The detection device is made of silicon diodes of 0.3 mm thickness proper to measure the positrons emitted by the radiotracer contained in arterial blood flowing in a thin-wall microtube. Such diodes are poorly efficient for the 511 keV gammas from the rodent and thus require a rather light lead shielding and allow operating very close by to the animal. The detectors, the front-end electronics (for signal preamplification, shaping, and discrimination) and the acquisition circuits are mounted on a single card. The device is connected directly to a portable computer via an USB port.

Such a design provides a compact, rugged and portable device for working close to a small animal PET camera. Preliminary results show the performances of this counting system with 18F solution and a time–activity curve for FDG blood samples (with |~30 μL/samples) from a rat.

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Keywords: Positron emission tomography; Arterial blood radioactivity; Input function

1. Introduction

Animal models reproducing the characteristics of human diseases such as cancers, and neuro-degenerative diseases, have been developed in recent years. Most of them are based on small rodents (mice and rats) [1]. Positrons Emission Tomography (PET) is a powerful tool for in vivo imaging of these diseases [2]. Actually, it seems to be the sharpest method of quantitative exploration of molecular processes on the scale of the femto mole. Moreover, it is possible to follow the evolution of diseases and treatments. The project presented here aims to bring solution to the challenge of the quantitative PET imaging of the rodent. The development of new tracers for PET imaging requires knowledge of the kinetics of the tracers in the body and especially in arterial blood and plasma. The kinetics of the tracer in the plasma is usually referred to as Plasma Input Function. The most common approach to obtain the input function is to sample the blood and measure the activity of plasma samples as a function of time, in a gamma counter.

Our project, named ART, from a French acronym, consists of a blood pump and an activity counter. During PET examination, the controlled pump takes automatically a sequence of small blood samples from the animal. Simultaneously, the system measures online radioactive concentration of the samples.

This paper presents the device and the results of the physical tests performed using radioactive liquid sources. One study was also performed on a rat after the injection of [18F]FDG.

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2. System overview

A perfusion needle is introduced in the caudal artery of the animal and connected through a catheter to the detector. Inside the detector the blood flows through a specific low-attenuation micro tube. The output of the device is connected to a peristaltic pump (Fig. 1).

The micro tube must have such a diameter that the total quantity of taken blood remains lower than 1.5 ml for a rat (0.2 ml for a mouse) for a study. A PET study requires approximately 20–30 measurements in the time course. Consequently, the blood volume sample is restricted to 8 μl for mice and 30 μl for rats.

2.1. Detector setup

We did select the detection of the positrons because this solution has the following advantages:

- It can be carried out by using very compact detectors because of the high probability of interaction of electrons with matter. Consequently, one may use a low-density and low thickness detector that has a low efficiency for γrays.
- The device, thus, does not require heavy shielding against γescaping from the body of the animal.

We chose silicon diodes because the positrons of fluorine-18 and carbon-11, main radioisotopes used for PET medical imaging, are detectable in 300 μm thickness of this material. The configuration selected for the detector includes six silicon diodes ($10 \times 10 \times 0.3\,mm^3$). The inner micro tube is a polyimide tubing (density $\rho = 1.42\,g/cm^3$) with a wall thickness of 25 μm. These characteristics minimize the energy loss and the rate of annihilation of the positrons in the walls. This tube is tightened between two boards made up of 3 diodes each (Fig. 2).

A two-centimetres-thick lead shielding protects detectors against γ escaping from the body of the animal.

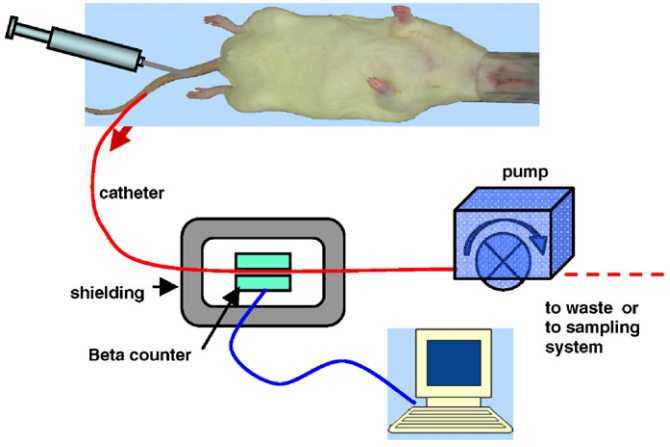

Fig. 1. System overview of the ART project.

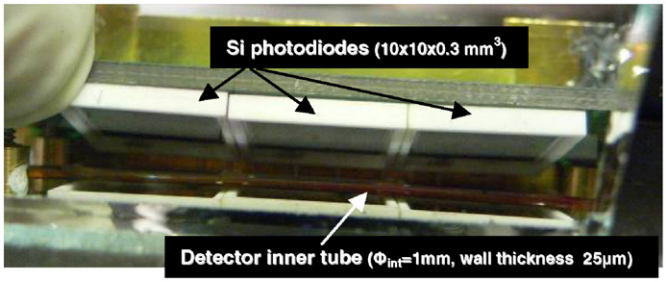

Fig. 2. The inner tube is tightened between two layers of three diodes. This configuration covers a wide geometric acceptance for the beta detection going out of the tube.

2.2. Electronics

A printed circuit board was especially designed for this device in order to minimize the size of the unit. It includes the readout electronics of the detectors and the acquisition of the data. The front-end electronics is based upon the SFE16 ASIC (Application Specific Integrated Circuit), previously developed for a nuclear physics experiment [3]. It contains signal preamplification, shaping, and discrimination in a 16-channel chip. Only 6 channels are used for our application. An internal Digital to Analog Converter (DAC) provides a common threshold for all the channels.

The acquisition is managed via a general purpose USB configurable interface previously developed in the Physics Department [4]. This interface is fully programmable and allows a versatile driving of the system and connection to the USB port of a PC.

2.3. Pump characteristics

A PC-controlled peristaltic pump (Ismatec Reglo-digital 832) with adjustable sampling volume is connected on the output of the counter box (Fig. 1) with a plastic tube, of inner diameter 0.51 mm for 8 μl and 0.89 mm for 30 μl sample volumes. The pump may operate in a sequential sampling mode. In order to minimize the total blood volume taken from the animal, we chose this sampling mode. The measurement of a time–activity curve (TAC) requires fast sampling and counting in the first phase of the radiotracer dilution following the injection. Then the times between samples may be increased during the uptake and elimination phase. The total time of measurement may be around 1h following the radiotracer injection. In the rapid sampling mode ($\approx$1 sample/s), the diffusion of activity between consecutive blood samples is low and no correction is necessary. On the contrary, this diffusion has to be taken into account for the late times [5].

The distance between the cannulation point and the detector was minimized in order to reduce the propagation delay. There are only four pumping samples to reach the detector. The correction for this delay depends on the sampling time interval and its automatic correction will be implemented.

3. Detector characterization

3.1. Energy calibration

An energy calibration was performed using a ^{241}Am source (γ ray of 60 keV) and a ^{57}Co source (γ ray of 122 keV), giving a conversion law defined by

$$E_{(\mathrm{keV})} = 0.81 * \mathrm{threshold}_{(\mathrm{DAC\ unit})} - 10.66.$$

Above a threshold of 70 DAC units (corresponding to 46 keV of deposited energy), the electronic noise is lower than 4 Hz.

3.2. Detection efficiency measurement

As the range of the emitted positrons is a function of the positron energy, the energy loss in the material and the deposited energy in the diodes change with radio-isotopes. The counting efficiency needs to be measured for each isotope. Counting efficiency is defined as the ratio of counting rate recorded by the detector over the actual activity contained in the inner micro tube.

We performed this measurement for ^{18}F. Three solutions of ^{18}F of known activity concentrations (0.23, 0.51, 2.48 kBq/μl) were flown into the inner tube of the counter box. The counting rate was recorded for different threshold values (Fig. 3). The experimental plot indicates an efficiency of 32.5% for ^{18}F at a threshold value of 46 keV, which is in good agreement with the Monte Carlo simulation of the device. As expected, the efficiency does not depend on the activity.

The same data set provides an estimation of the linearity of the rate measured by the counter as a function of the activity (less than 0.9% deviation from a linear fit).

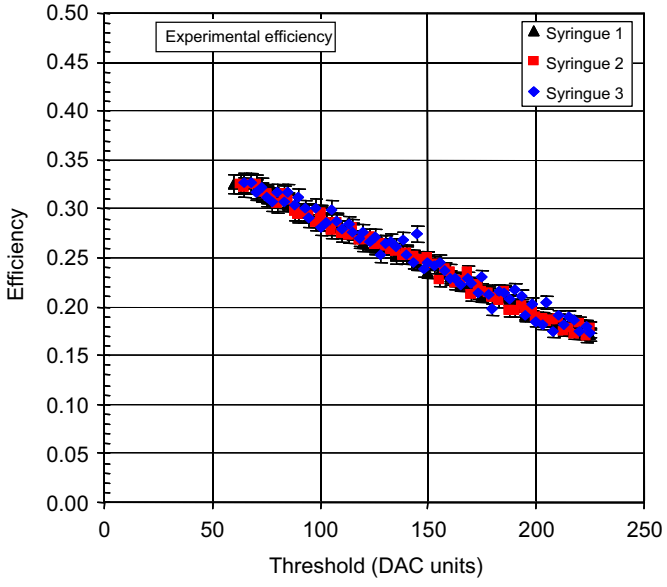

Fig. 3. Experimental efficiency as a function of the threshold in DAC units for ^{18}F isotope for three different injected activities varying from 6 to 70 kBq.

4. First animal study

A first animal study was performed for biological validation. a one millimeter of a heparin solution (250 U/ml) was injected to the animal before FDG injection. The needle (0.6 mm) and all tubes were also flushed with heparin before the tracer injection. An FDG solution of 43.3 MBq was injected as intra venous bolus to a 492 g rat. This is equivalent to a blood activity peak around 1270 kBq/ml (average rat blood volume $\approx$ 7 ml/100g). Fifties samples of 30 μl each were automatically taken at discrete times from the rat. The experimental time–activity curve is showed in Fig. 4. The data are corrected from radioactive decay, γ background ($<$20 cps), and detection efficiency ($\varepsilon = 32.5\%$). Additional corrections should be performed to compare with known FDG time–activity curve from the literature. These corrections include delay (between blood extraction and blood counting) and dilution between samples. For this first test, two manual samples were taken at late times, counted in a γ counter (efficiency 100%) and compared successfully with ART measurements. In addition, the time activity curve maximum is compatible with the theoretical blood activity concentration at injection.

5. Conclusion and perspectives

The operation of our system prototype and the first attempt of biological validation are encouraging. In the near future, we plan to perform more animal studies to validate the automatic sampling system including tests on mice. More operator-friendly software will be developed with automatic corrections, data analysis, and display.

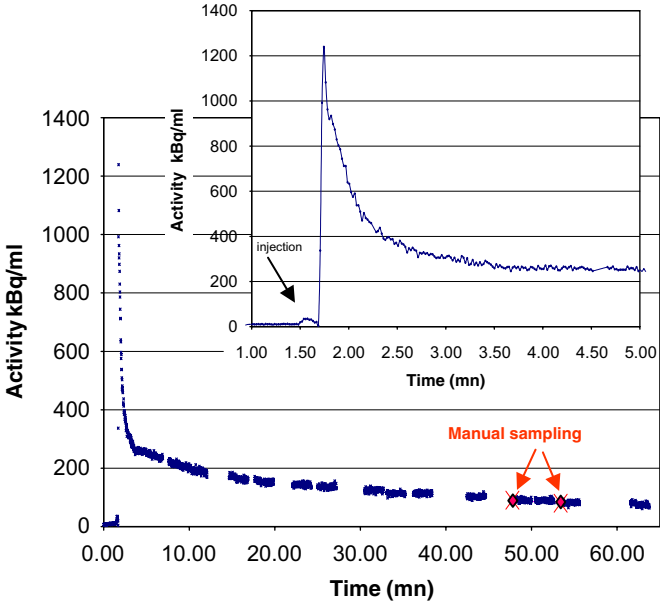

Fig. 4. TAC corrected for radioactive decay only. The propagation delay was applied to the two manual samples in order to be compared with the non-corrected experimental curve. The superposed figure is a close-up of the main curve at prompt time.

Concurrently, we continue to study an automatic online blood-separating system.

Acknowledgments

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