Biofísica Magazine

BEYOND BIOPHYSICS

Medical Physics and Biophysics

A conversation with José Bernabéu

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Medicine and physics have always been interconnected. Physics is at the ground of all natural sciences, of which medicine is arguably the most impacting one since health is a priority for people. Advances in physics mean new ways to interpret Nature and often give rise to new concepts and methodologies which allow advances in other branches of science. Among them, medicine enjoys a privileged attraction by physicists. This alone explains the *synergy* between Physics and Medicine, at least during the last century.

In fact, looking back in history, we find that the birth of particle and nuclear physics, which are two landmarks of modern science, gave rise to the development of new medical applications. Thus, medical physics was born and grew, hand by hand, with the understanding and capacity to manipulate radiations, which were employed for medical purposes even before the discovery of their nature. The synergy persists today but with renewed forces and like in the past the thrust comes from new advances in physics, put to the service of human health. Modern medical physics is still based mainly on applications of radiation, but now incorporates different types of it and is used for a variety of clinical purposes, from diagnosis to therapy. The contributions of physics have also expanded. Radiation therapies have evolved to use high energy sources based on protons and ions which combine effectiveness, specificity and very low side effects. Moreover, instruments used for particle detection in modern particle and nuclear physics have been the basis for the development of a new generation of detectors for medical uses which allow in situ non-invasive functional imaging on real time.

> **Rediations were employed for medical purposes even before the discovery of their nature**

Worldwide, top level physics institutions, like CERN and Fermilab, have been and continue being capital for new developments in medicine. A privileged witness and actor of past and recent achievements in medical physics is José Bernabéu, professor at the *Instituto de Física Corpuscular* – IFIC (University of Valencia and *Consejo Superior de Investigaciones Científicas* – CSIC). As specialist in physics of elementary particles, he has dedicated the last years to the creation of IFIMED (*Instalación de Física Médica*), a unique Facility in Spain meant to explore new methods for treatment and diagnosis of cancer and degenerative diseases using *proton therapy* and including also the development of accelerators, detectors and medical image equipment.

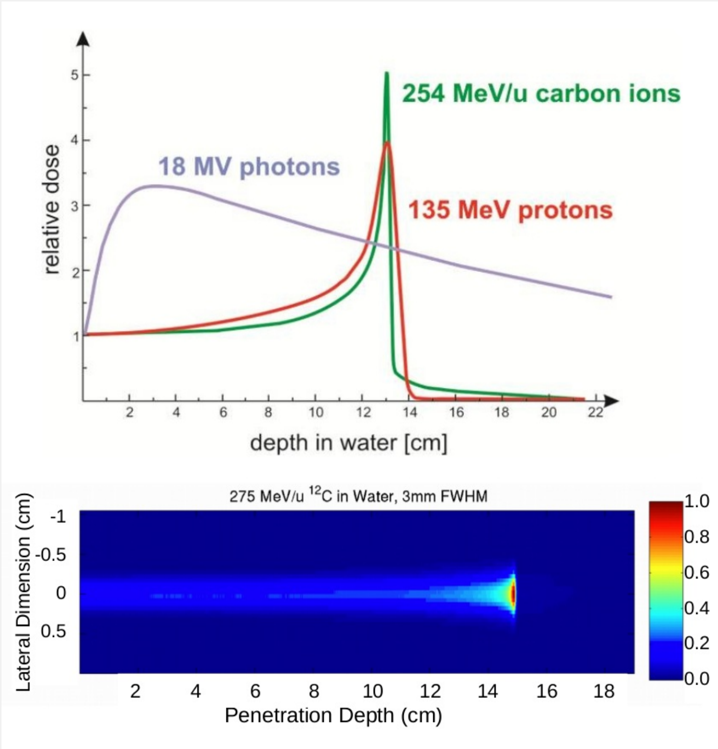
> **"Physicians are more conservative than physicists. That is understandable, but how do you get proofs for something without trying it!"**

I meet professor Bernabéu for an over-lunch conversation about medical physics and biophysics in the cafeteria of our common campus. A priori, one would probably expect some overlap between the two fields, and I start, quite naïvely, pointing this out to prof. Bernabéu. He has a clear and immediate answer: "There can, of course, be some level of coincidence, like there is between biology and medicine, but you would not mix these two either". Then, I realize throughout the conversation that there are important differences between the two fields: Medical physics works always close to medical problems. Physicists tailor physical phenomena to develop and fine tune new methods, to be used in the clinic. Their end goal is research oriented to cure people and they often work in collaboration with medical doctors and radiophysicists. A fruitful joint environment of research and clinic results in a desirable synergy. Biophysics, in contrast, uses a much broader approach and is more pluridisciplinary because the studies are oriented to all life sciences, not just medicine.

> **The cure of cancer has been, and continues to be, the major driving force of medical physics**

The close connection with hospitals and collaboration between physicists and medical doctors are influential characteristics for the development and implementation of medical physics projects. Professor Bernabéu says that "physicists and medical doctors have often different points of view and different ways to solve problems. Their scientific language is also different, which sometimes hinders communication. Physicians are more conservative than physicists. That is understandable, as they are used to work with patients, but how do you get proofs for something without trying it!" Medical doctors base diagnosis and prognosis on recognisable patterns (symptoms) from different types of observations. They are normally very focussed specialists on particular organs or pathologies, but they also must deal the patient as a whole. On the other hand, physicists may not be aware of all the physiological details of the human body and its parts. However, they can represent it as a complex system, made of a hierarchical collection of nested complex sub-systems, from cells to tissues, to organs to the complete organism, and with a list of associated properties, organised as a dynamic network, exhibiting emergent behaviour, with feedback loops and non-linear relationships between parts… "For a physicist cancer is a complex adaptive system, which evolves as a results from the redundancy and multiplicity of subclones and interactions at different scales. Heterogeneity, metastases and evolution towards resistant states can be seen as emergent properties of such a system. This is where biological and physical sciences converge."

The reference to cancer does not come out by chance. In fact, the cure of cancer has been, and continues to be, the major driving force of medical physics. The main outcome has been the development of a variety of therapeutic methods based on the use of radiation and known collectively as radiotherapy. The idea behind these methods is to use a penetrating radiation to eliminate malignant cells. It should be sufficiently energetic to reach the tumour and should ionize molecules which then produce cascading effects and ultimately trigger cell death. But ideally the radiation should have a localized action, like surgery, with no effects on healthy tissues. This seems a complicated issue!



New radiation sources allow conformal dose distributions, which concentrate energy in a reduced volume along the penetration pathway and minimize the effect on healthy tissues. Image courtesy of prof. José Bernabéu.

I ask prof. Bernabéu about the limitations of classical radiotherapy and the solutions introduced by new developments in recent years. "The two requirements, strong power and selectivity, turn out to be difficult to achieve simultaneously." This has limited the use of radiotherapy, depending on the localization and distribution of tumours. Conventional, external radiotherapy nowadays is still based on the use of *X-rays*, mainly produced by linearly accelerated particles (linacs). These are penetrable sources but weakly selective. On the other hand, a classical problem has been the precise localization of the tumours. The introduction of imaging techniques in the 80's allowed the control of the position and size of tumours and to calculate adequate radiation doses. "But an important breakthrough has been the use of beams of accelerated protons and ions (like carbon and neon ions). The advantage is that with these beams the dose keeps low for much of the penetration path and then peaks to reach a maximum at a narrow position which decays steeply from that point. This allows deposition of high energy in a small volume with minimal effects on surrounding areas." Prof. Bernabéu explains to me that the energy maximum corresponds to the Bragg peak of the radiation (see accompaning Figure) and its position can be adjusted to coincide with the position of the tumour.

The phenomenon was well known from early studies with cyclotron accelerators and had been applied to patients already since 1957. However, the use of protontherapy is only extending in recent years. "Nowadays this therapy is possible in more than 30 specialized centres in America, Japan and Europe and there are many others under construction. These are mostly particle physics research laboratories and there are also some installations in hospitals. The ideal site is a joint medical physics research facility associated to a hospital."

In Spain IFIMED, coordinated by Professor Bernabéu, "has completed in its Phase I the infrastructure for research in Imaging and Accelerators applied to Medicine, and contemplates in its Phase II an accelerator delivering protons up to 230 MeV -MeV is a million of electron-Volts, the eV being the energy acquired by an electron when 1 Volt is applied. This proton accelerator can be used for research and for protontherapy, the Bragg Peak for reaching tumours being located up to 32 cm deep in the human body." He points out that this is not a hospital but a research centre. In parallel, it can also be used for treatment of patients in cases where conventional radiotherapy is either inefficient or inconvenient due to side effects. Professor Bernabéu gives us an example. "Eye tumours, where conventional radiotherapy is of no use because the effect on healthy cells ends up destroying the function of the eye. Other cases are solid resistant tumours, for which it is important to apply concentrated energy in a small area, and early detected isolated tumours." This ambitious project is also conceived as a facility for users and teams up with other projects in Europe. "IFIMED is member of ENLIGHT, the European platform of particle therapy centres for activity in medical physics, coordinated by CERN. This includes other projects like PARTNER, the particle training network of European radiotherapy, ENVISION, the on-line non-invasive monitoring of the application of hadrontherapy to patients (imaging in real time), OMA, the optimization of medical accelerators and OpenMED, the design of a prototype of an ideal accelerator for particle therapy taking advantage of the Bragg Peak."

Detection and imaging are also of the interest of medical physics. The first medical images were based on X-rays but nowadays a variety of types of signals, detectors and mathematical and computerized treatments of data have given rise to a long list of sophisticated imaging methods. Classical imaging provides structural information (form). This, in principle, has also functional importance, since structure and function are correlated at all levels in biology (from molecules to cells to organs). However, modern medical imaging is designed to provide high level functional information, like the spatial distribution of specific molecules in the body. Again, the development and generalization of functional image methods for their use in medicine has a lot to do with advances in physics. Two of them are magnetic resonance imaging (MRI) and positron emission tomography (PET). Although the physical basis of the two methods are very different, in both cases the atoms responsible of the signals are naturally present in the body (hydrogen atoms from water, in the case of MRI) or can be easily incorporated to normal organic molecules (positron emitting isotopes, for the case of PET) and thus the images inform directly about the physical and physiologic (metabolic) state of the tissue.

> **Scientific progress consists mainly in finding the right questions: the answers just follow**

Professor Bernabéu stresses that imaging is not only important for diagnosis. "Detection and imaging can complement protontherapy. With an appropriate detection, imaging can inform in real time about the therapeutic mechanism. For example, cell death triggering may not be due to the direct action of the proton beam but to the effect of secondary electrons ejected from cell molecules as they are hit by the radiation. For this reason, integration of particle acceleration, detection and imaging at IFIMED is an important innovative aspect, not common in other medical physics infrastructures."

Professor Bernabéu is also an enthusiastic defender of basic research: "All great developments originate in basic research, without ever suspecting about their possible applications. This is, for example, how the world-wide-web started at CERN with a purpose very different from that we give it today. It was invented there, not at IBM!". Along the same lines, he also likes to say that scientific progress consists mainly in finding the right questions (the answers just follow). Medical physics is a good example where a few scientific questions pertaining to the field of particle and nuclear physics have yielded a benefit for people as invaluable as curing cancer. Then, I ask him to tell us a question that will motivate medical physics research in the coming years.

> *Protontherapy can be even more efficient with low dose if we know the precise position of the tumour at each moment during the application of the therapy. As we have moving organs, is it possible to integrate Imaging with Therapy in order to monitorize on-line, in real time, both the accelerator energy and the effects of therapy?*

Yes, this is a really big question! I am sure medical physicists will soon provide good answers to it.

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ISSN 2445-4311

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