TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

School of Nuclear Science & Engineering

Field of training (specialty) 14.04.02 Nuclear physics and technology

Division for Nuclear-Fuel Cycle

MASTER'S GRADUATION THESIS

Topic of research work
Application of detector technologies for heavy-ion nuclear experiment and for irradiation of brain tumor cells

UDC 539.16.04:539.1.074

Student

Group	Full name	Signature	Data
0AM8M	Danilova Irina Borisovna		

Scientific supervisors

Position	Full name	Academic degree, academic rank	Signature	Data
Leading Researcher	Svetlana Kushpil	CSc.		
Leading Researcher	Ing. Marie Davidkova	CSc.		

Adviser

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Verigin D.A.	Ph.D.		

ADVISERS:

Section "Financial Management, Resource Efficiency and Resource Saving"

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Menshikova E.V.	Ph.D.		

Section "Social Responsibility"

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Verigin D.A.	Ph.D.		

ADMITTED TO DEFENSE:

Director of programme	Full name	Academic degree, academic rank	Signature	Data
Nuclear Medicine	Cherepennikov Yu.M.	Ph.D.		

Tomsk – 2020

LEARNING OUTCOMES

Expected learning outcomes

Learning outcome (LO) code	Learning outcome (a graduate should be ready)	Requirements of the FSES HE, criteria and / or interested parties
	Professional competencies	
LO1	To apply deep mathematical, scientific, socio-economic and professional knowledge for conducting theoretical and experimental research in the field of the use of nuclear science and technology.	FSES HE Requirements (BPC-1,2, PC-3, UC-1,3), Criterion 5 RAEE (p 1.1) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO2	To demonstrate ability to define, formulate, and solve interdisciplinary engineering tasks in the nuclear field using professional knowledge and modern research methods.	FSES HE Requirements (PC-9,10,13,14,15, BPC-1,3), Criterion 5 RAEE (p 1.2) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO3	To plan and conduct analytical, simulation and experimental studies in complex and uncertain conditions using modern technologies, and to evaluate critically research results.	FSES HE Requirements (PC-1,13,22, UC-2, BPC-1), Criterion 5 RAEE (p 1.3) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"

LO4	To use basic and special approaches, skills and methods for identification, analysis, and solution of technical problems in the field of nuclear science and technology.	FSES HE Requirements (PC-2,4,6,8, UC-2, BPC-1), Criterion 5 RAEE (p 1.4) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO5	To operate modern physical equipment and instruments, to master technological processes in the course of preparation for the production of new materials, instruments, installations, and systems.	FSES HE Requirements (PC-5,7,11,12, UC-2, BPC-1), Criterion 5 RAEE (p 1.4) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO6	To demonstrate ability to develop multi-option schemes for achieving production goals with the effective use of available technical means and resources.	FSES HE Requirements (PC-16-21,23), Criterion 5 RAEE (p 1.5) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
Cultural competencies		
LO7	To demonstrate ability to use a creative approach to develop new ideas and methods for designing nuclear facilities, as well as to modernize and improve the applied technologies of nuclear production.	FSES HE Requirements (BPC-1,3, UC-3), Criterion 5 RAEE (p 2.4,2.5)

Basic professional competencies		
LO8	To demonstrate skills of independent learning and readiness for continuous self-development within the whole period of professional activity.	FSES HE Requirements (UC-3, PC-1, BPC-1), Criterion 5 RAEE (p 2.6) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO9	To use a foreign language at a level that enables a graduate to function successfully in the international environment, to develop documentation, and to introduce the results of their professional activity.	FSES HE Requirements (PC-11,16,17, BPC-3), Criterion 5 RAEE (p 2.2) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"
LO10	To demonstrate independent thinking, to function efficiently in command-oriented tasks and to have a high level of productivity in the professional (sectoral), ethical and social environments, to lead professional teams, to set tasks, to assign responsibilities and bear liability for the results of work.	FSES HE Requirements (PC-18,23, UC-2), Criterion 5 RAEE (p 1.6,2.3) requirements of the Ministry of Health and Social Development of the Russian Federation under the unified skills guide for positions of managers, specialists and non-manual workers for the position of "medical physicist"

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School of Nuclear Science & Engineering
Field of training (specialty) 14.04.02 Nuclear physics and technology
Division for Nuclear-Fuel Cycle

APPROVED BY:
Director of the programme
_____ _____ Cherepennikov Y.M.
(Signature) (Date) (Full name)

ASSIGNMENT
for the Graduation Thesis completion

In the form:

Master's thesis

For a student:

Group	Full name
0AM8M	Danilova Irina Borisovna

Topic of research work:

Application of detector technologies for heavy-ion nuclear experiment and for irradiation of brain tumor cells	
Approved by the order of the Director of School of Nuclear Science & Engineering (date, number):	

Deadline for completion of Master's Graduation Thesis:	19.06.2020

TERMS OF REFERENCE:

Initial data for research work: *(the name of the object of research or design; performance or load; mode of operation (continuous, periodic, cyclic, etc.); type of raw material or material of the product; requirements for the product, product or process; special requirements to the features of the operation of the object or product in terms of operational safety, environmental impact, energy costs; economic analysis, etc.)*	Beam test data taken at PS CERN in 2018; ALPIDE sensors; off-line data collected at the ITS of the ALICE experiment at CERN in 2020; raw data analysis by ROOT framework, created at CERN; monolayer cultures of brain tumor cells; irradiation source from Chisostat SO 01 (Nuclear Physics Institute of the CAS, Czech Republic); System QUANTUM and BioVision software framework for counting and analyzing of cells; water phantom.

List of the issues to be investigated, designed and developed *(analytical review of literary sources with the purpose to study global scientific and technological achievements in the target field, formulation of the research purpose, design, construction, determination of the procedure for research, design, and construction, discussion of the research work results, formulation of additional sections to be developed; conclusions).*	Get familiar and analysis with the literature on the topic of work; work with experimental data from beam test taken at PS CERN (detector efficiency at selected settings); laboratory measurements of FHR and Thresholds for selected sensors; comparison of the results with experimental results from previous chips, investigated by the ITS team; off-line analysis from the commissioning process of new ITS; conduction experiments to determine the radiosensitivity of medulloblastoma cell lines; clonogenic assay for DAOY and ONS-76 cell lines irradiated by ^{60}Co; formulation of conclusions; financial management, resource efficiency and resource saving; social responsibility.

Advisors to the sections of the Master's Graduation Thesis

(with indication of sections)

Section	Advisor
Financial Management, Resource Efficiency and Resource Saving	Menshikova E.V.
Social Responsibility	Verigin D.A.

Date of issuance of the assignment for Master's Graduation Thesis completion according to the schedule	

Assignment issued by a scientific supervisor / advisor (if any):

Position	Full name	Academic degree, academic rank	Signature	Data
Leading Researcher	Svetlana Kushpil	CSc.		
Leading Researcher	Ing. Marie Davidkova	CSc.		
Associate Professor	Verigin D.A.	Ph.D.		

Assignment accepted for execution by a student:

Group	Full name	Signature	Data
0AM8M	Danilova Irina Borisovna		

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

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School of Nuclear Science & Engineering

Field of training (specialty) 14.04.02 Nuclear physics and technology

Level of education Master Degree Program

Division for Nuclear-Fuel Cycle

Period of completion fall / spring semester 2019 /2020

Form of presenting the work:

Master's thesis

SCHEDULED ASSESSMENT CALENDAR
for the Master's Graduation Thesis completion

Deadline for completion of Master's Graduation Thesis:	19.06.2020

Assessment date	Title of section (module) / type of work (research)	Maximum score for the section (module)
15.02.20	Drawing up and approving the terms of reference	7
03.03.20	Selection and study of materials on the topic	10
10.03.20	Choice of research area	5
27.04.20	Conducting experiments	42
17.05.20	Analysis and description of results	27
01.06.20	Preparing for thesis defense	9

COMPILED BY:
Scientific supervisor

Position	Full name	Academic degree, academic rank	Signature	Data
Leading Researcher	Svetlana Kushpil	CSc.		
Leading Researcher	Ing. Marie Davidkova	CSc.		

Adviser (if any)

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Verigin D.A.	Ph.D.		

AGREED BY:
Director of the programme

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Cherepennikov Yu.M.	Ph.D.		

TASK FOR SECTION
"FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE SAVING"

To student:

Group	Full name
0AM8M	Danilova Irina Borisovna

School	Nuclear Science & Engineering	Division	Nuclear-Fuel Cycle
Degree	Master Degree program	Education Programme	Nuclear medicine (medical physicist)

Input data to the section "Financial management, resource efficiency and resource saving":	
1. Resource cost of scientific and technical research (STR): material and technical, energetic, financial and human	Depreciation and amortization of equipment and electricity costs 9215.88 rubles Main salary of performers 348533.62 rubles Additional salary of performers of the project 34853.36 rubles Contributions to extrabudgetary funds 67962.62 rubles
2. Expenditure rates and expenditure standards for resources	Tariff for industrial electricity 10.18 per 1 kW Tomsk city district coefficient - 1,3 District coefficient of the city of Prague is 1
3. Current tax system, tax rates, charges rates, discounting rates and interest rates	The amount of insurance premiums is 30% Reduced rate in Tomsk - 27,1% Reduced rate in Prague - 15%
The list of subjects to study, design and develop:	
1. Assessment of commercial and innovative potential of STR	Competitive technical solutions evaluation map
2. Scheduling of STR management process: structure and timeline, budget, risk management	Hierarchical structure of work
3. Determination of resource, financial, economic efficiency	Evalution of technical solutions competitiveness SWOT Matrix Schedule and budget for the scientific research Gantt Chart
A list of graphic material *(with list of mandatory blueprints):*	
1. Evaluation of the competitiveness of technical solutions *2. SWOT- analysis* *3. Gantt chart and budget of scientific research* *4. Assessment of resource, financial and economic efficiency of STR* *5. Potential risks*	

Date of issue of the task for the section according to the schedule	

Task issued by adviser:

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Menshikova E.V.	Ph.D.		

The tast was accepted by the student:

Group	Full name	Signature	Data
0AM8M	Danilova Irina Borisovna		

TASK FOR SECTION
"SOCIAL RESPONSIBILITY"

To the student:

Group	Full name
0AM8M	Danilova Irina Borisovna

School	Nuclear Science & Engineering	Division	Nuclear-Fuel Cycle
Degree	Master Degree Program	Education Programme	Nuclear medicine (medical physicist)

Topic of research work:

Application of detector technologies for heavy-ion nuclear experiment and for irradiation of brain tumor cells
Objects of study: ALPIDE sensors and brain tumor cells

Initial data for section "Social Responsibility":	
1. Information about object of investigation (matter, material, device, algorithm, procedure, workplace) and area of its application	Investigation of effect of coolant injection parameters on mitigation of core melting accident by simulation on PC. Application area: safety of nuclear reactor
List of items to be investigated and to be developed:	
1. Legal and organizational issues to provide safety: *– Special (specific for operation of objects of investigation, designed workplace) legal rules of labor legislation;* *– Organizational activities for layout of workplace.*	Labour code of Russian Federation ♯197 from 30/12/2001 GOST 12.2.032-78 SSBT Sanitary Rules 2.2.2/2.4.1340-03. Hygienic requirements for PC and work with it
2. Work Safety: *– Analysis of identified harmful and dangerous factors* *– Justification of measures to reduce probability of harmful and dangerous factors*	Enhanced electromagnetic radiation level Insufficient illumination of workplace Excessive noise Deviation of microclimate indicators Electric shock Ionizing radiation
3. Ecological safety:	Indicate impact of gamma-radiation on hydrosphere, atmosphere and lithosphere Indicate impact of plastics production on hydrosphere, atmosphere and lithosphere
4. Safety in emergency situations:	Fire safety

Assignment date for section according to schedule	

The task was issued by adviser:

Position	Full name	Academic degree, academic rank	Signature	Data
Associate Professor	Verigin D.A.	Ph.D.		

The tast was accepted by the student:

Group	Full name	Signature	Data
0AM8M	Danilova Irina Borisovna		

ABSTRACT

Master's Graduation work 112 p., 55 fig., 29 tab., 68 sources.

Keywords: ITS ALICE, CERN, ALPIDE, detector, medulloblastoma, cell line, radiosensitivity, cell survival curve, clonogenic assay.

Objects of research are ALPIDE sensors and medulloblastoma cell lines.

Purpose of work includes a complex investigation of the characteristics of the ALPIDE pixel detector which is currently applied in the ALICE experiment at CERN, and the determination of survival curves chosen cell lines of brain tumor.

In the process of research were carried out: got familiar and analysis with the literature, work with experimental data from beam test taken at PS CERN (detector efficiency at selected settings), laboratory measurements of FHR and Thresholds for selected sensors, comparison of the results with experimental results from previous chips, investigated by the ITS team, off-line analysis from the commissioning process of new ITS, conduction experiments to determine the radiosensitivity of medulloblastoma cell lines, a clonogenic assay for DAOY and ONS-76 cell lines irradiated by ^{60}Co, result analysis.

As a result of the study, an installation was proposed using the ALPIDE detector for irradiating cells which allows on to determine the location of charged particles and how many cells were irradiated.

Degree of implementation: the research is currently under development.

Application area: medicine, high energy physics, scientific research.

Planned in the future to take measurements using the proposed installation for irradiation cells with the use of ALPIDEs sensors.

List of abbreviations

Abbreviations used in the work:
ALICE – A Large Ion Collider Experiment;
ALPIDE – ALICE Pixel Detector;
ATRT – Atypical Teratoid Rhabdoid tumors;
CNS – Central Nervous System;
CSF – Cerebrospinal fluid;
CT – Computed Tomography;
DAQ – Data AcQuisition;
DNA – Deoxyribonucleic acid;
DSB – Double-standed breaks;
ETANTR – Embryonal tumor with abundant neuropil and true rosettes;
FBS – Fetal bovine serum;
FHR – Fake Hit Rate;
HCL – Hierarchical clustering;
HU – Hounsfield Units;
IAEA – International Atomic Energy Agency;
IB – Inner Barrel;
IMEM – Improved Minimum Essential Medium;
IP – Interaction point;
ITS – Inner Tracking System;
LCA – Littoral cell angiomas;
LINAC – Linear accelerator;
LHC – Large Hadron Collider;
LQM – Linear-Quadratic model;
MAPS – Monolithic Active Pixel Sensor;
MB – Medulloblastoma;
MBEN – Medulloblastoma with extensive nodularity;
NIEL – Non-Ionizing Energy Loss;
OB – Outer Barrel;
PBS – Phosphate-Buffered Saline;
PCA – Principal component analysis;
PE – Planting efficiency;
PID – Proportional Integral Derivative;

PMMA – Polymethyl methacrylate;
PS – the Proton Synchrotron;
P/S – Penicillin-streptomycin;
RMS – Root mean square;
RSP – Relative stopping power;
SAD – Source-to-axis distance;
SF – Surviving fraction;
SSB – Single-standed breaks;
SSD – Source-to-skin distance;
Stv – Stave;
TCGF – T-cell growth factor;
TID – Total ionizing dose;
TN – Temporal noise;
TOF – Time of flight;
TPC – Time-Projection Chamber;
TRD – Transition Radiation Detector (TRD);
UV – Ultraviolet.

Contents

Introduction

Radiation therapy is one of the most effective ways against cancer. In order to successfully irradiate tumor within target volume and minimize the damage of healthy tissue, there is a need to control the dose rate delivery. Today, irradiation is carried out using photons or charged particles (for example, protons). Proton therapy has the potential to deliver better dose distributions than radiotherapy by photon/electron beams, as the proton lose most all of energy at the end of range, producing the Bragg peak [1]. Therefore, the absorbed dose for healthy tissues after irradiation with protons is less than after photons.

The accurate determination of the Bragg peak position within a target volume needs to know the information from one of the photon attenuations to one of proton energy loss for different organs and tissue patients [2]. This requires an X-ray computed tomography (CT) numbers (HU – Hounsfield Units) to be converted into relative stopping powers (RSPs). At the moment this process is done through using a calibration curve [3]. This process contributes 0.5-1.8% to the proton beam range uncertainty, depending on whether the uncertainties in the mean ionization energies are considered [2, 4] . Therefore, to reduce uncertainty at positioning in hadron therapy it is proposed to use ALICE PIxel DEtector (ALPIDE) [5].

Particle physics experiments depend on the ability to accurately track the paths of particles produced in high-energy collisions. Frontier experiments demand ever-higher collision rates both to maximize sensitivity to rare processes and subtle effects and to minimize the statistical errors on measurements. The high-rate capability, tracking precision, sensor granularity, readout speed, and radiation resistance of the current generation of silicon detectors has led to their widespread adoption, particularly in collider experiments (which typically require the most demanding specifications). New technologies are emerging, both from within particle physics and through the design of specialist variants of commercial optical sensors, which offer significant improvements in terms of particle-track spatial resolution, fast-timing capability, detector radiation hardness, scattering material and cost per unit area. Other disciplines that already use particle physics silicon tracking technologies can only benefit from adopting these developments as they become available.

ALPIDE pixel chip is the Monolithic Active Pixel Sensor (MAPS) for the Upgrade of the Inner Tracking System (ITS) of the ALICE experiment at the CERN Large Hadron Collider. ALPIDE is based on the TowerJazz 180 nm CMOS imaging

process and is produced on wafers with a high resistivity (> 1 kΩ·cm) 25 μm p-type epitaxial layer on a p-type substrate. In combination with a small size of pixel implements high density and low power digital circuits. The chip has a size is 15 mm × 30 mm and a matrix of 512 × 1024 pixels with a pitch of 28 μm [6]. Each pixel of the ALICE PIxel DEtector has an analog front-end circuit for signal amplification, hit discrimination, and multi-event buffering. Radiation tolerance of ALPIDE up to 1.7×10^{13} 1 MeV neq/cm^2 non-ionising energy loss (NIEL) and up to 2700 krad total ionizing radiation (TID) including an additional safety factor equal to 10 [7, 8]. ALPIDE has a detection efficiency above 99%, a spatial resolution of about 5 μm and noise level less 10^{-6} hits/event/pixel [5] allowing a precise positioning of a particle beam in hadron therapy [9].

Goal of my diploma thesis includes a complex investigation of the characteristics of ALPIDE which is currently applied in the ALICE experiment at CERN and assessing of possible application of these detectors at experiments studying radiosensitivity of brain tumour cells. Radiobiology part of the diploma thesis was focused to determine radiosensitivity of selected meduloblastoma cell lines DAOY and ONS-76 using clonogenic assays. The final step is to propose an experimental setup, where ALPIDE detectors can be used for radiobiology research.

To achieve this goal it was necessary to perform the following objectives:

1) In detector technology:

– Get familiar with the principle of ALPIDE operation for ITS upgrade;

– Study of detection efficiency of ALPIDE, using PS beam data;

– Laboratory investigation of Fake-Hit Rate (FHR) and Thresholds for selected sensors;

– Perform off-line analysis of the FHR for the ALPIDE from commissioning process of new ITS;

– Compare the results with experimental results from previous chips of the final design, investigated by the ITS team.

2) In radiobiology:

– Get familiar with a cellular response to ionizing radiation;

– Study of the process of the clonogenic assay;

– Conduct experiments to determine the radiosensitivity of medulloblastoma cell lines;

– Execute process of the clonogenic assay for DAOY and ONS-76 cells;

– Irradiate the chosen cell lines by ^{60}Co;

– Construct cell survival curves for brain tumor cells;

– Determine parameters of Linear-Quadratic model (LQM) for DAOY and ONS-76 cells.

1 Detector technologies

1.1 The ALICE experiment

The ALICE experiment (ALICE – A Large Ion Collider Experiment) is one of four large experiments located at the Large Hadron Collider at CERN [10]. This experiment is designed to study the physics of strongly interacting matter and in particular the properties of the Quark-Gluon Plasma, using proton-proton, proton-nucleus and nucleus-nucleus collisions [11].

The ALICE LHC experiment is currently in the process of upgrading subsystems. After the second long shutdown of the LHC in 2019–2021, ALICE will focus on high-precision measurements. The major upgrade part is a high resolution, low material budget ITS system. ALICE will carry out high-precision measurements of strongly scattered hadrons, quarkonium, and dileptons with low mass at small transverse momenta.

A schematic view of the ALICE detectors during the second shutdown of the LHC is shown in Figure 1.1. This setup consists of a Muon Spectrometer [12], which is used to detect muons, and a Central Cylinder, which is necessary for the detection and construction of collision vertices [11]. The ALICE collaboration uses the 10,000-tonne ALICE detector 26 m long, 16 m high, and 16 m wide.

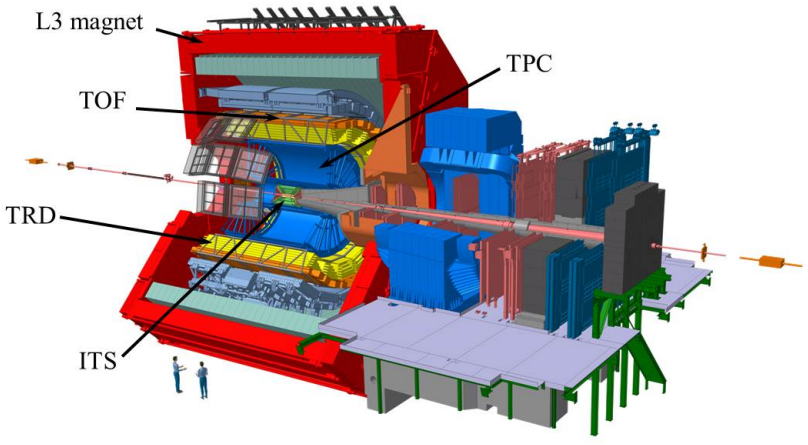

Figure 1.1 – Schematic view of the ALICE experiment and its sub-detectors, modified from [13]

The ALICE detector is placed in a moderate (0.5 T) magnetic field, provided by the L3 magnet. Detectors in the central barrel part cover the pseudorapidity range $|\eta| < 0.9$. The main detectors for charged particle tracking are the ITS, Time Projection Chamber (TPC), Time Of Flight (TOF), and Transition Radiation Detector (TRD).

1.2 Upgrade of ITS ALICE

The ALICE major upgrade is a new inner tracking system (ITS) with a new high resolution, low-material-budget silicon tracker [7]. The new ITS replacement by a new detector based on CMOS monolithic active pixel sensor (MAPS) covering the mid-rapidity ($|\eta| < 1.3$) region. In the MAPS technology, both the sensor for charge collection and the readout circuit for digitization are hosted in the same piece of silicon. The sensor developed by ALICE is called ALPIDE. The sensor technology is based on a 180 nm CMOS process provided by Tower Semiconductor. With this chip, the silicon material budget per layer is reduced of seven compared to the previous ITS [5]. The ALPIDE chip is 15×30 mm^2 in size containing more than half a million pixels organized in 1024 columns and 512 rows. Its low power consumption (< 40 mW/cm^2) and an intrinsic spatial resolution (~ 5 mm) are perfect for the inner tracker of ALICE [14]. The next parameters will be discussed in the section 1.4.

The ITS consists of seven cylindrical layers of ALPIDE chips summing up a total area of 10 m^2 and 12.5 billion pixels (see Fig. 1.2). The pixel chips are installed on staves with radial distances ranging from 22 mm to 405 mm from the interaction point (IP). The beam pipe is also newly designed with a smaller radius of 18.6 mm, allowing the first detection layer to be placed closer to the IP at a radius of about 22 mm compared to the presently 39 mm.

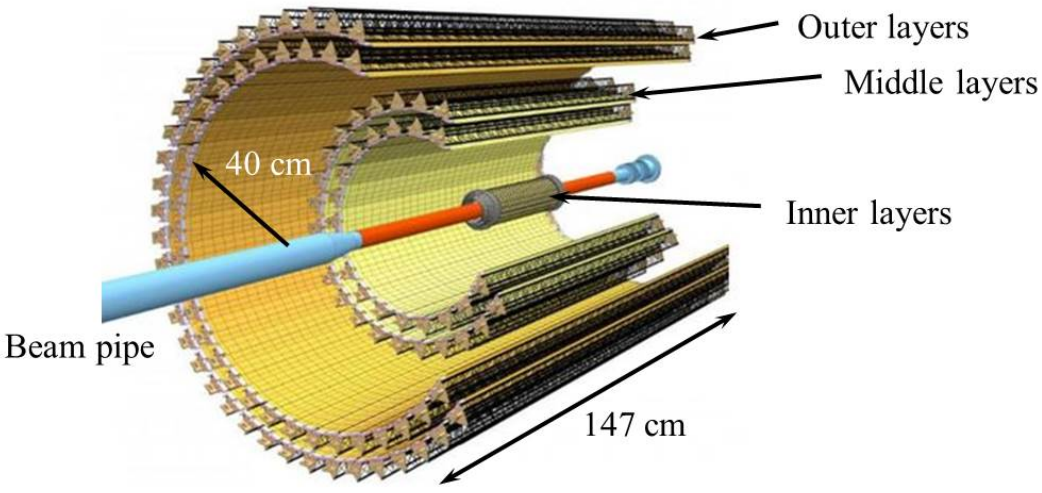

Figure 1.2 – Layout of the new ITS ALICE, taken from [7]

Sensors with thickness 50 µm and 100 µm are utilised for IB and OB, respectively. When a particle passes through a thinner detector it loses lower energy and can be therefore detected with chips in the OB, which improves track reconstruction.

The basic improvements of the ITS done the requirements ALICE technical design report:

– six cylindrical layers of silicon pixel, drift and strip detectors replaced with seven concentric cylindrical layers of MAPS cover 10 m^2 area;

– the current beam pipe with a radius of 29 mm replaced by a beryllium beam pipe having a radius of 17.2 mm;

– distance between the first layer and the interaction point reduced from the current 39 mm to 22 mm;

– material budget per layer reduced in comparison from 1.14 % to 0.3 % X/X_0 for inner layers and to 1% for outer layers;

– read the data in a continuous readout or a triggered mode up to a rate of 100 kHz for Pb–Pb collisions and 400 kHz for proton-proton collisions;

– pixel size reduced from 50×425 μm^2 to 29×27 μm^2 (a total number of pixels $\approx 12.5 \times 10^9$).

The characteristics listed of the new ITS ALICE above will enable impact parameter resolution for 500 MeV/c to be improved by a factor of about 3 and 6 in the spatial resolution (r_φ) and the transverse plane (z), respectively [15].

1.3 MAPS

For the ITS upgrade, ALICE applies Monolithic Active Pixel Sensor technology combined front-end circuitry and manufactured in Tower-Jazz 180 nm CMOS. Some benefits of 0.18 μm CMOS technology are with a transistor feature size of 0.18 μm and gate oxide thickness below 4 nm. CMOS process becomes substantially more robust to TID than other technologies. This technology provides 6 metal layers that allow implementing high density and low power digital circuits with a reduced area for the digital circuitry at the periphery of the pixel matrix. As a consequence insensitive area of the pixel chip is reduced.

Epitaxial layers can be developed with resistivity from 1 KΩcm to 6 KΩcm. This makes bigger depletion area in the epitaxial layer and improves the signal to noise ratio of the sensor as well as its resistance to non-ionizing radiation.

The Material Budget can be reduced to a great extent by producing wafers with an epitaxial layer from 18 μm to 40 μm thicknesses and making chips thin up to 50 μm.

The most important feature of this technology is the use of a deep p-well. Parasitic charge collection by n-wells is a problem that the front-end electronics

surface. Deep p-well is used to eliminate this problem. The PMOS transistor embedding in n-well is assembled on top of the deep p-well. The stitching technology is one of the unique features of sensors production through which matrices are manufactured up to one matrix per 200 mm in wafer diameter.

MAPS technology uses a few metal layers which in combination with a small size of pixel implements high density and low power digital circuits. The thickness of the sensitive layer is 18-30 µm. First, the charge is collected on the collection diode or injected through the capacitance. The generated current causes a voltage drop on the PIX_IN node. After that the signal is amplified and discriminated against with respect to the chosen threshold level. The binary signal is then sent to the in-pixel memory. Each pixel of the ALPIDE has an analog front-end circuit for signal amplification, hit discrimination and a 3 hit buffer. Figure 1.3 shows the sensor structure schematically and charge collection.

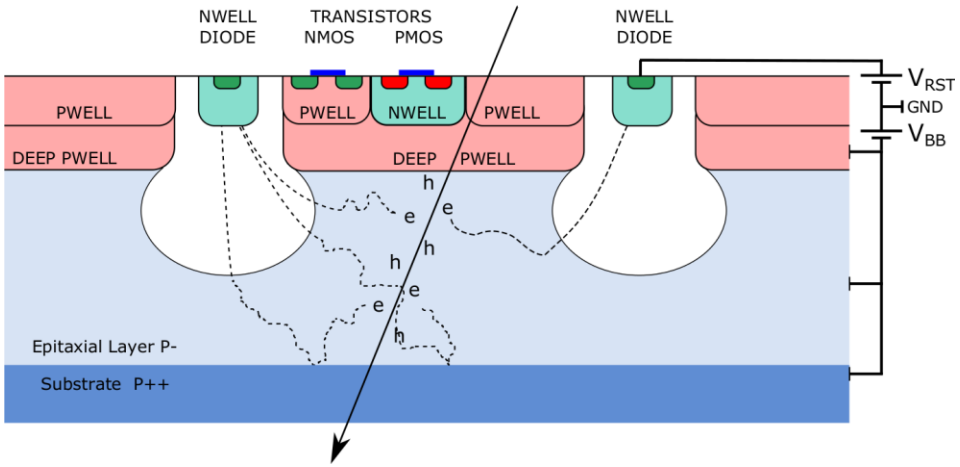

Figure 1.3 – A cross-sectional view of the pixel of ALPIDE sensor with the TowerJazz 180 nm technology and the corresponding charge collection, taken from [16]

Therefore, the MAPS are applicable for creating very thin detectors since the sensor and readout electronics are integrated inside the same silicon matrix, which allows reducing the material costs for producing such a sensor, as well as to simplify their production in comparison with expensive hybrid pixel sensors.

1.4 The ALPIDE sensor

ALPIDE is the pixel chip development carried out for the ALICE ITS upgrade. Size of ALPIDE sensor is shown in Figure 1.4. The general requirements and current performance of the ALPIDE chips for Inner and Outer Barrels are outlined in Table 1.1. ALPIDE of final design will be chosen 25 µm thick size.

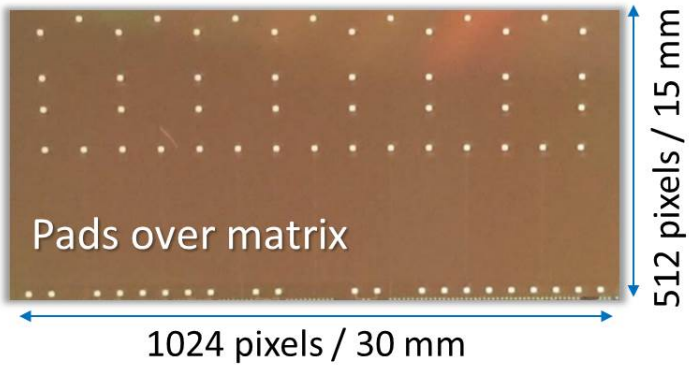

Figure 1.4 – Photo of the ALPIDE sensor

Table 1.1 – General pixel-chip requirements [7] and current performance of ALPIDE prototypes

Parameter	Inner Barrel	Outer Barrel	ALPIDE
Sensor thickness (μm)	50	100	✓
Spatial resolution (μm)	5	10	≈ 5
Chip dimension (mm)	15×30		✓
Detection efficiently (%)	> 99		✓
Fake-hit rate (event^{-1} pixel^{-1})	$< 10^{-6}$		$< 10^{-10}$
Event-time resolution (μs)	30		≈ 2
Power density (mW/cm^2)	< 300	< 100	< 40
TID (krad)[a]	270	10	✓
NIEL (1 MeV n_{eq}/cm^2)[a]	1.7×10^{12}	1×10^{11}	✓

[a] Not including an additional safety factor of 10

Figure 1.5 shows a schematic view of the in-pixel signal processing in ALPIDE chip. First, the charge is collected on the collection diode or injected through the capacitance (C_{inj}). In the analog front-end of the chip, the signal is amplified and discriminated against relatively chosen threshold level. The generated current causes a voltage drop on the PIX_IN node. If there is a hit, the voltage at OUT_A node increases. After that, the signal discriminates at the OUT_D node. The binary signal sent to the in-pixel memory.

Voltage V_{CASN} and current I_{THR} define the baseline value of OUT_A node. Increasing I_{THR} leads to the increase of the charge threshold while increasing V_{CASN} reduces the threshold. In other words, the charge threshold is influenced by two

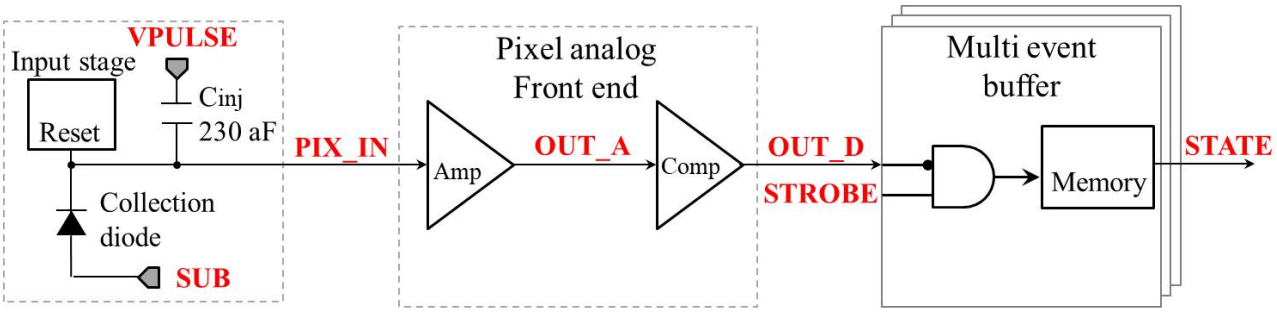

Figure 1.5 – Scheme of the in-pixel signal processing, taken from [17]

parameters: V_{CASN} and I_{THR}. The analog signals required by the front-ends are generated by a set of on-chip 8-bit DACs, which are implemented in a chip. All notations of the voltages are beginning with V (V_{CASN}, V_{CASN2}, V_{CASP}) and currents with I (I_{THR}, I_{DB}, etc.).

2 Cell radiobiology

2.1 Start from the beginning of the line

Cells are the structural, functional, and biological units of all living matter and contain fundamental molecules of life that all living things are made up of. The cell has linear dimensions of about 10-50 microns. Figure 2.1 shows a scheme of mammalian cell with organelles. Each cell contains a nucleus fulfilled with cell genome that stores hereditary information, transfers this information from cells to cells, from organism to organism. This information is encoded in DNA macromolecule, which is organized into special structures – chromosomes. An ordinary human cell contains 23 pairs of chromosomes (46 chromosomes).

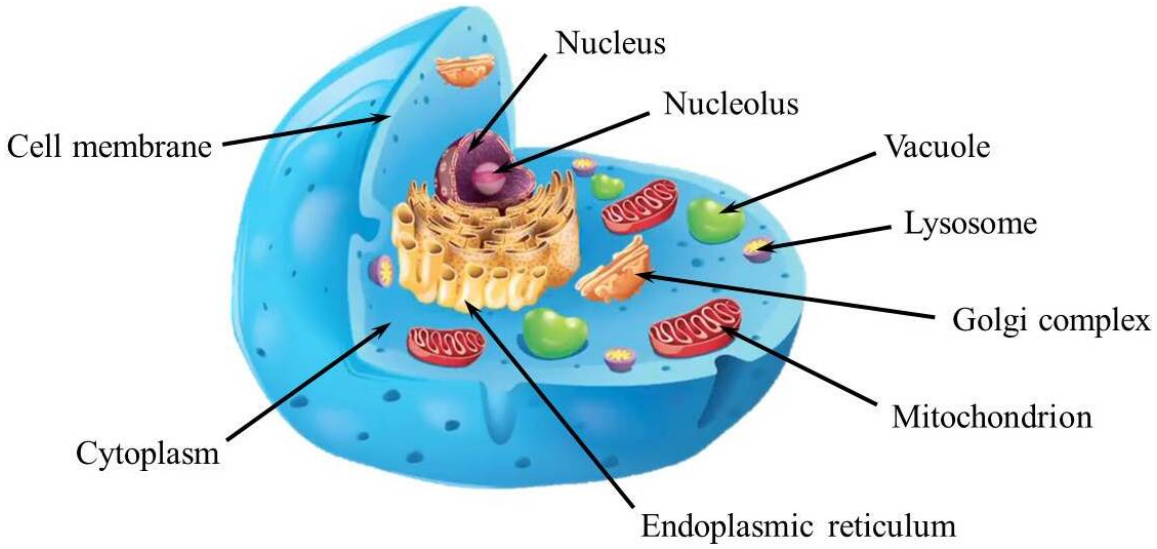

Figure 2.1 – Mammalian cell with organelles, modified from [30]

Mammalian cells multiply during mitosis [31]. After a certain period, each offspring may undergo further division. The time between successive divisions is known as the time of the mitotic cycle, or, as it is commonly called, the time of the cell cycle. Immediately before the cell divides, forming two hereditary cells, the chromosomes condense into clearly distinguishable forms. The whole process of mitosis, during the preparation of which rounding of the cell takes place, the chromosomal material condenses, and the cell divides into two parts, and then stretches again and attaches to the surface of the culture vessel, lasts about 1 hour. The rest of the cell cycle, interphase, occupies the entire inter mitotic period. If a population of dividing cells is observed with a conventional light microscope, the only event in the entire cell cycle that can be identified and distinguished is mitosis, or division itself.

The cell cycle consists of four phases for actively growing mammalian cells: M, mitosis; S is the synthetic phase of DNA; G_1 and G_2 – periods of apparent inactivity between the main distinguishable events in the cycle (see Fig. 2.2). Mitosis consists of 4 phases is Prophase, Metaphase, Anaphase, and Telophase.

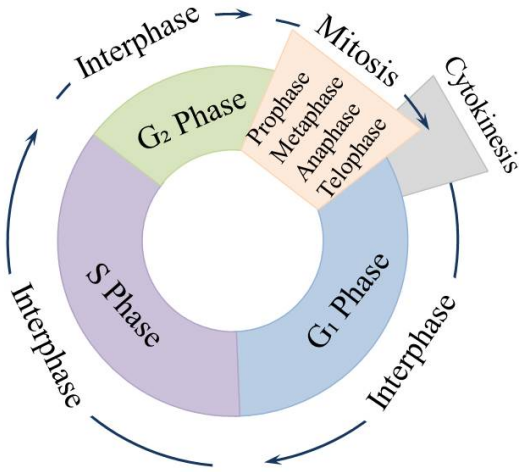

Figure 2.2 – The basic cell cycle machinery in mammalian cells

After some time, each of the progeny may incur a further division. The cell cycle time or the mitotic cycle time is a time between successive divisions. The fastest cycling mammalian cells in culture have cycle times as 9 to 10 hours. Stem cells in the resting mouse skin may have cycle times of more than 200 hours [32]. This difference is linked to the varying length of the most variable phase of the cycle G_1.

Research disciplines, for example, biology, cancer, genetics, reproductive functions, and neurobiology the importance has awareness of the structural and functional relationships of cells and tissues. Significant components of cells and tissue analysis are cell viability and proliferation, cell signaling pathways, cell cycle analysis, and cell structure.

2.2 Damage of cell organelles

The severity of a reaction cell to radiation depends on the stage of the cell cycle. The result of exposure on cells can be delayed division (when exposed to the nucleus), suppression of DNA synthesis, damage to a membrane, restoration, and maintenance of cell viability, impaired functioning, or death. If a cell has lost the ability to divide, that it does not always show signs of damage. A cell can live long after exposure irradiation. The main types of structural radiation damage are presented in Figure 2.3.

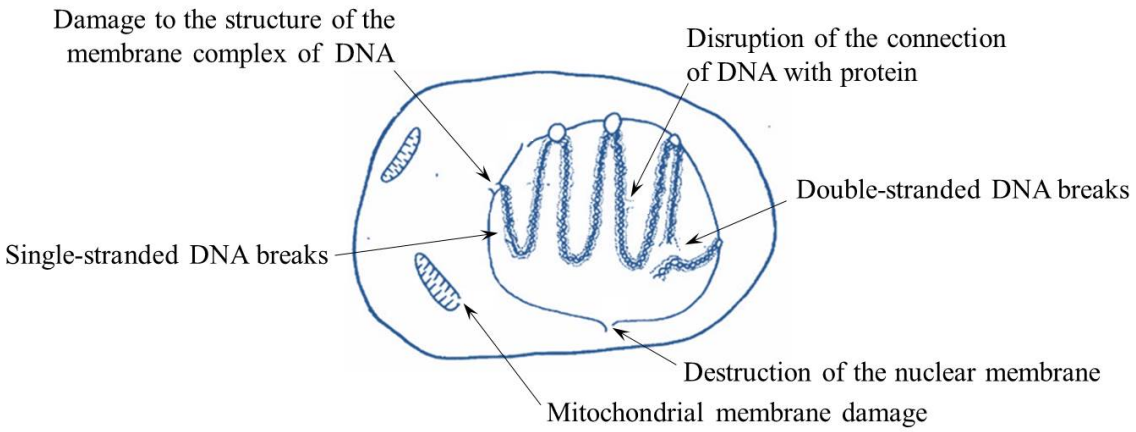

Figure 2.3 – Types of structural damage to the cell, modified from [33]

Most acute and long-term effects are the result of the death reproductive cells that occur in affected cells at an attempt to cleave occurs. The ability of cells to divide and form a colony is a sign of survival.

2.3 Cell response to radiation

Cell death in radiobiology is a loss of a cell's ability to proliferate. Surviving cells are cells that retained the ability to reproduce unlimitedly, i.e., clone formation. Thus, we are talking about reproductive cell death.

The main potential consequences of the effects on cells of ionizing radiation are normal cell division, aging caused by DNA damage, apoptosis, or cell death associated with mitotic processes. These manifestations of DNA damage may occur within one or two cell divisions or may happen at a later time after many cell divisions. Effects that appear in later times have been called delayed reproductive cell death and may also depend on secreted factors that are induced in response to radiation.

Mitotic death is death when trying to divide (dominant after irradiation). Apoptosis is programmed cell death. Autophagy is a digestive process that uses lysosomal degradation of long-lived proteins and organelles to restore or maintain cellular homeostasis. Cell senescence is a programmed cellular response to the accumulation of damage in the cell.

In most cases, cells die after trying to enter mitosis. Improperly repaired or unrepaired DNA damage causes a mitotic catastrophe, which results in cell death. It may occur after the first attempt to enter the mitosis, or after several mitoses have passed. This form of cell death is called late death [34]. In the absence of protein p53 cell loses the ability to enter apoptosis, which reduces its radiosensitivity. This leads to an early form of cell death.

On the whole, healthy and tumor cells die not immediately after irradiation, but after several attempts to enter mitosis. Therefore, although a radiation-induced delay in the cell cycle, most cells resume proliferation, although their death usually occurs at a fission attempt.

2.4 Clonogenic assay

The clonogenic cell is a cell that has retained its reproductive integrity and to proliferate indefinitely to produce a large clone or colony [35]. After irradiation some cells lose their ability to proliferate indefinitely, that is, its reproductive integrity. A total dose of 100 Gy is necessary for destroying cell functions in nonproliferation systems. The mean lethal dose for loss of proliferative capacity is usually less than 2 Gy [36].

2.4.1 *In vitro* Survival Curve

A clonogenic analysis is an *in vitro* cell survival analysis based on the ability of an individual cell to grow into a colony. An important condition of growing cell colonies is a culture medium which provides the necessary nutrients, growth factors, and hormones for cell growth, as well as regulates the pH and the osmotic pressure of the culture [37]. Most mammalian cell lines grow well at pH 7.4 and temperatures between 36°C and 37°C. Changes in atmospheric CO_2 can alter the pH of the medium. Therefore necessary to use exogenous CO_2 and control percent concentration carbon dioxide in the air especially if the cells are cultured in open dishes. For most cell culture experiments is common to use 5-7% CO_2 in the air.

The analysis tests every cell in the population for its ability to undergo division. A clonogenic analysis is a method for determining death reproductive cells after irradiation [38]. Also, this method can be used to determine the effectiveness of other cytotoxic agents. Only a fraction of the selected cells save the ability to produce colonies after irradiation. Figure 2.4 shows a technique to generate a cell culture survival curve.

Cells from the initial culture are irradiated dose from 0 Gy to 8 Gy and are detached into a cell suspension by trypsin. Then cell concentration is counted. After, exact number of cells are seeded into the Petri dishes and incubated for growth for 1-2 weeks until the surviving cells form colonies that can be easily counted. Cells that do not retain proliferative capacity following irradiation may divide a few times, but form only very small colonies. If a colony contains more than 50 cells, it is

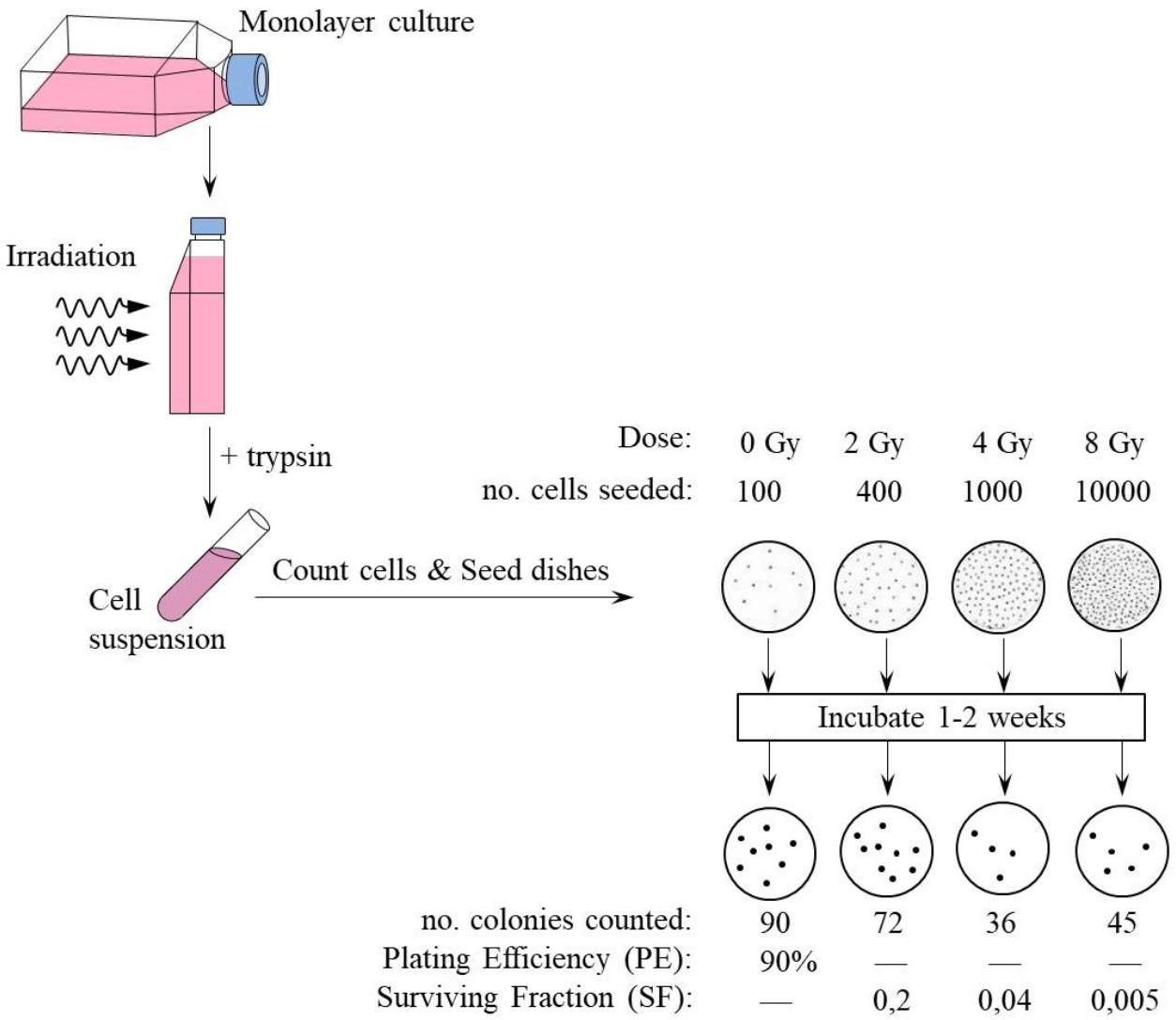

Figure 2.4 – Cell culture technique used to generate a cell survival curve

usually capable of continued growth and can be regarded as having arisen from a surviving cell. These cells can divide repeatedly and form discrete colonies of cells. Always there is a control dish to determine planting efficiency (PE). After that also is determined surviving fraction (SF) of cells.

PE is the percentage of cells that form colonies. In other words, those cells that survive the plating process can be close to 100% in some established cell lines, but 1% or less for fresh human cell explants. After this, the surviving fraction of cells is also determined. PE is then defined as:

$$PE = \frac{\text{Number of colonies counted}}{\text{Number of cells seeded}} \times 100. \tag{2.1}$$

SF is the ratio of passaging colonies to the planted cells, with the correction for the planting efficiency (not all passaging cells grow in the colony even in the absence of radiation). Surviving fraction cell is given by:

$$SF = \frac{PE \text{ of treated sample}}{PE \text{ of control}} \times 100. \tag{2.2}$$

2.4.2 The Shape of the Survival Curve

There are many different models of cell survival in the literature. The most frequent for mammalian cells are the Multi-target model and the Linear-Quadratic model (LQM) [32]. These models shows on the Figure 2.5.

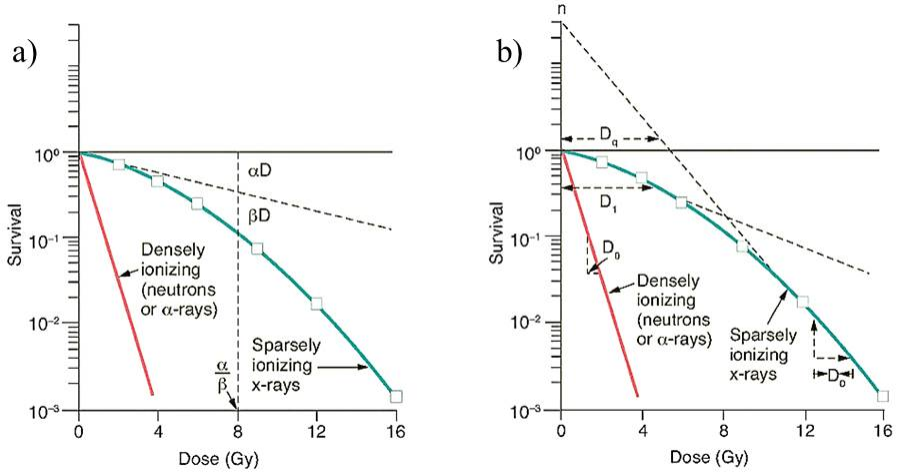

Figure 2.5 – The cell culture technique used to generate a cell survival curve: a) - The Linear-Quadratic model, b) - The Multitarget model, modified from [32]

There are two components of cell killing in LQM. The first component (αD) is proportional to dose or is equal to the probability of hitting a critical target. And the second component (βD^2) is proportional to the square of the dose or is equal to the probability of hitting two critical targets. In LQM the dose is the ratio α/β in which the linear and quadratic components are equal. The formula finds for the cell survival curve in this model is as follows:

$$\mathrm{S} = \exp(-\alpha D - \beta D^2). \tag{2.3}$$

An analysis of survival curves for mammalian cells exposed to radiation by the multitarget model is described by: 1) D_1 is dose to decreased survival to 37% on the initial portion of the curve; 2) D_0 is dose to decrease survival from starting point to 37% of that point on straight line portion; 3) n is an estimate of the width of the shoulder.

Cell survival in this model is described by the expression:

$$S = 1 - \left(1 - \exp\left(-\frac{D}{D_0}\right)\right)^n . \tag{2.4}$$

The parameter n is called the extrapolation number and is determined by the value cut off on the ordinate axis by the straight line segment obtained by extrapolating the rectilinear section to the intersection with this axis.

2.5 Tumors

Tumor cells are cells divide relentlessly and are a part of a benign or malignant tumor. The tumor cell is characterized by the acceleration cell cycle, genome change, invasive grow, high mobility cells, chemotaxis, change on the cell surface, and etc. [39]. Morphologically a tumor cell has a big nucleus, wrong size, and form, nucleoli noticeable, cytoplasm rare and intensely colored or, conversely, pale.

2.5.1 Tumor cell growth

The growth of solid tumors needs own blood supply system. In the absence of blood supply, the tumor can grow into a mass of about 10^6 cells, approximately a sphere with a diameter of 2 mm (see Fig. 2.6). However, most tumors cause the formation of new blood vessels, which penetrate into the tumor and nourish it, this process is called angiogenesis [40]. This process is divided into several stages: the degradation of the basal plate that surrounds the adjacent capillary, the migration of the endothelial cells lining the capillary into the tumor, the division of these endothelial cells, and the formation of a new basement membrane around the recently elongated capillary.

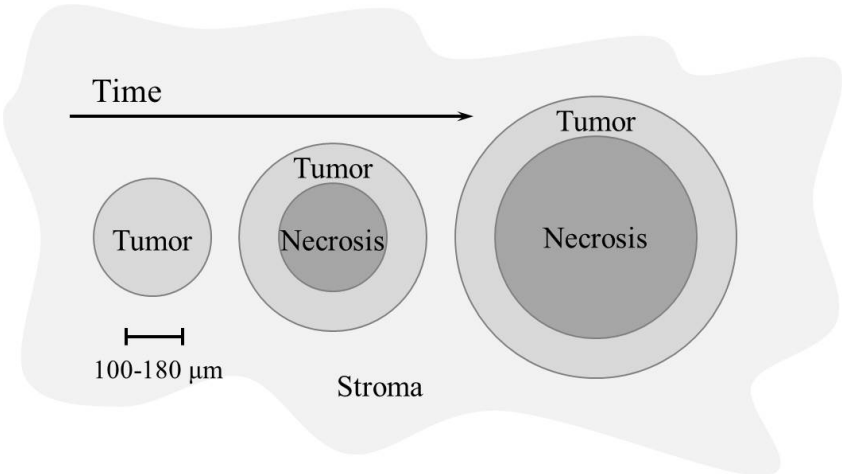

Figure 2.6 – Process of growing tumor cells hypoxia

Tumors consist of parenchyma and stroma. Tumor's parenchyma is the tumor cells formed as a result of the malignant transformation of the ancestor cell and its clonal proliferation. Stromal elements of the tumor are represented by cells and extracellular matrix of connective tissue, vessels, and nerve endings [41].

2.5.2 The 5 R's of radiobiology

Determining the effectiveness of tumor irradiation and including four processes, the name of which begins in English with the letter 'R': Reoxygenation (hours to few days), Repair (few hours), Repopulation (5-7 weeks), Radiosensitivity, and Redistribution in the cell cycle (few hours) [42].

Reoxygenation is a phenomenon by which hypoxia cells become oxygenated after a dose of radiation. Figure 2.7 shows the process of reoxygenation cells during and after radiation. With a single dose in a large dose, the death of oxygenated cells occurs and the proportion of hypoxic cells increases. Surviving cells are closer to a blood supply and reoxygenate.

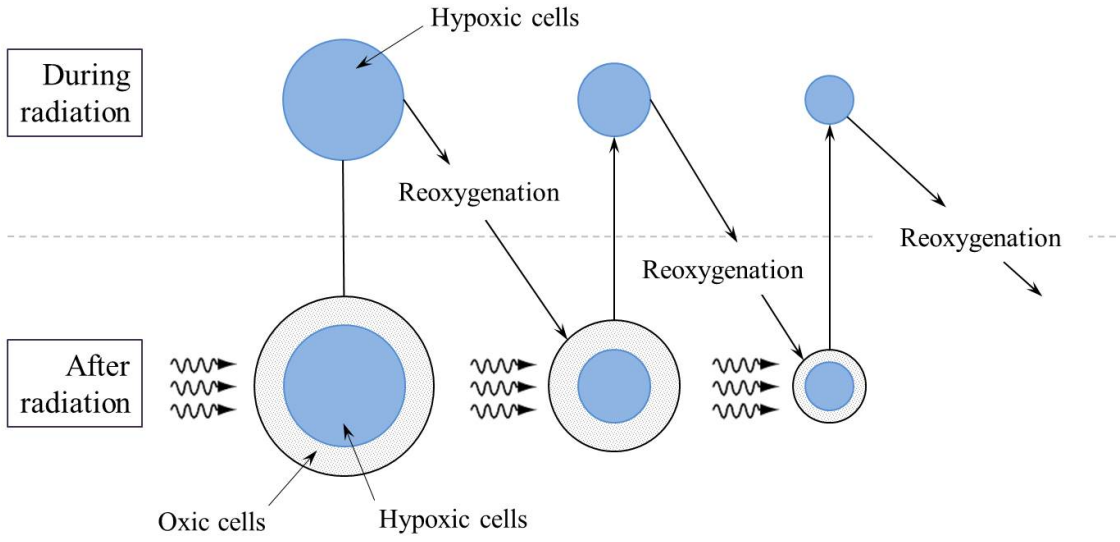

Figure 2.7 – Process of reoxygenation

Repair is a restoration of the integrity of damaged macromolecules. This process is one of the primary reasons why radiotherapy consists of fractions. The damages after irradiation may divide into two groups: non-repairable (lethal) and repairable (sublethal). Using small fractions into radiotherapy, cells can repair sublethal damages, whose number depends on the ability cell to recognize the damage and activate pathways to restoring. Normal tissue cells are able to repair the sublethal damage between fractions.

Repopulation is an increased cell division that occurs in clonogenic tumor cells between two consecutive fractions in radiotherapy [32]. Each fraction of radiation therapy results in a decrease in the number of surviving clonogenic tumor cells. If cells survive after irradiation, then they can repopulate the tumor by increasing their rate of proliferation and/or reduced cell loss. This process leads to an increase in tolerance with increasing overall treatment time. Repopulation is most important in early-responding normal tissues (e.g., skin, intestinal epithelium, bone marrow), or in malignant tumors.

Cellular radiosensitivity is a relative susceptibility of cells, tissues, organs, or organisms to the effects of ionizing radiation [32]. Radiosensitive cells include basal cells of the skin, epithelial stem cells, gametes, and tumor cells from hematological or sex organ origin. Radioresistant cells include myocytes, neurons, and tumor cells, such as melanoma or sarcoma.

During the cell cycle, the radiosensitivity of cells is changed. Cells in S phase (especially in late S phase) are most resistant. In the late G_2 and in M phases, cells are most sensitive to radiation. Radiation causes accumulation cells at specific cell cycle phases. After irradiation, cells in the sensitive phase are killed, and surviving cells become more synchronized. This process is called redistribution. It makes the cell population more sensitive to fractionated treatment as compared with a single dose.

Those Rs are very important in determining the time dose and fractionation of radiotherapy [43]. The optimal combination of the total dose, the dose per fraction, the span of time between fractions, and the overall treatment time must be determined in the treatment plan.

3 Financial management, resource efficiency and resource saving

The purpose of this section discusses the issues of competitiveness, resource efficiency, and resource-saving, as well as financial costs regarding the object of study of Master's thesis. Competitiveness analysis is carried out for this purpose. SWOT-analysis helps to identify strengths, weaknesses, opportunities, and threats associated with the project, and give an idea of working with them in each particular case. For the development of the project requires funds that go to the salaries of project participants and the necessary equipment, a complete list is given in the relevant section. The calculation of the resource efficiency indicator helps to make a final assessment of the technical decision on individual criteria and in general.

3.1 Pre-project analysis

Nowadays the perspective of scientific research is determined not so much by the scale of discovery, which is difficult to estimate at the first stages of the life cycle of a high-tech and resource-efficient product, but by the commercial value of the development. Assessment of the commercial value of the development is a necessary condition when searching for sources of financing for scientific research and commercialization of its results. It is important for developers, who should represent the state and prospects of ongoing scientific research.

It is necessary to understand that the commercial attractiveness of scientific research is determined not only by the excess of technical parameters over previous developments but also by how quickly the developer will be able to find answers to such questions - whether the product will be in demand in the market, what will be its price, what is the budget of the scientific project, how long it will take to enter the market, etc.

The achievement of the goal is ensured by solving the tasks:

– evaluation of the commercial potential and prospects of scientific research;

– identifying possible alternatives to scientific research that meets current resource efficiency and resource conservation requirements;

– research planning;

– resource (resource-saving), financial, budgetary, social, and economic efficiency of research.

3.1.1 Competitiveness analysis of technical solutions

In order to find sources of financing for the project, it is necessary, first, to determine the commercial value of the work. It is important to realistically assess the strengths and weaknesses of competitor designs. Analysis of competitive technical solutions from the standpoint of resource efficiency and resource saving allows us to assess the comparative effectiveness of scientific development and determine the directions for its future improvement.

Today, proton radiation therapy has been performed using X-ray computerized tomography (P_{i1}) and less frequently using images taken on magnetic resonance imaging (P_{i2}). Images obtained by such methods make an error of 2-3% (depending on the type of organ and tissue) in the calculation of relative stopping power of heavy charged particles. This error can be is reduced by performing a CT using protons (P_f). Measurements will be made using an ALPIDE pixel detector, which will reconstruct the proton path at the irradiation volume. This potentially makes this method more convenient and less expensive than most existing analogs.

This analysis was carry out using an evaluation card (see Table 3.1). Two competitive developments were selected for this. The criteria for comparing and evaluating resource efficiency and resource conservation, shown in Table 3.1, were selected based on the selected objects of comparison, taking into account their technical and economic features of development, creation and operation.

Evaluation map analysis presented in Table 3.1. The position of your research and competitors is evaluated for each indicator by you on a five-point scale, where 1 is the weakest position and 5 is the strongest. The weights of indicators determined by you in the amount should be 1.

Analysis of competitive technical solutions is determined by the formula:

$$C = \sum W_i \cdot P_i; \tag{3.1}$$

where C – the competitiveness of research or a competitor;

W_i – criterion weight;

P_i – point of i-th criteria.

This analysis suggests that the study is effective because it provides acceptable quality results. Further investment in this development can be considered reasonable.

Table 3.1 – Evaluation card for comparison of competitive technical solutions

Evaluation criteria	**Criterion weight**	**Points**			**Competitiveness**		
		P_f	P_{i1}	P_{i2}	C_f	C_{i1}	C_{i2}
1	2	3	4	5	6	7	8
Technical criteria for evaluating resource efficiency							
1. Data processing time	0.2	4	4	2	0.8	0.8	0.4
2. Interference immunity	0.06	3	4	1	0.18	0.24	0.06
3. Safety	0.1	4	3	5	0.4	0.3	0.5
4. Resource requirement for memory	0.02	4	4	3	0.08	0.08	0.06
5. Functional capacity (opportunities provided)	0.1	5	4	4	0.5	0.4	0.4
6. Easy to use	0.05	5	5	3	0.25	0.25	0.15
7. Availability of expensive equipment	0.1	4	3	5	0.4	0.3	0.5
Economic criteria for performance evaluation							
1. Development cost	0.1	5	4	3	0.5	0.4	0.3
2. Product competitiveness	0.04	5	4	2	0.2	0.16	0.08
3. Popularity of the method	0.03	3	5	4	0.09	0.15	0.12
4. Interest in scientific development	0.2	5	4	4	1	0.8	0.8
Total	1				4.4	3.88	3.37

3.1.2 SWOT analysis

Complex analysis solution with the greatest competitiveness is carried out with the method of the SWOT analysis: Strengths, Weaknesses, Opportunities and Threats. The analysis has several stages. The first stage consists of describing the strengths and weaknesses of the project, identifying opportunities and threats to the project that have emerged or may appear in its external environment. The second stage consists of identifying the compatibility of the strengths and weaknesses of the project with the external environmental conditions. This compatibility or incompatibility should help to identify what strategic changes are needed.

The SWOT analysis of this research project is presented in Table 3.2.

Table 3.2 – SWOT Matrix

	Strengths: S1: High precision; S2: Reducing the dose load on critical organs; S3: A local increase in tumor energy release; S4: The relevance of work is associated with the modification of ALICE ITS, in checking the performance of chips experiment ALPIDE and constant contact with CERN; S5: The developed algorithms of data processing of tests ALPIDE sensors can be used in further studies.	**Weaknesses:** W1: Necessary to conduct research on several radiation sources; W2: Instability of Accelerators; W3: The high cost of the system under development.

Table 3.2 – SWOT Matrix

Opportunities: O1: Use of financial aid NPI CAS; O2: Possibility to use medical accelerators; O3: Using ALPIDE detectors not only in high energy physics experiments; O4: The development of nuclear medicine will lead to the modernization of standard treatment methods; O5: Applying is written software to a new set of data.	1. Similar experiments with other sources of radiation will lead to an expansion of the consumer market; 2. Reduced dose loads on critical organs and local increases in proton energy production in tumors will reduce interest in standard treatments; 3. The possibility of using the measurement results in further research in various fields of science.	1. As part of the development of nuclear medicine, it is possible to conduct additional research to reduce the uncertainty of the resulting biological effect; 2. Need to model the shape and size of the device in order to be able to be used for medical purposes; 3. Possible reduction of the cost of the system by obtaining financial support, due to the prospect of possible applications.

Table 3.2 – SWOT Matrix

Threats: T1: The existence of a classic method of imaging in medicine; T2: The difficulty of implementation in medical institutions; T3: Mechanical damage to the chip during experiments in the laboratory.	1. The developed algorithm of ALPIDE sensor test data processing is universal, so in a break down of chip is possible to re-examine with new detectors; 2. Increased competitiveness by reducing radiation exposure to the patient; 3. Reduced costs for experimental materials by expanding the scope of applicability; 4. A decrease in the cost of a radiation therapy session will lead to increased competitiveness in the market for these products.	1. The classical method is based on obtaining CT images using photons, which is not accurate when planning proton irradiation; 2. Introduction into medical facilities is complicated by the high cost of the system being developed; 3. Additional research on ALPIDE sensors will increase demand; 4. Writing articles and speaking at conferences will increase the number of stakeholders and raise awareness of the project.

Based on the results of the analysis of this matrix, it can be concluded that the difficulties and challenges that this research project may face in one way or another can be addressed by the existing strengths of the research.

3.2 Project Initiation

The initiation process group consists of processes that are performed to define a new project or a new phase of an existing one. In the initiation processes, the initial purpose and content are determined and the initial financial resources are fixed. The internal and external stakeholders of the project who will interact and influence the overall result of the research project are determined.

3.2.1 Project objectives and results

This section describes the project stakeholders, the hierarchy of project objectives and the criteria for achieving the objectives.

Project stakeholders refer to individuals or organisations that are actively involved in the project or whose interests may be affected positively or negatively during project implementation or completion. Information on project stakeholders shows in Table 3.3.

Table 3.3 – Stakeholders of the project

Project stakeholders	**Stakeholder expectations**
Cancer clinics and dispensaries	A new innovative technique for positioning the particle beam in hadron therapy, easy to use, and inexpensive.
Cancer Research Institutes	Improved proton-computed tomography capabilities and a basis for new research in this field.
Oncology physicians	Implementation of radiation treatment with less dose load on critical organs and structures. Increased control of the tumor and, as a result, reduces the probability of relapse.
Patients with cancer	Reducing the risk of late radiation reactions in the body. Reduced recovery time after radiation treatment, due to reduced radiation load.

Table 3.4 shows information on the hierarchy of project objectives and criteria for achieving the objectives.

Table 3.4 – Purpose and results of the project

Purpose of project	Study of the characteristics of pixel ALPIDE detector used in the ALICE CERN experiment to study the survival of tumor cells.
Expected results of the project	1. Study of detection efficiency of ALPIDE, using PS beam data, taken at large thresholds. 2. Determination of the fake-hit rate of ALPIDE sensors with different settings back-bias voltage at large thresholds. 3. Learning basic methods of work with tumor cell lines. 4. Clonogenic assay of DAOY and ONS-76 tumor cells. 5. Determination of the radiosensitivity of selected cell lines.
Criteria for acceptance of the project result	1. The detection efficiency of ALPIDE sensors is greater than 99%. 2. The fake hit rate of ALPIDE sensors is less than 10^{-6}/pixel/ event. 3. Reduction in survival fraction of DAOY and ONS-76 cells compared to the control group.
Requirements for the project result	1. The research carried out under this project should be completed by June 1, 2020. 2. The results obtained must meet the criteria for accepting the project result. 3. If unsatisfactory results are obtained, additional studies should be conducted using other versions of ALPIDE sensors, cell lines, or radiation sources.

3.2.2 The organizational structure of the project

At this stage of the work, it was necessary to solve the following questions: who will be a member of the working group of the given project, to define the role of each participant in the given project, and also to prescribe the functions carried out by each of the participants and their labor input in the project. This information is presented in tabular form (see Table 3.5).

Table 3.5 – Project working group

№	Participant	Role in the project	Functions	Labor time, hours.
1	Kushpil Svetlana, CSc., Senior Physicist, NPI CAS	Supervisor (1)	She is responsible for the project implementation within the set resource constraints, coordinates the activities of the project participant.	416
2	Ing. Davidkova Marie, CSc.,SS Head of Department of Radiation Dosimetry, NPI CAS	Supervisor (2)	She is responsible for the project implementation within the set resource constraints, coordinates the activities of the project participant.	424
3	Danilova Irina, Master, TPU	Executor	Review of literary sources and technical literature; Experimental measurements of ALPIDE sensors characteristics and processing of received data; Cell irradiation in a cultural vial and processing of data on survival curves; Writing the master's thesis.	784
4	Verigin Dan, Docent, TPU	Consultant	Responsible for assisting the Master in the preparation of documentation and protection of the diploma	80
Total				1704

3.2.3 Limitations and assumptions of the project

Project restrictions are all factors that may serve to limit the degree of freedom of the project team members, as well as "project boundaries" - parameters of the project or its product that will not be implemented within the project. Table 3.6 shows the main limitations of this work.

Table 3.6 – Project limitations

Factors	**Limitations / Assumptions**
1. Project budget	531960 RUB
1.1 Source of financing	NPI CAS funding
2. Project time limits	27.01.2020 – 01.06.2020
2.1 Date of project management plan approval	03.02.2020
2.2 Project completion date	01.06.2020
3. Other restrictions and assumptions	The limit of acceptable effective dose for the personnel of group B is not more than 12.5 mSv per year; Epidemiological situation (Coronovirus)

3.3 Scientific research planning

The Graduate Qualification Study (GQR) is a work of a scientific nature related to scientific inquiry, research to obtain scientific generalizations, to find principles and ways of creating (modernizing) products, it includes:

1. fundamental research carried out with a view to enhancing scientific knowledge, phenomena and patterns of their development without regard to their specific practical application;

2. search research carried out with the purpose of finding ways to use the revealed phenomena and regularities in a concrete field of science and technology for creation of principally new products, materials and technologies;

3. applied research aimed at solving scientific problems, improvement of methods in order to obtain specific results used in experimental and design developments in the creation of scientific and technical.

3.3.1 Structure of work within the scientific research

Planning of the complex of proposed works is carried out in the following order:

- determination of the structure of works within the scientific research;
- definition of participants of each work;
- determination of the duration of work;
- construction of the schedule for scientific research.

To carry out scientific research, a working group is formed, which may include researchers and teachers, engineers, technicians, and laboratory technicians, the number of groups may vary. For each type of work to be carried out, an appropriate position for the executors shall be established. In this section, it is necessary to make a list of stages and works within the framework of scientific research, to make a distribution of performers by type of work. An approximate order of drawing up stages and works, distribution of performers by these types of work is shown in Table 3.7.

The table contains a list of the main stages of the study, the work performed in the study, and the distribution of roles of the work performers.

3.3.2 Development of a schedule for scientific research

During the performance of the thesis, for convenience and clarity, a ribbon schedule of scientific works is constructed in the form of a Gantt chart. The works on the topic are presented as long sections of time, characterized by the start and end dates of these works.

For the convenience of drawing a chart, the duration of each stage of work should be translated from working days to calendar days. To do this, you are should use the following formula:

$$T_{Ki} = T_{Pi} \cdot k_{cal}; \tag{3.2}$$

where T_{Ki} – the duration of the i-th job in calendar days;

T_{Pi} – duration of the i-th job in working days;

k_{cal} – calendar factor.

Table 3.7 – List of stages, works and distribution of performers

Main steps	**№**	**Contents of work**	**Executor's position**
Terms of reference development	1	Drawing up and approving the terms of reference	Supervisors, Consultant, Executor
Determination of research direction and study of technical literature	2	Selection and study of materials on the topic	Executor
	3	Choice of research area	Executor
	4	Calendar work planning on the subject	Supervisors, Executor
Experimental researches	5	Development of experimental setups	Supervisors, Executor
	6	Conducting an experiments	Supervisors, Executor
	7	Analysis and processing of experimentally obtained data	Executor
Synthesis and evaluation of results	8	Comparison of results obtained	Executor
	9	Evaluation of the effectiveness of the results obtained	Supervisors, Executor
Development of technical documentation and design of project	10	Experimental design	Supervisors, Executor
	11	Design selection and calculation	Executor
	12	Evaluation of the effectiveness of proposed methods	Executor
Production of an experimental setup	13	Select samples to conduct experiments	Supervisors, Executor
	14	Determination of characteristics of ALPIDE sensors	Supervisor (1), Executor
	15	Tumor cell irradiation in a cultural bottle	Supervisor (2), Executor
Registration of final qualifying work	16	Drawing up an explanatory note	Executor
	17	Preparing to defend a diploma thesis	Supervisors, Consultant, Executor

The coefficient of calendar is determined by the following formula:

$$k_{cal} = \frac{T_{cal}}{T_{cal} - T_{weekend} - T_{hol}} = \frac{366}{366 - 52 - 14} = 1.22; \quad (3.3)$$

where T_{cal} – calendar day amount per year;

$T_{weekend}$ – a number of days off per year;

T_{hol} – a number of holidays per year.

All calculated values are summarized in Table 3.8.

On the basis of Table 3.8, a time schedule is constructed (see Table 3.9). The schedule is constructed for the maximum duration of the research project by months and decades (10 days) for the period of writing the diploma. At the same time, the works on the schedule should be distinguished by different shading depending on the executors responsible for this or that work (– Supervisors, – Consultant, – Executor).

Table 3.8 – A project timeline in working days

№	Labour intensity			Participants	T_{Pi}	T_{Ki}
	t_{min}	t_{max}	t_{expi}			
1	1	5	3	Supervisors, Consultant, Executor	3	4
2	4	9	6	Executor	6	7
3	2	6	4	Executor	4	5
4	3	9	6	Supervisors, Executor	6	7
5	5	11	7	Supervisors, Executor	7	9
6	6	10	8	Supervisors, Executor	8	10
7	2	7	4	Executor	4	5
8	2	5	4	Executor	4	5
9	2	7	3	Supervisors, Executor	3	4
10	4	9	5	Supervisors, Executor	5	6
11	2	6	4	Executor	4	5
12	3	7	5	Executor	5	6
13	2	8	5	Supervisors, Executor	5	6
14	4	13	8	Supervisor (1), Executor	8	10
15	5	11	9	Supervisor (2), Executor	9	11
16	6	14	10	Executor	10	12
17	4	13	7	Supervisors, Consultant, Executor	7	9
Total	57	150	98		52/53/10/98	65/66/13/121

Table 3.9 – Calendar plan-graph in the form of a Gantt chart

№	T_{Ki}	Duration of the project											
		February			March			April			May		
		1	2	3	1	2	3	1	2	3	1	2	3
1	4												
2	7												
3	5												
4	7												
5	9												
6	10												
7	5												
8	5												
9	4												
10	6												
11	5												
12	6												
13	6												
14	10												
15	11												
16	12												
17	9												

3.4 Scientific and technical research budget

The amount of costs associated with the implementation of this work is the basis for the formation of the project budget. This budget will be presented as the lower limit of project costs when forming a contract with the customer.

To form the final cost value, all calculated costs for individual items related to the manager and the student are summed.

In the process of budgeting, the following grouping of costs by items is used:

– material costs of scientific and technical research;

– costs of special equipment for scientific work (Depreciation of equipment used for design);

– basic salary;

– additional salary;

– labor tax;

– overhead.

3.4.1 Material cost calculation

This item includes the cost of purchasing all types of materials, components, and semi-finished products required to perform work on the subject. Calculation of the cost of material expenses is made at current price lists or contractual prices. The results of this cost item are recorded in Table 3.10.

Table 3.10 – Costs of materials

Name	**Brand, size**	**Quantity**	**Price per unit, rub.**	**Amount, rub.**
Multiwell	TPP	34 pcs.	310	10540
Culture flask	TPP	36 pcs.	104	3744
Glove	Labs	18 pcs.	44	792
Paper	SvetoCopy	1 packet	210	210
Pen	Erich Krause	3 pcs.	15	45
The sum of all for the materials				15331
Transportation and procurement costs				0
Total				15331

3.4.2 Calculation of equipment costs

This article includes all costs associated with the acquisition of special equipment (devices, control and measuring equipment, stands, devices and mechanisms) required to carry out work on the subject of the diploma thesis.

The equipment has not been specifically purchased for this work, therefore it is necessary to calculate depreciation of used equipment. The annual sum of depreciations is calculated as follows:

The depreciation costs of equipment are calculated using a formula:

$$A = \frac{C_{eq} \cdot N_{am}}{100}; \tag{3.4}$$

where A – annual the depreciation;

C_{eq} – cost of equipment in rubles;

N_{am} – norm of the depreciation.

The norm of the depreciation are equal:

$$N_{am} = \frac{100}{T_{lt}}; \tag{3.5}$$

where T_{lt} – equipment lifetime.

In order to find the depreciation charge per day, A divided by the number of days per year (in 2020, 366 days).

Measurements characteristics ALPIDE sensor with using a voltage source lasted about 456 hours (19 days). Tumor cell survival curves of Cell culture hood were measured in 120 hours (5 days), irradiation source Chisostat SO 01 - 12 hours (half day), System QUANTUM and Water Bath-VWB2 2S - 24 hours (1 day), IncuSafe MCO-5M-PE Multigas Incubator - 648 hours (27 days). Also, in our work was used cell analyzer Muse and cell counter Scepter which measured cells summarily of about 48 hours (2 days).

Accordingly, the total cost of the equipment used in this diploma thesis is presented in Table 3.11.

Thus, the cost of depreciation and electrical equipment in the performance of this diploma work amounted to 9215.88 RUB.

Table 3.11 – Calculation of the budget of expenses for equipment for scientific works

Name	**Quantity**	**Price per unit, thous. rub.**	**Service life, year**	**The depreciation, rub.**
ALPIDE sensor	3 pcs.	68.4	10	355.08
Voltage source HAMEG HMP2030	1 pcs.	161	8	1044.75
Cell culture hood	1 pcs.	323.6	10	442.08
γ-irradiation source Chisostat SO 01	1 pcs.	25000	30	1138.43
System QUANTUM	1 pcs.	746	5	407.65
Cell counters	2 pcs.	1547	8	1056.69
IncuSafe MCO-5M-PE Multigas Incubator	1 pcs.	643	10	4743.44
Water Bath-VWB2 2S	1 pcs.	50.8	5	27.76
Total				9215.88

3.4.3 Basic and additional salary

This point includes the amount of payments stipulated by the legislation on labor, for example, payment of regular and additional holidays; payment of time associated with state and public duties; payment for work experience, etc.

This point includes the basic salary of participants directly involved in the implementation of work on this research. The value of salary costs is determined based on the labor intensity of the work performed and the current salary system. The basic salary (S_{base}) is calculated according to the following formula:

$$S_{base} = S_{day} \cdot T_w, \tag{3.6}$$

where S_{day} – an average daily salary of an participant, rub;

T_w – a duration of the work performed by the scientific and technical worker, working days.

The average daily salary (S_{day}) is calculated by the formula:

$$S_{day} = \frac{S_{month} \cdot M}{F_V}; \tag{3.7}$$

where S_{month} – a monthly salary of an participant, rub.;

M – a average daily salary of an participant, rub.;

F_V – valid annual fund of working time of scientific and technical personnel (247 days).

The number of months of work without vacation during the year is calculated as follows: at 24 working days of vacation M = 11.2 months, 5-day week, and at 48 working days of vacation M = 10.4 months, 6-day week. Table 3.12 calculates the actual annual fund of scientific and technical staff.

Table 3.12 – The valid annual fund of working time

Working time indicators	**Supervisors**	**Student**	**Consultant**
Calendar number of days	366	366	366
The number of non-working days			
– weekend	52	52	52
– holidays	14	14	14
Loss of working time			
– vacation	48	48	48
– sick absence	0	0	0
The valid annual fund of working time	252	252	252

Monthly salary is calculated by formula:

$$S_{month} = S_{base} \cdot (k_{premium} + k_{bonus}) \cdot k_{reg}; \quad (3.8)$$

where $k_{premium}$ – premium rate;;

k_{reg} – bonus rate;

k_{bonus} – regional rate.

Table 3.13 below calculates the base salary of the supervisors, the consultant, and the executor.

Additional salary include the amount of payments stipulated by the legislation on labor, for example, payment of regular and additional holidays; payment of time associated with state and public duties; payment for work experience, etc.

Additional salaries (S_{add}) are calculated on the basis of 10-15% of the base salary of workers:

$$S_{add} = S_{base} \cdot k_{extra}; \quad (3.9)$$

Table 3.13 – Calculation of the basic salary

Performers	**Salary, rub.**	**k$_{reg}$**	**S$_{month}$, rub.**	**S$_{day}$, rub.**	**T$_{w}$, work-days**	**S$_{base}$, rub.**
Supervisor 1	52100	1	52100	2315.56	52	120409.12
Supervisor 2	63500	1	63500	2822.22	53	149577.66
Consultant	22480	1.3	29224	1206.07	10	12060.70
Executor	12664	1.3	16463.2	678.43	98	66486.14

where k$_{extra}$ – additional salary coefficient (10%);

S$_{base}$ – base salary, rubles.

k$_{bonus}$ – regional rate.

The additional salaries are equal to:

1) Supervisor 1:

$$S_{add} = S_{base} \cdot k_{extra} = 120409.12 \cdot 0.1 = 12040.91 \text{ RUB}; \quad (3.10)$$

2) Supervisor 2:

$$S_{add} = S_{base} \cdot k_{extra} = 149577.66 \cdot 0.1 = 14957.77 \text{ RUB}; \quad (3.11)$$

3) Consultant:

$$S_{add} = S_{base} \cdot k_{extra} = 12060.70 \cdot 0.1 = 1206.07 \text{ RUB}; \quad (3.12)$$

4) Executor:

$$S_{add} = S_{base} \cdot k_{extra} = 66486.14 \cdot 0.1 = 6648.61 \text{ RUB}. \quad (3.13)$$

3.4.4 Labor tax

Tax to extra-budgetary funds is compulsory according to the norms established by the legislation of the Russian Federation to the state social insurance (SIF), pension fund (PF), and medical insurance (FCMIF) from the costs of workers.

Payment to extra-budgetary funds is determined of the formula:

$$P_{social} = k_b \cdot S_{base} + S_{add}; \quad (3.14)$$

where k_b – coefficient of deductions for labor tax.

In accordance with the Federal law of July 24, 2009 No. 212-FL, the amount of insurance contributions is set at 30%. Institutions conducting educational and scientific activities have rate - 27.1%. In the Czech Republic, the amount of insurance contributions for scientific is set at 15%.

The labor tax is presented in Table 3.14.

Table 3.14 – Labor tax

Performers	Supervisor 1	Supervisor 2	Consultant	Executor
Coefficient of deductions	0.15		0.271	
Salary, rub.	132450.03	164535.43	13266.77	73134.75
Labor tax, rub.	19867.50	24680.31	3595.29	19819.52
Total, rub.	67962.62			

3.4.5 Overhead costs

Overhead costs include other management and maintenance costs that can be allocated directly to the project. In addition, this includes expenses for the maintenance, operation and repair of equipment, production tools and equipment, buildings, structures, etc.

The work was performed using a stationary computer with an average power of 550 W (0.55 kW). If we assume that all the work was done on it, then everything was spent:

$$E = P \cdot F_{sum} = 0.55 \cdot 292 = 160.6 \text{ kW·h}; \quad (3.15)$$

where P – equipment power is measured in kW;

F_{sum} – time of use of the equipment in hours.

Electricity costs are calculated using a formula:

$$C_{el} = T_{el} \cdot E = 10.18 \cdot 160.6 = 1634.91 \text{ RUB}; \quad (3.16)$$

where T_{el} – tariff for industrial electricity (10.18 rubles per 1 kW·h).

When measuring the characteristics of the ALPIDE sensors, a voltage source HAMEG HMP2030 of 0.18 kW was used. Therefore, the energy costs are equal:

$$C_{el} = T_{el} \cdot P \cdot F_{sum} = 10.18 \cdot 0.18 \cdot 64 = 117.27 \text{ RUB.} \quad (3.17)$$

For incubate cells was used IncuSafe MCO-5M-PE Multigas incubator with an average power of 0.23 kW. The energy costs using an incubator are equal:

$$C_{el} = T_{el} \cdot P \cdot F_{sum} = 10.18 \cdot 0.23 \cdot 648 = 1517.23 \text{ RUB.} \quad (3.18)$$

Chisostat SO 01 (Nuclear Physics Institute of the CAS, Czech Republic) accelerator with an average power of 50 kW were used in the experiments on cell irradiation. The electrical power consumption of the Accelerators is calculated by the formula:

$$C_{el} = T_{el} \cdot P \cdot F_{sum} = 10.18 \cdot 50 \cdot 16 = 8144 \text{ RUB.} \quad (3.19)$$

A month of Internet use costs 900 rubles, in this work Internet was used for 4 months, so the cost of the Internet was 3600 rubles.

The overhead costs in this work amounted to 15013.41 RUB.

3.4.6 Other direct costs

The diploma work was done abroad, so the student was paid a daily subsistence allowance, which can be attributed to direct costs. The student was paid 50 rubles per day. The term of stay abroad is 104 days. Thus, the student was paid 6050 roubles. In addition, TPU allocated money to pay for travel to the place of practice, which is equal to 35000 rubles.

3.5 Formation of budget costs

The calculated amount of research and development work costs is the basis for forming the project cost budget. The definition of the research project cost budget for each option is given in Table 3.15.

Table 3.15 – The budget for scientific and technical research

Name of expenditure items	**Cost, rubles**
Material costs	15331
Costs of special equipment	9215.88
Basic salary	348533.62
Additional salary	34853.36
Labor tax	67962.62
Overhead	15013.41
Other direct costs	41050
Total planned cost	531959.89

3.6 Project risk register

Identified project risks include possible undefined events that may occur in the project and cause unintended consequences. Information on this section is presented in Table 3.16.

Table 3.16 – Register of risks

№	Risk	Potential effects	Probability (1-5)	Effect of risk (1-5)	Level of risk	Ways to mitigate risk	Conditions of occurrence
1	Break down of accelerators	Impossibility of conducting experiment irradiation of cells	3	5	High	Implementation of works according to the instruction	Improper handling of the irradiation system
2	Mechanical damage to the chip during laboratory experiments	Internal influence	3	5	High	Parallel study of multiple chips	Careless in removing the chip from the reading board
3	Break down of additional equipment	Impossibility of conducting an experiment to determine the characteristics of ALPIDE sensors and to obtain tumor cell survival curves	2	4	Med	Use of equipment according to the technical documentation	Careless handling of auxiliary equipment
4	Mismatch of data received with expected results	Failure to meet project objectives	3	2	Low	Better analysis of literary sources	Error in predicting expected results

3.7 Determining research resource efficiency

Determination of efficiency is based on the calculation of the integral indicator of scientific research efficiency. Its location is related to the definition of two weighted average values: financial efficiency and resource efficiency.

The integrated indicator of resource efficiency of variants of execution of the object of research can be defined as follows:

$$I_{pi} = \sum a_i \cdot b_i; \tag{3.20}$$

where I_{pi} – integral resource efficiency index for the i-th variant of development execution;

a_i – development weighting factor;

b_i^a, b_i^b – an evaluation of the i-th variant of the development's execution is set by the expert by the selected evaluation scale.

The calculation of the integral resource efficiency index of this study is presented in the form of Table 3.17.

Table 3.17 – Comparative assessment of the characteristics of the project implementation options

Criteria	**Parameter weighting factor**	**Current project**	**Analog 1**	**Analog 2**
Helps to increase user productivity	0.1	5	4	2
Convenient operation (meets customer requirements)	0.15	4	5	3
Interference immunity	0.15	4	4	2
Energy saving	0.20	5	4	3
Reliability	0.25	4	4	4
Material capacity	0.15	4	3	4
Total	1	4.3	4	3.15

An integrated financial indicator for development is defined as:

$$I_f^p = \frac{F_i}{F_{max}}; \tag{3.21}$$

where F_i – a cost of the i-th option;

F_{max} – a maximum cost of execution of the scientific and technical research (including analogues).

$$I_f^p = \frac{F_p}{F_{max}} = \frac{531960}{554200} = 0.96; \tag{3.22}$$

$$I_f^{a1} = \frac{F_{a1}}{F_{max}} = \frac{543100}{554200} = 0.98; \tag{3.23}$$

$$I_f^{a2} = \frac{F_{a2}}{F_{max}} = \frac{554200}{554200} = 1. \tag{3.24}$$

The integrated index of efficiency of development variants (I_{fin}^p) and analogues (I_{fin}^a) is determined on the basis of the integrated index of resource efficiency and integrated financial index by formulas:

$$I_{fin}^p = \frac{I_m^p}{I_f^p} = \frac{4.3}{0.96} = 4.43; \tag{3.25}$$

$$I_{fin}^{a1} = \frac{I_m^{a1}}{I_f^{a1}} = \frac{4}{0.98} = 4.06; \tag{3.26}$$

$$I_{fin}^{a2} = \frac{I_m^{a2}}{I_f^{a2}} = \frac{3.15}{1} = 3.15. \tag{3.27}$$

Comparison of the integral performance indicator of the current project and its analogues will allow to determine the comparative efficiency of the project (see Table 3.18).

Comparative effectiveness of the project:

$$C_{Eff} = \frac{I_{fin}^p}{I_m^p}. \tag{3.28}$$

Based on the calculation of the integral indicator with the definition of two weighted average values: financial efficiency and resource efficiency of scientific

Table 3.18 – Comparative development efficiency

Indicators	**Current project**	**Analog 1**	**Analog 2**
Integral resource efficiency indicator	4.3	4	3.15
Integral performance indicator for variants	4.43	4.06	3.15
Comparative performance of the variants	1.04	1.01	1

research, we can conclude that the comparative assessment of the current project is higher than other analogs.

Thus, in this section was developed stages for design and creation competitive developed that meet the requirements in the field of resource efficiency and resource-saving.

3.8 Conclusions under financial management

These stages include:

– development of a common economic project idea, the formation of a project concept;

– organization of work on a research project;

– identification of possible research alternatives;

– research planning;

– assessing the commercial potential and prospects of scientific research from the standpoint of resource efficiency and resource-saving;

– determination of resource (resource-saving), financial, budget, social, and economic efficiency of the project.

In the course of performing the economic part of the diploma work, calculations were made of the planned cost of research and the time spent.

The total cost of work is 531959.89 RUB, the main component of which is the cost of wages to perform scientific and technical research. The time required to perform the work was 121 calendar days.

4 Social responsibility

4.1 Introduction

Research on the topic diploma thesis seek to study the characteristics of the ALPIDE which is currently applied in the ALICE experiment at CERN, and determination of survival curves chosen cell lines of brain tumor. These research aim at developing an experimental setup, where ALPIDE detectors can be used for radiobiology research, for example, for precise positioning of a particle beam in hadron therapy. In this way, the application area result of the diploma work includes fundamental and applied research in the physics and medical fields.

The research work was performed in the Nuclear Physics Institute of the Czech Academy of Sciences (NPI CAS, Czech Republic). The main characteristics of ALPIDE sensors were determined from the Řež research centre. The irradiation and seeding cells were carried out in the department of radiation dosimetry in Prague.

Potential users of the project are cancer clinics and dispensaries, cancer research institutes, oncology physicians, and patients with cancer. A new method positioning of a particle beam in hadron therapy will improve proton-computed tomography capabilities and a basis for new research in this field. Also, it will allow as to implementation of radiation treatment with less dose load on critical organs and structures and increase control of the tumor. In addition, the results of this study will allow daily dosimetric monitoring before irradiating patients with a beam of charged particles.

4.2 Legal and organizational items in providing safety

Nowadays one of the main way to radical improvement of all prophylactic work referred to reduce Total Incidents Rate and occupational morbidity is the widespread implementation of an integrated Occupational Safety and Health management system. That means combining isolated activities into a single system of targeted actions at all levels and stages of the production process.

Occupational safety is a system of legislative, socio-economic, organizational, technological, hygienic and therapeutic and prophylactic measures and tools that ensure the safety, preservation of health and human performance in the work process [65].

According to the Labor Code of the Russian Federation, every employee has the right:

– to have a workplace that meets Occupational safety requirements;

– to have a compulsory social insurance against accidents at manufacturing and occupational diseases;

– to receive reliable information from the employer, relevant government bodies and public organizations on conditions and Occupational safety at the workplace, about the existing risk of damage to health, as well as measures to protect against harmful and (or) hazardous factors;

– to refuse carrying out work in case of danger to his life and health due to violation of Occupational safety requirements;

– be provided with personal and collective protective equipment in compliance with Occupational safety requirements at the expense of the employer;

– for training in safe work methods and techniques at the expense of the employer;

– for personal participation or participation through their representatives in consideration of issues related to ensuring safe working conditions in his workplace, and in the investigation of the accident with him at work or occupational disease;

– for extraordinary medical examination in accordance with medical recommendations with preservation of his place of work (position) and secondary earnings during the passage of the specified medical examination;

– for warranties and compensation established in accordance with this Code, collective agreement, agreement, local regulatory an act, an employment contract, if he is engaged in work with harmful and (or) hazardous working conditions.

The labor code of the Russian Federation states that normal working hours may not exceed 40 hours per week, The employer must keep track of the time worked by each employee.

Rules for labor protection and safety measures are introduced in order to prevent accidents, ensure safe working conditions for workers and are mandatory for workers, managers, engineers and technicians.

4.3 Basic ergonomic requirements for the correct location and arrangement of researcher's workplace

The workplace when working with a PC should be at least 6 square meters. The legroom should correspond to the following parameters: the legroom height is at least 600 mm, the seat distance to the lower edge of the working surface is at least

150 mm, and the seat height is 420 mm. It is worth noting that the height of the table should depend on the growth of the operator.

The following requirements are also provided for the organization of the workplace of the PC user: The design of the working chair should ensure the maintenance of a rational working posture while working on the PC and allow the posture to be changed in order to reduce the static tension of the neck and shoulder muscles and back to prevent the development of fatigue.

The type of working chair should be selected taking into account the growth of the user, the nature and duration of work with the PC. The working chair should be lifting and swivel, adjustable in height and angle of inclination of the seat and back, as well as the distance of the back from the front edge of the seat, while the adjustment of each parameter should be independent, easy to carry out and have a secure fit.

4.4 Occupational safety

A dangerous factor or industrial hazard is a factor whose impact under certain conditions leads to trauma or other sudden, severe deterioration of health of the worker [65].

A harmful factor or industrial health hazard is a factor, the effect of which on a worker under certain conditions leads to a disease or a decrease in working capacity.

4.4.1 Analysis of harmful and dangerous factors that can create object of investigation

The object of investigation is "Application of detector technologies for heavy-ion nuclear experiment and for irradiation of brain tumor cells". Therefore objects of the investigation itself cannot cause harmful and dangerous factors.

4.4.2 Analysis of harmful and dangerous factors that can arise at workplace during investigation

The working conditions in the workplace are characterized by the presence of hazardous and harmful factors, which are classified by groups of elements: physical, chemical, biological, psychophysiological. The main elements of the production process that form dangerous and harmful factors are presented in Table 4.1.

The following factors effect on person working on a computer:

– physical:

◦ temperature and humidity;

Table 4.1 – Possible hazardous and harmful factors

Factors (GOST 12.0.003-2015)	Work stages			Legal documents
	Devel-opment	Manu-facture	Exploi-tation	
1. Deviation of microclimate indicators	+	+	+	Sanitary rules 2.2.2 / 2.4.1340–03. Sanitary and epidemiological rules and regulations "Hygienic requirements for personal electronic computers and work organization." Sanitary rules 2.2.1 / 2.1.1.1278–03. Hygienic requirements for natural, artificial and combined lighting of residential and public buildings. Sanitary rules 2.2.4 / 2.1.8.562–96. Noise at workplaces, in premises of residential, public buildings and in the construction area. Sanitary rules 2.2.4.548–96. Hygienic requirements for the microclimate of industrial premises. Sanitary rules GOST 12.1.038-82 SSBT. Electrical safety. Maximum permissible levels of touch voltages and currents. Sanitary Rules 2.6.1. 2523 -0 9. Radiation Safety Standards (NRB-99/2009).
2. Excessive noise		+	+	
3. Increased level of elec-tromagnetic radiation	+	+	+	
4. Insufficient illumination of the working area		+	+	
5. Abnormally high voltage value in the circuit, the closure which may occur through the human body	+	+	+	
6. Increased levels of ionizing radiation	+	+	+	

- noise;
- static electricity;
- electromagnetic field of low purity;
- illumination;
- presence of radiation;

– psychophysiological:

- psychophysiological dangerous and harmful factors are divided into: physical

overload (static, dynamic) and mental stress (mental overstrain, monotony of work, emotional overload).

Deviation of microclimate indicators

The air of the working area (microclimate) is determined by the following parameters: temperature, relative humidity, air speed. The optimum and permissible values of the microclimate characteristics are established in accordance with [66] and are given in Table 4.2.

Table 4.2 – Optimal and permissible parameters of the microclimate

Period of the year	Temperature,°C	Relative humidity,%	Speed of air movement, m/s
Cold and changing of seasons	23-25	40-60	0.1
Warm	23-25	40	0.1

Excessive noise

Noise and vibration worsen working conditions, have a harmful effect on the human body, namely, the organs of hearing and the whole body through the central nervous system. It result in weakened attention, deteriorated memory, decreased response, and increased number of errors in work. Noise can be generated by operating equipment, air conditioning units, daylight illuminating devices, as well as spread from the outside. When working on a PC, the noise level in the workplace should not exceed 50 dB.

Increased level of electromagnetic radiation

The screen and system blocks produce electromagnetic radiation. Its main part comes from the system unit and the video cable. According to [66], the intensity of the electromagnetic field at a distance of 50 cm around the screen along the electrical component should be no more than:

– in the frequency range 5-2000 Hz – 25 V/m;
– in the frequency range 2-400 kHz – 2.5 V/m.

The magnetic flux density should be no more than:

– in the frequency range 5-2000 Hz – 250 nT;
– in the frequency range 2-400 kHz – 25 nT.

Abnormally high voltage value in the circuit

Depending on the conditions in the room, the risk of electric shock to a person increases or decreases. Do not operate the electronic device in conditions of high humidity (relative air humidity exceeds 75% for a long time), high temperature (more than 35°C), the presence of conductive dust, conductive floors and the possibility of simultaneous contact with metal components connected to the ground and the metal casing of electrical equipment (see Fig. 4.3). The operator works with electrical devices: a computer (display, system unit, etc.) and peripheral devices. There is a risk of electric shock in the following cases:

– with direct contact with current-carrying parts during computer repair;
– when touched by non-live parts that are under voltage (in case of violation of insulation of current-carrying parts of the computer);
– when touched with the floor, walls that are under voltage;
– short-circuited in high-voltage units: power supply and display unit.

Table 4.3 – Upper limits for values of contact current and voltage

	Voltage, V	Current, mA
Alternate, 50 Hz	2	0.3
Alternate, 400 Hz	3	0.4
Direct	8	1.0

Insufficient illumination of the working area

Light sources can be both natural and artificial. The natural source of the light in the room is the sun, artificial light are lamps. With long work in low illumination conditions and in violation of other parameters of the illumination, visual perception decreases, myopia, eye disease develops, and headaches appear.

According to the standard, the illumination on the table surface in the area of the working document should be 300-500 lux. Lighting should not create glare on the surface of the monitor. Illumination of the monitor surface should not be more than 300 lux.

The brightness of the lamps of common light in the area with radiation angles from 50 to 90° should be no more than 200 cd/m, the protective angle of the lamps should be at least 40°. The safety factor for lamps of common light should be assumed to be 1.4. The ripple coefficient should not exceed 5%.

Increased levels of ionizing radiation

Ionizing radiation is radiation that could ionize molecules and atoms. This effect is widely used in energetics and industry. However, there is a health hazard. In living tissue, this radiation could damage cells that result in two types of effects. Deterministic effects (harmful tissue reactions) due to exposure with high doses and stochastic effects due to DNA destruction and mutations (for example, induction of cancer).

To provide radiation safety with using sources of ionizing radiation one must use the next principles:

a) keep individual radiation doses from all radiation sources not higher than permissible exposure;

b) forbid all activity by using radiation sources if profit is low then the risk of possible hazard;

c) keep individual radiation doses from all radiation sources as low as possible.

There are two groups of people related to work with radiation: personnel, who work with ionizing radiation, and public. Table 4.4 shows the recommended dose limits in planned exposure situations.

Effective dose for personnel must not exceed 1000 mSv for 50 years of working activity, and for population must not exceed 70 mSv for 70 years of life.

In addition, for women from personnel of age below 45 years there is limit of 1 mSv per month of equivalent dose on lower abdomen. During gestation and breast feeding women must not work with radiation sources.

For students older than 16, who uses radiation sources in study process or who is in rooms with increased level of ionizing radiation, dose limits are quarter part of dose limits of personnel.

Table 4.4 – Dose limited for occupations and public

Type of limit	Ocupational, mSv in a year	Public, mSv in a year
Effective dose	20, averaged over 5 years, with no more then 50 mSv in any one year	1 (exceptionally, a higher value of effective dose could be allowed in a year provided that the average over 5 years does not exceed 1 mSv in a year)
Equivalent dose:		
to a lens of the eye	150	15
to skin	500	50
to hands and feet	500	50

4.4.3 Justification of measures to reduce the levels of exposure to hazardous and harmful factors on the researcher

Deviation of microclimate indicators

The measures for improving the air environment in the production room include: the correct organization of ventilation and air conditioning, heating of room. Ventilation can be realized naturally and mechanically. In the room, the following volumes of outside air must be delivered:

– at least 30 m^3 per hour per person for the volume of the room up to 20 m^3 per person;

– natural ventilation is allowed for the volume of the room more than 40 m^3 per person and if there is no emission of harmful substances.

The heating system must provide sufficient, constant and uniform heating of the air. Water heating should be used in rooms with increased requirements for clean air.

The parameters of the microclimate in the laboratory regulated by the central heating system, have the following values: humidity 40%, air speed 0,1 m/s, summer temperature 20-25°C, in winter 13-15°C. Natural ventilation is provided in the laboratory. Air enters and leaves through the cracks, windows, doors. The main disadvantage of such ventilation is that the fresh air enters the room without preliminary cleaning and heating.

Excessive noise

In research audiences, there are various kinds of noises that are generated by both internal and external noise sources. The internal sources of noise are working equipment, personal computer, printer, ventilation system, as well as computer equipment of other engineers in the audience. If the maximum permissible conditions are exceeded, it is sufficient to use sound-absorbing materials in the room (sound-absorbing wall and ceiling cladding, window curtains). To reduce the noise penetrating outside the premises, install seals around the perimeter of the doors and windows.

Increased level of electromagnetic radiation

There are the following ways to protect against EMF:

– increase the distance from the source (the screen should be at least 50 cm from the user);

– the use of pre-screen filters, special screens and other personal protective equipment.

When working with a computer, the ionizing radiation source is a display. Under the influence of ionizing radiation in the body, there may be a violation of normal blood coagulability, an increase in the fragility of blood vessels, a decrease in immunity, etc. The dose of irradiation at a distance of 20 cm to the display is 50 μR/h . According to the norms [66], the design of the computer should provide the power of the exposure dose of x-rays at any point at a distance of 0.05 m from the screen no more than 100 μR/h. Fatigue of the organs of vision can be associated with both insufficient illumination and excessive illumination, as well as with the wrong direction of light.

Increased levels of ionizing radiation

In case of radiation accident, responsible personnel must take all measures to restore control of radiation sources and reduce to minimum radiation doses, number of irradiated persons, radioactive pollution of the environment, economic and social losses caused with radioactive pollution.

Radiation control is a main part of radiation safety and radiation protection. It is aimed at not exceeding the established basic dose limits and permissible levels of radiation, obtaining the necessary information to optimize protection and making

decisions about interference in the case of radiation accidents, contamination of the environment and buildings with radionuclides.

The radiation control is control of:

– Radiation characteristics of radiation sources, pollution in air, liquid and solid wastes.

– Radiation factors developed with technological processes in working places and environment.

– Radiation factors of contaminated environment.

– Irradiation dose levels of personnel and population.

The main controlled parameters are:

– annual effective and equivalent doses;

– intake and body content of radionuclides;

– volume or specific activity of radionuclides in air, water, food products, building materials and etc.;

– radioactive contamination of skin, clothes, footwear, working places and etc.;

– dose and power of external irradiation;

– particles and photons flux density.

Radiation protection office establish control levels of all controlled parameters in according to not exceed dose limits and keep dose levels as low as possible. In case of exceeding control levels radiation protection officers start investigation of exceed causes and take actions to eliminate this exceeding.

During planning and implementation of radiation safety precautions, taking any actions about radiation safety and analysis of effectiveness of mentioned action and precautions one must value radiation safety with next factors:

– characteristics of radioactive contamination of the environment;

– probability of radiation accidents and scale of accidents;

– degree of readiness to effective elimination of radiation accidents and its aftermathches;

– number of persons irradiated with doses higher than controlled limits of doses;

– analysis of actions for providing radiation safety, meeting requirements, rules, standards of radiation safety;

– analysis of irradiation doses obtained by groups of population from all ionizing radiation sources.

Abnormally high voltage value in the circuit

Measures to ensure the electrical safety of electrical installations:

– disconnection of voltage from live parts, on which or near to which work will be carried out, and taking measures to ensure the impossibility of applying voltage to the workplace;

– posting of posters indicating the place of work;

– electrical grounding of the housings of all installations through a neutral wire;

– coating of metal surfaces of tools with reliable insulation;

– inaccessibility of current-carrying parts of equipment (the conclusion in the case of electroporating elements, the conclusion in the body of current-carrying parts) [67].

Insufficient illumination of the working area

Desktops should be placed in such a way that the monitors are oriented sideways to the light openings, so that natural light falls mainly on the left.

Also, as a means of protection to minimize the impact of the factor, local lighting should be installed due to insufficient lighting, window openings should be equipped with adjustable devices such as blinds, curtains, external visors, etc.

4.5 Ecological safety

4.5.1 Analysis of the impact of the research object on the environment

Sources of ionizing radiation used in medicine could be divided into two groups: radioactive substances and radiation generators. The difference is that radiation generators like accelerators and x-ray tubes emit ionizing radiation only when they are turned on. In ordinary work with necessary safety precautions, there are insignificant impact of using sources of ionizing radiation on environment. The immediate effect of ionizing radiation is ionization of air in room, but after a specified time the ionization disappears. The danger of using radioactive materials could occur only in accidents with stealing and loosing these materials due to high toxicity.

The using of radio waves gives to industry great possibilities and finds a wide range of applications. The most known are communications. As energy of radio waves is dissipated with distance effect of irradiation by radio waves was thoroughly study by scientist. There are a series of standards and legal notes to limit power of radio

waves sources due harmful effect on biological tissues. The impact on hydrosphere, atmosphere and lithosphere is a question to debate because of a small number of investigations in this field. Main impact could be only from powerful sources like radiolocation stations.

Mass production of plastic began only 60 years ago. During this time, its output increased 180 times. Recycling takes only 9% of the plastic. Another 12% is burned, and 79% goes to landfills and the environment. As a result, there is pollution by debris of the lithosphere and hydrosphere. Due to the circulation of currents in the oceans, "garbage islands" are formed. At the same time, plastic not only drifts on the surface, but sinks to the bottom.

In addition to large plastic wastes, there are also wastes due to microplastics. According to international classification, any plastic particle less than 5 mm in length falls into this category. Microplastic is divided into primary and secondary. Primary is most often fibers added to synthetic clothing. When rubbing on a surface or washing, thousands of fibers are separated from it, “hanging” in the air or washed off into the sewer. The second most important source is particles of artificial rubber from tires, which each car leaves 20 grams per 100 km of track. In addition, cars erase markings from roads, which also contain plastic. Secondary microplastic is added to this - “large” debris, broken up into small pieces. As you know, plastic has decomposed for centuries. But it can quickly degrade to tiny parts, while maintaining its molecular structure. The solutions to the plastic problem today are legislative restrictions on the use of plastic and disposable products, sorting and processing of waste. But they are still not effective solutions to the problem.

4.5.2 Analysis of the environmental impact of the research process

Process of investigation itself in the thesis do not have essential effect on environment. One of hazardous waste is fluorescent lamps. Mercury in fluorescent lamps is a hazardous substance and its improper disposal greatly poisons the environment.

Outdated devices goes to an enterprise that has the right to process wastes. It is possible to isolate precious metals with a purity in the range of 99.95–99.99% from computer components. A closed production cycle consists of the following stages: primary sorting of equipment; the allocation of precious, ferrous and non-ferrous metals and other materials; melting; refining and processing of metals. Thus, there is an effective disposal of computer devices.

4.5.3 Justification of environmental protection measures

Pollution reduction is possible due to the improvement of devices that produces electricity, the use of more economical and efficient technologies, the use of new methods for generating electricity and the introduction of modern methods and methods for cleaning and neutralizing industrial waste. In addition, this problem should be solved by efficient and economical use of electricity by consumers themselves. This is the use of more economical devices, as well as efficient regimes of these devices. This also includes compliance with production discipline in the framework of the proper use of electricity.

Simple conclusion is that it is necessary to strive to reduce energy consumption, to develop and implement systems with low energy consumption. In modern computers, modes with reduced power consumption during long-term idle are widely used.

4.6 Safety in emergency

4.6.1 Analysis of probable emergencies that may occur at the workplace during research

The fire is the most probable emergency in our life. Possible causes of fire:

– malfunction of current-carrying parts of installations;
– work with open electrical equipment;
– short circuits in the power supply;
– non-compliance with fire safety regulations;
– presence of combustible components: documents, doors, tables, cable insulation, etc.

Activities on fire prevention are divided into: organizational, technical, operational and regime.

4.6.2 Substantiation of measures for the prevention of emergencies and the development of procedures in case of emergencies

Organizational measures provide for correct operation of equipment, proper maintenance of buildings and territories, fire instruction for workers and employees, training of production personnel for fire safety rules, issuing instructions, posters, and the existence of an evacuation plan [68].

The technical measures include compliance with fire regulations, norms for

the design of buildings, the installation of electrical wires and equipment, heating, ventilation, lighting, the correct placement of equipment.

The regime measures include the establishment of rules for the organization of work, and compliance with fire-fighting measures. To prevent fire from short circuits, overloads, etc., the following fire safety rules must be observed:

– elimination of the formation of a flammable environment (sealing equipment, control of the air, working and emergency ventilation);

– use in the construction and decoration of buildings of non-combustible or difficultly combustible materials;

– the correct operation of the equipment (proper inclusion of equipment in the electrical supply network, monitoring of heating equipment);

– correct maintenance of buildings and territories (exclusion of the source of ignition - prevention of spontaneous combustion of substances, restriction of fire works);

– training of production personnel in fire safety rules;

– the publication of instructions, posters, the existence of an evacuation plan;

– compliance with fire regulations, norms in the design of buildings, in the organization of electrical wires and equipment, heating, ventilation, lighting;

– the correct placement of equipment;

– well-time preventive inspection, repair and testing of equipment.

In the case of an emergency, it is necessary to:

– inform the management (duty officer);

– call the Emergency Service or the Ministry of Emergency Situations - telephone no. 112;

– take measures to eliminate the accident in accordance with the instructions.

4.7 Conclusions under social responsibility

In this section about social responsibility the hazardous and harmful factors were revealed. All necessary safety measures and precaution to minimize probability of accidents and traumas during investigation are given. Possible negative effect on environment were given in compact form describing main ecological problem of using nuclear energy.

It could be stated that with respect to all regulations and standards, investigation itself and object of investigation do not pose special risks to personnel, other equipment and environment.

Conclusion

Radiation therapy is currently carried out using beams of photons or charged particles such as protons. The main advantages of proton therapy are a decrease in the total energy of particles in comparison with photon methods and a limited range of the proton beam [1]. The latter adds an extra degree of freedom to treatment planning [2]. The range in the tissue is associated with significant uncertainties caused by imaging, patient placement, particle beam location, and dose calculation. Decreasing uncertainty will reduce the amount of treatment and increase the use of protons.

The accuracy of proton radiotherapy treatment planning depends on the accuracy of the information used to calculate the properties of the brake the ability of the tissue in the patient's body. This information is from computed tomography images using the calibration curve for converting Hounsfield units to relative values of the proton stopping power [3]. It leads to large uncertainty in planning and therefore to the necessary expansion of the treatment area. This uncertainty can be reduced by performing a CT using protons [9].

In the course of the master's work:

1) In detector technology:

– Got familiar with the principle of ALPIDE operation for ITS upgrade;

– Studied of detection efficiency of ALPIDE, using PS beam data;

– Carried out laboratory investigations of FHR and Thresholds of selected ALPIDE sensors;

– Performed off-line analysis of the FHR for the ALPIDE from commissioning process of new ITS;

– Compared the results with experimental results from previous chips of the final design, investigated by the ITS team.

2) In radiobiology:

– Got familiar with a cellular response to ionizing radiation;

– Studied of the process of the clonogenic assay;

– Conducted experiments to determine the radiosensitivity of DAOY and ONS-76 cell lines;

– Executed process of the clonogenic assay for DAOY and ONS-76 cells;

– Irradiated the chosen cell lines by ^{60}Co;

– Constructed cell survival curves for brain tumor cells;

– Determined parameters of LQ model for chosen cell lines.

In this thesis, I have conducted a study of the ALPIDE sensors used in the upgrade of the ALICE Inner Tracking System. The Fake-Hit Rate/pixel/event was measured for non-irradiated ALPIDE sensors at V_{BB} = -3 V. The tests were performed for three chips, labeled W15R23, W15R25 and W15R34 at the laboratory of the Nuclear Physics Institute of the Czech Academy of Sciences in Řež. FHR values for non-irradiated ALPIDEs obtained from laboratory measurements are lower ALICE request. In addition, I analyzed the output data of the detection efficiency of five chips characterizing by 6 GeV/c pion beam taken at PS CERN. Detection efficiency obtained from PS beam test data corresponds to ALICE request at large thresholds. Also, in this work stable of FHR were obtained for different staves in the off-line analysis in during the commissioning process. The received parameters of ALPIDE sensors are applicable for radiobiology experiments.

As part of diploma work was to determine radiosensitivity of DAOY and ONS-76 cell lines of medulloblastoma. These cells were irradiated to gamma radiation ^{60}Co at doses ranging between 0 and 8 Gy. After cells fixation and standing was created the survival curves. Survival fractions of chosen cells are significantly reduced for doses that are higher than 1 Gy. Parameters α and β for chosen cell lines were found. For DAOY cells α is equal to (0.22±0.08) Gy^{-1} and β is equal to (0.05±0.02) Gy^{-2}. ONS-76 cell line α and β are equal to (0.23±0.05) Gy^{-1} and (0.08±0.02) Gy^{-2}, respectively.

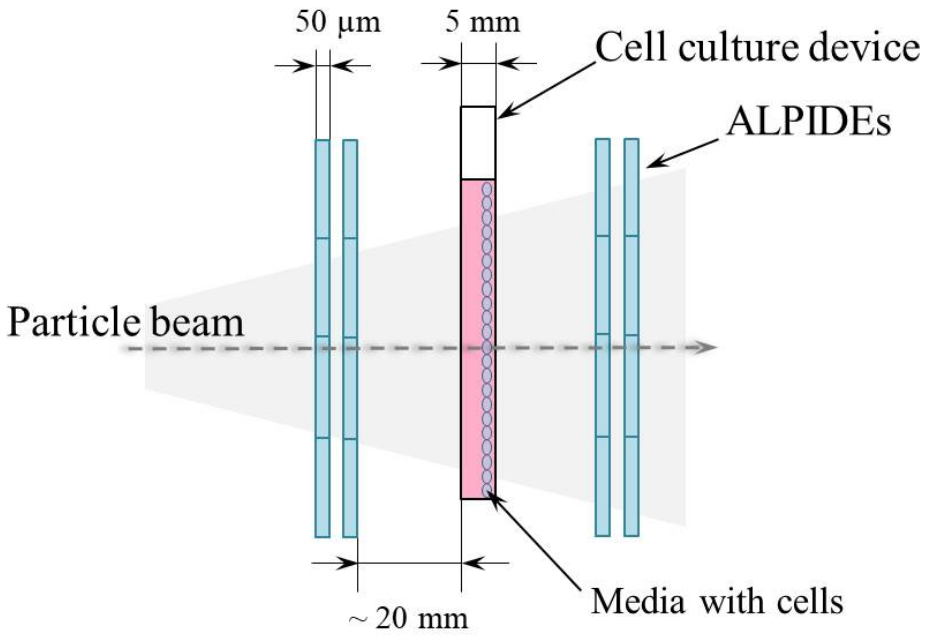

Figure 4.1 – Scheme of the future experimental setup with ALPIDEs and cells

Further work is aimed at an experimental design of radiobiology experiments that will be designed where ALPIDE detectors can be applied to perform microdosimetry measurements. In a future experiment, a tissue flask with cell monolayer with a cell culture will be placed between the ALPIDE sensors (see Fig. 4.1). Then on an output signal from the detector track of ionizing particles will be reconstructed. This will enable us to determine the the quality of radiation field or beam at the position of cell culture and therefore describe and understand better the corresponding biological response. These results will be useful when planning for tumor cells irradiation.

List of references

[1] Jeyasingam J., Peterson S.W. Evaluation of proton inelastic reaction models in Geant4 for promptgamma production during proton radiotherapy. – Phys. Med. Biol. 2015. – pp. 7617-7635.

[2] H. Paganetti Range uncertainties in proton therapy and the role of MC simulations. – Phys. Med. Biol., 2012, issue number 99-117.

[3] Hurleyet R.F. al. Water-equivalent path length calibration of a prototypeproton CT scanner. – Med. Phys. 2012. – pp. 2438-2446.

[4] Schaffner B. The precision of proton range calculations in proton radiotherapy treatment planning. – Phys. Med. Biol. 1998. – pp. 1579-1592.

[5] ALICE Collaboration. The ALPIDE pixel sensor chip for the upgrade of the ALICE Inner Tracking System. Nucl. Instrum. Methods Phys. Res. Sec. A Accel. Spectrom. Detect. Assoc. Equip. 2017, 845, 583–587.

[6] Prabket J. et al. Resistivity profile of epitaxial layer for the new ALICE ITS sensor. – JINST 14, 2019.

[7] B. Abelev et al. (ALICE Collaboration), Technical Design Report for the Upgrade of the ALICE Inner Tracking System, J.Phys.G 41 (2014),087002.

[8] Kushpil S. (Rez, Nucl. Phys. Inst.) Characterization of ALPIDE Monolithic Active Pixel Sensor for the ALICE Inner Tracking System Upgrade Using the PS Facility at CERN. – IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC 2017), Atlanta, Georgia, USA, 2017. – pp. 853-940.

[9] Monika Varga-Kofarago (on Behalf of the Bergen pCT Collaboration) Medical Applications of the ALPIDE Detector. – Universe, 2019.

[10] CERN Accelerating science [Electronic resource]. – Access mode: https://home.cern/science/accelerators/large-hadron-collider.

[11] Carminati F. et al. ALICE: Physics performance report. – J. Phys. G. volume I, 2004. – pp. 1517-1763.

[12] ALICE Muon Spectrometer: The muon spectrometer of the ALICE. – J. Phys. Conf. Ser., 2006. – pp. 397-401.

[13] L. Valencia Palomo The ALICE experiment upgrades for LHC Run 3 and beyond: contributions from mexican groups. – IOP Conf. Series: Journal of Physics: Conf. Series, 2017.

[14] S. Kushpil (ALICE Collaboration). Upgrade of the ALICE Inner Tracking System. – Journal of Physics: Conference Series, 2016.

[15] E. Garcia-Solisa (ALICE Collabaration) Perspectives of the ALICE Experiment and Detector Upgrade. – Nuclear and Particle Physics Proceedings, 2015. – pp. 382-391.

[16] K. Aamodt (ALICE collaboration), The ALICE experiment at the CERN LHC, JINST 3 (2008) S08002.

[17] M. Varga-Köfaragó, Anomalous Broadening of Jet-Peak Shapes in Pb–Pb Collisions and Characterization of Monolithic Active Pixel Sensors for the ALICE Inner Tracking System Upgrade. – CERN-Thesis, 2018.

[18] F. Reidt, Studies for the ALICE Inner Tracking System Upgrade. – PhD thesis. CERN-THESIS-2016-033, 2016.

[19] R.M. Smith, D. Hale, P. Wizinowich Bad Pixel Mapping. – High Energy, Optical, and Infrared Detectors for Astronomy VI, Proc. of SPIE, 2014. – Vol. 9154.

[20] S. Kushpil, F. Krizek, A. Isakov, Recent results from beam tests of the ALPIDE pixel chip for the upgrade of the ALICE Inner Tracker Nuclear Physics Institute CAS, for the ALICE Collaboration.

[21] I. Rubinskiy, EUTelescope. Offline track reconstruction and DUT analysis software. EUDET-Memo-2010-12.

[22] CERN ROOT [Electronic resource]. – Access mode: https://root.cern.ch/.

[23] Lazareva T. Analysis of test beam data of ALPIDE, the Monolithic Active Pixel Sensor (MAPS) for the ALICE ITS upgrade. – CERN-STUDENTS-Note-2017-246, 2017.

[24] C. Kleinwort, General Broken Lines as advanced trade fitting method. – In: NIM A673, 2012. – pp. 107-110.

[25] D. Colella et al. (ALICE Collaboration), ALICE Inner Tracking System Upgrade:construction and commissioning, arXiv:1912.12188 (2019).

[26] M. Buckland et al. (ALICE collaboration), Series Production and Test of Hybrid Modules for the ALICE ITS Upgrade (2019) PoS, to be published in proceedings of Vertex 2019.

[27] D. Andreou et al. (ALICE collaboration), The upgrade of the ALICE Inner Tracking System, JINST 14 (2019) p. C05004.

[28] ALICE general figures [Electronic resource]. – Access mode: https://alice-figure.web.cern.ch/generalfig, [Online 24.02.2018].

[29] Shift report 19.March, CERN surface laboratory.

[30] Animal cell [Electronic resource]. – Access mode: https://byjus.com/biology/animal-cell/.

[31] Gray J.W., Dolbeare F., Pallavicini M.G., Beisker W., Waldman F. Cell cycle analysis using flow cytometry. – Int J Radiat Biol Relat Stud Phys Chem Med. 1986. – pp. 237-255.

[32] Eric J. Hall, Amato J. Giaccia Radiobiology for the radiologist. – Wolters Kluwer Health, 2018. – 624 pp.

[33] Davydov M.G., Buraeva E.A. et al. Radioecology: a textbook for universities. - Rostov-on-Don: Phoenix, 2013. – 635 pp. [in Russian]

[34] Joiner M.C., Kogel A.J. Basic Clinical Radiobiology. – CRC Press, 2018. – 350 pp.

[35] Munshi A., Hobbs M., Meyn R.E. Clonogenic cell survival assay. – Methods Mol. Med. 2005, 110, 21–28.

[36] Mirza Q.B. Practical Radiotherapy and Chemotherapy Planning. – Jaypee Brothers Medical Publishers Pvt Ltd; 1 edition, 2017. – 552 pp.

[37] Gibco Handbook for cell culture basics. Invitrogen Life Technologies. 2014 Nov 25; B-087243 0110.

[38] Franken N.A., Rodermond H.M., Stap J., Haveman J., van Bree C. Clonogenic assay of cells in vitro. – Nat Protoc 2006;1:2315-9.

[39] Baba AI, Câtoi C. Comparative Oncology. – The Publishing House of the Romanian Academy; 2007.

[40] Lodish H., Berk A., Zipursky S.L., et al. Molecular Cell Biology. – 4th edition, New York: W.H. Freeman; 2000.

[41] Bekhtereva I.A., Sudilovskaya V.V. The role of epithelial-vascular relationships in the formation and development of cervical cancer. - Bulletin of the National Medical and Surgical Center named after N.I. Pirogov, vol. 6, 2011. – pp. 98-104. [in Russian]

[42] Harrington K., Jankowska P, Hingorani M. Molecular biology for the radiation oncologist: the 5Rs of radiobiology meet the hallmarks of cancer. – Clinical oncology (Royal College of Radiologists (Great Britain)); 2007.

[43] Mallick S., Rath G.K., Benson R. Practical Radiation Oncology. – Springer Nature Singapore Pte Ltd. 2019. – 300 pp.

[44] Mayo Clinic Care Network: Medulloblastoma [Electronic resource]. – Access mode: https://middlesexhealth.org/learning-center/diseases-and-conditions/medulloblastoma.

[45] Rossi A., Caracciolo V., Russo G., Reiss K., Giordano A. Medulloblastoma: from molecular pathology to therapy. – Clin. Cancer Res. 2008. – pp. 971-976.

[46] Michael D. Taylor, Paul A. Northcott et al. Molecular subgroups of medulloblastoma: the current consensus. – Acta Neuropathol; 2012.

[47] Jacobsen P.F., Jenkyn D.J., Papadimitriou J.M. Establishment of a human medulloblastoma cell line and its heterotransplantation into nude mice. – J Neuropathol Exp Neurol, 1985. – pp. 472-485.

[48] Tamura K., Shimizu K., Yamada M. et al. Expression of major histocompatibility complex on human medulloblastoma cells with neuronal differentiation. – Cancer Res, 1989.

[49] Zanini C., Ercole E., Mandili G. et al. Medullospheres from DAOY, UW228 and ONS-76 cells: increased stem cell population and proteomic modifications. – PLoS One, 2013.

[50] Water baths, VWB2 series [Electronic resource]. – Access mode: https://uk.vwr.com/store/product/20352380/water-baths-vwb2-series.

[51] MCO-5M-PE IncuSafe Multigas Incubator [Electronic resource]. – Access mode: https://www.phchd.com/eu/biomedical/incubation/multi-gas-incubators/mco-5m.

[52] Catalog: Cell Culture CO2 Incubators MCO-19AIC(UV)/19AIC [Electonic resource]. – Access mode: https://pdf.medicalexpo.com/pdf/phc-europe-bv-phcbi/cell-culture-co2-incubators-mco-19aic-uv-19aic/70908-123785.html.

[53] Fast, Accurate, Innovative Cell Counting and Analysis [Electronic resource]. – Access mode: https://www.abacusdx.com/media/MP_Catalogue_MuseScepter_2014.pdf.

[54] Guava easyCyte [Electronic resource]. – Access mode: https://www.luminexcorp.com/guava-easycyte-flow-cytometers/.

[55] VILBER Smart Imaging [Electronic resource]. – Access mode: https://www.vilber.com/quantum/down.

[56] INTERNATIONAL ATOMIC ENERGY AGENCY, Absorbed Dose Determination in Photon and Electron Beams: An International Code of Practice, Technical Reports Series No. 277 (2nd edn in 1997), IAEA, Vienna (1987).

[57] INTERNATIONAL ATOMIC ENERGY AGENCY, The Use of Plane-parallel Ionization Chambers in High-energy Electron and Photon Beams. An International Code of Practice for Dosimetry, Technical Reports Series No. 381, IAEA, Vienna (1997).

[58] INTERNATIONAL ATOMIC ENERGY AGENCY, Absorbed Dose Determination in External Beam Radiotherapy: International Atomic Energy Agency, Technical Reports Series No. 398, IAEA, Vienna (2000).

[59] RTD Dosimetry Phantom Solutions [Electronic resource]. – Access mode: http://www.activeradsys.com/tp/images/Ambrinf/ rtddosimetryphantomsovervie.pdf.

[60] EASY SLAB [Electronic resource]. – Access mode: https://www.lap-laser.com/products/easy-slab.

[61] van Leeuwen C.M., Oei A.L., Crezee J. et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. – Radiat Oncol 13, 2018.

[62] Qi X.S., Schultz C.J., Li X.A. An estimation of radiobiologic parameters from clinical outcomes for radiation treatment planning of brain tumor. – International Journal of Radiation Oncology Biology Physics, 2006. – pp. 1570–1580.

[63] Tubiana M. Introduction To Radiobiology. – CRC Press, 2005. – 269 pp.

[64] OriginLab Releases Origin 8.5 [Electronic resource]. – Access mode: https://www.originlab.com/index.aspx?go=PRODUCTS/Origin

[65] Federal Law "On the Fundamentals of Labor Protection in the Russian Federation" of 17.07.99 number № 181 – FZ;

[66] SanPiN 2.2.2 / 2.4.1340-03. Sanitary-epidemiological rules and standards "Hygienic requirements for PC and work organization"

[67] GOST 12.1.038-82 Occupational safety standards system. Electrical safety

[68] Fire and explosion safety of industrial facilities. GOST R12.1.004-85 Occupational safety standards system. Fire Safety Rules in Russian Federation.