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Atoms for Health Physics applied to medicine

*From elementary particles
to surgical knives*

*LHC calorimeters
for medical diagnostic*



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When united we stand... Physics and medicine allied against cancer

In the last decades of the Western World, *tumour* raised its ranking among the principal causes of death, and even though this term is used in many ways it has a sharp definition in biology: “an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimulus which evoked the change.” (R.A. Willis) The large variety in typologies of tumours leads to a huge number of different ways through which this condition of disease can either evolve or extinguish. *Oncology* is the branch in medicine that engaged this challenge: to recognise the tumour (diagnosis), and to *cure* it (therapy).

In the first step, its precise *visualization* is mandatory, and it could be located either on the surface of human body or in a deeper position. For the second step, the most successful and mainly adopted strategy is its removal: since the cells have been triggered in an abnormal reproductive activity, their destruction is the most effective result. How to achieve such a result? Considering that the most dated documented evidence of malignant tumour was reported more than 3000 years ago (in the *Edwin Smith Papyrus*, written during the Dynasties 16-17 of the Second Intermediate Period in Ancient Egypt), it is easy to understand the fact that so many techniques have been introduced while tackling this problem throughout the centuries. Surprising is the fact that, in the most recent decades, particle physics played the role as a pivotal actor in this – apparently – eternal struggle, developing both advanced techniques and equipment at the cutting edge of medicine, that is why we asked Nicolas Di Vara how the *LHC’s calorimeters are used in medical diagnosis!*

Terms like *particle accelerator*, *LHC*, *Higgs boson* are nowadays becoming more and more famous among the mass audience, mostly because at the CERN in Geneva so many researchers work hard to give their contribution. Conversely, less known is the fact that scientific exotic objects like electron and proton beams, high energy radiation, nuclear decays, antimatter are all potential candidates as effective weapons in this fight. Thus, if we have to locate cancer in the patient’s body we can trace the cancer’s need for chemical energy with radioactive molecules, and if we want to evict it we can bomb diseased cells with particle beams!

Physics and medicine are perfect allies. As Francesco Collamati explains in his journey *from elementary particles to the operating room*, it is a long path but as promising as few others are. As a matter of fact, the European Union is investing so much effort in this technological transfer from laboratories to clinics, as Manjit Dosanjh, the project coordinator for ENLIGHT, tells us. At european level (and not only), many projects are focused on this goal, from different points of view: Manuela Cirilli, from CERN, tells us about real-time monitoring techniques; Frauke Roellinghoff tells us about *single photon emission computed tomography*; Thiago Lima tells us about *clinical phantoms*; Garcia Ortega and Carlo Mancini tell us about the crucial role of computer simulation for therapeutic treatment.

Where do we hold all these secret weapons? Well, among the most worldwide successful research centers we find the italian National Center for Hadrontherapy (CNAO) based in Pavia, as Roberto Orecchia and Sandro Rossi tell us, it is fast growing center for what it concerns clinical trials and quality certifications: not just a center for research and for the cure, but also a role model for institutional and international collaboration.

Medical Physics is a cross-disciplinary science, and it goes far beyond any academic or geographical boundary. In this sense, here is our small contribution: this time our magazine made the grade as well, since for the special occasion of the european Researcher’s Night 2013, accastampato is going published in four different idioms (italian, english, french, spanish). You can find it either online www.accastampato.it or trough the AppStore for iPad and iPhone experience, and also as a printed version, distributed in Rome, Geneva, Paris, Barcelona, ...

Enjoy your reading, buona lettura, bonne lecture, feliz lectura!

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From elementary particles to the operating room

Achievements and frontiers in the fight against cancer

Francesco Collamati
(Sapienza, University of Rome)

Behind the significant improvement of the survival rate after 5 years from tumor diagnosis, raised from the 49% of 1975 to the 68% of 2009 (U.S. data [1]), several scientific progress of the last decades are enclosed, not only in the medical field. In fact, if on one hand a fundamental role was played by molecular biology, that giving us a more and more clear picture of tumors and of their behavior allowed us to understand the functioning and in some cases even their cause¹, on the other hand there are some technical innovations that we tend to confine to different importance, that instead played an important role as well in this context. It's indeed known that the spread of refrigerators contributed to reduce the incidence of stomach tumors [2].

Several steps of a long lasting struggle

Beside great steps made by surgical techniques, allowing today highly precise diagnosis (e.g. biopsies) able to address the patient towards the most effective treatment, remarkable efforts have been made in prevention, awareness and screening of the population. If we think about *imaging techniques*, that are those allowing us to *see inside* the patient *from outside*, for example by means of radiations, it is pretty clear how today's tools in the fight against cancer are infinitely more advanced and powerful than those of just some decades ago. Nevertheless, there is still much to do, if we consider that every year in Italy about 150 thousand people die because of tumor [3]. Luckily, we still have a lot of possibilities to explore! Biologists and immunologists today can create particular antibodies able to attack with high selectivity target molecules characteristic of the tumor. Heavy ion radiotherapy (the so called *hadrontherapy*) allows us to hit diseased cells in depth leaving practically unhurt those healthy nearby. All this without forgetting that a big and concrete improvement would come from a deep change of our lifestyles...!

It shows clearly off that all the human sciences have much to say in this fight. However, it is when they merge and intersect each other that new horizons and possibilities unfold. In such a way, it may happen that a remarkable and unexpected aid to surgery comes from elementary particle physics. That physics that builds enormous accelerators, giant spatial telescopes and curious observatories under oceans and mountains. Centuries of discoveries, decades and decades of researches that become big and little

¹ Like in the case of *Papilloma Virus*, which is responsible for nearly all the cervix tumors and for which today we have a vaccine.

tools in the hands of the surgeon. Notwithstanding great progress of radio and chemotherapy, surgery remains in fact the primary therapy in cancer patients, that undergo surgical procedure in 90% of the cases. It is clear that the aim of the procedure is the resection of diseased cells, and that the more complete the resection, the higher is the possibility of having actually eradicated the tumor. Cancer cells, in fact, by their nature tend to reproduce in an uncontrolled manner, and even small amounts of residual cells could bring to new diseases, the so called *recurrences*, that become more and more difficult to treat and significantly diminish the life expectancy of the patient.

When physics meet surgery

Thanks to actual imaging techniques (CT, NMR, PET, see Figure 1), today we are generally able to know where a tumor is located before the surgical procedure with high precision. However, the problem arises when the surgeon has to explore the operating field looking for *by eye* what he saw clearly in the images before. Usually, the so called *bulk tumor* is quiet easy to identify even by the naked eye: it is indeed a particular kind of tissue, characterized by an increased and chaotic development with respect to the normal one. Unfortunately, this main mass rarely presents

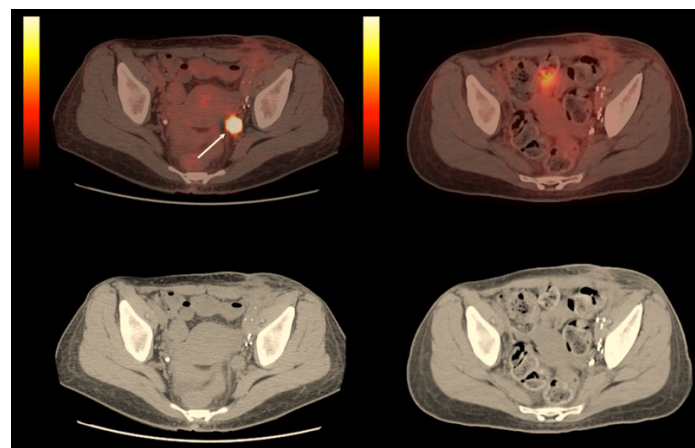


Figure 1 – Examples of *imaging* techniques: on the bottom CT images, that provide informations about density of tissues, thus showing bones with great detail. On the top, PET images, where we get information about metabolic activity of tissues, that is how much glucose they consume: in such a way we are able to identify zones of abnormal activity, that often are tumors, as indicated by the white arrow.



Figure 2 – Prototype of the probe that, enveloped in a sterile covering, should be used by the surgeon during the procedure to verify the completeness of the tumor resection.

well defined borders from the surrounding healthy flesh. Quiet often, after the excision of the tumor the surgeon has the necessity to scan inch by inch the edge of the removal zone, trying to identify possible residuals of cancer cells. To now, the efficacy of this scanning is strictly tied to the surgeons' experience and skill, which however, being him after all a human, has substantial probability of errors (even of 30%).

Just a spoonful of sugar...

In this context of operating rooms and scalpels, which contribution can be given by nuclear physics? Well, to be honest, a certain (and fundamental) role is played by chemistry (together with biology) as well. There exist in fact particular molecules which have high affinity with tumoral cells. Simple example: *sugar*. It is pretty comprehensible that the more effort and fatigue we make, the more sugar we will consume. And in this way it also works for our cells: the ones with particularly elevated metabolism consume much more sugar than those with normal metabolism. Tumoral cells, differently from healthy ones, spend their time in reproducing more and more, with a huge expense in term of energy consumption: hence tumoral cells will be much more avid of glucose than normal ones! Sadly, *bombing* with sugar cancer cells will hardly help our surgeon... we are indeed missing a last essential step.

Once established that tumors are more avid of glucose than healthy tissue, why don't we think to feed them, instead of normal sugar, with a *radio-marked* sugar molecule? It is sufficient to take a glucose molecule and to replace one of its atoms with a radioactive one, that sooner or later will decay emitting a particle, for example an electron. In such a way, when we see this particle somewhere we know that a molecule of this radioactive sugar was over there: if we see a lot of particles, we know that in that place there is a lot of sugar, thus suggesting it can be a diseased zone!

All this story of molecules and radioactive atoms, despite seeming something like science fiction, is already today widely spread even at industrial level, and are there numerous centers in the

world producing every day ^{18}F -FDG (code name for this *radioactive glucose*), even to be exported (once a day from Tor Vergata Hospital in Rome a plain brings this sugar to Malta!). ^{18}F -FDG is indeed today fundamental in many field of nuclear medicine, starting from PET imaging [4], that contributes to save every year millions of human lives, so many that it is difficult to quantify! And it is right from this established reality that it is possible to imagine new ways to investigate. In fact, aside from sugar it is possible to conceive a lot of these molecules to be used as *trackers*, as well as several other isotopes can be used as *spy* of the presence of such radio-marked molecules. The idea behind this innovative technique, named *radio-guided surgery*, is (apparently) simple: by injecting into the patient a small dose of this radioactive material just before the operation itself, the surgeon is able via a small probe (sized like a pen, see Figure 2) to scan *on-line* the tumor zone to understand if the tissue he is studying is diseased (if *spy particles* are seen), and thus should be removed, or not, having to be left there. There exist cases, like cerebral tumors, in which a complete resection of the lesion can change dramatically the patient outcome and life expectancy even of years. It is right on this project that together with a group from Physics Department of the University of Rome Sapienza we are working, availing of several medical collaborations (Pediatric Hospital Bambin Gesù from Rome, Neurological Institute Carlo Besta from Milan), of outmost importance in perspective of such an intersection of knowledges and skills.

It would perhaps be excessive to conclude that "just a spoonful of sugar"! Though, we must avoid the erroneous thought that to improve our life and our condition we need more and more new things to discovery. There is an infinity of possibilities that arise just from the wise and courageous blending of skills, ideas and technologies we already have. In the words of Marcel Proust: "le véritable voyage de découverte ne consiste pas à chercher de nouveaux paysages, mais à avoir de nouveaux yeux".



Figure 3 – The actress Julie Andrews in a shot of Mary Poppins (1964).

Bibliography

- [1] Howlader N., Noone A., Krapcho M. *et al.* *SEER Cancer Statistics Review 1975-2009*. National Cancer Institute (2010)
- [2] La Vecchia C., Negri E., D'Avanzo B. e Franceschi S. *Electric refrigerator use and gastric cancer risk*. In *British Journal of Cancer*, vol. 62(1):136–137 (lug. 1990). URL <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1971721/pdf/brjcancer00215-0144.pdf>
- [3] AAVV. *I numeri del cancro in Italia* URL <http://www.registri-tumori.it>
- [4] AAVV. *Positron emission tomography*. In *Wikipedia*. URL http://en.wikipedia.org/wiki/Positron_emission_tomography

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ENLIGHT: European hadrontherapy

The ENLIGHT network is to bring together the excellence in hadron therapy in Europe

Manjit Dosanjh
(CERN, Geneva)

Cancer is a major societal health problem and each year over 3 million Europeans develop malignant tumours and about 50% these are cured. Traditional X-ray radiotherapy accounts for 40 ÷ 50% of this cure rate, either used alone or in combination with other therapies. Radiotherapy also plays an important role in symptom control and pain relief for incurable patients. It is by far the most cost-effective modality for cancer treatment with the added advantage of conserving normal tissue function. More than 10,000 electron linear accelerators (linacs) are used worldwide by radiation oncologists to treat patients. However, conventional X-ray radiation therapy is characterised by almost exponential attenuation and absorption, and consequently delivers the maximum energy near the beam entrance, but continues to deposit significant energy at distances beyond the cancer target. The maximum, for X-ray beams with energy of about 8 MeV, is reached at a depth of 2 ÷ 3 cm of soft tissue. To compensate for these disadvantages of X-rays and to better target the radiation dose distribution to the shape of the tumours, the radiation oncologists use complex Conformal and Intensity Modulated techniques. These involve the use of computerized treatment plan optimization tools achieving a better dose conformity and minimizing the total energy deposition to the normal tissues.

Visionary physicist and founder of Fermilab, Robert Wilson proposed the use of the Bragg peak effect of hadrons for cancer treatment in 1946. For protons, alpha particles, and other ions the peak of energy loss occurs immediately before the particles stop. This is called the Bragg peak. The use of this peak was first applied at the Lawrence Berkeley Laboratory (LBL).

Beyond X-rays: the particle therapy

Particle Therapy is a precise form of radiotherapy that uses charged particles instead of X-rays to deliver a dose of radiotherapy for patients. Radiation Therapy with hadrons or particles (protons and other light ions) offers several advantages. It can overcome the limitations of X-rays since hadrons/particles deposit most of their energy at the end of their range and these beams can be shaped with great precision. Hence it allows for a more accurate treatment of the tumour destroying the cancer cells more precisely with minimal damage to surrounding tissue therefore sparing the healthy surrounding tissue. Particle therapy is being increasingly used, with about 100 thousands patients treated worldwide. Several dedicated hospital-based centres with

significant capacity for treating patients are now replacing the first generation RD facilities hosted by the physics research laboratories. However, only small percentage of these patients have been irradiated with the more technologically advanced active scanning techniques, which are an exclusive European contribution developed at PSI (Villigen) for protons and at GSI (Darmstadt) for carbon ions.

Carbon ions treatment

Carbon ions deposit over 20 times more energy in a cell than protons but with similar range and precision. However with carbon at the end of the range the Linear Energy Transfer is much larger than the one of X-rays and protons (low-LET radiations). The resulting DNA damages include more complex double strand breaks and other lethal damage, which cannot be repaired by the normal cellular mechanisms. The effects produced at the end of the range by particles such as carbon are qualitatively different from those produced by the other classes of radiations and open the way to a strategy to overcome radio-resistance, often due to hypoxia of the tumour cells. For these reasons carbon and other heavier ions with their higher relative biological effectiveness (RBE) at the end of their range can control tumours that are normally resistant to X-rays and possibly protons. Such ions can lead to more effective/improved treatment and reduced number of treatment fractions and treatment times. This has been shown by



Figure 1 – The Dresden proton therapy facility is under construction on the campus of the University Hospital Carl Gustav Carus, and will host the first patient treatments in spring 2014. Credit: ENLIGHT.

using carbon over the last ten years with the first 10 thousands patients mostly treated at HIMAC (Japan), at GSI (Darmstadt) and HIT (Heidelberg) in Germany, and recently at CNAO (Pavia, Italy). However carbon ions are still in the experimental stage and more clinical studies are needed.

Currently Japan is the leader in treatment with carbon ions, Europe however, is playing a key role in the development of ion therapy. In 1997 for the first time treatments with actively scanned carbon ions were performed at the GSI (Gesellschaft für Schwerionenforschung) centre in Germany. Light ion therapy dual centres (for both carbon ions and protons) are presently under construction in Heidelberg (Germany) and Pavia (Italy) and proton centres for the therapy of deep seated tumours and malformations are running in France, Switzerland and Sweden while new centres will become operational soon. Additional dual hadrontherapy centres have been approved in Austria, France, and Germany and a number of other European countries are interested in establishing more proton and ion therapy centres, e.g. Belgium, Czech Republic, Denmark, Greece, The Netherlands, Spain, Sweden, and the UK. The European Network for Research in Light-Ion Hadron Therapy (ENLIGHT)¹ which had its inaugural meeting at CERN in February 2002, was established to coordinate European efforts in using light-ion beams for radiation therapy. Funded by the European Commission for three years, ENLIGHT has created a multidisciplinary platform, uniting traditionally separate communities so that clinicians, physicists, biologists and engineers with experience in ions could work together with a common goal.

The European Network for Research in Light-Ion Hadron Therapy

In 2006, a brainstorming amongst clinicians, oncologists, physicists, radiobiologists, information and communication technology experts and engineers – from around 20 European countries – took place at CERN. The community felt that ENLIGHT was a key ingredient for future progress, and therefore should be maintained and broadened, called ENLIGHT++. The aim of ENLIGHT++ network is twofold: to maintain and enlarge the European network of institutions and specialists which work in the field of Light Ion Therapy and to sponsor the research in fields of common interests for the development of the cutting edge and technically advanced clinical facilities.

It provides a common European platform for fostering and coordinating collaborations between national research activities related to hadrontherapy, encompassing such various fields as proton and light ion accelerators, detectors, image reconstruction and processing, radiobiology, oncology, and clinical research. ENLIGHT permits a critical mass of physicians, radiobiologists,

medical physicists and biomedical engineers from different European countries, involved in the development of hadrontherapy. Under the umbrella of ENLIGHT, there are currently four EC funded projects: PARTner Training Network for European Radiotherapy (PARTNER), Union of Light Ion Center in Europe (ULICE, 2009), European NoVel Imaging System for ION therapy (ENVISION) and Research Training in 3D Digital Imaging for Cancer Radiation Therapy (ENTERVISION). All these projects are directed towards the various aspects of developing, establishing and optimising hadron therapy. The initiatives involve integrating clinical, biological and technical knowledge as well as training the future generation at a European level, so that hadron therapy becomes widely available for the benefit of all European inhabitants. Specifically it aims to:

- identify the critical topics and focus the research on key-areas in order to define and develop particle therapy and extend its benefits throughout Europe and eventually worldwide, complementary to other treatments;
- develop a common European platform to validate the efficacy of hadron therapy, starting first with the most advanced facilities, in Heidelberg and Pavia;
- develop the technical expertise and widespread knowledge for a therapeutic use of particle therapy and create the appropriate professional know-how needed for European-wide expansion;
- enhance the cost effectiveness of hadron therapy by improving quality of life and reducing the overall cost of treatment;
- integrate hadron therapy within the best available multidisciplinary management of cancer treatment;
- train the future scientists needed for this emerging field.

ENLIGHT's key vision is the promotion and the optimisation of hadron therapy for cancer treatment at a pan-European level.

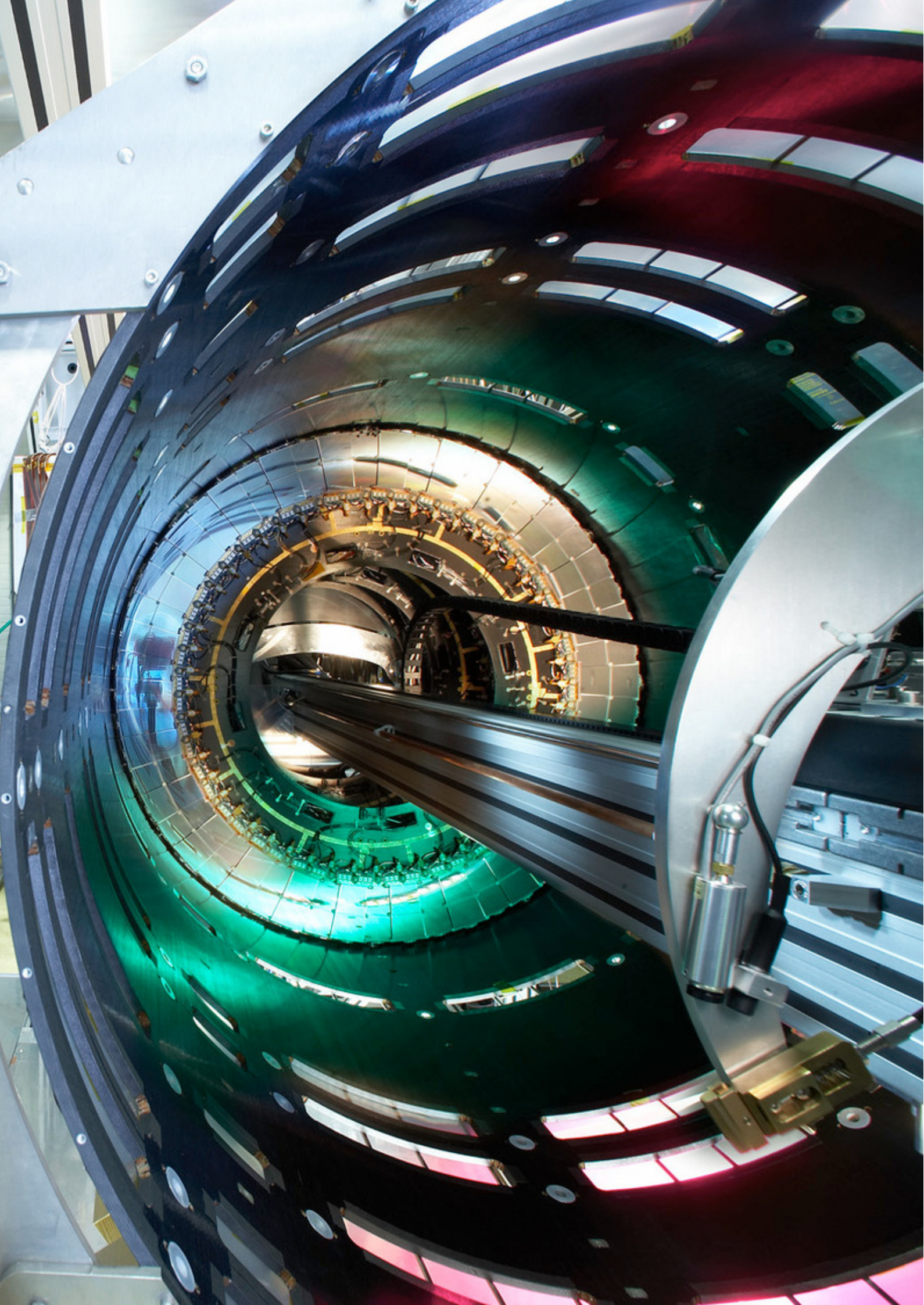
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¹ Official page: www.cern.ch/ENLIGHT.



Striving for precision

Monitoring and therapy from ENVISION project

Manuela Cirilli
(CERN, Geneva)

The clinical interest of hadron therapy resides in the fact that it delivers precision treatment of tumours, exploiting the characteristic shape of the Bragg curve for hadrons, i.e. the dose deposition as a function of the depth of matter traversed. While X-rays lose energy slowly and mainly exponentially as they penetrate tissue, hadrons deposit almost all their energy in a sharp peak – the Bragg peak – at the very end of their path.

The cancer revealed

The Bragg peak makes it possible to target a well defined cancerous region at a depth in the body that can be tuned by adjusting the energy of the incident particle beam, with reduced damage to the surrounding healthy tissues. The dose deposition is so sharp that new techniques had to be developed in order to treat the whole target. These fall under the categories of *passive scattering*, where one or more scatterers are used to spread the beam, and *spot scanning*, where a thin pencil-like beam covers the target volume in 3D under the control of sweeping magnets coupled to energy variations. The latest generation of hadron therapy treatments aims at achieving the level of sophistication of intensity modulated (conventional) radiation therapy: IMPT (Intensity Modulated Particle Therapy) would allow to adjust the beam dose and depth and hence to *paint* the tumour more accurately. These refined methods require state-of-the-art medical imaging techniques, not only prior to the treatment, but ultimately also in real-time, while the dose is being delivered, in order to provide fast feedback to the treatment planning system. In fact, uncertainties in the actual range of the particle beam inside the patient and factors related to the patient set-up or dose calculation may lessen the inherent

accuracy of particle therapy. Advanced imaging is also key to address the issue of organ motion, such as in lung cancer, and to redefine the target volume as the tumour shrinks with treatment.

The ENVISION project

The crucial challenge of quality assurance during hadron therapy is addressed by the EC funded project ENVISION¹, an R&D consortium of sixteen leading European research centres and one industrial partner, co-ordinated by CERN and supported by the ENLIGHT network. The project aims at developing solutions for real-time non-invasive monitoring and response to moving organs, quantitative imaging, precise determination of delivered dose, and fast feedback for optimal treatment planning. In order to achieve its goals, ENVISION pursues the development of innovative detector solutions, motion monitoring techniques, and simulation studies, and aims at integrating the dosimetric information from these tools into the treatment planning system.

Non-invasive monitoring systems

The first aim of ENVISION is to accurately monitor in-beam (i.e. during irradiation) the actual dose delivered to the patient. A method first attempted at LBNL (Berkeley, USA) and then clinically implemented at GSI (Darmstadt, Germany) makes use of Positron Emission Tomography (PET). PET is routinely used in hospitals to obtain 3D images of the functional processes inside the body. In this standard PET implementation, a radioactive tracer is injected into the patient, concentrates in the tissues of interest, and undergoes positron emission (i.e. β^+ decay); the positron annihilates in the body, and the PET system detects the two photons emerging from this process, thus allowing to reconstruct the annihilation vertexes. The distribution of the vertexes gives us an image of the tracer distribution in the tissues. In-beam PET (ibPET) for hadron therapy monitoring relies on the β^+ activity induced by the hadrons themselves, with no need for an injected radioactive tracer. The quality of the images suffers from the lower counting rate with respect to conventional PET, and from the open geometry needed to accommodate the beam nozzle: instead of a ring of photon detectors surrounding the body, the set-up will be composed of two detector *heads*, leading to dead areas and hence to imaging artefacts.



Figure 1 – Official logo of the ENVISION project.

¹ See the official page: <http://cern.ch/ENVISION>.

ENVISION aims at improving the image quality by limiting the region of interest with a measurement of the time difference between the photons (Time-of-Flight Positron Emission Tomography, TOF-PET). The achievable image improvement depends on the accuracy of the TOF determination. The ENVISION project intends to compare different detector technologies (scintillating crystals and Resistive Plate Chambers, or RPCs), to design, build, and test dual-head demonstrators including read-out electronics and data acquisition systems, to simulate a full TOF-PET set-up and to develop fast image reconstruction algorithms exploiting TOF for in-beam PET.

A recent approach to in-beam monitoring of the delivered dose is based on the detection of prompt radiation emitted immediately following the nuclear reactions induced by the therapeutic hadron beam. ENVISION investigates the feasibility of using prompt photons or protons for online quality assurance during hadron therapy, an innovative approach called *in-beam single particle tomography* (SPAT). In-beam SPAT (ibSPAT) is not influenced by metabolic processes, and thus should provide more precise information on the deposited dose distribution with respect to in-beam PET. The intensity of prompt photons emitted orthogonally to the beam direction exhibits a peak structure, which is correlated with the Bragg peak. *Single photon emission tomography* (SPECT) is widely used in nuclear medicine to obtain 3D images through the injection of a gamma-emitting radioisotope, but the challenge for the ENVISION project is to design and build a system adapted to the special requirements of in-beam applications in particle therapy. In fact, the typical device used for SPECT imaging is the so-called *gamma camera*. However, the gamma cameras for nuclear medicine are not suited for the detection of photons at the energies relevant in hadron therapy, mainly between 0 and 7 MeV. The ENVISION consortium is therefore comparing different detection technologies, and developing different prototypes being tested on suitable hadron beams. In-beam dose monitoring with prompt charged particles, in particular protons, has not been attempted so far. Fragmentation measurements performed at GSI have shown that light charged particles can be recorded outside the patient's body, with a maximum intensity in the forward direction, i.e. in the direction of the beam. ENVISION is investigating the feasibility of this approach, building and testing various detector systems.

Hadron therapy in 4D

In parallel to the development of non-invasive, real-time monitoring systems that will be able to provide an accurate in-vivo measurement of the actually delivered dose, ENVISION is tackling the issue of effectively and safely irradiating tumours subject to physiological motion. Hadron therapy, due to the high dose at the Bragg peak, is particularly sensitive to movements and changes in the anatomy, as the dose could be accidentally delivered out-

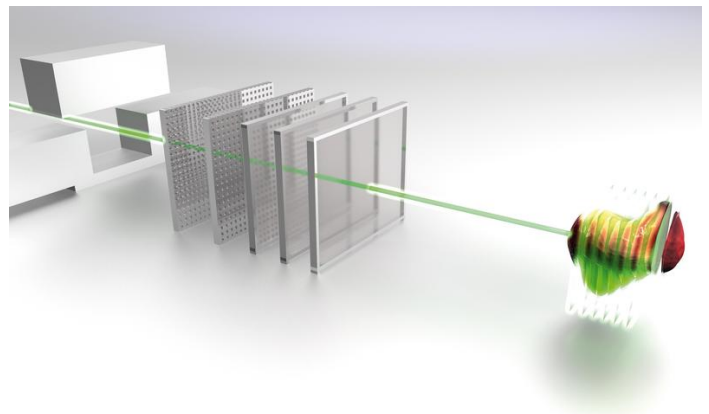


Figure 2 – Precise irradiation of tumour using with beams of hadrons using the raster scanning technique. Credit: GSI/HIT/Siemens.

side of the target. This could have severe consequences especially when tumours are close to critical organs that must be preserved. State-of-the-art beam delivery *paints* the tumour in 3D, i.e. covers the entire tumour region in subsequent passes of the beam, and therefore poses the challenge of delivering a moving beam to a moving anatomy. ENVISION explores software and hardware solutions that would improve the quality and reliability of hadron therapy in the case of moving targets. This means first of all moving from 3D to 4D monitoring, including time evolution in addition to the spatial dimensions. Within ENVISION, for the first time, the potential of different implementations of in-vivo PET imaging for a motion-mitigated delivery of hadron beams is assessed. This will allow to identify the specific requirements for 4D in-beam PET imaging for hadron therapy. Also, since most of the upcoming European hadron therapy facilities will not be directly equipped with ibPET instrumentation, but will have availability of nearby nuclear medicine PET/CT scanners, the potential of post-irradiation 4D PET/CT imaging is also being investigated.

In parallel, ENVISION explores enhanced non-invasive 4D motion monitoring techniques, which could be applied to all the different dosimetric technologies being developed within the project or routinely available. All of these developments will be meaningful only if they can be integrated in the clinical setting. For this reason, ENVISION also focuses on developing and fine-tuning the techniques required to automatically integrate dosimetric information from ibPET and ibSPAT into the treatment planning and the whole beam delivery workflow. Such tools will facilitate the prompt detection of treatment delivery errors and permit adaptive radiotherapy, meaning that the treatment plan can be modified to account for changes in patient anatomy and tissue dosimetry. As an example, when using PET for dosimetry checks, the verification of treatment plans is ensured by the comparison between a measured and a simulated β^+ -activity distribution, where the latter is acquired from the treatment plan. This comparison is per-

formed by well-trained observers, so it's a subjective, time consuming and expensive procedure. Automated comparisons would allow a more efficient and cost saving treatment workflow.

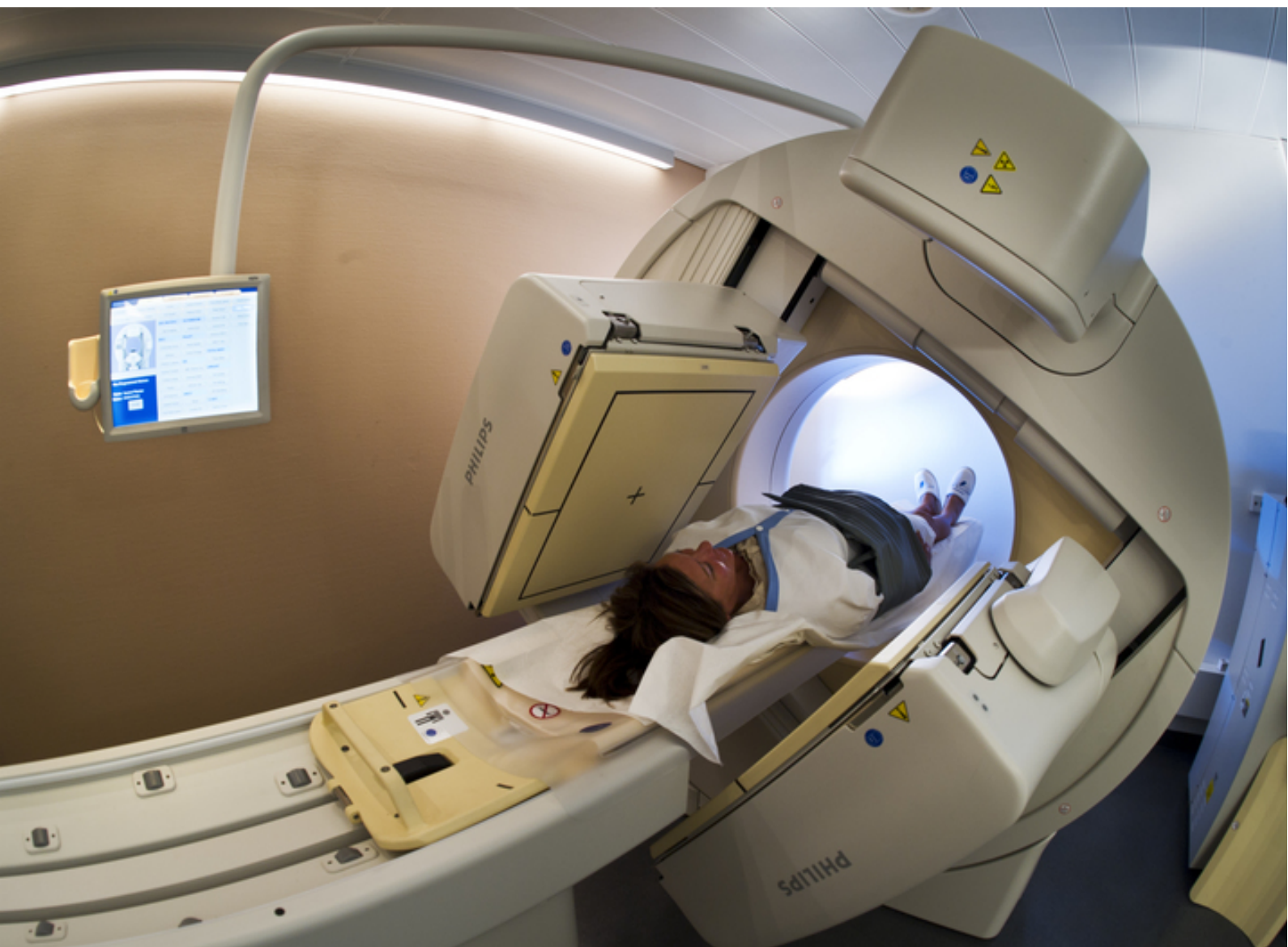
ENVISION also aims at developing dedicated simulation tools for hadron therapy applications, in order to reliably predict and understand all possible signals and effects that could be crucial for treatment monitoring. At present, the most reliable calculation models in the context of in-vivo dosimetry are based on Monte Carlo simulations. This approach can model the interactions of the hadron beam with matter, and the resulting production of radioactive nuclides and secondary particles. However, at this time, nuclear interactions cannot be described by well-established calculable models, and therefore different phenomenological models have been proposed. These phenomenological models depend on parameters that have to be set using experimental data as a reference, and one of the challenges for ENVISION is to review the status of available data and to make a thorough comparison of the different existing models with the data. The ENVISION consortium is also working on the accurate description of the detection of emitted secondary particles and the production of beta+ emitters, and is putting together all the tools and procedures needed to describe realistic patient treatments in all their steps.

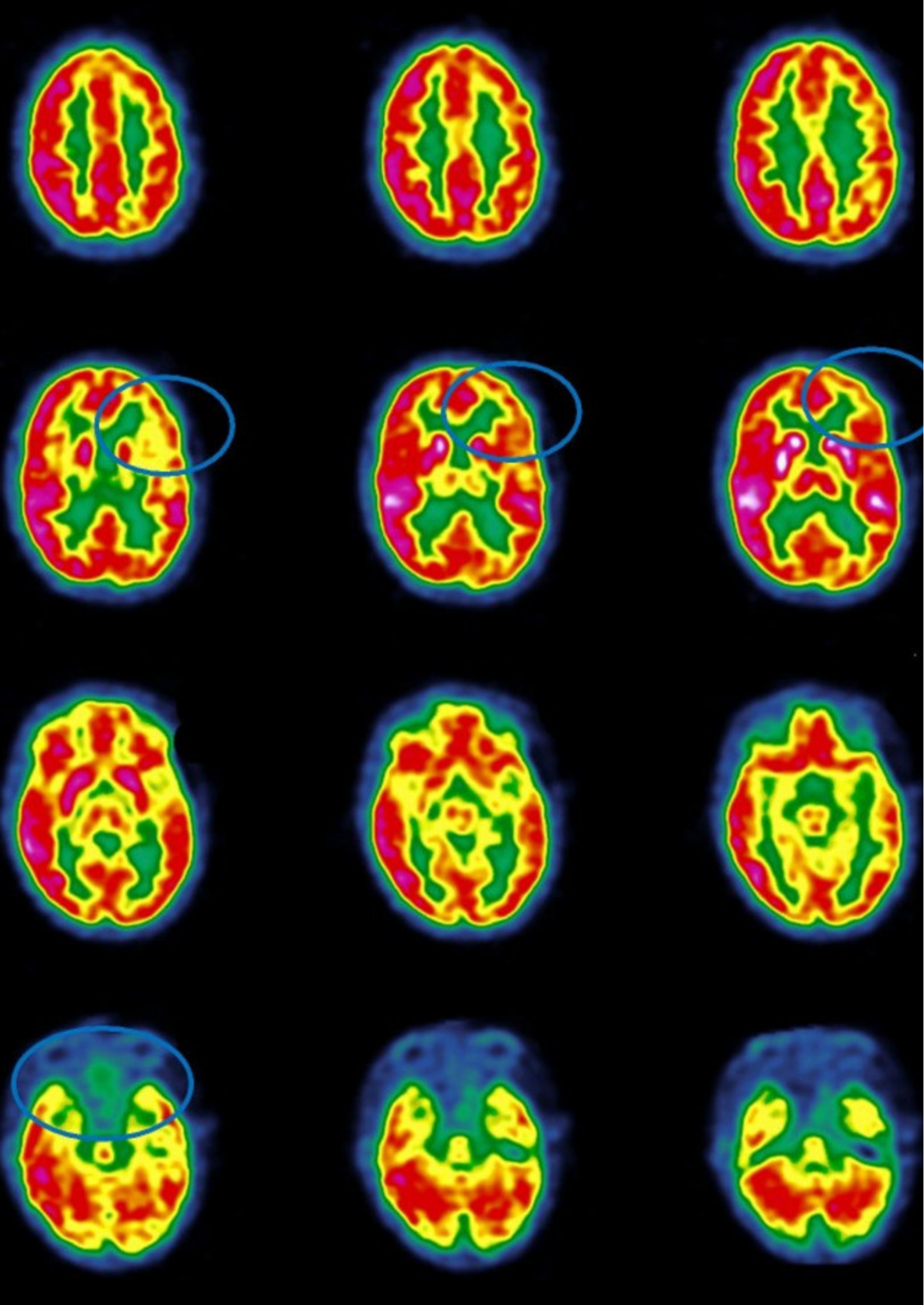
All of the developments within ENVISION are meant to find application in the clinical setting, and to provide solutions to some of the crucial issues in state-of-the-art hadron therapy: the project has now entered in its final year, and we are all eager to see the final results.

On-line discussion: http://www.accastampato.it/2013/09/envision_en/

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The calorimeters at LHC for medical diagnostics

The tools of particle accelerators applied to PET

Nicolas Di Vara
(University of Milano-Bicocca)

W

hen Sir Joseph Johnson identified the first electron, in 1897, he definitely did not think about electronics. And he could not imagine the impact of this discovery in the following decades.

The relationship between Nature's regularity and its applications is still the most natural approach when trying to improve our life conditions through technology. This link between fundamental research and technological solutions becomes evident in a classical domain of applied physics: medicine. About this, we must remind the experience of the European greatest research lab, the CERN in Geneva, and the so-called *technology transfer*, from elementary particles physics to nuclear medicine applications.

Similar solutions stem from the same problems

Great particle physics experiments need parameters, facilities and accuracy, not much different from those requested by a medical physics machinery. In detail, we need accelerated particle beams, techniques to control and manage the impacts, detecting systems and electronics to measure the particles' parameters emerging from the collisions, softwares to analyse data. These factors are crucial also in nuclear medicine, both in diagnostic and treatment. For instance, energy measuring systems for electromagnetic particles, called *electromagnetic calorimeters*, have similar features to *CAT scan's* detecting systems (Computerized Axial Tomography): in both cases we have to resolve incident particles' energy with a reasonable cost effectiveness, eventually with a high time precision. Detector's structure is similar: materials able to turn the incident energy into an easily measurable parameter. For example, a material which emits light when interacting with radiation, in its own crystalline structure.

So, medical physics research is strictly bound to particle physics research: the first taking significant advantages from the several innovations granted by the second. To cutting-edge questions there are always cutting-edge innovations, with following applications in similar or derivate branches. It's interesting to take a look in detail and say something about physical main contribution, in this case nuclear and subnuclear, to medicine.

Diagnostic nuclear medicine

The concept of radiographic exam is certainly the eldest and the most common triumph of applied physics, the possibility to diag-

nose with images. From the most trivial radiographic exams to the more complex tomographic concepts, using ionizing radiations to obtain images of patient's body strata and sections is nowadays a common routine in clinical structures. The principle is based on photons behaviour (in this case energetic photons, called X-rays) which go across the matter. These are attenuated in a decreasing exponential way, depending on the material which they go through. Consequently, the material chosen and the thickness crossed influence on the number of photons detected. When using a CAT scan, since the images are taken from different positions, we are able to reconstruct the density profiles within the body, that is visualizing body structures. This kind of clinical exam is often used as an alternative, or with other diagnostic techniques such as the *magnetic resonance* or the PET.

The PET, *Positron Emission Tomography*, is a nuclear medicine technique of the diagnostic branch. Nowadays it is largely used in oncological diagnosis since, thanks to the peculiar features of some radioactive decays, it allows to map the cells metabolic activity and target more easily tumors. In particular, the patient is given a drug to which a radioisotope is bound, the *Fluorine-18*. When swallowed, this drug, chemically similar to a sugar, is accepted by cells with a high usage of sugar, particularly from those tumorous. Once we have reached, in a partial selective way, the tumorous cells, we must define a way to detect them with a scanner outside the body. In this perspective, we are advantaged by a specific kind of decay: the β^+ . This phenomenon, which characterises a radioisotope such as *Fluorine-18*, determines the production of a subatomic particle, the positron, the electron's anti-particle. This particle, meeting one of the electrons of the surrounding matter, reacts through the annihilation mechanism. For cinematic reasons¹ the result of this process is a photons couple, emitted in opposite directions. We are able to detect this photons with detectors similar to those used in great particle physics experiments. Thanks to the detection of these two photons, it is possible to follow again the line along which the two photons have been emitted and so find where was the sugar which emitted the positron. Accumulating such measures we are able to reconstruct a series of lines, realizing a map of radioactive sugar concentration within the patient. Areas which reveal a higher sugar concentration point out an anomalous metabolism, and consequently they can indicate the presence of tumours.

One of the most promising fields in PET's branch is the so-called *time of light PET*. To improve the relation between interesting

¹ Because of impulse's conservation.

photons detected and those who emerge from other sources, it is possible to exploit the time information which they deliver. Thanks to very quick electronics and crystals, besides the response line identified by the two detectors, we have a second information, the arrival time of the single photon² This permits to narrow, along the line, the position of the specific event source. The advantages produced by this approach have consequences on the entire diagnostic chain: improving the image quality we are able to reduce the exposition time, so that the exams are quicker and the patient is given a smaller dose of radioactive drug.

With respect to this, many lines of research are opened, in a joint effort of european projects involving the most important research institutions. As a first example we report the material ingeneering of the future detectors, in particular the study of the lattice where the particles interact giving origin to the measurable light. This light production is determined by the specifi properties of the material, its composition, its density and the optical properties of the bulk. Moreover, given the objective of extreme timing resolution, an important attention is put on the electronics, considering both analogic and digital approaches, to transduce the light signal in a usable electric signal. These projects ambitiously aim to improve up to five times the timing resolution of commercially available machines.

Therapy based on radiations

Even in tumor treatment physics has been able to deeply modify clinical approaches. The possibility to use ionizing radiations to hit tumors has established itself with different aims, both therapeutical and palliative. Once again the functioning principle derives directly from particle and matter's interaction features. Radiations, a more or less energetic particle beam, elementary (photons, electrons) or not (protons, neutron), are able to damage the DNA of the target tissue. A certain number of damaged cells are not able to repair themselves, so they die. Obviously the relevant parameters in this case are two: the number of diseased cells destroyed with success and the number of healthy cells damaged by radiation. The first mostly influence patient's probability to recover from the tumor, while the second is the responsible for side effects, as the growing of a new tumor in a mid-long term. The main used therapies in clinical areas are based on photons and electrons, and nowadays they are considered standard approaches for tumor treatment. Thanks to the develop of accelerating technologies, not different from those which let the protons run inside LHC, new frontiers have been opened, such as *hadrontherapy*, which uses protons beams, neutron or heavier atoms (such as oxy-

² The difficulty of the measurement is obviously that photons run at the speed of light, and the detecting systems can't be too far from the patient, consequently these ones are measures which must have very high time resolution.



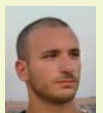
Figure 1 – Scintillating crystals for particle detectors (in this example, for CMS experiment at LHC) are also used in PET scanners. Photo by Peter Ginter (2004). Credit: CERN (cds.cern.ch/record/808282).

gene). The advantage is mainly to provide proper treatments, that is granting the right equilibrium between the radiations dose given and the tumor volume, with a lower irradiation in the surrounding areas.

On-line discussion: <http://www.accastampato.it/2013/09/calorimeters-lhc-and-pet/>

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Single photon emission computed tomography

The challenge to send and collect light through a human body

Frauke Roellinghoff

(Claude Bernard Lyon University and Ion Beam Applications S.A.)

One of the greatest challenges in medicine is to be able to see what goes on inside the human body. For millenia, the only way to do this was pretty drastic: you had to cut, open and look. Then came the invention of the X-rays and since then, we have seen the development of a plethora of imaging options. This abundance can often seem confusing and mysterious from the patient point of view. Well, let me lift at least some of the mystery for you today. We are looking at an imaging process called SPECT [5].

The S.P.E.C.T.

The acronym (medical physicists really love acronyms!) stands for *single photon emission computed tomography*. Let's decompose it's meaning from the end. Tomography stands for any type of imaging where you are using some kind of penetrating waves – remember, in modern physics any particle can also be considered a wave – to make images of slices or sections of an object or patient. The word *computed* would indicate that some kind of complicated reconstruction is required to obtain an image. *Photon emission* hints at the fact that the waves in question are high-energy electromagnetic waves¹ that originate in the patient. And *single* serves to distinguish this type of imaging from PET, a similar technique in which pairs of photons are being detected. From a physicists view, there are two challenges in SPECT. How do I get the photons inside the patient? And how do I image them in the most precise way while limiting the amount of radiation dose? So how do you get photons inside the human body? Well, usually, by ingesting or injecting radioisotopes into the body. These radioisotopes are made to be part of molecules typically found in biology and the path of these molecules can then be traced as they travel through the human anatomy. The way they travel, and where they accumulate can give us information on the function and metabolism of the tissue that is imaged. For example, iodine isotopes will accumulate in the thyroid gland. The distribution throughout this gland will show if it is working properly or if there is for example a tumour growing inside. This is what is called an *emission imaging*. Often a second, *transmission imaging* – using a source of known location and activity that is located outside the

¹ In physics the energy of radiations and particles is often misured in electronvolt (eV): it is the amount of energy gained (or lost) by the charge of a single electron moved across an electric potential difference of one volt (in vacuum). The SI prefixes most commonly used are keV (10^3 eV) and MeV (10^6 eV).

body and radiates through the body – is also made to be able to measure the attenuation of the photons by tissue and correct the emission images accordingly.

Isotope	Energy (keV)	Half life
Technetium-99m	140	6 hours
Iodine-123	159	13 hours
Iodine-131	159	8 days
Indium-111	171	67 hours
Thallium-201	167	3 days
Gallium-67	93 ÷ 393	3.3 days

Since the photons used for SPECT are much more energetic than visible light, obtaining an image is much more challenging. The same physical properties that allow them to travel through the body and show us the organs inside also make it difficult to stop them to get an image! For one thing, you cannot use a glass lens to focus them and simple film does not suffice to detect them. To focus high energy photons several techniques can be used. The simplest approach is what is commonly called an *Anger camera*, after an idea first developed by Hal Anger in 1958 [6]. Basically, some dense, radiation absorbent material (such as lead or tungsten) is put in front of the detector in a way only allows photons coming in a certain way to pass through it. For example, a pinhole aperture consists of a simple hole in a metal sheet. All photons are obliged to pass through this hole, that is, approximately through a single point, thus making a reversed projection of the image. A parallel-hole collimator consists of slits that only let those photons that come in at nearly 90 degrees pass and so directly projects

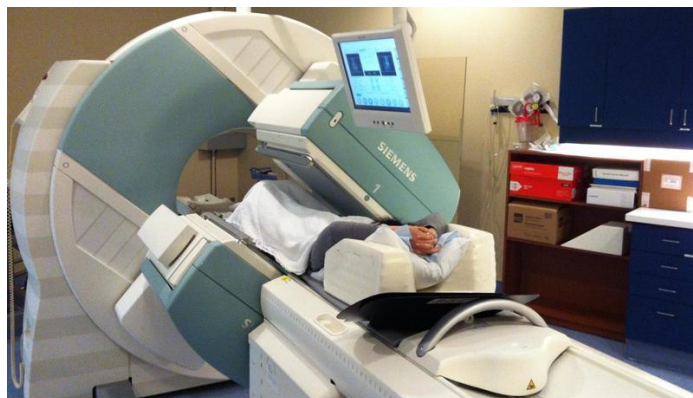


Figure 1 – Example of a commercial SPECT scanner. Credit: Wikimedia.

the image. For any of these collimators, there is what is called a trade-off: if the collimator is too restrictive, very few photons pass and you will get a very dim image. If you open it up too wide, you get a bad resolution. Most of the effort in development is spent on finding the right equilibrium. To detect the photons, one has to rely on interactions of the photons with the detector. Typical interactions at these types of energy are Compton scattering, photoelectric effect and coherent scattering. Any of these interactions deposit energy inside the detector, which will then convert this into an electronic signal. Since the energy of the photons is known, one can select the detected events that correspond to this energy. This both reduces random noise and discards most of those photons that have already scattered in the patient or the collimator.

For the moment, we have only talked about planar images, that is flat, 2D images of the patient. These show the integral of all emission along the direction the camera is looking! The solution is to take a lot of images from different angles, either by using several cameras around the patient, or, to be more cost effective, by rotating one or two camera heads around. One can then reconstruct what had been emitted by each voxel (think it as a kind of three-dimensional pixel) and have a nice 3D picture of the patient.

Not just photons

SPECT is a pretty well established technique, but this doesn't mean research is not still being done. The project I am working on, for example, is not classical SPECT, but the transfer of SPECT principles to a slightly different application [7]. I work in a field called hadrontherapy, which consists of irradiating tumorous cells with hadrons (typically protons or light ions).

This type of therapy allows targeting the tumour very precisely while sparing healthy tissue around it, but it has one flaw: there is at this time no way to know that the irradiation was delivered exactly as it should be! While the aim of these machines is very precise, there is always the possibility of a small misalignment or even of anatomical changes within the patient, all of which can sum up to errors of up to one centimeter. To deal with this, physicists add margins around the tumour volume to be sure that it gets completely irradiated. Luckily, there is a phenomenon that we can take advantage of: the particles, as they react with the matter inside the patient, leave behind excited nuclei, which emit photons. Some of these, called *prompt gamma* are emitted very quickly – in times under one nanosecond – and allow imaging to be made in real time, as shown schematically in Figure 2. These photons can be detected in much the same way as classical SPECT.

There are differences which make it much more challenging though. One is the limited time available for the acquisition. Since the main aim is treatment, not imaging, of course irradiation is stopped as soon as the goal dose is delivered, and the total

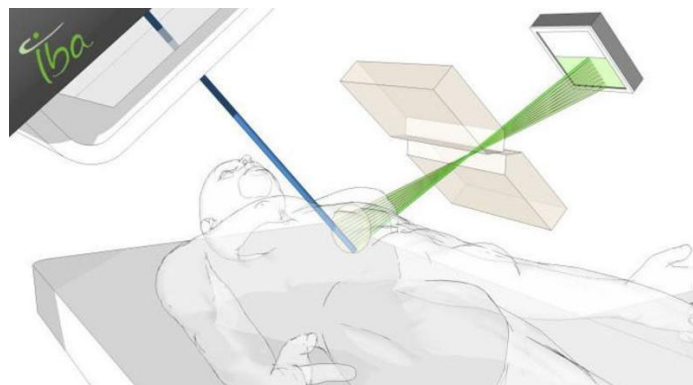


Figure 2 – Concept sketch of the prompt gamma imaging. Credit: medicalphysicsweb.org.

number of photons acquired in this way can be quite low. Another difference is that unlike when radioisotopes are used, the energy spectrum is continuous, so there is no way to do selection of the energy. The energy spectrum also goes to relatively high values (over 10 MeV), so optimizing a collimator can be quite challenging. There are several projects working on this at the very moment, most of which are still in the development and prototyping stage. We hope that sometime soon, there will be one of these in each treatment center so that targeting becomes more precise, margins can be made smaller and side-effects reduced.

Bibliography

- [5] Wernick M. e Aarsvold J. *Emission tomography: the fundamentals of PET and SPECT*. cap. 7: Single photon emission computed tomography, pp. 127–151 (2004)
- [6] Anger H. *Scintillation Camera with Multichannel*. In , pp. 515–531 (1964)
- [7] Freeman T. *Can prompt gammas monitor in real time?* In *Medical Physics web*. URL <http://medicalphysicsweb.org/cws/article/research/49909>

On-line discussion: <http://www.accastampato.it/2013/09/single-photon-tomography/>

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Clinical phantoms

Translating research into clinical practice:
test treatments on synthetic organs

Thiago V.M. Lima
(CERN, Geneva)

At hospitals, physicists need to safely verify how the diverse treatment options translate into improving the patients' treatment outcome. The complexity of these innovative treatments comes in different shapes and forms like using different particles to treat patients (carbon, protons and other ions are used in hadron therapy) or how these particles are delivered. And the main way to do so is to reproduce the treatment without harming the patients, which is the case of the use of medical phantoms. Phantoms are objects that are specially designed in order to evaluate the performance of specific equipment. They are used for both imaging and treatment equipment. There are different phantom types that are used clinically: some precisely represent the human anatomy while others are more concerned with reproducibility and reliability. The different phantoms will try to mimic different scenarios that need to be evaluated, like different density materials in order to study the effects of inhomogeneities (human chest comprising high density materials like bones, low density lungs filled with air and mid range density like other tissues and organs). Other phantoms are interested in studying the physiology of certain structures, for example the cardiac cycle (heart contractions). Some examples are shown in Figure 1.

Experimenting on phantoms

Radiotherapy aims to kill the cancerous cells by damaging its' DNA. When a damaged has occurred, the cell has the capability to repair it but this will depend on the extent of these damages. Hadron therapy is a modality of radiotherapy that uses heavier than electron particles and uses the principle that a heavier particle (the mass of carbon is 12 times the proton mass which is 10,000 times the mass of electron) has increased probability of interacting on its path through the matter (higher ionization density = more damages, see Figure 2). These interactions are responsible for the dose given and the damage created.

Hadron therapy uses the principles of better dose conformity and biological effects in comparison to conventional X-rays treatments. There are several forms of treatments using X-rays present in most hospitals around the world and they received different names like simply radiotherapy, brachytherapy, teletherapy, tomotherapy, etc. But currently, the knowhow in how the given dose will affect the clinical outcome (in how different cancers react to the given dose) is mainly known for X-ray therapy therefore a conversion of this knowledge into hadron therapy is done. For

that a quantity called relative biological effectiveness (or RBE) was introduced in order to evaluate the effectiveness of different radiation types. RBE is the ratio of the given X-ray dose over the dose given by the ions to achieve the same biological effect. The RBE varies with many factors like dose, particle type, cell type, etc. Although being complicate to calculate clinically, it is the only way to transfer the clinical experience from X-ray therapy to other types of radiation. In clinical practice, very complicated extrapolations of concerning factors are required for therapeutic dose calculations.

Presently there are two different approaches being used clinically to calculate the RBE-weighted dose, one by HIMAC, Japan [8] and one adopted in Europe which was developed by the Gesellschaft fur Schwerionenforschung (GSI) [9]. At HIMAC, RBE-weighted dose is calculated by an empirically established



Figure 1 – Different types of phantoms, both representing the human chest. The one at the top represents the anatomical structures of the chest with the bones, lung and other soft-tissues. Credit: www.kyotokagaku.com. The one at the bottom is a dynamic cardiac phantom representing the physiology of the human heart. Credit: www.ptw.de.

equivalence between NIRS' experience with both carbon and neutrons. GSI developed their own biophysical model called local effect model (LEM) which calculates the biological damage by the products of the local physical dose and cell characteristics hence the name. But in order to fully benefit from hadron therapy's advantages research is needed.

The European project ENTERVISION

ENTERVISION is an European project which wants to tackle this need. ENTERVISION (Official page: entervision.web.cern.ch) is divided into 4 work packages (WP) from studying new concepts and materials for imaging devices for best monitoring the tumour location and treatment delivery (WP1 and WP2), to calculating the delivered dose and physical processes in order to verify its biological effects (WP3 and WP4). As part of the WP4, I am involved in developing a biological dosimetric phantom in order to study these biological effects of the radiation and translate this into better treatments. When developing a phantom a good amount of work goes on the design phase with different scenarios to be considered like the material used detectors type and quantity, final shape, mobility, costs, etc. For example, will the selected material best represent what you want to measure? Which detectors will you use and how they will be accommodated? For the WP4 in ENTERVISION some of the answers were clearer than others for example the use of ionization chambers as detectors. They are the most available and studied detectors in the hadron therapy as they are already in used for the routine quality assurance. In relation to the chosen material, for hadron therapy the scatter equivalence with water is very important in order to obtain the correct depth dose calculations. This is measured as water equivalent path length or WEPL, which translate into how thick a block of water would need to be to have the same attenuation effect as the thickness used of the selected material. Although in the ideal scenario the material WEPL would be the closest as possible to 1, the cost of material and the difficulty of manipulation (cutting, drilling, etc.) will be taken into consideration as during the development of a phantom several prototypes are needed.

There isn't an universal agreement on which method of calculating the biological dose is correct and which is wrong and different studies showed that they can be biological identical but a factor need to be applied in order to translate the obtained results [10]. This uncertainty explains the need for further research into how to improve the patients' treatment outcome. With the WP4 biological phantom we are trying to answer this. Once the final prototype is ready, we will be able to test different scenarios by evaluating some of the factors that contribute for the biological dose calculation like different radiation types and the different cells variables (cell type, oxygen level, temperature, etc.).

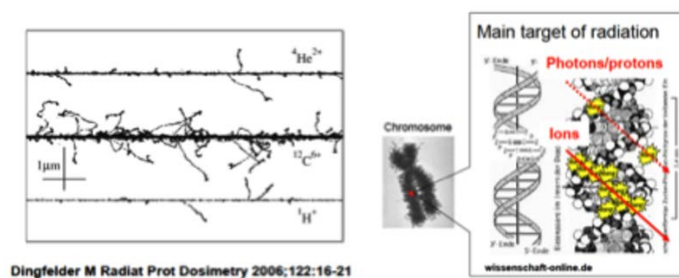


Figure 2 – Effects of different ionisation densities in the DNA.

Bibliography

- [8] Kanai T. *et al.* Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. In *Int J Radiat Oncol Biol Phys*, vol. 44:201–210 (1999)
- [9] Scholz M. *et al.* Computation of cell survival in heavy ion beams for therapy. The model and its approximation. In *Radiat Environ Biophys*, vol. 36:59–66 (1997)
- [10] Uzawa A. *et al.* Comparison of biological effectiveness of carbon-ion beams in Japan and Germany. In *Int J Radiat Oncol Biol Phys*, vol. 73:1545–1551 (2009)

On-line discussion: <http://www.accastampato.it/2013/09/clinical-phantoms/>

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Monte Carlo and hadrontherapy

Reality simulation to better control a real experiment

Pablo Garcia Ortega, Carlo Mancini
(CERN, Geneva)

No, there is no error: the title does not refer to the city of the principality of Monaco. It refers to a technique used to simulate complex processes that gets its name from the city worldwide known for its Casino.

The Monte Carlo method is an algorithm which reproduces a range of possible realizations of the phenomenon to be studied, in which every eventuality appears with the probability it has in reality¹.

Suppose we want to calculate the probability that the ball of a pinball falls directly between the two flippers without the player can intervene (see Figure 1). The dynamic of such a system is too complicated to be analyzed from a mathematical point of view (analytical) as smaller variations in the initial energy could change the trajectory of the ball. Therefore, we should carry out an experiment, throwing many balls with a real pinball machine. However, our experiment would require a lot of time and we wouldn't be able to tell whether placing an additional element on the playing surface increases the probability or not. The alternative is to do a *virtual* experiment, a Monte Carlo. We need therefore to develop a program that simulates our experiment by reproducing the interaction of the ball with all the parts of the surface, then virtually launch several balls with different energies. As the energies of launch are not necessarily equiprobable, we also have to consider the probability distribution of the initial energy of the ball. The accuracy of the result (the number of times that the ball passes through the flippers divided by the number of launches) depends on the number of launches we do. Once a fairly large number of *events* has been done, we can do *measures*, i.e. we can simulate the response of the measuring instruments on our series of events. For example, we could measure the average number of interactions with an element of the playing surface, or (virtually) measure the energy transferred from the ball to one of the bumpers. A measure, the latter, that would be very difficult to achieve with a real experiment.

The Monte Carlo allows not only to estimate what will be the result of an experiment before it has been carried out, but also to interpret the data and to optimize the experiment itself. After all, virtual reality has become part of our lives, video games simulate reality in a surprising way and almost all game consoles integrate processors for the simulation of physical processes. Therefore it is not so surprising that simulations play a crucial role in physics experiments.

¹ Or with a statistical weight.



Figure 1 – A pinball of 1995: “Theatre of magic”. Credit: Wikipedia.

The origins of the Monte Carlo can be traced back to the first half of the '40s when it was formalized by Enrico Fermi, John von Neumann and Stanislaw Marcin Ulam as part of the Manhattan Project. The name Monte Carlo – which refers to the tradition of gambling – was given later by Nicholas Constantine Metropolis. The simulation technique, spread after the spread of computers, is now in almost all physics experiments.

The design of an experiment

As in the example of the pinball, MC simulations are extensively used also when designing real experiments to evaluate the characteristics that the experiment needs to measure the wanted quantities. Afterwards, MC simulations are used to design and optimize the detectors and to interpret their signals. For example, the Figure 2 shows the experimental data measured during the ATLAS experiment and the predictions of the Monte Carlo simulation. It is very important that the simulation reproduces as precisely as possible the data that will result from the experiment, otherwise it would be almost impossible to go back from the signals produced by the detector to the processes that generated them. In

fact, the development of software that reconstructs the event that generated the signals is based on the simulation.

The Monte Carlo in Physics

Many programs have been developed over the years to obtain realistic simulations. Concerning simulations for particle physics experiments, these programs simulate what happens in millions of interactions in which, depending on the energy involved, some particles can be annihilated and others created. New particles can decay and, as they pass through a material, they interact with its atoms and can produce electric current, flashes of light or an increase in temperature.

MC techniques are also used to estimate the amount of radiation produced, not only in the experiments but also in any type of structure that uses radioactive sources for designing screens and safety procedures.

Medical applications of MC

In addition to basic research, Monte Carlo codes are currently being applied to an enormous variety of fields, from Biology to Telecommunications, Mathematics and of course Medical

Physics. In particular, the use of Monte Carlo transport codes is of relevant importance in many steps of cancer treatment. The basic idea behind radiotherapy is to use ionizing particles to damage the DNA of tumor cells, with the aim of killing them in the process. Independently of the particle used for treatment, the physical principle is the same, i.e., deposit sufficient dose (defined as energy per unit mass) in order to cause the death of all the tumoral cells. The key point now is to find a method to predict where these particles will deposit their energy, so we can focus our beams to the tumor area, reducing as much as possible the irradiation of healthy tissues. The transport of particles in the body tissue is a complex problem, not only because of the complexity of describing particle transport through the resolution of the Boltzmann transport equation². Traditionally, medical physics use Treatment Plan Systems (TPS), a specialized software based on analytical models which helps to obtain a 3D distribution of the dose to be applied to the patient. The use of approximate analytical solutions is useful for some problems. They are fast and accurate enough for traditional radiotherapy, based on X-rays and electrons. However, in the last decades, the use of protons and ions is becoming a popular alternative to the latter particles. If we study the dose delivered along the travelled distance inside a material before a particle stops, the so-called particle's range, we will see that the profile is quite different depending on the particle type. For electrons and X-rays, the dose maximum is obtained at the entrance of the media. On the other hand, for protons and ions, the maximum is located near the end of the particle's range, close to where the particle stops, creating a peak structure called *Bragg peak*, in honour of William Henry Bragg who first described this effect in 1903. This special dose distribution, where most of the energy is deposited inside the media is very interesting if you have to treat a deep-located tumor surrounding by healthy tissue, even more if this healthy tissue is a sensitive organ. It is evident that the depth of penetration reached by the beam particles depends on their energy, so modifying the energy of the beam we can cover a wide range of positions inside the patient.

Of course, the precise location of where the dose is released is essential for this type of treatment and a Monte Carlo simulation is the ideal tool for this kind of predictions, especially for what concerns heavy ions such as carbon, that in addition to interact with the medium can fragment.

For now, the Monte Carlo simulations are used to monitor treatment plans made with numerical algorithms, similar to those used for the treatments with X-rays and electrons. Indeed, it would take too much time to optimize the treatment plan directly with a full simulation.

² It is an equation that describes the statistical distribution of particles in a fluid and is used in the context of non-equilibrium statistical mechanics to study how a fluid transports physical quantities such as the heat, charge, or, in fact, particles of various kinds.

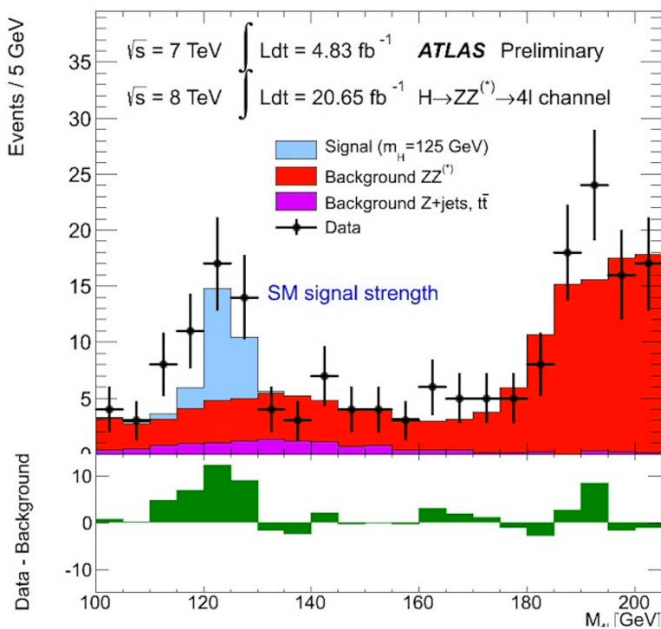


Figure 2 – The black points are the data measured in the ATLAS experiment: the red and the purple show the predictions of the Monte Carlo simulation of events caused by other processes already known; the green shows the difference between the prediction of the simulation and the data actually measured. The excess is consistent with the signal that would be obtained if it was produced by the Higgs boson and if it weighed 125 GeV, as seen in the simulation in blue.

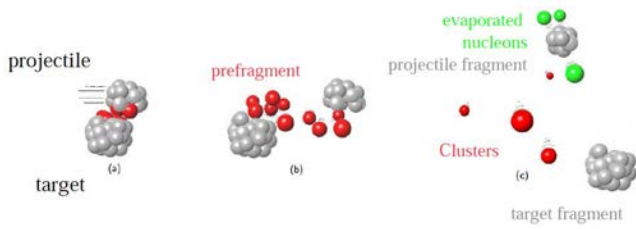


Figure 3 – Sketch of carbon fragmentation.

The prediction of the fragmentation of carbon, which forms part of our work, is one of the main points on which the research focuses. Its importance derives from the fact that the fragmentation of the carbon distorts the dose released (see Figure 3) since the fragments move more in the body. In addition, as Frauke Roellinghoff explains in his article, we are looking for a way to use these fragments to obtain real-time images of the area we are working on to enable the direct control of the location and quantity of the dose released.

The use of a MC simulation to verify the dose deposited in the

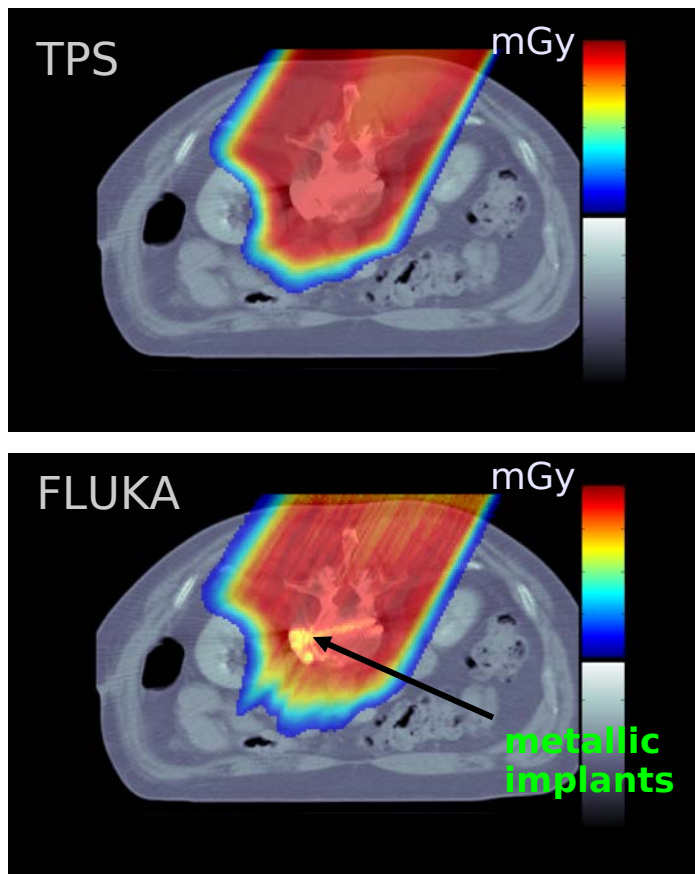


Figure 4 – Comparison between the dose provided by a numerical software and a Monte Carlo (FLUKA) if there are metal implants. Credit: K. Parodi et al, IJROBP 2007.

patient is particularly important in case of sudden changes in density, for example near the lungs or if there are metal implants, as seen in Figure 4.

A never-ending story...

In conclusion, the MC technique is used to simulate the processes that are too complex for us to treat analytically. Concerning the particle therapy, MC simulations are used in both research and clinics to design experiments, screens and security procedures, to verify treatment plans and explore new techniques for evaluation of treatments.

On-line discussion: <http://www.accastampato.it/2013/09/montecarlo-and-hadrontherapy/>

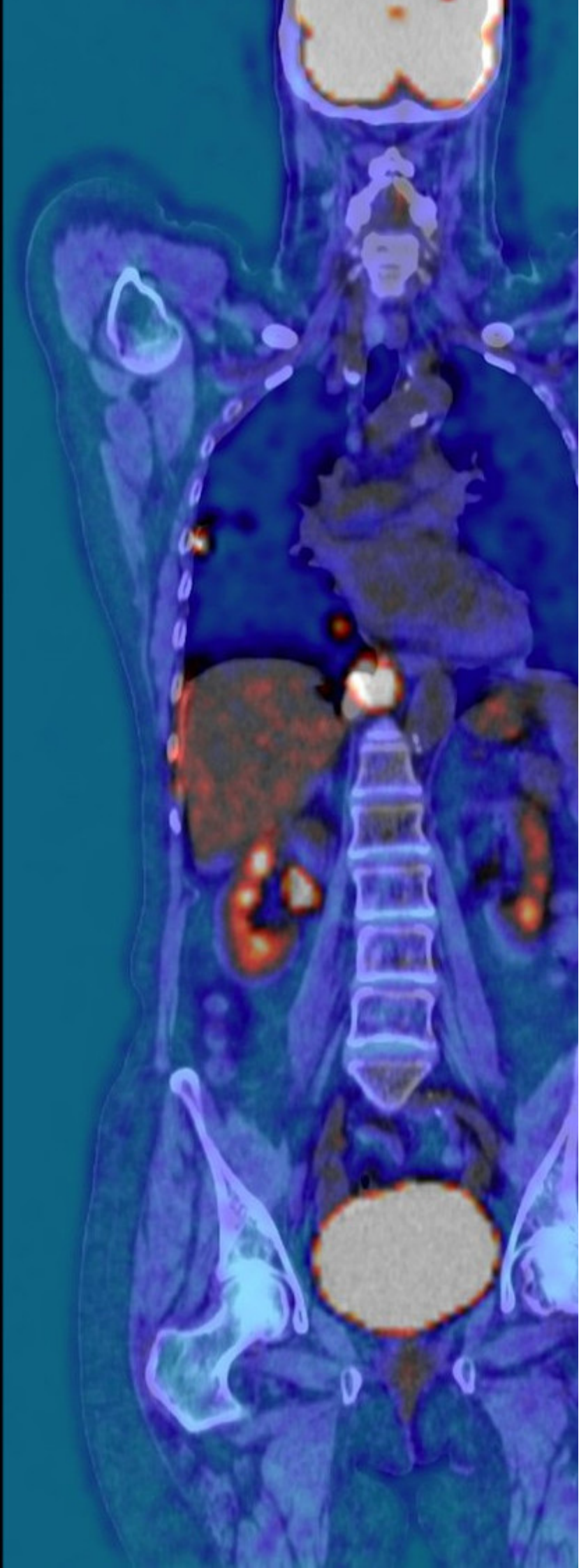
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The National Centre for Oncological Hadrontherapy

An international center of excellence for cancer hadron therapy

Roberto Orecchia, Sandro Rossi
(CERN, Geneva)

The CNAO (Italian acronym that stands for National Centre for Oncological Hadrontherapy) began its clinical activity in September 2011 with the first experimental treatments with proton beams and the very first patient was treated with carbon in November 2012. Both events represented an absolute novelty on the landscape of Italian healthcare.



Figure 1 – Top view of the area occupied by CNAO. At the front the hospital building and the entrance, in the back the power station and the roof of the synchrotron vault. Credit: ENLIGHT.

The foundation

The end of construction phase of the centre was marked with the inauguration of CNAO, on February 15th 2010, and the second phase, of clinical trials began. This phase takes place over 2010-2013, and will allow to scientifically validate hadrontherapy applied to the cure of tumours with a range of many clinical protocols. It will also lay the foundation for the subsequent phase of optimising the number of patients treated as outpatients, a few thousands patients per year and gradually expanding the clinical indications and introducing clinical, radiobiological and translational research¹.

The treatment of patients with carbon ions was approved in July 2012 by the Italian Ministry of Healthcare, following a detailed review of the data presented by CNAO on dosimetry and radiobiology with carbon ions, both in-vitro and in-vivo. These experimental activities were performed in the first part of 2012

¹ In the field of oncology, translational research verifies the ability to translate scientific breakthroughs that come from the laboratory into clinical applications to reduce the incidence and mortality of cancer.

also thanks to the collaboration of the Italian Institute of Nuclear Physics (INFN) and the Japanese National Institute of Radiological Sciences (NIRS). The data presented at the National Health Council confirmed the expected beam parameters specifications and also demonstrated the high standards of safety and quality achieved at CNAO.

The first months of 2012 were also important to adopt a quality management of the CNAO procedures, and in July the certifications ISO9001 and ISO13485² were obtained. This represented a fundamental step in view of the CE marking of CNAO. In fact, the CE marking of the different clinical protocols is mandatory to begin routine hadrontherapy treatments.

The numbers

At the end of April, 89 patients completed their treatment, 75 within clinical trials, 14 within the framework of solidarity treatment approved on a case-by-case basis by the Ethical Committee and by the Ministry. Among them, 59 patients have been treated with protons and 30 with carbon ions. Patients were referred to CNAO by around thirty hospitals from throughout the country, which demonstrates that an oncological network for patient referral is beginning to take shape and operate effectively. This aspect is crucial to establish CNAO as a national structure, and represents one of the key elements to ensure an efficient recruitment of patients who are eligible for this type of treatment.

In February 2013, clinical results of the first protocol (CNAO 01/2011 v2.0), concerning treatments with protons of 30 patients with chordomas and chondrosarcomas of the skull base³, were submitted for approval to the National Health Council. These clinical results are very positive, and they reach the target goals of the protocol. A peer review commission will examine these results and will deliver the CE marking of CNAO as a medical device for these protocols. The CE procedure foresees to complete other protocols, and to obtain each authorisation on a one by one basis by the health authorities.

² They are rules and guidelines developed by the International Organization for Standardization. The 9001 defines the requirements for a quality management system for an organization: they are general requirements and can be implemented by any type of organization. The 13485 explicitly refers to medical equipment.

³ They are both rare forms of malignant bone tumor: the chordoma arises from the cells residues of the embryonic notochord, chondrosarcoma arises from cartilage tissue.



Figure 2 – Patient positioning and patient verification systems in one of the three treatment rooms of CNAO. Credit: ENLIGHT.

The place

The facility is located in an area of Pavia that hosts other hospitals and the University campus (see Figure 1). The realization of CNAO is based on a close collaborative network, which links CNAO with the most important institutions in Italy and abroad. In particular, for the cutting-edge technologies, fundamental contributions came from INFN, that shared the management of the realisation, and also from CERN and GSI. This network has ensured collaboration of experts at CNAO in the past, and it will continue to do so in the future.

In 2013, a study programme for the design of a dedicated experimental beam line has been launched. Within three years a dedicated research facility for radiobiology, detector developments, clinical research and translational research will become operational at CNAO. CNAO's main objective of 2013 will be the increase of the patients' throughput and the approval of most of the on-going clinical trials. At the beginning of the year, the third treatment room became operational and it added one horizontal and one vertical beam lines to the already active treatment rooms (two rooms with one horizontal beam each, see Figure 2). Figure 2 shows a treatment room, with the systems used for patient positioning and verification of the correct alignment with the beam port. (cfr. Figure 2).

Reprinted of "The Status of CNAO at the beginning of 2013" published in ENLIGHT HIGHLIGHTS, June 2013: enlight.web.cern.ch/media/highlights.

On-line discussion: http://www.accastampato.it/2013/09/cnao_en/

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How do we measure a sound?

Intensity, pressure and relative units

Martina Pugliese

(Physics Department, Sapienza, University of Rome)

We usually identify a sound stimulus through (among other features) its *loudness*. But what does this exactly represent, and how is it measured? We use the *decibel*, shortened as *dB*, as the unit of measurement of sound loudness, so that the value in decibels of the loudness of a sound is defined through the *intensity level* (IL) as

$$\text{Loudness in decibels}_{IL} = 10 \log_{10} \left(\frac{I}{I_0} \right),$$

where I is the *intensity* of the sound, given by the power (energy of the sound wave transmitted into one unit of time) divided by the surface the wave passes through. It is indeed the energy that a sound wave carries in the unit of time and per unit of surface. I_0 is a sound intensity value universally adopted as a reference point, fixed at $I_0 = 10^{-12} \text{ W/m}^2$.

This value refers to the minimal intensity that, on average, a human ear can detect and is estimated as the minimal air pressure value that can put the eardrum into vibration. This means that the value in decibels is directly proportional to the logarithm (with base 10) of the ratio of the sound intensity we are seeking and that of a standard reference sound. Calling u a generic acoustic wave that propagates through time, if we depict its temporal trend we define its *period* as the time interval between two peaks (or between any two corresponding points), i.e., it is the time elapsed to have a complete oscillation. The *amplitude* of the wave, which is directly linked to the sound intensity, is its maximal values range. A wave propagating into a medium transmits the stimulus so the sound intensity is also related to the wave pressure p via a square relation:

$$I \propto p^2.$$

This means that, given that $\log(x^2) = 2\log(x)$, we can also write the value in decibels by means of the *sound pressure level* (SPL):

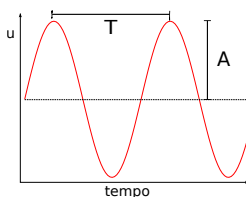


Figure 1 – An example of an acoustic wave: T is the *period* and A its *amplitude*.

$$\text{Loudness in decibels}_{SPL} = 20 \log_{10} \left(\frac{p}{p_0} \right).$$

Here we are using a reference pressure of $p_0 = 20 \text{ }\mu\text{Pa}$ ($20 \text{ }\mu\text{Pa}$, equal to $20 \cdot 10^{-6} \text{ Pa}$). It is then clear that the value in decibels of a sound can be negative: if, for instance, a sound has a loudness of -40 dB , it means that

$$-40 \text{ dB}_{SPL} = 20 \log_{10} \left(\frac{p}{p_0} \right) \Rightarrow p = \frac{p_0}{10^2},$$

that is, its pressure is 100 times lower than that used as a standard. We report here a table with typical values, in decibels, of commonly heard sounds (values are approximate).

Sound	dB _{SPL}
Whispering	30
Ordinary conversation	65
Phone ring	80
Motorcycle	100
Rocket take-off	180

Around 135 dB_{SPL} there is the so called *pain threshold*: the human ear, due to the excessive pressure experiences real pain (it is not recommendable to put it under such a stress!). This value depends of course on the particular couple of ears and on their history (on how long and how often they have been hearing *loud* sounds) and on their age.

Bibliography

- [11] Frova A. *Armonia celeste e dodecafonìa*. BUR (2006)
 - [12] Wolfe J. URL <http://www.animations.physics.unsw.edu.au/jw/dB.htm>
- On-line discussion: <http://www.accastampato.it/2013/09/loudness/>

About the author

Martina Pugliese (m.letitbe@gmail.com), graduated in Physics at Sapienza, University of Rome, is currently a PhD student from the same university. It mainly deals with modeling of the dynamics of language, but playing the piano for years she's also very interested in the profound relationship between music and science.





Magnetic levitation

The technology of high-speed trains with a turntable

by Paola Malacari

It is common to hear about *magnetic levitation* related to superconductors. Can we reproduce the same effect at home without a superconductor? If you have a record player you actually can! Hang the magnet to the far end of the paper strip. Put the aluminum disk on the record player. Turn on the record player to rotate the aluminum disk. Move the paper strip with the magnet close to the disk. You will observe that the disc rotation will make the magnet levitate above it!

What happened?

The disk rotation creates a variable magnetic field on the magnet, caused by its relative motion with respect to the impending magnet. The magnetic field variation produces an induced current, called *Foucault currents*, inside the disk. These currents origin a repulsive magnetic force on the magnet according to the *Lenz law*.



What is the electromagnetic induction? The phenomenon of electromagnetic induction takes place inside an electric circuit when immersed in a *variable* magnetic field: an induced current is created by the variable field and endures as long as the variation lasts. Moreover, the conservation energy principle imposes that the direction of current is such that opposes the variation of the flux that has generated it (Lenz law). The whole phenomenon is known as Faraday-Neumann-Lenz law:

$$\Delta V = -\Delta\Phi/\Delta t, \quad (1)$$

where $\Delta\Phi$ is the variation of the magnetic field flux inside the circuit in the time interval Δt , and ΔV is the electromotive force caused by the electromagnetic induction.



What are the Foucault currents? The Foucault currents are induced currents generated inside massive metallic units, just like in our experiment. According to the Lenz law, they create a repulsive magnetic force towards the magnet that makes it levitate above the aluminum disk.

Applications

The magnetic induction and the resulting magnetic levitation has many applications. In particular, one of the main utilizations is in the railway system. By using this effect, one can get rid of the contact between the train and the rail, thus reducing friction and resistance in the train motion. One of the techniques employed to realize these systems is indeed the electromagnetic induction, and they consequently take the name of Electrodynamic Suspension (EDS) railways. Here one exploits the opposite forces between the magnets placed on the vehicle and the conductive coils on the track. Thus the levitation is a direct outcome of the vehicle movement. To improve the stability the EDS trains use very light and powerful superconductor magnets, more expensive than conventional magnets and that require a refrigeration system placed on the train to keep them cooled.

SKETCH



MATERIALS

- 1 turntable
- 1 aluminum disk
- 1 strong magnet with small mass
- 1 thin paper strip

TOPICS

- Magnetic levitation
- Electric current
- Electromagnetic induction

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