Biofísica Magazine

May - Aug 2018
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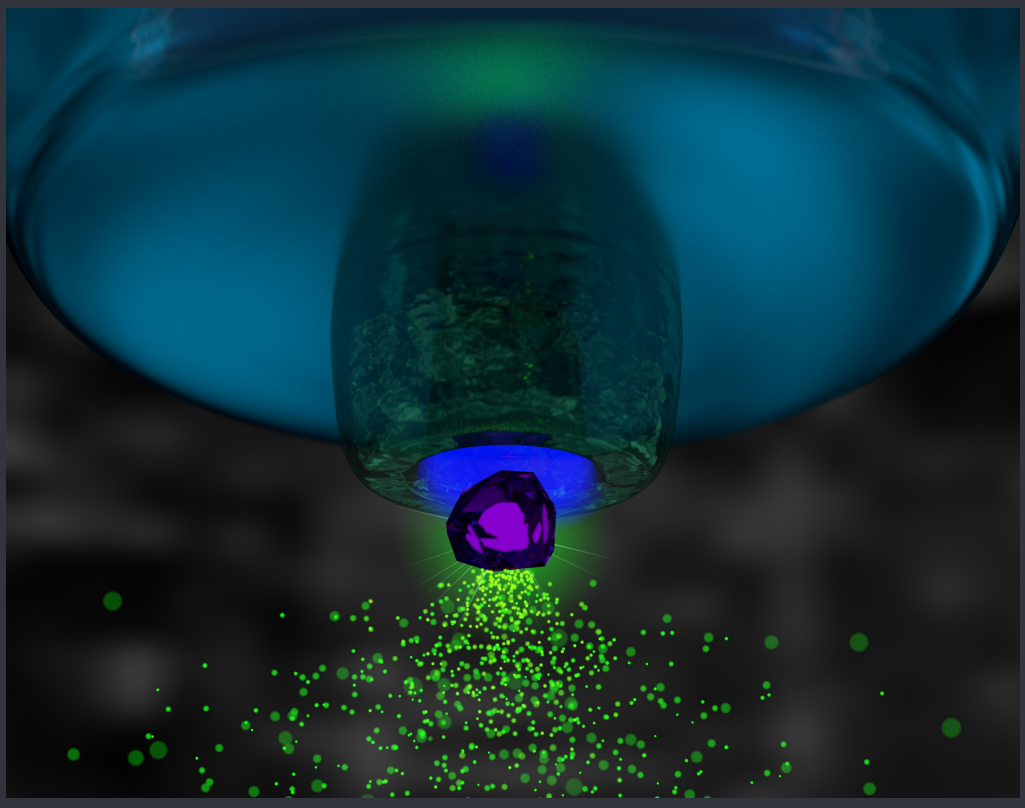

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ISSN 2445-43111

ISSN 2445-4311

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EDITORIAL / ANALYSIS

A view on peer review

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Scrutiny of scientific work is a fundamental pillar of Science. It is not only needed for correctness, in a purely technical sense, but also takes care of originality, novelty and significance, ensuring that the scientific work contributes to generating new knowledge. There are two stages where this task is especially important: before the start of a scientific investigation (*projects*) and when the investigation yields results (*publications*). At both stages the dominant (almost exclusive) method for evaluation is reviewing by peers.

A precursor of peer review began in England in the early 19 th century, with referees commissioned by the Royal Society of London to write reports on manuscripts sent for publication in Philosophical Transactions [1]. A standardized *referee* system developed from this point among the English scientific societies and slowly spread to independent journals and outside the Anglophone world. However, it was in the 1960s when refereeing propagated as the method to objectively judge Science (although the embracement of this system was delayed by some journals, like Nature, which adopted it in 1973) [1]. During that period of the 20 th century the scientific activities experienced a huge expansion, especially in the USA, with a massive increase in public funding and a parallel social and political demand for objective methods to judge scientific quality. In fact, the term peer review was first used in evaluation procedures by American funding agencies of that time and was later used as a synonym of refereeing for the case of revision of publications. Thus, classical peer review, either of projects or papers, is a relatively young system. But perhaps most importantly, it has never consolidated as a unique solid model and was, from the beginning, put into question [1]. It is then not surprising that in current times, with technological changes affecting the ways of communicating Science, the future of peer review is subject of a particularly vivid debate.

Classical peer review is relatively young. It was questioned from the beginning and has never consolidated as a unique model

Overflowed system

Today, the discussion about peer review connects with multiple other problems of Science [2] as well as with profound changes affecting modern publishing [3, 4]. With the dominance of *bibliometrics* as the measure to evaluate scientific performance, publishing has acquired a tremendous importance [5] and peer review, as the method employed to control what is published (and where), has become a crucial variable. Added to this, complex problems have emerged that affect directly to the quality of Science and thus uncover inefficiencies of the evaluation mechanisms, like poor reproducibility, fabrication of data, plagiarism or even direct corruption of the peer review system [6]. One would expect that the response of the scientific community to the clear need of stronger and more effective evaluation procedures would be to strengthen peer review, or even to evolve it into a new system, adapted to the challenges of the present and the future. However, in the vast majority of cases peer review continues being performed as it was conceived more than 50 years ago, despite its well known weaknesses.

> **Peer review, as the method to control what is published (and where), has become a crucial variable**

The bibliometric *epidemy* [5] contributes to inflate the number of publications, and with that, the numbers of publishers and journals have also grown exponentially. This process is fuelled by digitalization and automation, which makes publishing easier, cheaper and quicker than ever. But can proper assessment, criticism and discussion of scientific work be similarly escalated and accelerated? Obviously not. First, this part of the business cannot be easily automatized and needs the cautious time and attention of expert human readers / *evaluators*. Furthermore, the scientific methodology is quickly changing and becoming more and more sophisticated. All branches of natural sciences (including, of course, Biophysics) are increasingly becoming multidisciplinary, meaning that diverse and well prepared experts are needed to judge the scientific work. With this requirements it is easy to visualize that the pool of possible (capable) referees must be of smaller size than the pool of their peer authors. In practice, the pool of reviewers is further reduced because of the lack of incentives to perform difficult, time constrained and barely recognized reviewing tasks. This all makes finding adequate referees an herculean exercise and accentuates the weakness of the system, in a vicious circle.

Blindness *vs* transparency?

In the scientific community there is consensus about the importance of a solid peer review system and the need to tailor its traditional scheme for current and future exigencies. However, there is no clear consensus yet about the actions to take –more than paying homage to the stoic anonymous reviewers (**Fig. 1**) [7].

Figure 1. Homage to an anonymous peer reviewer
The monument was placed in May 2017 in the courtyard of the Institute of Education at Moscow's Higher School of Economics – HSE [7].

A major discussion is settled about the convenient level of transparency [8]. First, we remind that the pioneer refereeing English system, as conceived and exercised originally by William Whewell [1], started being completely open, with reports published and signed by the referee (in a especial *Proceedings* journal). But it was soon realized that such an option prevented criticism and discouraged negative reports. Thus, after a couple of years of openness, refereeing became anonymous and reports were no longer published [1]. Today's classical peer review is still mainly *single blinded*, with the identity of the authors know by reviewers, who remain unknown to the authors. This system has been attacked in two opposing directions. On the one hand, it is argued that the uncovered identity of authors facilitates possible discrimination because of gender, ethnic background, country of affiliation, personal relations or prestige of previous work. This has led to defend a *double-blinded* system [9], with unknown identities of both authors and referees. Although this option is preferred, according to some studies, it is recognized that is very difficult in practice to implement, since in many cases the type of work, cited references and other details can betray the identity of authors [10].

> **Openness is seen as positive: Fits with tendencies of modern publishing, brings transparency and provides ways to reward reviewers**

On the other hand, it has been pointed out that a covered identity makes referees potentially immune from their possible unfair, harsh or unsound criticisms, which is used to defend a completely open system. Openness, at different levels, is gaining adepts as it fits well with new tendencies of open publishing and has a positive connotation, because is seen as a way to bring transparency to the publication process. It also can provide ways to reward the reviewers *via* publication of their reports along with authors' manuscripts, which helps visualizing the

usefulness of the peer reviewing process, even when the identity of the reviewer is kept anonymous. Although still a minority [11], an increasing number of journals are already experimenting with various degrees of openness. For instance, *Nature Communications* and the four journals published by *EMBO* offer the authors (and referees) the choice of open peer review, although the identity of the reviewers is not revealed. A number of medical journals like those from *BioMed Central* and *BMJ* have decided to go further and publish also the complete pre-publication and peer review history, including the name and affiliation of reviewers [8]. It is argued that this fully open model has the positive advantages of reviewers being more honest and constructive [12], although critics note that it may favour prestigious institutions from English speaking countries [13] or discourage criticism by junior researchers, who may fear retaliation by senior colleagues [14]. Despite this concerns, a majority of participants in the meeting on *Transparency, Recognition, and Innovation in Peer Review in the Life Sciences*, organized by ASAPbio, HHMI and Wellcome on February 7-9, 2018 at HHMI headquarters in Chevy Chase [14], (~81%, voting in person or through the internet) favoured the option of "publishing the content of peer reviews (with or without the reviewers' names) and making these reports a formal part of the scholarly record with an associated DOI". In line with this, a large survey published in *PLoS ONE* by the end of 2017 also shows support (~60%) among the scientific community to open peer review [15].

Incentives and rewards

Expert scientists are busy people with exhausting responsibilities. Is "sense of duty" enough to involve them in peer review?

We all know that the referee work is a voluntary "duty" with hardly any other motivation than the personal conviction to contribute to the soundness of one's scientific discipline. But, almost by definition, the required expert scientists are very busy people under strong stress and with exhausting responsibilities at their institutions and research groups. Is "sense of duty" enough to involve them in the huge task of peer review?

Although a study promoted by Taylor & Francis Group concluded that "receiving free access to the Journal is the factor that would incentivise people most to review" [16], according to a recent survey [17], researchers ask for other incentives (**Fig. 2**). Particularly, they would like that peer reviewing activities are "taken into consideration when they are evaluated for grants, jobs or promotions." The issue was among the ones discussed in the aforementioned ASAPbio meeting [14], where the majority of participants favoured a "formal recognition and credit for peer review activities from funding agencies and institutions, and acknowledging all contributors to a peer review report (such as students and postdocs) when submitting it to a journal."

The need for proper peer review recognition is intensively debated [18, 19]. It has even been argued that free reviewing (and editorial work) is "not fair in ethical terms", especially when publishing is such a profitable business [20]. Setting a standard mechanism for recognition of peer review activities is a main target of a partner initiative by F1000 and ORCID [21].

Meanwhile, Publons has created a data-base and a validation system to make possible that researchers who participate in peer review get credited from their effort [22]. The goal is double: On the one hand, it intends to work as a platform to share peer reviews and discussions, provided that their dissemination is not prohibited by the journals involved in the publications. On the other hand, researchers who register at Publons are able to show their record of verifiable peer review activities, so that they can get credit to be used in their individual evaluations, either for performance enquiries, promotions or grant applications. A few institutions, like Harvard, recognize already peer review and editorial activities,

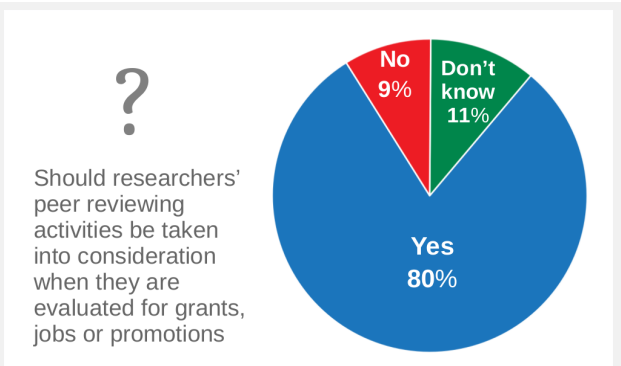

Figure 2. Opinion of scientists about recognition of their peer reviewing activities. Results of a survey carried out within the context of a recent ASAPbio | HHMI | Wellcome meeting on *Transparency, Recognition, and Innovation in Peer Review in the Life Sciences* (Chevy Chase, Maryland, February 7–9, 2018) [17].

which must be reported in annual evaluations. This is a big step forward, but needs to extend worldwide in order to exert a significant impact.

In summary, there is little doubt that a deep improvement of the strategies for assessing the quality of Science is a most urgent need. However, as we just discussed, the general perception is that this crucial and demanding task is not sufficiently rewarded. Very interesting initiatives exist to adapt, at multiple levels, classical peer review. Although the changes already in place seem mostly experimental, we can foresee that a renewed refereeing system, characterized by increased openness, rewarding and recognition, will soon crystallize.

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BEYOND BIOPHYSICS

Biophysics in microbiology

A conversation with Víctor de Lorenzo

Lucía García-Ortega, *UCM (Spain)*.

When I was proposed to write on this topic it sounded to me like a wonderful idea, since I thought that Víctor, like me, is a "side effect biophysicist". In my case, I got into biophysics as a consequence of my interest in molecular biology, proteins and their interactions with lipids. In Víctor's case, I considered his quantitative approach to microbiology to be highly biophysical. However, what a priori I thought it would be the *side effect* of a microbiologist, turned out to be an interesting description of microbiology from biophysical and mathematical points of view.

Victor de Lorenzo is the head of the Laboratory of Environmental Molecular Microbiology at the National Center of Biotechnology , an experimental isle within the ***Systems Biology*** Department, dominated by theoretical research groups. His laboratory is a mixture of biologists, engineers and network analysts dealing with the domestication of microorganisms for biotechnological purposes, like the elimination or transformation of pollutants by genetic and metabolic modifications of the soil bacterium *Pseudomonas putida*.

> **Biology needs to transform from a discipline based on phenomena description to one supported by general rules, standardized metrics and therefore able to make predictions**

Talking with him, one can feel his chemical background as he points out, with criticism, the "absence" of laws and theories in biology: How biology needs to transform from a discipline based on phenomena description to one supported by general rules, standardized metrics and therefore able to make predictions. This is a thought that I completely agree with, as I guess will also agree a majority of scientists from areas like mathematics, chemistry and physics: How tremendously is biology being enriched by their contribution! "Only physics is real science, the others are like collecting stamps", Víctor jokes, to illustrate his line of thought.

This new point of view in biology is developing fast now, and Víctor is a perfect example. Genetic engineering has moved from what it was back in the 80s to what it is nowadays: a precise methodology for designing genetic tools in a logical way for multiple applications. In fact, it can be argued that this more systematic point of view of environmental microbiology has prevented it from disappearing, since previous approximations gave results difficult to extrapolate to naturally occurring environments. As it happens in clinical biology, where unexpected results appear when translating hypotheses from simplistic laboratory experiments to living organisms, in bioremediation a multitude of variables have to be considered. These variables involve, not only single organisms, but also their interactions with a widely diverse surrounding population in a changing environment, where physical and chemical properties affect and constrain their behavior.

Systems biology emerged from the application of network theory to biological processes and became a new conceptual framework for understanding biology, playing an essential role in describing its complexity, by defining behavior patterns

and finding logical connections in biological processes. Even today, when the rate of published scientific results is overwhelming, biology still needs to convert vast amounts of information from particular cases to either integrated or transferable ones. Hand in hand goes synthetic biology, which applies similar strategies to modify and create new functions in life.

Prof. Víctor de Lorenzo, National Center of Biotechnology – CNB | CSIC, Madrid.

> **Besides the Evolution Theory and the Central Dogma, what else do we have?**

Víctor pioneered this technological handling of microbiology and proudly recalls the first European workshop organized in Spain in 2005 (*Constructing and deconstructing life*). However, more than thinking of complexity, he pursues optimization through simplification by a systematic genetic manipulation of microorganisms. In contrast to the paradigmatic goal of synthetic biology, that is the creation of an artificial living cell from scratch, he sounds more pragmatic: "Better if we take advantage of millions of years of evolution to our benefit by modifying and controlling already living organisms".

He is very enthusiastic with this new concept of biology. "Synthetic biology attracts lots of talent, mainly physicists and engineers, since it is a very creative field, where rules and parameters are still to be defined". But he observes that *languages* are still very different and communication is not always easy. Other aspects are also under construction; for example, the perspective of classical biology as a descriptive science sometimes underestimates the work of biologists, considered by theorists as mere data generators. As member of several international research boards, he recognizes the effort that physicists, engineers and all those dedicated to synthetic biology are making in finding and defining metrics useful in biology, as something essential for this transformation if we want to standardize laws, rules and metric units. "Besides the Evolution Theory and the Central Dogma, what else do we have?" Víctor says. That being said, more biologists need to populate this area of knowledge for a more integrative development. However, although he acknowledges the great influence of physics over biology, he is more skeptical with some other contributions of biophysics leading to sophisticated techniques; in particular, those related to imaging. In his opinion, we are converting the study of biology into a "sequence of images"; high quality images, but still surrounded by arbitrary units and qualitative conclusions difficult to reproduce. This worries him and reinforces his idea of working hard in the direction of standardizing and quantitatively measuring biological events.

> **Basic knowledge in transversal subjects has to be conveyed in all Science degrees: Experimental handling in biochemistry for physicists and a good basis in mathematics for biologists**

Is education in biology envisioning this transformation? From my experience at the Complutense University, biophysics and systems biology have minor roles in biology and biochemistry degrees. Víctor recognizes that there is no trivial solution for that. It remains an open discussion and the best model is not yet defined. Postgraduate courses specialized in these areas, when offered to students with very different backgrounds, have very good results in terms of promotion of creativity. However, from Víctor's experience, the basic knowledge in transversal subjects has to be conveyed in all Science degrees, i.e. experimental handling in biochemistry for physicists and a good basis in mathematics for biologists. Nevertheless, the systematic approach to biology needs to be promoted even more among biologists. For Víctor de Lorenzo, systems and synthetic biology are the latest revolution in biology, essential to universalize hypothesis, create biological theories and make reliable predictions. This latter, however, is the main handicap so far and where most of the criticisms focus on.

And now that I am writing and reflecting on this inspiring conversation, a final question comes to my mind: Would it be possible to predict the great ability to adaptation of living beings?

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Biofísica Magazine

COOL BIOPHYSICS

The eyes of chemistry

(Dedicated to Geoffrey Roughton)

Isabel Usón[1,2] & Claudia Millán,[2]
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For most humans, *vision* constitutes the main way to apprehend the world. We understand information best when we can see it in a three-dimensional frame. This explains the impact of X-ray crystallography from its onset, a century ago, as it allows seeing in atomic detail the main players in chemical and biological processes. However, deriving a three-dimensional structure from the diffraction experiment requires overcoming *the phase problem*. The evolution of crystallographic methods along the quest to retrieve the phases, which are lost in the diffraction experiment, has been linked to milestones in chemistry and biology. The field of crystallography has arguably been marked by the character of its pioneers, which possibly determined the percentage of women scientists, the collaborative spirit or the support of education and science in emergent economies.

Our group has developed structural methods to exploit the stereochemical knowledge present in small, yet very accurate, fragments. Their use to solve the central problem of crystallography, the phase problem, is implemented in our software ARCIMBOLDO. We are extending the use of fragments to map interpretation, other diffraction methods currently undergoing exciting development and structural bioinformatics. As illustrated in the painting by Giuseppe Arcimboldo, the information content derived from a correct combination of fragments goes beyond their simple addition.

This article reflects the “Ellerslie talk” held jointly (alternated contributions) by Claudia Millán and Isabel Usón at 9 Adams Road, Cambridge, on the 28th July 2017.

An image is worth a thousand spectra

In 1991, towards the end of my Ph.D. after the usual four years of dedicated work, I was starting to panic that what I could write in the thesis would be more fitting for the XIX than for the XX century. I had accumulated a lot of information on the synthesis and properties of organometallic platinum clusters but paradoxically, I did not know what they were or how to explain their properties. For example, I knew that from the reaction:

$$Pb^{2+} + [Pt(C_6F_5)_4]^{2-} \longrightarrow bright - green \quad (1)$$

I could isolate this luminescent cluster, which I had characterised by its spectra and determining its elemental composition. In solution, it was elusive, its instability precluding the use of solvents needed for NMR. I also had probed its reactivity but… I had no clue of what was happening at the molecular level. I knew all along that a *crystal structure* was needed. Indeed, solving the problems to obtain stable crystals, to measure the diffraction intensities and to determine the atomic structure displayed in **Fig. 1**, allowed placing all previous information in a visual framework and settled conclusively our many questions [**1**]. The structure confirmed the intended direct bonds between both types of metal centres and the interactions to the fluorine substituents in the ligands. I was delighted, and I thought about how

many others before me must have shared this same joy of literally seeing the answers so long pursued. But the structure also raised new questions: why was the coordination around lead, in oxidation state II, linear? Should there not be a stereochemically active lone pair of electrons? Why then was the structure not bent around the lead centre?

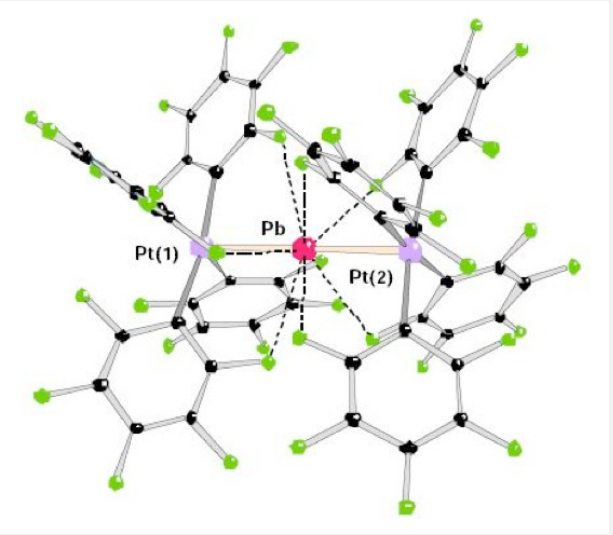


Figure 1. The three-dimensional view of a molecule in atomic detail. It provides a visual framework to all functional knowledge associated, as in the case of the anion $[Pt(C_6F_5)_4]^{2-}$ [1].

The Braggs shaped the character of crystallography

About one hundred years earlier, in 1895, X-rays had been discovered by Röntgen [2]. Their ability to penetrate matter and yield image information (**Fig. 2**, *left*) had been patent from the onset. Diffraction by crystals, by Max von Laue, Walther Friedrich and Paul Knipping, served to simultaneously establish the nature of X-rays and crystals [3]. From these findings, William Bragg and his son, sir Lawrence Bragg realized that in the case of molecules, the natural grating provided by crystals would be required to amplify the scattering signal, by bringing a large number of equivalent atoms to add their contributions [4]. We cannot see X-rays and if we want to experiment with light scattering on macroscopic objects and how it reflects periodicity and the underlying blocks making up the periodic object, we should choose the appropriate wavelength: monochromatic visible light. Among much excellent material available on-line to visualize diffraction on gratings, we would suggest a YouTube video [5] (**Video 1**) showing green light scattered on ***periodic***, everyday objects, such as spans of thread, strings of beads, screws, spiral springs mimicking the double helix structure adopted by DNA or sieves illustrating lattices! As can be appreciated in the video, we are not seeing an image of the illuminated items, but the pattern is obviously related to the periodicity and to the underlying structure of the object.

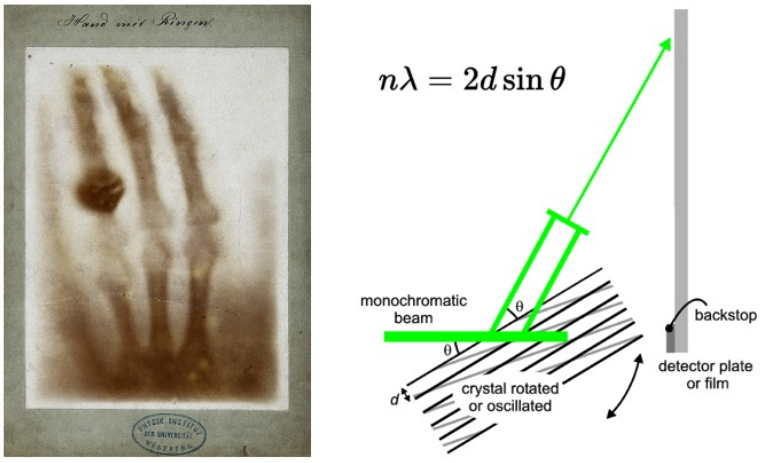


Figure 2. Röntgen's discovery and geometric illustration of Bragg's Law. **Left**, image recorded by Conrad Röntgen on 22nd December 1895 showing the hand of his wife, Anna Bertha Ludwig. **Right**, constructive interference geometry of X-rays incident to a crystal sample.

The fundamental law of diffraction is named *Bragg's Law*, and establishes the geometry of the diffraction pattern (**Fig. 2**, *right*). We can think of diffraction as reflection on sets of planes running through the crystal. Only at certain angles are the waves diffracted from different planes shifted by a whole number of wavelengths apart, i.e. in phase. For such angles, the intensity of the diffracted beams can be recorded on a detector. At other angles, the waves reflected from different planes are out of phase and cancel out.

Lawrence Bragg, was the first to perform structural analysis by X-ray crystallography, determining the structures of various inorganic salts, such as NaCl [6]. The Braggs analysed the diffraction pattern and figured out how it related to the structure in real space, placing the atoms that composed structures. Their work established the grounds for X-ray crystallography, as we know it today and was awarded a Nobel Prize in 1915,

following Max von Laue's prize from 1914.

Mentoring crystallographers regardless of their gender

The Braggs were not only pioneers in scientific terms. They also shaped the field by mentoring and influencing a new generation of crystallographers. In particular, support of women scientists can be appreciated in their scientific descent and in the opportunities they promoted women to, thus treating them as equals for the first time [7]. Prominent examples comprise Joan Evans, who was invited in 1923 by William Bragg to be the first woman to ever deliver a Discourse at the Royal Institution; Lucy Wilson, who was Lawrence Bragg's first research student in 1923-1924; Kathleen Lonsdale, one of the first two female Fellows of the Royal Society elected in 1945, had been a student in the group of William Bragg; Helen Megaw, the first female staff member in Cambridge's legendary Cavendish Laboratory, was appointed in 1946 by Lawrence Bragg.

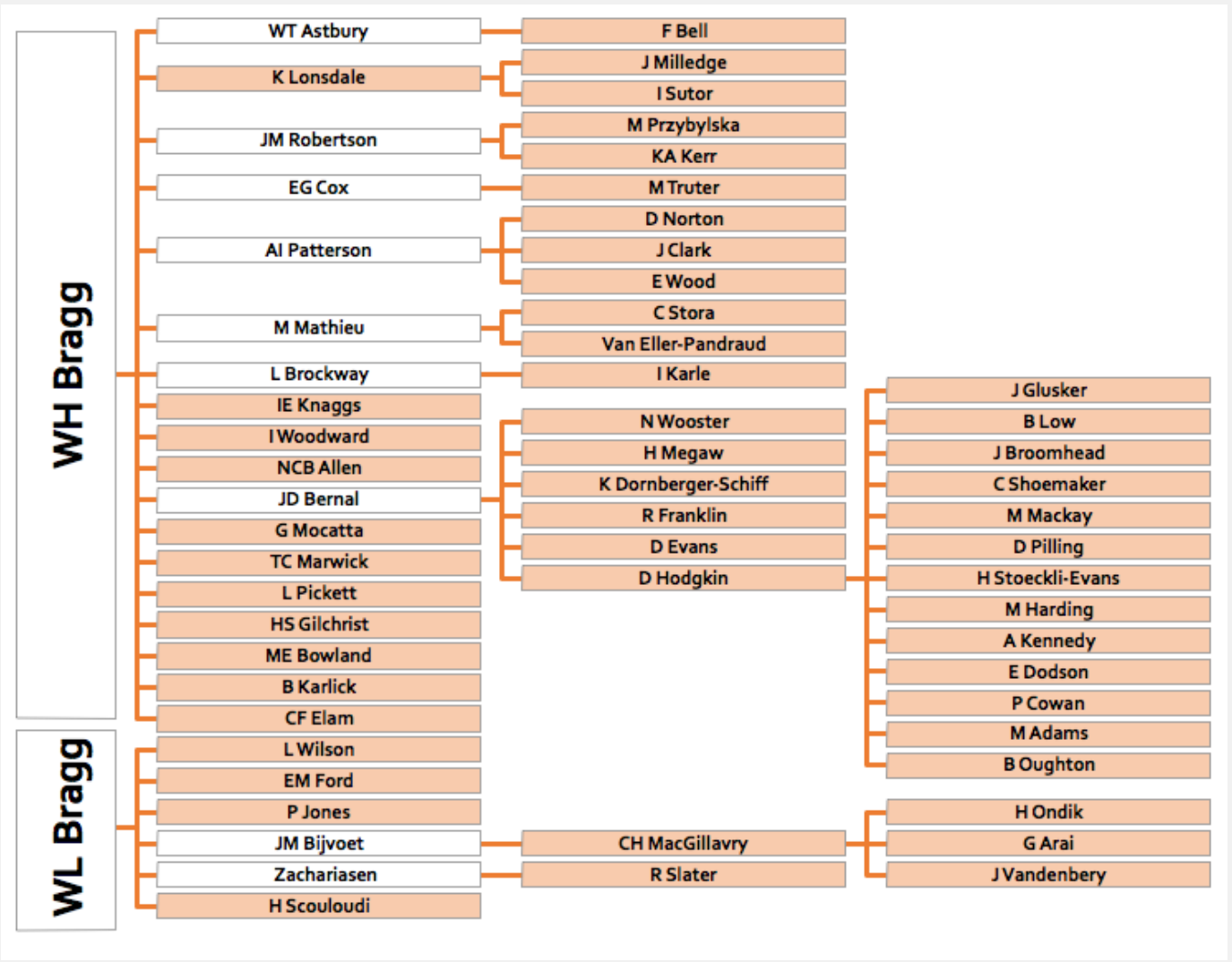


Figure 3. Partial scientific genealogy of the Braggs Female scientists are highlighted in sepia. Based on [7].

In the genealogy reproduced on **Fig. 3**, displaying part of the scientific descent of the Braggs it is noticeable the unusually high numbers of distinguished women scientists. In fact, possibly due to the Braggs' direct intervention, crystallography has been differentiated from other scientific fields by a higher participation of women, providing role models for young scientists and also for the collaborative, open, joy-in-discovery attitude in many of its distinguished members. However, the actual percentage of women in crystallography was much lower than the one commonly perceived. While the popular feeling is that nearly half of the researchers in this field were women, in truth they amounted to less than 15% of entries in the World directory of crystallographers by the year 1981 (updated figures are available but crystallography is currently practised by many scientists who do not define themselves primarily as

crystallographers).

This biased perception must have been brought about by having such prominent figures in the field as Dorothy Hodgkin Kathleen Lonsdale, Rosalind Franklin, Isabella Karle and still active in the present, Ada Yonath or Eleanor Dodson. Even in Spain, where the incorporation of women to academia cannot be compared with the UK, Sagrario Martínez-Carrera pioneered the development of crystallographic computing from the 50s on [8]. Nobel laureate Dorothy Hodgkin, who determined such key structures as penicillin and vitamin B12, was determinedly involved in the cause of scientists from, at the time, developing countries, in particular India and China. Eleanor Dodson, nucleated the "collaborative computing project number 4" (CCP4), which has provided a unique model of cooperation in crystallography and done much to actively support science and mentoring worldwide.

Regarding relatives, the wife of Lawrence Bragg was Alice Hopkinson. She and her cousin happened to share the same maiden name and both families used to live in the same street in Cambridge. The other Alice Hopkinson married Francis John Worsley Roughton. Alice Roughton was the first woman to obtain a Ph.D. in psychiatry in Cambridge. Not only did she study: she practised taking her commitment to an extreme. She was literally living with her patients, including psychotic cases or prospective convict teenagers, which she brought into her home. After World War II, she heard of the German physicists imprisoned in Farm Hall, near Cambridge. She contrived to reach an agreement whereby Hahn, Heisenberg and their colleagues would be fetched and brought to Cambridge every evening to participate in the academic life and dinner provided in high tables. Later on, she continued throwing her house open to refugees from every conflict, scholars, artists and stranded people from every nationality. Alice Roughton was a psychiatrist, a medical campaigner, a pioneer in the movement against nuclear weapons and a conservationist and her inspiring biography has been recently published [9]. But the story of structure and chemistry brings us back to Jack Roughton, professor of Colloidal Science at Trinity College.

The physiology of respiration

The role of atomic structure in providing a visual framework to all our indirect information and prompting new questions extends to many chemical contexts: for instance, something as immediate as the physiology of respiration, which we all exercise 13 times in a minute. Much was known of this process, thanks to the works of the physiologist Jack Roughton in Cambridge, before an atomic model could be envisaged. As a result of his efforts (which required constructing the apparatus to measure the reactions of haemoglobin with gases) the oxygen equilibrium curve, the thermodynamics and some of the kinetics of the reaction with oxygen seemed to be well understood. Also established were the binding of oxygen at the iron centre, whereas carbon dioxide was binding a different site, in the peptide chain, or the cooperativity among the four different haemoglobin subunits in the active species [10]. The Bohr effect, first discovered by physiologist Christian Bohr in 1904, explained how hydrogen ions and carbon dioxide affect the affinity of oxygen in haemoglobin. If the pH was below the normal physiological pH of 7.4, haemoglobin would not bind oxygen as well. But some vital gaps and anomalies remained by the time the structure was determined by Max Perutz [11].

Again, relating the previous knowledge to a three-dimensional frame provided conclusive information about the mechanism and the large structural changes involved, but opened new questions. For example, it was totally unexpected that the active sites, which were acting in cooperation, would be separated by large distances, rather than in immediate proximity. With this new structural insight, Jack Roughton continued researching the biochemistry of respiration from a new perspective [12].

The phase problem

As mentioned above, crystallography does not render a direct image, and no lenses for X-rays are available to reconstruct it. In order to calculate an electron density map, both the intensities (proportional to the squares of the *amplitudes F*) and the *phases φ* of the scattered beams, *hkl*, would be required, but only the former are recorded in the diffraction experiment:

$$\rho(xyz) = \frac{1}{V} \sum_{hkl=-\infty}^{+\infty} |F(hkl)| \, . \, e^{-2\pi i[hx+ky+lz-\phi(hkl)]}$$

Amplitudes — Phases?

The problem of phasing is highly non-linear and has a very poor radius of convergence, thus search, rather than minimisation methods are needed. Chemical structures can usually be solved *ab initio*, not requiring previous structural knowledge of the unknown structure or collection of additional experimental data. Directly solving the phase problem for small chemical structures, with up to 200 atoms is possible due to the excellent diffraction properties of typically well ordered crystals, allowing the measurement of many more independent reflections. This highly overdetermined problem, requiring comparatively few parameters, can be solved by computational brute force direct methods. The assumption of atomicity imposes statistical restraints on the phases. For the development of their equations to derive phases from the intensities, Herbert Hauptman and Jerome Karle received the Nobel Prize in 1985 [**13**]. It has been often rued, that Isabella Karle, who actually got the method to work and solved the first structures this way [**14**], did not get to share in the award.

Alternatively, the presence of a few heavy atoms can be used to solve the structure of chemical molecules by the Patterson function (the Fourier transform with F2 as coefficients), which can be calculated directly from the experimental data and gives information about interatomic distances, relating atoms with significantly more electrons than the rest of the structure [**15**].

In the case of macromolecules, the larger number of parameters and lower proportion of independent measurements accessible makes *ab initio* methods unsuccessful. Crystals tend to be less perfect, as half of the volume is filled by disordered water, but this in turn opens the door to new phasing methods [**16**]. Experimental phasing is based on inducing or differentiating a small molecule within the macromolecule. For instance, by introducing heavy atoms like Hg. Because of the many electrons at these atoms, the X-ray intensities from derivatives differ sensibly from their native counterpart and these differences can be exploited to determine the structure of the heavy atoms, which in turn can be used to provide reference phases for the whole macromolecule. The first protein structures, those of myoglobin and haemoglobin, were so determined. Alternatively, a related structure can provide starting phases for the unknown one through Molecular Replacement: this requires placing the related structure in the unit cell of the target one, to best match the data.

Antibiotics constitute a class of molecules typically falling in between small molecules and macromolecules. They tend to give crystals with more than 200 independent atoms but so compactly packed that no space is left for disordered solvent. Too large for classic direct methods, these crystals could not be modified diffusing solutions with chemicals and closely enough structures would not be available. The structure of many antibiotics was only achieved in the 90's, after 50 years had passed from the determination of the structure of penicillin. These and other "large small molecules" needed recycling between the real space and reciprocal space formulation of the problem, constraining atomicity in both. For instance, vancomycin, a last resort antibiotic administered in hospitals against particularly resistant strains to common antibiotics, had not seen its structure determined until 1996, even though crystals diffracting to atomic resolution had been available for over two decades. Such direct methods-based dual-space recycling methods finally succeeded in obtaining the vancomycin structure [**17**].

Fragments in phasing, map and structure interpretation

It is not surprising that in the absence of atomic resolution, enforcing atomicity is of limited use. Therefore, dual space recycling methods succeeded in extending the scope of direct methods to larger structures but remained tied to the requirement of exceptionally good data and heavily overdetermined problems, i.e. data to atomic resolution. Instead, they became essential in the solution of substructures of heavy atoms and anomalous scatterers required in experimental phasing [**18**]. For such substructures, resolution is still "atomic" in the sense that their components are separated by longer distances and thus, resolved.

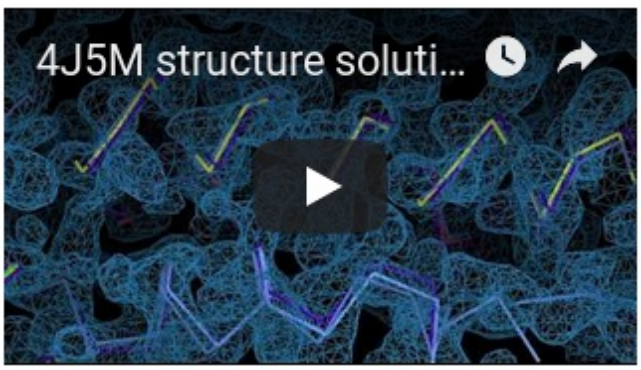
At the typical resolutions reached in macromolecular crystallography, rather than exploiting atomicity as a constraint, it was necessary to resort to the fact that macromolecular structures contain fragments of known geometry. Therefore, our group developed methods to exploit the stereochemical knowledge present in small, yet very accurate, structural units such as secondary structure fragments and their association into local folds [19]. Their use to solve the phase problem is implemented in our software *ARCIMBOLDO*, named in analogy to the portraits this artist painted in the XVI th century out of common objects such as fruits and vegetables. We assemble structural hypotheses out of common fragments of secondary structure or small local folds, such as alpha helices or small beta sheets. This is achieved with the molecular replacement methods implemented in *PHASER* based on Bayesian statistics [20], which provide a sensitive guide to decision making. If one of such substructures, comprising some 6% of the total structure, is correct and accurate to 0.5Å rmsd to the true structure, density modification and automatic map interpretation with *SHELXE* [21] reveals the "portrait" of our protein. As most trials remain a still life, massive, parallel computing is needed in difficult cases. A video reproducing the process can be seen in our YouTube channel [22] (**Video 2**). As illustrated in the painting by Giuseppe Arcimboldo, the information content derived from a correct combination of fragments goes beyond their simple addition. This has required developing our own particular toolbox for the very detailed view required in phasing [23], which can be extended to the solution of other problems. In particular, we are also extending this view to map interpretation in autotracing and general structure interpretation. The recent resolution revolution experimented in electron diffraction methods [24], has brought cryo-electron microscopy into the world of high resolution, and thus quantitative structure determination and many computing methods are being developed starting from crystallographic ones.

Acknowledgments

Airlie McCoy is gratefully acknowledged for her lecture on the Bragg symposium, at the ECM 28 in Warwick, UK. We thank Nicolas Soler for expert feedback.

Movies

Video 1. Diffraction gratings. Experiments with diffraction gratings made from everyday objects. A telescope magnifies small bending angles of light so the diffraction patterns can be easily observed on a screen. Standard YouTube License 2014 [5].



Video 2. 4J5M structure solution using ARCIMBOLDO_SHREDDER spheres. In this video, we describe schematically the process of structure solution with ARCIMBOLDO_SHREDDER using the x-ray diffraction data from the cargo binding domain from human myosin Vb. Standard YouTube License 2017 [22].

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Biofísica Magazine

CONFERENCE REPORT

On the 6th International Iberian Biophysics Congress & X Iberoamerican Congress of Biophysics

Vicente M. Aguilella, *Chair of the Organizing Committee, UJI, Castellón (Spain)*.

The XVII Annual Meeting of the Spanish Biophysical Society (SBE) took place at the Campus of Universitat Jaume I in Castellón, on June 20–22, 2018. This year, the SBE, the Portuguese Biophysical Society (SPBf) and the Latin American Federation of Biophysical Societies (LAFeBS) jointly organized this Scientific Conference, so that it was named as 6th International Iberian Biophysics Congress and X Iberoamerican Congress of Biophysics.

Over 200 scientists, from nearly 20 countries, gathered in Castellón to discuss the state-of-the-art in Biophysics during three days. They presented nearly 170 communications, 70 of them in Talks and around a hundred Posters in two sessions. As expected, young participants (PhD students and postdocs) were by far the major part of the audience. Their participation was greatly facilitated by nearly 40 bursaries kindly offered by the SBE, the SPBf, the European Biophysical Societies Association (EBSA), the International Society of Magnetic Resonance (ISMAR) and the Biophysical Society International Relations Committee.

Group picture of 2018 IIBC attendees

Two satellite meetings took advantage of the IIBC-2018 celebration to attract attendees. On June 19th, Members of the *Spanish Ion Channel Initiative* had a scientific session in Castellón with a good representation of the groups that form this Scientific Network. Right after the congress, the *Summer School MemBiophysics* 2018, was held from 25th to 29th June in Oporto, Portugal. The Scientific Programme included six parallel symposia on the second and third day of the Conference, covering the main research topics in Molecular Biophysics. Renowned speakers delivered five Plenary Lectures. Sergey Bezrukov, Jordi García Ojalvo, Rosangela Itri, Celerino Abad Zapatero and Fred Mackintosh stimulated the discussion during and after their talks. The first day was devoted to a special session on New and Notable Biophysics —with speakers selected by their recent outstanding contributions— followed by a new stand alone symposium on Physics in Biology. With this symposium, highly successful looking at the number of abstracts submitted, and with the selection of the Plenary Speakers, we wanted to highlight this year the key role of Physics for quantitative understanding of biological problems, not only focused in the Experimental Methods and Simulation but also, and particularly, on the theory. As some highly reputed biophysicists wrote,

> *The connection between biology and physics is a two way street. However, the heavy traffic has gone one way.*

> *Many tools from physics have been adopted by researchers in the biological sciences. The return traffic, where biological ideas motivate physical considerations, has been less visible.*

Three of the plenary lectures focused on this *return traffic* from different perspectives: diffusional transport of single particles, electrical signaling in bacteria and phase transitions were the topics chosen by the speakers. The RSEF-SBE plenary lecture took a step further in strengthening the ties between the two Spanish societies and attracting towards the SBE physicists who are actually working on biological problems.

Pianist Patrizia Marcatello and clarinetist Antonio Amanti

Not all activities were strictly scientific. At the end of the first Symposium, on the very first day of the Meeting, the participants could enjoy a Clarinet and Piano recital, sponsored by the Small Biosystems Lab from the University of Barcelona, performed by two talented Italian musicians, the clarinetist Antonio Amanti and the pianist Patrizia Marcatello. Prof. Félix Ritort introduced the artists and the repertoire: Clarinet Concerto No.1 in F minor by Carl Maria Von Weber; Sonata in B-Flat Clarinet and Piano by Francis Poulenc and Sholem-alekhem, Rov Feidman for Clarinet and Piano by Bela Kovacs. After this relaxing session, there was ample time for networking during the welcoming reception, although some participants rushed to the nearby classrooms to watch on TV the a football match of the Spanish national team participating in the World Cup.

This Congress edition awarded a prize to the three best posters, sponsored by FEBS Letters, Biopolymers and Peptide Science, respectively, and the Imagin'Action prize sponsored by Hamamatsu. There was also an award to the best oral communication presented by a young researcher member of the SBE or SPBf, offered by the *Luis de Camoens Chair* of the University Carlos III of Madrid, together with Banco de Santander and Ramón Areces Foundation. Three SBE awards (Bruker-Manuel Rico, Enrique Pérez-Payá and SBE-33) and the SPBf award to the best Young Researcher recognized the scientific trajectory of four outstanding researchers in our field, who delivered their talks in the Awards Symposium on Friday 22. During the closing ceremony, the SBE payed a warm tribute to one of his members, Prof. Carlos Gómez-Moreno, from the University of Zaragoza, for his long scientific trajectory and contributions to the advance of Biophysics in Spain.

As Chair of IIBC-2018, I would like to thank all participants in the Meeting. In particular to the chairs of the sessions, who selected an excellent list of speakers for their respective symposia. All of them contributed to setting high standards in the scientific level of the Meeting. Also the collaborative effort of all members of the Laboratory of Molecular Biophysics in Universitat Jaume I was essential the preparation and development of the Congress. In addition, I would like to thank ALÓ Congress SL, for their support with logistics, Technical Secretary and Website of the Congress. Last, but not least, I could not forget to mention SBE and SPBf for their support and Universitat Jaume I for the use of its facilities. There were several Institutional and Commercial sponsors that made possible the celebration of the Meeting. I am deeply grateful for their economic support: Generalitat Valenciana, Ministerio de Ciencia, Innovación y Universidades, UJI, Small Biosystems Lab, EBSA, ISMAR, Biophysical Society, Cátedra Luis de Camoens UCIII (B. Santander and Areces Foundation), Nanion, Wyatt Technology, Dynamic Biosensors, Elsevier, iesmat, LabClinics, NanoTemper, Hamamatsu, Lasing, Paralab BIO, AntalGenics, PrimaDerm, BCNPeptides and Bruker.

Biofísica Magazine

SPECIAL RECOGNITION

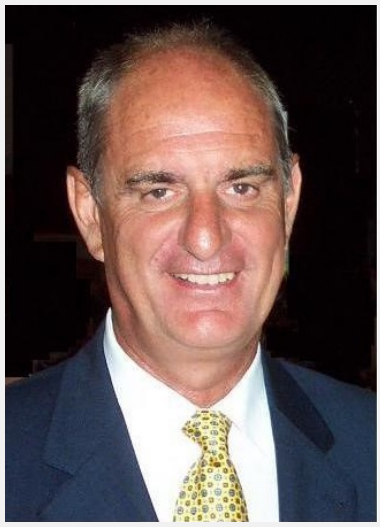
Tribute to Carlos Gómez-Moreno

Milagros Medina & Javier Sancho, *BIFI & UNIZAR, Zaragoza (Spain)*.

When Carlos Gómez-Moreno assumed his *Cátedra* (full Professorship) at the University of Zaragoza (1983) he may not have imagined the future of the Structural Biology and Biophysics in this city. This makes us look back to see the very long road that he has travelled and that, fortunately for us, we have in many occasions intensely walked with him. Carlos has lived, and keeps living, by pushing on each of the turns of life to come out in the best possible way; forcing himself to work hard, to make his ideas and actions valuable for all of us.

He did his doctorate in Seville, moving latter to the USA for two postdoctoral periods, first in Ohio and later in San Francisco. As he likes to say:

> *Four years, two postdocs, two sons, many experiences, much of training, a new vision of life and ideas in science to develop onwards, first in a short period in Granada, and latter, for 35 years in Zaragoza, where I developed most of my scientific life, as well as my family and personal life.*



Prof. Carlos Gómez-Moreno

In 1983 Carlos arrived to the recently founded Department of Biochemistry and Molecular and Cell Biology at the University of Zaragoza (DBMCB-UNIZAR), with 35 years, a brand new full Professorship and a test tube containing a sample of *Anabaena variabilis*, the microscopic organism on which he has been working during all this time. When he came to Zaragoza, he joined a department that was active in two lines of research, metabolism of lipids and cell biology, both of them very different from his own expertise. In this context, he founded his research group with the biological material he brought and with many ideas to elucidate the reaction mechanisms of photosynthetic enzymes. This laid the foundations of Structural Biology and Biophysics at the University of Zaragoza and in the whole region of Aragón, and some of us had the fortune to be there almost from the very beginning. One of us (Javier) joined first, and as Carlos recalls, “he was not only a brilliant student, but also strong and able to handle the 600 liters of cultures that we needed to produce proteins, working long days, if you were feeding him well.” He also attracted to this nascent group a new lecturer in Plant Physiology at DBMCB, Maria Luisa Peleato, and continued with his “psychological” task to convince the rest of us to carry out our PhD under his supervision. In his first 10 years in Zaragoza, Maria Fillat, José Javier Pueyo, Milagros Medina and Teresa Bes, in addition to Javier Sancho, got their PhD in Carlos’ group, and many more scientists came later on. These were the fruitful seeds that he planted for Structural Biology and Biophysics in Zaragoza, since most of us have made our scientific career and created our own research groups in these areas, in many cases remaining at UNIZAR, thus spreading the field in the form of numerous talented Carlos’ “grandsons” and “granddaughters” PhDs, doctorated with us.

He can also be very proud of having contributed to the development of two biotechnological companies, based in Aragón, that today are selling to hundreds of countries and employing many people trained at UNIZAR. In Carlos own words:

> *I have fulfilled the main objectives of a University Professor: To educate people, who help improving the living conditions of their territory, through the development of knowledge and entrepreneurship.*

Carlos Gómez-Moreno addresses the public at the "Special Recognition" act during the 6th IIBC / X ICB 2018 in Castellón. Left to right, Carlos Gómez-Moreno, Vicente Aguilella, Jesús Pérez-Gil, Nuno Santos and António J. da Costa-Filho.

But he did not only plant the seeds, he has also remained watering them along these 35 years. From the very beginning he showed us the importance to open up to the world. He started collaborations with different groups in the USA and Europe, which helped us, young people at that time, to visit other laboratories, learn new techniques and meet illustrious scientists; who, in turn, made us realize that our work was relevant. Carlos also showed us that "not everything is abroad." Indeed, he has been strongly committed with the Spanish science in general, and particularly at UNIZAR and with national Bioscience related Societies. Among them, our Spanish Biophysical Society (SBE) has been very important for him. In fact, as we learnt from Felix Goñi at the 2018 IIBC Congress in Castellón, Carlos was there from the very beginning and he has always transmitted to us the importance of supporting the societies. Thus, since the beginning of our careers he had the grace to introduce us to his/her respected colleagues, in such a sympathetic way that made us feel their respect, support and friendship until today. At the local level, he also contributed to the foundation and development of new research institutes at UNIZAR, particularly, the Institute for Biocomputation and Physics of Complex Systems (BIFI) and more significantly the Institute of Nanoscience of Aragon (INA).

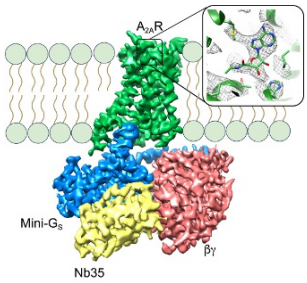
Some of us also have had the privilege to continue working closely with Carlos during the last 25 years, particularly Marta Martínez-Júlvez and myself (Milagros). During this time we implemented fast kinetic methods and other biophysical tools to characterize the mechanisms of interaction between electron-transfer proteins from the photosynthetic chain and also actively worked to obtain X-ray crystal structures from our biological molecules. Always opening new frontiers, more recently, and together with Ana Isabel Gracia-Lostao, Carlos research activity has been primarily aimed at the use of atomic force microscopy for the study of interactions between proteins at the single molecule level.

At the point of slowing down his scientific career, Carlos must be proud of himself, not only because of the many things he achieved in Science, but also because at the same time he has been hard-working, noble, loyal and generous to us. We know for sure that he will keep looking at the future with the same passion and personality that he has shown along his professional life.

Biofísica Magazine

HIGHLIGHTED PUBLICATIONS: MAY - SEPTEMBER 2018

Papers of the month by SBE members



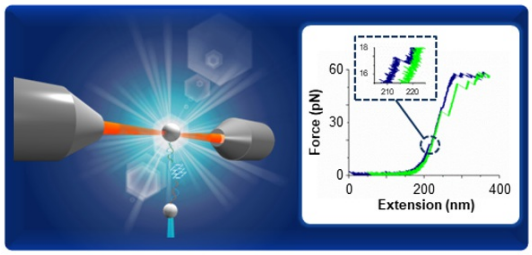
Garcia-Nafria...Tate {*eLife* 7: e35946}

HIGHLIGHTS 2018 | MAY.

Cryo-EM structure of the adenosine A2A receptor coupled to an engineered heterotrimeric G protein

García-Nafría J, Lee Y, Bai X, Carpenter B, Tate CG

eLife **2018** (May), 7:



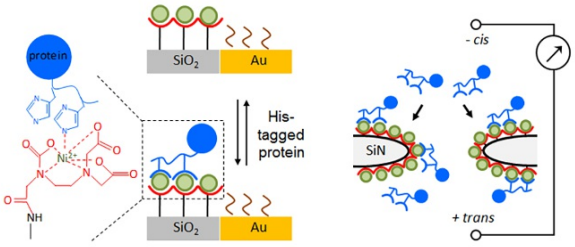
Gutierrez...Arias-Gonzalez {*J Phys Chem Lett* 9: 2498}

HIGHLIGHTS 2018 | MAY.

Single-Stranded Condensation Stochastically Blocks G-Quadruplex Assembly in Human Telomeric RNA

Gutiérrez I, Garavís M, de Lorenzo S, Villasante A, González C, Arias-Gonzalez JR

J Phys Chem Lett **2018** (May), 9: 2498



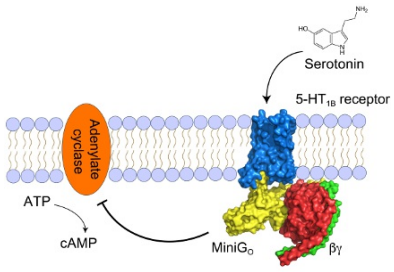
Ananth...Richter, Gorlich {*Small* 14: e1703357}

HIGHLIGHTS 2018 | MAY.

Reversible Immobilization of Proteins in Sensors and Solid-State Nanopores

Ananth A, Genua M, Aissaoui N, Díaz L, Eisele NB, Frey S, Dekker C, Richter RP, Görlich D

Small **2018** (May), 14: 1703357



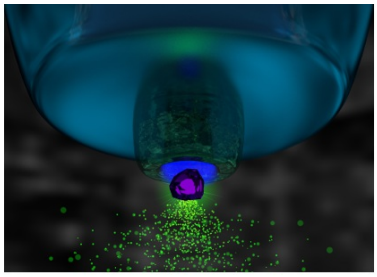
Garcia-Nafria...Tate {*Nature* 558: 620}

HIGHLIGHTS 2018 | JUN.

Cryo-EM structure of the serotonin 5-HT1B receptor coupled to heterotrimeric Go

García-Nafría J, Nehmé R, Edwards PC, Tate CG

Nature **2018** (Jun), 558: 620



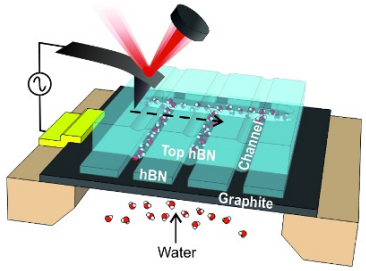
Sanz-Paz...Mivelle {*Nano Lett* 18: 3481}

HIGHLIGHTS 2018 | JUN.

Enhancing Magnetic Light Emission with All-Dielectric Optical Nanoantennas

Sanz-Paz M, Ernandes C, Esparza JU, Burr GW, van Hulst NF, Maitre A, Aigouy L, Gacoin T, Bonod N, Garcia-Parajo MF, Bidault S, Mivelle M

Nano Letters **2018** (Jun), 18: 3481



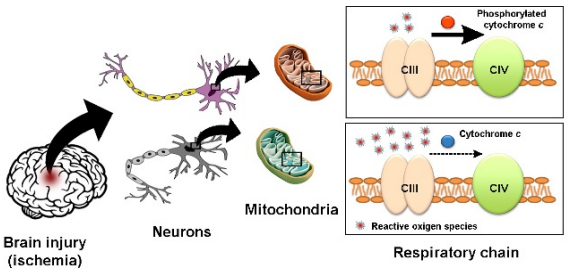
Fumagalli...Geim {*Science* 360: 1339}

HIGHLIGHTS 2018 | JUN.

Anomalously low dielectric constant of confined water

Fumagalli L, Esfandiar A, Fabregas R, Hu S, Ares P, Janardanan A, Yang Q, Radha B, Taniguchi T, Watanabe K, Gomila G, Novoselov KS, Geim AK

Science **2018** (Jun), 360: 1339



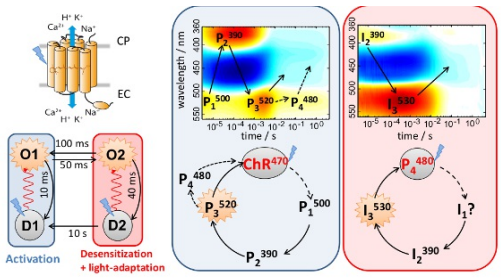
Guerra-Castellano...Diaz-Moreno {*Proc Natl Acad Sci USA* 115: 7955}

HIGHLIGHTS 2018 | JUL.

Oxidative stress is tightly regulated by cytochromecphosphorylation and respirasome factors in mitochondria

Guerra-Castellano A, Díaz-Quintana A, Pérez-Mejías G, Elena-Real CA, González-Arzola K, García-Mauriño SM, la Rosa MAD, Díaz-Moreno I

Proc Natl Acad Sci USA **2018** (Jul), 115: 7955



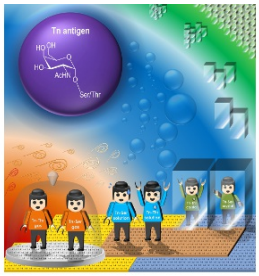
Saita...Lorenz-Fonfria {*J Am Chem Soc* 140: 9899}

HIGHLIGHTS 2018 | AUG.

Photoexcitation of the P4480 State Induces a Secondary Photocycle That Potentially Desensitizes Channelrhodopsin-2

Saita M, Pranga-Sellnau F, Resler T, Schlesinger R, Heberle J, Lorenz-Fonfria VA

J Am Chem Soc **2018** (Aug), 140: 9899



Bermejo...Cocinero, Corzana {*J Am Chem Soc* 140: 9952}

HIGHLIGHTS 2018 | AUG.

Water Sculpts the Distinctive Shapes and Dynamics of the Tumor-Associated Carbohydrate Tn Antigens: Implications for Their Molecular Recognition

Bermejo IA, Usabiaga I, Compañón I, Castro-López J, Insausti A, Fernández JA, Avenoza A, Busto JH, Jiménez-Barbero J, Asensio JL, Peregrina JM, Jiménez-Osés G, et al

J Am Chem Soc **2018** (Aug), 140: 9952