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Medica-Plus: a novel Micromegas detector for high-resolution β imaging for improved pharmacological applications

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Abstract. For many years ³H and ¹⁴C labelling of molecules of pharmaceutical interest has been performed to study their in vivo biodistribution on animal tissue sections through β -particles detection. Film autoradiography has progressively been replaced by digital β -imagers capable of high sensitivity, real-time imaging and activity counting for absolute quantification of radioactive compounds in tissue sections. After the discovery of the tumor heterogeneity phenomenon, research efforts for characterizing cell heterogeneity have been at the heart of oncology research, aiming at a better understanding of the causes and progression of the disease. This new perspective has also allowed for cell-targeting drugs, and radically changed both sample sizes and radiotracer activities. In this context, Medica-Plus, a transversal project gathering biologists, microfluidics specialists and detector developers, intends to perform quantification of low dose ³H- or ¹⁴C-labelled drugs inside single cells. This article reports preliminary results obtained with a prototype detector measuring tritium-generated signal.

1. Introduction

In the past 50 years, cancer death rates have barely decreased, despite a better understanding of the biological processes underlying the disease, and contrary to other major causes of death such as cardiovascular diseases which plummeted, benefiting from the overall progresses of medicine [1]. More concerning, the overall share of population with cancer worldwide has increased in the last 30 years. If, for certain types of cancers the improvement of surgical techniques has allowed to decrease drastically the death rate, for other types the treatment relies on radiations or chemotherapy, both of which, by design, are toxic to human cells. Drug toxicity induces a number of undesirable side effects which can be the cause of health degradation by themselves especially among elders which represent the majority of cancer incidence. Side effects also imply the use of smaller drug doses, which decreases the treatment efficiency [2]. The past 20 years have seen the appearance of a diversity of novel antitumor agents aiming at targeting

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specific tumoral functions; however the dream for a "magic bullet" faded after the discovery of tumor resistance to those treatments. Up to then, the tumoral tissue was considered as a uniform body, and drug targeting was looked at a large scale using drug labelling techniques, including ^3H and ^{14}C or by attachment of a fluorescent group, followed by a relatively large scale detection: autoradiography on sections (not always quantitative) or ex vivo or in vivo fluorescence respectively. However recent discoveries in oncology have demonstrated that different tumor cells can exist in tumoral tissue just like in normal host cells, showing distinct morphological and phenotypic profiles, including gene expression, metabolism, proliferation or metastatic potential [3]. This phenomenon, called tumour heterogeneity, occurs both between and within tumors and is caused by environment and genetic factors. It is at the origin of acquired drug resistance and limits the precision of histological diagnoses (biopsy) or molecular prognostic markers for classifying patients that might benefit from specific therapies. Thus, for therapeutic index optimization, the assessment of drug distribution within cancer cells (increasing toxicity) and host-cells (limiting side toxicological effects) is essential.

Unit cells with incorporated labelled drugs have been observed, often using fluorescence techniques[4], but those are not ideal for the pharmacological industry since fluorescent groups are relatively large molecules which change the drug molecule dynamics and make difficult to prove that the labelled molecule has the same cell-interactions properties. Thus for this type of pharmaceutical applications, radiolabelling is preferred, that is replacing one of the molecule constituents with one of its radioactive isotopes or an element decaying into the original atom. ^{14}C , ^3H , ^{35}S , ^{18}F , all beta emitters, are often used for this purpose. One team has mentioned the radioactive labelling by ^{18}F [5][6], which has a relatively high energy decay product (0,63MeV) allowing for its detection by radioluminescence, but is still not representative (in terms of metabolic activities), and also brings heavy constraints of working near a medical isotopes facility, due to the short lifetime of ^{18}F (1.8 h half-life). For now, the observation of ^3H or ^{14}C labelled drugs in unit cells has not been made due to a number of challenges linked to the low energy of the decay products of those two isotopes (weighted mean energies of 6 keV and 49 keV respectively) as well as their relatively low specific activities.

The idea of the Medica-Plus project thus originated from the concrete need for a beta imager at the cell level for pharmaceutical applications in particular in the field of anticancerous drug studies in the animal model and in humans. In this project, Micromegas detectors are foreseen to tackle the aforementioned issues. In the next sections, we will briefly explain why. Then preliminary results obtained with a prototype detector measuring tritium-containing dummy samples will be shown. Finally, conclusions and perspectives for this work will be presented.

2. Medica-Plus and interaction between the teams

In this section the steps involved upstream from detector development are briefly described to give an idea of the constraints brought by the interdisciplinary aspects of this project to the detector design and performance. The project relies on several teams with specific skills in relation to the different backgrounds involved in this complex subject: biology, microfluidics, detector development, and signal processing. The relationships are more or less linear but with feedback loops to accommodate the technical requirements of each party, which are not always compatible. Simply put, the upstream parts of the project involves:

2.1. Obtaining single cells with radiolabelled drugs

In the biology department the cells from an animal model of tumor progression which received an injection of a radiolabelled drug, are sampled. Then, they are prepared, separated and conditioned as a suspension of unit cells in an aqueous solution. The cell size is on average 20 μm for the tumor model envisaged in this project. The betas originating from tritium decay have a relatively low energy and their interaction with the cells themselves is expected to

decrease strongly the particles' energy to be detected and their further interactions with matter. Accordingly the detector should have a low energy threshold, and be able to reconstruct the short tracks arising from the betas. Also, to avoid any further energy losses, the sample holder should be inside the gas volume of the detector. Consequently, the drift cathode has been adapted into a sample holder. Furthermore, the tritium activity per cell might depend strongly on the type of drug and cell, deriving from cell heterogeneity itself. The target activity per cell is of the order of 10 pCi (~ 0.37 Bq) but there are large uncertainties and the activity could be one or two orders of magnitude higher. From the detector point of view, this means that all background rejection capabilities will be needed. Both of those constraints are well handled by Micromegas detectors coupled to suitable electronics.

2.2. Sorting and deposition of the cells on the analysis support

The microfluidists receive the cells in suspension and sort them before depositing them on a sample holder. For statistical significance, high-throughput screening of cell heterogeneity and routine generation of large-scale single-cell arrays with high precision and efficiency, single-cell resolution, multiple cell types are needed. In the context of this project, two concurrent techniques are currently studied. On one hand, continuous flow (and phase) mechanical trapping via the so-called "Block cell printing"[7]. This technique consists in flowing a suspension of unit cells through an array of micro-sized tubes with side anchor hooks to trap cells. Then, the microfluidic device is left untouched for a while so that the cells can slide down and adhere on the underlying surface (the sample holder). Its mechanics are easy, no complex physics are involved but high resolution lithography ($3\ \mu\text{m}$) is required. In this case the distance between hooks and channels set the pitch between the deposited cells. Alternatively, a sorting technique based on Deterministic Lateral Displacement (DLD)[8] is studied. Droplet-based microfluidics show unique characteristics compared to the typical continuous flow, such as rapid mixing, splitting, and trapping. Nevertheless, the design mechanics and the microfluidic phenomena involved are more complex (and depend on relative properties of the fluids such as viscosity, which can raise issues for the cell integrity during the manipulation or on the detector part where remaining traces of those fluids are not desired). After encapsulation the cells are deposited by fast droplet deposition on the sample holder. In both cases the cells are deposited following a known pattern, a few hundreds of microns apart from each other. Thus a detector with good spatial resolution is required; here again Micromegas detectors are adapted and provide good results even for very short tracks arising from low energy particle interaction with gas.

3. Preliminary results

To investigate the feasibility of tritium detection with Micromegas-based detectors, a preliminary simulation work was performed. It will be displayed in the next subsection and followed by a presentation of the first tritiated samples measurements obtained with a prototype detector.

3.1. Feasibility simulations with Geant4 and the REST software

To investigate the project feasibility, a simulation based on GEANT4[9] and the REST framework [10][11] was performed. The samples consist of an array of 11×11 cells of $20\ \mu\text{m}$ diameter and $500\ \mu\text{m}$ pitch, and an activity per cell of 100 pCi (3.7 Bq). Each cell is located in a $20\ \mu\text{m}$ thick layer of water, supported by a glass support. The samples are thus located inside the drift gap and the drift gap itself is 10 mm wide. The active area of the detector is $60 \times 60\ \text{mm}^2$ with a 2-dimensional readout plane with a $350\ \mu\text{m}$ interstrip pitch. The simulation gas is a mixture of Argon and 5% Isobutane. The detector gain is 10^4 and its energy resolution is 13% FWHM at 5.9 keV. The electronics response is simulated with the REST software: the AFTER-chip [12] was used with a strip gain of 240 pF and a 100 ns integration time. No noise component was taken into account. Figure 1 shows the geometry principle and the results of the

simulation: the position and activity of each cell can be determined. To optimize this result, a complete simulation study will be made in order to refine the various parameters of the beta imager (gas, drift space, readout plane, position and holding of the biological sample in the detector enclosure). Optimization of the topological capabilities of the Micromegas detector should allow to improve the assessment of the radioactivity in each cell.

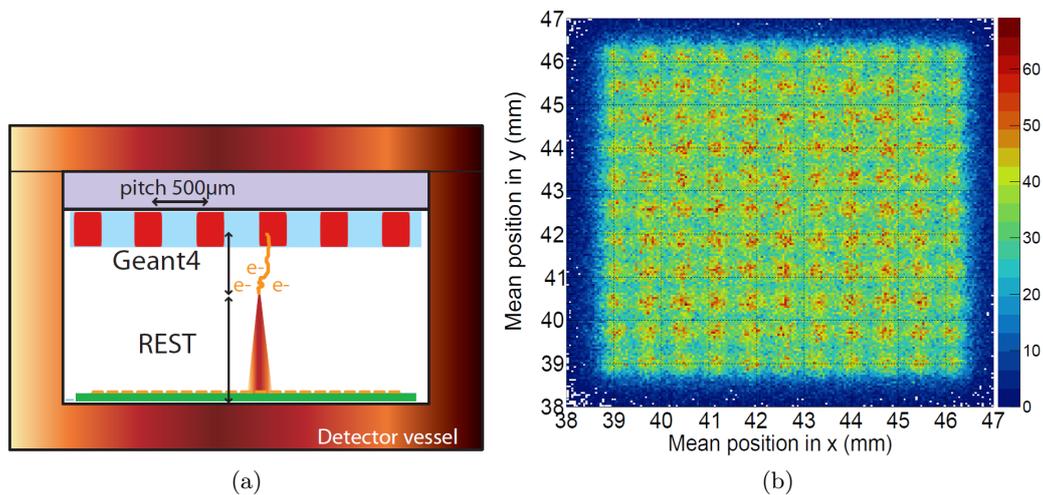


Figure 1: Schematics of the detector geometry (a); Simulated detector image for an exposition time of 2 days (b) (detector and electronics parameters described in the text).

3.2. First prototype detector performance

The first prototype is a bulk Micromegas detector with an amplification gap of $128 \mu\text{m}$, and a drift gap of 5 mm. The readout plane is made of $370 \mu\text{m}$ large copper unidirectional strips with a $500 \mu\text{m}$ pitch. A first characterization in 95% Argon - 5% Isobutane mixture has been made in mesh-reading configuration, grounding all the strips and reading the mesh signal globally. The voltages were independently applied by a CAEN N471A module. The avalanche signal is read out by an ORTEC 142C preamplifier. The preamplifier output was fed into a CANBERRA 2022 spectroscopy amplifier and subsequently into a multichannel analyzer AMPTEK MCA-8000A for spectra building. No specific control of pressure or temperature was made. A coarsely collimated ^{55}Fe source was used to obtain the detector characteristics. In Figure 2, the energy spectrum of this source is presented along with a gaussian fit allowing one to determine the FWHM resolution to be 28% which is average but does not impair the detector performance as to tritium detection (conditions : voltages optimized to be on the electron transparency plateau with a gain of 3.10^4 ; 600s acquisition time per spectrum). Using the ^{55}Fe peak one can also calibrate the Multi Channel Analyser to deduce its energy threshold, here around 700 eV.

As both biologists and microfluidists are still developing their techniques to provide the future radiolabelled sorted cells, the first measurements were obtained with tritiated glucose deposits used as dummy samples. Five droplets of respectively 1, 2, 5, 7 and 10 nCi nominal activity were deposited on the drift cathode, facing the readout-plane, and left drying before closing the detector. The total activity obtained is thus 25 nCi (925 Bq), the equivalent activity of an array of cells deposited every $500 \mu\text{m}$ on a $25 \times 25 \text{mm}^2$ surface, and with an activity of 10 pCi each. Two profiles (for reproducibility) as well as the expected tritium profile [13] (arbitrarily scaled to guide the eye for interpretation) are shown in Figure 3(a). Compared

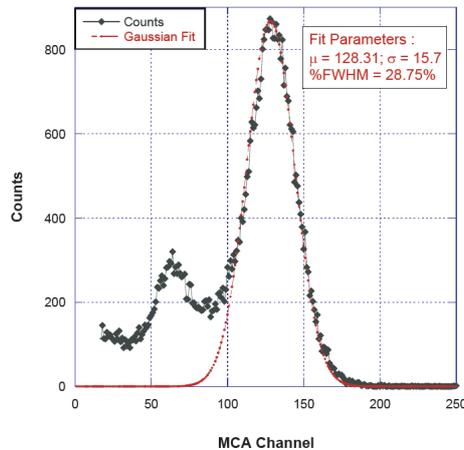


Figure 2: Energy spectra obtained with the ^{55}Fe source (squares), and a gaussian fit allowing for energy resolution calculation (red line).

with the theoretical tritium decay profile, a shift towards lower energies is observed, as well as a greater number of low energy events. Also, the total count rate is 317 ± 6 counts/s, thus giving an apparent efficiency of 34% if comparing to the nominal activity deposited. However, the profile shape change rather suggests more an effect of self-absorption of the β 's by the sample. To investigate this hypothesis, a simple simulation was performed, using the glucose stopping power from the NIST database [14], a simplified geometry and a basic electron/sample interaction. The geometry used is a rectangular shaped sample in which 1000 decays per grid point are simulated along a regular grid. For each decay, a β particle energy is randomly selected (respecting the theoretical distribution), as well as an angle of emission, and the distance to get out from the sample is calculated assuming a strictly linear trajectory. The stopping power curve is then used to calculate the energy loss, along the trajectory with 100 steps on the way, except if the β intersects the drift cathode support, in which case it is considered fully stopped. The sample dimensions are chosen after a microscope observation of the cristallized glucose deposited in the 10 nCi case, to be 500 nm long (pixel limit) \times 5 nm thick (calculated) with a likely error of 100%. The theoretical tritium decay profile is compared in Figure 3 (b) to the profile of the β s successfully exiting the sample for this geometry and a 1 μm long sample.

A similar energy distribution shift is observed, with an apparent efficiency between 31% and 41% respectively for the two geometries. However, this effect does not fully depict what is observed in the experiment, especially the low energy counts. If a noise contribution is expected from Figure 2, other physical phenomena such as the excitation peak from the aluminium at the cathode surface (added in Figure 3(b)), and also a contribution of β s crossing the 4 μm thick mylar foil are contemplated. Fortunately, those effects can be easily discarded by drift cathode modifications, which will be tested soon.

4. Conclusions

Medica-Plus is a transdisciplinary project for pharmacological applications involving teams from biology, microfluidics, detectors and signal processing backgrounds. New challenges and team enrichment arise from the several technical and technological lock-ins that need to be released in each project field while accomodating other fields-related constraints. Encouraging simulation results for low radiomarkers activities distributed on a regular grid pattern are confirmed by first measurements with tritiated samples. Preliminary tests with a tritiated glucose deposit

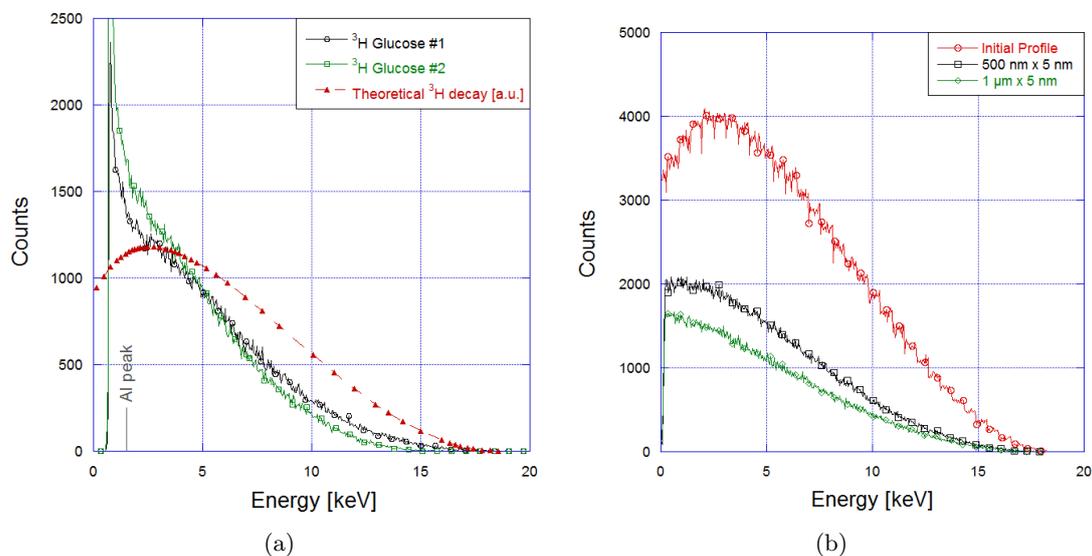


Figure 3: Two mesh-read measurement of 25 nCi of tritiated D-glucose with the prototype detector compared to theoretical tritium spectra (a). Evaluation of the effect of self-absorption on the final energy profile with the simplified simulation model (b).

have been performed allowing the measurement of a first ^3H spectrum. Factors influencing the detected signal have to be understood and modeled while getting closer to target activities.

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