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PHYSICS OF THE LIVING STATE AT ICTP

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THE ORIGIN OF THE PROGRAMME

Fifteen years ago the programme "Physics of the Living State" was suggested and strongly supported by the first Director of the International Centre for Theoretical Physics (ICTP), Professor Abdus Salam, who in recent years, as we shall see below, made some significant contributions to the life sciences. During this period the programme has gained a position in the Academic Calendar that is greatly appreciated, particularly by over thirty Associate Members who are specifically involved in this activity, as well as by numerous scientists coming under an agreement with almost 300 Federated Institutes from developing countries. We intend to discuss the bases that led to the inclusion of the life sciences in the activities of the Centre.

THE GROWTH OF BIOLOGICAL THOUGHT

In his very influential book (with the same title of this section) Ernst Mayr argues, correctly in our view, against biology being an imperfect stepchild of the physical sciences. The history of taxonomy is a good point in question, for its traditional functions have been the identification of particular specimens and the classification of living things into a satisfactory conceptual order. From the time of Aristotle the basis of such order was not understood. For deep insights we had to wait for the advent of the birth of modern biology in the middle of the Nineteenth Century with the work of Charles Darwin.

In his *Origin of Species* a true revolution was brought about by incorporating a very wide range of biological phenomena within the scope of natural explanation, including an appropriate approach to taxonomy.

Darwin's theorizing in biology may have begun in 1838 (in his Notebook D), although for reasons that have been well documented elsewhere, the publication of his seminal book was delayed until 1859. The intellectual revolution initiated by Darwin has produced a far-reaching change in our thinking, even outside the strict boundaries of the natural sciences, but the radical departure from the biological science of his time consisted in formulating a mechanism, natural selection, for the evolution of life. At a time when the prevalent ideas in the scientific community were mathematical principles and physical laws, biology was enriched by Darwin with the concepts of chance and probability.

ROLE OF PHYSICS IN BIOLOGY

In spite of the fact that it is widely appreciated that biology is not the imperfect stepchild of the physical sciences, physics itself has nevertheless had a valuable influence on the life sciences, particularly when a century after the publication of *The Origin of Species,* in the 1950s, the molecular bases of genetics were searched for with precise experiments.

During the 1940s physicists and physical chemists made vital contributions to the transition of biology into an experimental phase, in which traditional physical subdisciplines were to make modern molecular biology possible. The theoretical physicist Max Delbrück had contacts with radiation biologists. Learning about mutations, he foresaw the possibility of linking them to the lesions produced by a physical agent acting on the atoms of the still-to-be-discovered genetic material. This important step in the development of modern science was popularised by the theoretical physicist, Erwin Schrödinger, working during that decade at the Dublin Institute for Advanced Studies. He delivered at Trinity College, Dublin, a set of lectures, known to us through the influential book *What is Life?*

In those early years, when science was still ignorant of the chemical nature of the carrier of genetic information, a generation of physicists was responsible for the birth of the new biology, together with colleagues trained in the more traditional branches of the biological sciences. This group included, Sir Francis Crick, who graduated in physics at University College, London, whom Lewis Wolpert has referred to as "the genius theoretical biologist of our age" [1].

However, before we go further with a brief survey of the origins of the fruitful interaction between two of the basic sciences: biology and physics, we wish to consider in the context of our own ICTP the elements of science policy that influenced the development of the life sciences in Trieste.

MAIN OBJECTIVES OF THE ICTP PROGRAMME ON PHYSICS OF THE LIVING STATE

The insertion of the programme of Physics of the Living State into the Centre's activities goes back deep into its 30-year history: in the "Report of the *ad hoc* Consultative Committee" chaired by Professor Paul T. Matthews in 1983, it was pointed out that there had been a preliminary encouragement for the ICTP scientific programme to receive

Figure caption: *Sir Francis Crick and Professor Abdus Salam during a break at the Main Hall of the International Centre for Theoretical Physics (ICTP), at the International Symposium on Contemporary Physics, which took place in Trieste from 7 to 29 June, 1968, on the occasion of the inauguration of the elegant Main Building of ICTP in the grounds* ***o****f Miramare Park, near Grignano. This event took place only four years after the inauguration of ICTP had taken place in the building that had been assigned to it in Piazza Oberdan in the city of Trieste. Those of us that were fortunate enough to participate in the Miramare Symposium were particularly impressed with Salam's far-reaching vision of Physics, in which there are no artificial barriers between the basic sciences of biology and physics.*

"its strong support for the wide interpretation which the Centre has put, with the approval of the Scientific Council, on the recommendations of the Van Hove Committee (1974). This programme now includes activities in ... Physics of the Living State".

In the *Van Hove ad hoc Committee Report* itself we find that the authors of this document "believe that the overriding consideration in the subject matter programme of the Centre should continue to be the intellectual quality and generality of the work and its contribution towards exhibiting the intellectual unity of physical theory... The condensed matter programme offers good opportunities for branching out to additional topics of importance, such as solid state applied to biophysics. Many developing countries have strong traditional groups in biology and this topic would provide an important interdisciplinary activity".

FOUR AREAS OF THE LIFE SCIENCES AT ICTP: BIOPHYSICS, MEDICAL PHYSICS, NEUROPHYSICS, AND THE ORIGIN OF LIFE

Returning to the recent history of science, we now consider the particular areas in the biological sciences that have flourished at ICTP. When approaching the physical foundations of the life sciences (*biophysics)* Delbrück had to introduce precise methods of experimentation to study viruses, his chosen experimental system. A little later other physicists thought about various aspects of physiology, in particular focusing attention on haemoglobin, a blood protein of vertebrates made up of four subunits. In the 1940s biochemists realized that the method devised by the physicist Sir Lawrence Bragg to decode diffraction patterns of crystals might be equally well applied to protein crystals.

In 1959 Sir John Kendrew and co-workers solved the structure of the first protein molecule, myoglobin, similar to a subunit of haemoglobin and needed to bind oxygen in muscle. The time required for such structural investigations has been reduced with the advent of modern computers; it is even possible today to study the structure, amongst others, of a variety of complex biomolecules relevant to the fuctioning of the central nervous system. Thus the approach to *neurophysics* by means of modern molecular biology is one of the most exciting areas of research in the life sciences, and one that has been developed at ICTP through a series of colleges, in which participants from the Third World and industrialized nations have been able to present their work in oral and poster presentations (not only in these Colleges, but also in the other activities in the Programme of Physics of the Living State). Within this format it has been possible to consider neurophysics in a broad context of neuronal structure and function, as well as addressing the important issues of perception, learning and memory.

Advanced physical techniques have allowed the systematic study of all the main macromolecules of life: proteins and nucleic acids (DNA and RNA), as well as the important macromolecules of the cell membrane (lipids and polysaccharides). Throughout the 15 years since scientific activities began in the life sciences, the Biophysics Colleges have covered the study of these biomolecules. For the reasons mentioned above, protein crystallography has been emphasized in our Colleges. Specific topics have also been included in which physical processes are relevant, for instance, electron transfer in the reaction centres of bacteria, where the main intermediate steps of photosynthesis take place.

However, another aspect of biophysics is also relevant: at present there is a flood of data coming from the sequencing of the entire human genome (the sequencing of lower organisms is also currently in progress, such as the yeast *Saccharomyces cerevisiae* and the nematode *Caenorhabditis elegans,* the consideration of which was introduced into experimental biology by Sydney Brenner, who together with Crick participated in the Miramare Symposium (cf., figure caption). For these reasons biophysicists have to become computer literate and change our approach to the study of life. The starting point of research in biology, in the words of Walter Gilbert, "...will be theoretical. An individual scientist will begin with a theoretical conjecture, only then turning to experiment to follow or test that hypothesis" [2]. These factors have led to the introduction of the new subject of bioinformatics in our Biophysics Colleges.

A third way in which physics has had considerable impact in the life sciences is through the clinical application of physical techniques *(medical physics)*. For example, in dosimetry, by contributing to maintain safety standards in the various exposures that the normal population is currently being exposed to in dentistry, mammography, and normal routine scans with invasive techniques such as X-rays. Another major contribution of the physical sciences in the clinical sector is the problem of imaging for medical diagnosis: magnetic resonance imaging (MRI) responds to water because it focuses on the behaviour of hydrogen atoms in water molecules. This allows MRI to do certain things better than alternative scanners, such as distinguishing between the brain's white matter and water-rich gray matter. Bones, which contain little water, do not appear at all in MRI; this allows us to observe tissue surrounded by bone, such as the brain.

The ICTP Colleges of Medical Physics have covered both fields, dosimetry and imaging, including MRI and a whole variety of accessory techniques. Some of these have taken full advantage of progress in our understanding of elementary particle interactions, particularly synchrotron radiation with the experimental facilities that Trieste has provided in its Research Area; this consists of an intense form of electromagnetic radiation that spans all wavelengths, including X-rays. The early experiments on this extremely useful form of radiation were carried out at accelerators designed for the study of elementary particle physics, which emit synchrotron radiation as a by-product. The Trieste source has an advanced design that is contributing to both our Medical Physics as well as our Biophysics Colleges.

An additional technique includes computer tomography (CT), in which a fan-shaped X-ray beam produces a view of a cross-section of the body's interior; further techniques are positron emission tomography and single photon emission computed tomography. The ICTP Colleges of Medical Physics have emphasised quality control in X-ray imaging; a technique which is used extensively, but not always appropriate safety measures are taken regarding patient's doses, in both industrialized and Third World countries. CT image quality has also been highlighted in our recent Colleges. At a more fundamental level, the *origin of life* is currently one of the most attractive interdisciplinary fields, in which major components come from the physical, as well as the earth sciences. The most ancient life forms known are colonies of bacterial microfossils, discovered by J. William Schopf in Western Australia in the early 1990s, to which a date of some 3500 million years before the present (Mybp) may be assigned.

However, according to geochemical work of Manfred Schidlowski it is not to be excluded that photosynthetic bacteria might be as old as some of the oldest extant rocks available, following the field work in Western Greenland of Stephen Moorbath and others, retrieving rocks to which one may assign dates of the order of 3800 Mybp, from a very ancient geologic era, the early Archean; this date should be compared with the age of the Earth itself, of some 4600 Mybp. But the identification of the mechanism for the initiation of life has been in the minds of philosophers and theologians for as long as civilization has existed. In modern times with the pioneering work of Alexander Oparin, Sidney Fox, John Oro, Cyril Ponnnamperuma and others, the discipline has reached maturity as a research field, and the physics of the origin and evolution of life has become a valid topic of interdisciplinary research, to which the Fourth Trieste Conference on Chemical Evolution turned its attention.

ICTP SCIENTISTS IN PHYSICS OF THE LIVING STATE

With such clear and well defined objectives in the Programme of Physics of the Living State formulated by both the *Van Hove* as well as the *Matthews ad hoc Committees,* the personal interest of Abdus Salam, in the wide area of theoretical biology was a key factor in the development of the Programme. From the mid-1980s he encouraged some long-term visiting scientists, such as the present writer, to join him in sequences of seminars on basic topics in molecular biology with special emphasis on the origin of the genetic code, the dictionary that relates the four-letter language of the nucleic acids to the twenty-letter language of the proteins. Our discussions centred on the deviations of the "universal" code which have been observed in the protozoans and some bacteria. We were particularly delighted when two scientists from Brazil (Jose Eduardo and Yvone Maria Hornos) presented in an ICTP seminar, in early 1991, their preliminary steps in their eventually successful search for symmetries of the genetic code.

However, a bigger impact on the Centre's activities came at the beginning of the 1990s from Abdus Salam's deep interest in another topic in theoretical biology (closer in its content to the work that had earlier led to his Nobel Prize in Physics) namely, the role of symmetry in the living state, as we shall see below. He gave a strong impulse to the Programme with his own research in the topic of the asymmetry of the macromolecules of life, discussed in his five publications from 1990 till 1993. The first unifying principle in biochemistry is that the key molecules: amino acids, sugars, and natural lecithins (phospholipids), have the same 'handedness', or 'chirality'. Chiral molecules and their corresponding mirror images may be defined by left (L), or right (D) optical / rotatory dispersion.

Remarkably, this is true for all organisms with the exception of bacterial cell walls, which contain D-amino acids, as in the case of *Bacillus brevis* or *Lactobacillus arabinosus*. However, we may state in general that living systems translate their genes, following the rules of the genetic code, into proteins composed of twenty L-amino acids.

The search for the origin of chirality in the effects of the weak interaction started in the 1950s. In a substantial body of previous work by many authors, the parity-violating electroweak neutral current has been suggested as the main physical force inducing observed biochirality. Abdus Salam's approach also invoked the electroweak interaction, but was original in appealing to further physical concepts that may apply at the end of chemical evolution. He pointed out a particular cooperative phenomenon that may have taken place, namely, a phase transition beneath a certain critical temperature T_c. Amino acids that had been synthesized earlier from various precursors entered into a new phase which was a Bose condensed mode. Abdus Salam asked the present writer to prepare a paper for the Journal Chirality (1991) at the same time as his own paper in the

Journal of Molecular Evolution (1991), in order to reach a wider audience of scientists interested in the pharmacological, biological, and chemical consequences of molecular asymmetry, and some of the arguments in that paper may be relevant here.

The physical concepts: cooperative phenomena and condensation led Salam to suggest that the electromagnetic force is not the only force which can produce chemical effects: the Z^o component of the electroweak force, in spite of the fact that its effects appear to be negligible at low energies, may play an active role in chemistry.

The reasons for the proposed chemical role of the parity-violating weak interactions may be found in some calculations in quantum chemistry of Stephen Mason, Alexandra MacDermott and George Tranter working in the United Kingdom. More recently, the independent calculation of Ayaz Bakasov, Tae-Kyu Ha and Martin Quack from Zurich give some support to the previous assumptions that Salam had used from quantum chemistry in his own work. The results of these calculations indicate that amino acids, for which results have been completed are L-stabilized relative to their D-partners for configurations in aqueous media. This stability affects 1 out of 10^{17} molecules at room temperature, since

$$10^{-17} \approx (3\text{x}10^{-19} \text{ eV} / 300\text{K}k_B)$$

(where K denotes degrees Kelvin, and k_B denotes the Boltzmann constant), a small quantity that has deterred many chemists from accepting the effects of the electroweak interactions as a possible source of optical symmetry; nevertheless, in the conjectured phase transition, sufficiently large effects were obtained from the inclusion of the top quark (t) and top antiquark (t) in an enlarged version of the standard theory. He also suggested the extinction of further macroscopic quantum mechanical effects below T_c , such as the value of the critical magnetic field for the Meissner effect, which normally are nonvanishing only for temperatures above T_c.

Ponnamperuma, who was also attracted to this original approach to the question of chirality, proceeded to test these ideas in his own world-renowned Laboratory of Chemical Evolution at the University of Maryland. Although these experiments failed to detect the presence of the postulated phase transition, they have been continued by other groups, particularly by Wang Wenqing and co-workers in Beijing.

The interaction between Trieste and Maryland led Abdus Salam to propose the initiation of a sequence of high-level conferences on chemical evolution, centering not only on the specific relic of the origin of life, but from the beginning it was suggested that the Trieste Conferences on Chemical Evolution should cover the entire subject of the origin and evolution of life on Earth in regular meetings, not excluding the important component of exobiology, as understood in the well-known research work of extraterrestrial life by Frank Drake in California and Jean Heidmann in Paris, and of the atmospheres of Solar-System satellites by François Raulin in Paris.

When Abdus Salam asked the present author in the spring of 1991 to take charge of the organization of these conferences under the general direction of Ponnamperuma, we could not have forseen that we would have been able to maintain a series for four consecutive years. Sidney Fox referred to the Third Trieste Conference on Chemical Evolution as "a forward-looking meeting on The First Cell" [3].

CONFERENCES AND THE TRAINING PROGRAMMES: COLLEGES AND WORKSHOPS

The initiation of the Programme of Physics of the Living State found fertile ground in the ICTP structures and scientists that had come to Trieste in the previous fifteen years, since Professor Paolo Budinich had suggested to Salam in the early 1960s that Trieste should support the foundation of ICTP. From 1980 efforts to initiate work in Medical Physics, Biophysics, and Neurophysics had made Trieste the usual meeting ground for a large number of life scientists. This was only possible as there were permanent physicists at the Institute of Theoretical Physics of the University of Trieste who were interested in the application of physics to the life sciences and shared the original vision of Salam, notably Giorgio Alberi, Luciano Bertocchi, and Giancarlo Ghirardi. Support came also when Antonio Borsellino, a biophysicist who retired from the University of Genoa, took up a position at the Trieste Scuola Internazionale di Studi Avanzati, accepting the invitation from Budinich, its first Director.

This group of Italian scientists was joined by high-level international scientists who shaped the Trieste College of Medical Physics (Anna Benini, John Cameron, Roberto Cesareo, Horacio Farach, Sergio Mascarenhas and, more recently, Perry Sprawls), as well as the *Giorgio Alberi Memorial Conferences* on Medical Physics (Pietro Baxa, Bertocchi and Eduardo Castelli).

The early and subsequent stages of the Biophysics College were supported by the valuable work of Farach and Mascarenhas, and in subsequent years several scientists have collaborated including Kalpathy Easwaran, Jose Nelson Onuchic, Franco Quadrifoglio and, more recently, Sandor Pongor and the present writer. The Neurophysics work initiated by Borsellino in 1984 was turned into a successful activity with the collaboration of Gadi Geiger, Jon Kaas and Obaid Siddiqi. Currently the College bears the name of the *Antonio Borsellino College of Neurophysics*.

It was against this background that the Trieste Conferences on Chemical Evolution took place from 1992 till 1995. The success of these events is now widely recognised, and saw the participation, not only of Salam (1992) and Ponnamperuma, who directed the first three conferences, but also of two of the pioneers in the origin-of-life studies (Fox and Oro); to these we must add Gustaf Arrhenius, Harrick Baltscheffsky, Mohindra Chadha, Georgi Gladyshev, Vitali Goldanskii, J. Mayo Greenberg, Kaoru Harada, Otto Kandler, Mikhail Kritsky, Igor Kulaev, MacDermott, Moorbath, Alicia Negron-Mendoza, Tahiro Oshima, Raulin, Peter Schuster, Schidlowski, Schopf and Wang.

The Fourth Trieste Conference on Chemical Evolution, co-directed with Raulin, was devoted to Physics of the Origin and Evolution of Life. Amongst others, the invited participants included Baltscheffsky, George Coyne, David Cline, Drake, Fox, Greenberg, Heidmann, Yoji Ishikawa, Lajos Keszthelyi, Kensei Kobayashi, MacDermott, Moorbath, Koichiro Matsuno, Christopher McKay, Oro and Takeshi Saito, Jean Schneider and Joseph Seckbach. In all of these conferences there has also been a consistent group of Third World participants, including Chadha, Michael Eze, the Hornos, Jamal Islam, Narendra Kumar, Negron-Mendoza, Rafael Navarro-Gonzalez, Wang and Yu-Fen Zhao.

CONCLUSIONS

Some of the reasons for the success of the Programme are: the intrinsic social importance of the clinical applications covered by the activity of the seven Colleges on Medical Physics and the four *Giorgio Alberi Memorial Conferences;* the basic nature of the research reported in the six Colleges on Biophysics ; the implications of the studies of the brain considered in the four Colleges on Neurophysics and the *First Borsellino College of Neurophysics* and, finally, the universal appeal of the search for our own origins as it may be illustrated, for instance, with the work reported in the recent *Cyril Ponnamperuma Memorial Conference*.

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