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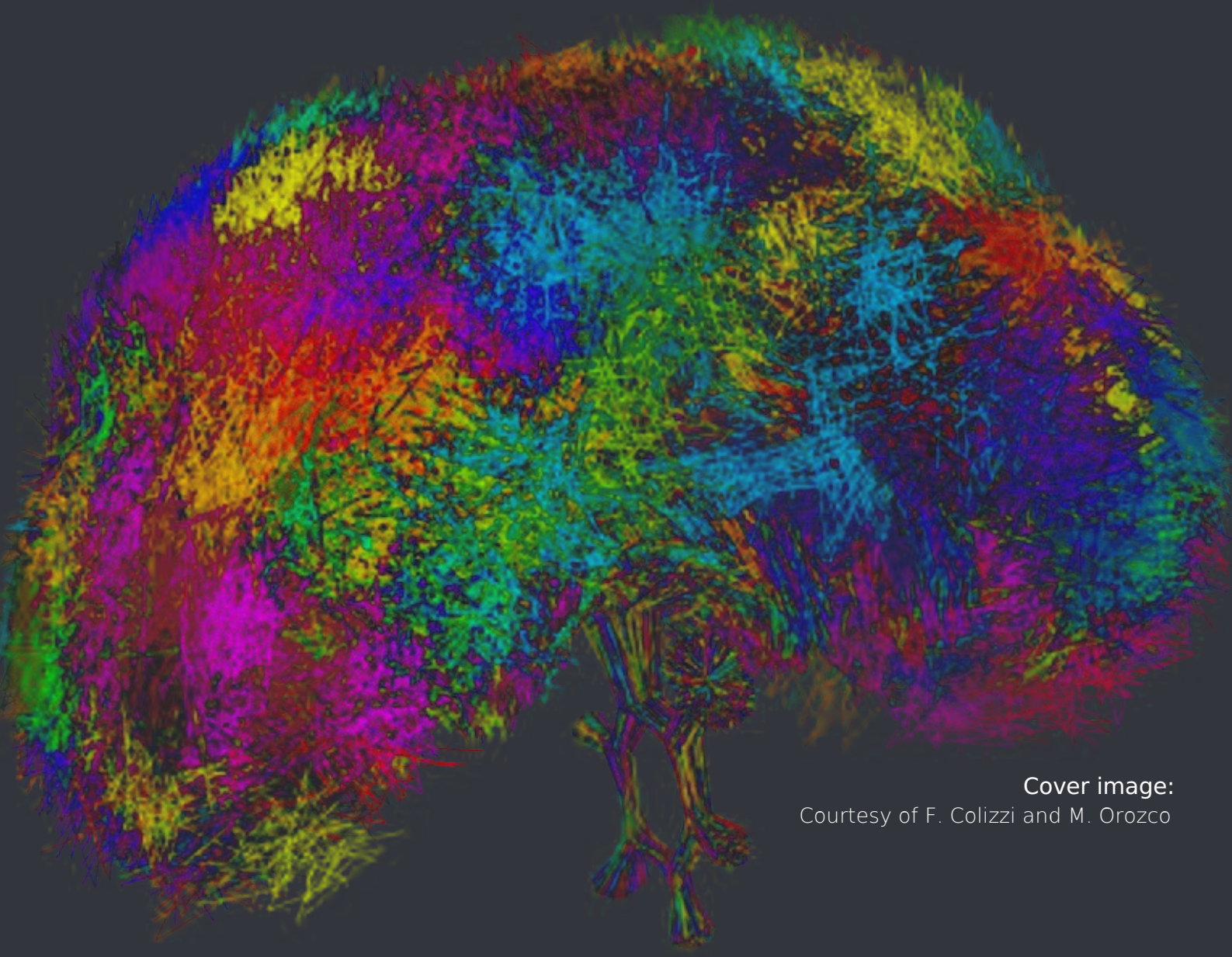

Cover image:
Courtesy of F. Colizzi and M. Orozco

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About the Cover Image:

Molecular dynamics simulations were used to sample the conformational space (in Figure) of flexible molecules and quantify their propensity to form intramolecular H-bonds in a variety of environments. The simulations quantitatively recapitulate experimental observables and provide insight on molecular behaviour in conditions not accessible experimentally.

Colizzi F, Hospital A, Zivanovic S, Orozco M, Angew Chem Int Ed Engl 2019, 58: 3759.

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EDITORIAL / INVITED OPINION

Are we ready for Plan S?

Paola Bovolenta,
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Academic publications reporting research advances, which have been obtained with the support of public funds, should be readily and freely available to the community and allowed to be used without restriction. Very few researchers, if any, would disagree with this basic concept given that it represents one of the fundamental principles underlying science and humanities progress. By and large, this is what "Plan S" expects to achieve by the beginning of 2020.

Plan S was launched in September 2018 as an initiative of the European Commission's Open Access Envoy, Robert-Jan Smits, to push the publication of scientific (including humanities) research towards a completely open access mode. Currently, a large fraction of research results –with differences across scientific domains– are unfairly retained behind pay-walls and often available only to members of institutions that can afford to pay expensive subscriptions to journals. Moreover, timing of accessibility to publications is rather variable because publishers impose different embargo' periods before allowing authors to making articles freely available through a repository. The option taken by a subset of journals –mainly established in recent years– of publishing in full open access guaranties that manuscripts become freely accessible from the moment of publication, without embargo periods. Unfortunately, this is again often highly expensive and is currently only at reach of institutions and research groups that can afford it. Furthermore, among other principles (see ref. [1] for full description), Plan S considers as non-compliant the model of publishing adopted by many other journals, in which articles can escape embargo periods by paying for gold open access (hybrid model). Finally, there are journals and platforms that are cost free for both authors and readers –the so-called platinum open access journal– in which costs are met by sponsoring organization; but, as far as I know, the list of these journals is rather short, at least in the life sciences domain.

In the current publishing system, the use and reuse of a large fraction of the published information is limited by copyright agreements, set for the benefit of the publishers

In the current publishing system, the use and reuse of a large fraction of the published information is limited by copyright agreements that are set for the benefit of the publishers and not, for example, of the authors or the institutions they belong to. Plan S also expects to tackle this issue by requiring that publicly funded authors (or their institutions, depending on the jurisdiction) retain their copyright and publish under a Creative Commons Attribution license (CC BY). This type of licence maximises research benefits because it implies the right to reuse, modify, and redistribute the information and, at the same time, requires that credits must be given to the authors in the terms that they establish. This means that the so-called green open access publishing system will often not be acceptable in Plan S. Indeed, in green open access, authors are allowed to make their work freely available, for example, through institutional repositories or similar platforms, but many legacy publishers require the transfer of the copyright agreement and limit the use and reuse of published results.

Although Plan S has just a few months of life its roots date back to the 2003 Berlin Declaration [2], when representatives of researchers and granting agencies openly formulated the need of regaining the right (and I believe it is a right) of

determining the rules for scientific dissemination. Thereafter, progresses have been slow until 2016, when the EU Competitiveness Council, composed of Science and Innovation Ministers or equivalent Secretaries of State, placed 2020 as the date for implementing immediate open access for the publication of research data obtained with public funds. The nominated Special Envoy on Open Access, Robert-Jan Smits, then set the basis of Plan S, which was further developed by the president of Science Europe (an association of research funding and research performing organisations to which, for example, the Spanish CSIC belongs) and has been adopted by the cOAlition S alliance. This alliance includes a growing number of European and non-European funding bodies, which are actively working towards the implementation of Plan S.

With such a history, Plan S should indeed be considered the response of policy makers to a need that scientists have spelt out during recent years. Yet, the scientific community has not unanimously greeted Plan S and much has been written either in favour or against Plan S, reflecting the existing diverse opinions among researchers from different fields. Physicists have a long-standing tradition of working in large and world-wide coalitions and they normally share their findings in open access repositories. Their view is, thus, largely in favour of a system that for them is already a routine. Yet, the governance of arXiv.org, a widely used pioneer international digital archive for open access distribution of pre-prints in the field of physics –now expanding also to mathematics, computer science, quantitative biology among others– has formulated a number of recommendations [**3**] to improve the current Plan S implementation guidance [**4**]. Many chemists across Europe have instead raised their voice against Plan S stating that it is "risky" and "goes too far" [**5**]. In their open letter [**6**], chemists, for example, underscore that the principles of Plan S seriously limit the freedom of researchers to publish in what are considered high quality journals, often belonging to the hybrid type. They also state that this limitation will seriously affect career progression, especially of the younger in the field.

Much has been written either in favour or against Plan S, reflecting the existing diverse opinions among researchers from different fields

Many funding bodies have expressed their support of Plan S. This is the case, for example, of the European Research Council – ERC, although the ERC has not joined cOAlition S. Since its foundation, the ERC has considered as part of its mission fostering open access publication for the research output of its grantees. Initially, grantees were strongly encouraged to have their manuscript available in open access. With time, the suggestion turned into an obligation that grantees and their institutions acquire when their contract is signed. Thus, in the latest calls, the ERC requires that manuscripts resulting from its support are deposited at the time of acceptance or publication in a repository for scientific publications, eventually accepting an embargo period of a maximum of six months (12 months for social sciences and humanities) before they are made openly accessible. There is also a pilot for exploring a similar requirement for research data deposition in open access repositories (for more information see [**7**]). Therefore, the current ERC policy does not fully match the requirements of Plan S. The ERC Scientific Council, composed of scientists from different disciplines, is currently actively debating Plan S. An ERC representative participates in the task force that is discussing its implementation, taking into account the feedback that a large number of stakeholders, including funders, libraries, scientific societies, publishers and many individual contributors have provided through an open call that closed in the first week of February [**8**].

As a member of the ERC Scientific Council and as a scientist, I support the fundamental principles of Plan S. However, as a biomedical researcher working in Spain, I have conflicting thoughts and wonder what will be the effect of Plan S on Spanish research. I have been complaining for years, as many other colleagues, about how abusive the biomedical publishing system is, in which a journal can ask for up to four different fees for publishing a manuscript, including fees for just reviewing the manuscript, for the cost of printed pages, for colour figures and for opting for gold open access. Or how unfair it is to require that you give away the copyright of your work for free or to ask you to dedicate time, again for free, to editorial work that ensures the quality control of the published work. Will Plan S really be able to modify this awkward system? Probably not. Likely much more needs to be done to change the

Will Plan S really be able to modify this awkward system? Likely much more needs to be done to change the economic model of publishers

economic model of publishers, and the changes might need to be implemented stepwise.

The Spanish national funding agencies have not adhered yet to Plan S, very likely because of the concerns raised by the costs that Plant S may imply. Indeed, Plan S indicates that funders, universities or research institutions, but not individual researchers, will be responsible for covering the fees of open access publication. In a recent interview that appeared in the national press, the current Secretary General for the coordination of scientific policies stated that the Ministry for Science, Innovation and Universities is currently evaluating whether to join cOAlition S, but research budget is a major limitation [**9**]. I cannot but agree. Governmental support to open access publication will require an initial dedicated budget, which on the long run could be recovered from saving on expenses to journals' subscriptions. In the present situation, trimming the already very limited funds dedicated to the Spanish national projects is not an option, because it will impoverish even further the current resources, with likely irreversible consequences for the generation of competitive research.

Unfortunately, if the Spanish national funding agencies do not join cOAlition S, the Spanish researchers will loose a great deal. Their research will be less visible than that of other European colleagues not subjected to embargo periods. Most Spanish laboratories lack the economic power to subtract from their research budget what is the equivalent of three months' salary of a technician or a graduate student, for publishing in open access. With the current shrinking of laboratories' man power –for both economical and contractual reasons– I will opt, like many other colleagues, to sacrifice visibility. As a predictable outcome, there will be a further separation between the very few financially potent groups and the rest of national scientific research. This unbalanced situation will likely and mainly impact in young scientists, given that they will start their independent groups with a significant disadvantage over their European colleagues. This disadvantage will then trigger a down spiral, preventing them, for example, to be competitive in ERC starting or consolidators calls.

Plan S states that scientists should be able to publish their work open access even if their institutions have limited means. Can different countries appeal to this principle?

Spanish universities and research institutions such as the CSIC or the ISCIII could assume the cost of Plan S and support their researchers, but this will not prevent increasing differences across the country. Spanish universities receive support from their communities and therefore policies and economical power are not uniform across the country. Richer universities may be able to assume the cost of Plan S, others not, thereby sacrificing the visibility of their researchers. Many CSIC research institutes are joint ventures with local universities. If some universities follow Plan S, what will be the policies in these mixed centres? To my knowledge, there is no publicly available information on the CSIC position on Plan S, although I expect its full support, given that the CSIC belongs to Science Europe and Science Europe is behind cOAlition S. Will CSIC financially support Plan S implementation among its researchers? I am confident that a clarification will come soon. In the meantime and without the willingness to invest much more in science, I, sadly, have to conclude that Spain is not ready for Plan S. Nor are a number of other EU countries, in which, for example, research freedom is in danger, placing open access publication, at best, in a secondary position. Plan S states that scientists should be able to publish their work open access even if their institutions have limited means. Can different countries appeal to this principle? Does cOAlition S have a plan to implement this statement?

My reservations about Plan S implementation are not limited to the predictable lack of Spanish institutional support but extend to the scientists' reaction to its principles. Biomedical researchers – and I refer to them because they are the ones that I know best- are unfortunately very much used to trust or appreciate research achievements according to the venue in which the research is published, rather than on their own merit. If immediate open access publication is mandatory, many of what we consider top journals will no longer be venues of choice, unless these journals change their policies. Will we be able to change our mentalities and judge research results with other parameters? Of course, we can easily determine new journal rankings and apply those instead of the current ones. In a true optimistic view, Plan S would be a great opportunity for reassessing our scale of value in research. This might be particularly important for young researchers, whose interest in a project is often strictly linked to the expected benefits, measured by their position in the

Will we be able to change our mentalities and judge research results with other parameters?

authorship list of the related publication. However, I do not entirely blame them for this attitude. Indeed, they have grown up with the current rules, in which academic positions, for example, are too often assigned on the basis of the number of publications in high impact factor journals. Changing this mentality is a question of time in many senses, including that of starting to read the publications of the researchers we evaluate or want to hire, instead of simply looking where their work is published. Will we be able to achieve that by 2020? I doubt it, but I hope that Plan S will be a reason to reassess our position towards research evaluation.

In conclusion, the Plan S initiative is conceptually important and I expect that, at the end, it will bring a refreshing spirit on the current mode of scientific publications and their relative value; we should be ready to take full advantage of it.

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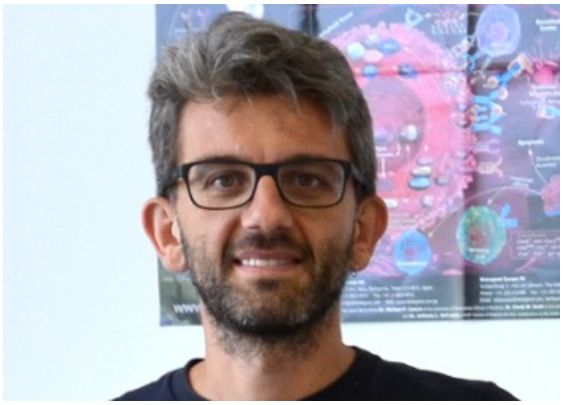
Biofísica Magazine

BEYOND BIOPHYSICS

Cell Biology and Biophysics

A conversation with Isabel Fabregat-Romero

Carlo Manzo, *UVIC-UCC, Vic (Spain)*.



Often, when asked by freshmen students what *Biophysics* is, I jokingly tell them to look at the Wikipedia. Those who go beyond the first sentence, containing a formal and rather obvious definition, can read: "Biophysical research shares significant overlap with biochemistry, molecular biology, physical chemistry, physiology, nanotechnology, bioengineering, computational biology, biomechanics, developmental biology and systems biology." But then I generally get a second question: "Does it mean that biophysics is *a bit of everything*?" My answer to this is obviously positive. However, I feel the need to add that being "a bit of everything" reflects the deep level of contamination and interdisciplinarity reached by life sciences in general, which I interpret as one of the strengths of modern research. In this scenario, barriers among scientific disciplines are getting fainter and precise definitions often still exist for mere practical purposes, such as labeling classes and departments.

Still, a superficial reading of the first paragraphs of the Wikipedia page might suggest that biophysics is just a container constantly being filled with whatever research goes beyond the good old biology that one can find in the textbooks, provided it has some mathematical formulas so to be associated to physics. In my personal (and obviously biased) opinion, this is a rather restrictive view, because it does not reflect one of the main contributions of biophysical research to the development of life sciences. I'll try to expose my point.

> **"In biology, we use several arguments to convince ourselves that problems that require calculus can be solved with arithmetic if one tries hard enough and does another series of experiments."**
> **Yuri Lazebnik [1]**

I'm sure many of you are familiar with the Yuri Lazebnik paper "Can a biologist fix a radio? – or, what I learned studying apoptosis" [1]. The paper consists of a cynical, although hilarious, critique deconstructing the methodological approach commonly used in biological investigations, which is often accused of lacking a standard and quantitative language to unambiguously describe and communicate results. In Lazebnik's words: "In biology, we use several arguments to convince ourselves that problems that require calculus can be solved with arithmetic if one tries hard enough and does another series of experiments." According to the author, this flaw has limited a faster and more efficient development of biology, as compared to e.g. engineering, that also involves complex systems but has managed to incorporate the necessary technical language. Opponents of Lazebnik's view tend to argue that developing such a mathematical description is an unrealistic effort and would instead require a lot of new experimental data.

I would not enter in the minefield of discussing whether this is actually the case or not. The fact is that an engineer-like approach that can really help to decipher all the details of living things has not been developed, at least to date. Among the multitude of bio-disciplines, the one offering the closest methodology to the one hoped for by Yuri Lazebnik is

probably represented by systems biology, which has helped to understand how molecules interplay in living systems. However, if we trust Richard Feynman quote "What I cannot create, I do not understand", to comprehend living organisms we must wait for a reverse-engineering approach, and for this, we must keep a close eye on research being conducted by the synthetic biologists.

Several universities worldwide offer courses, graduate programs, workshops or have departments of "Cell Biology and Biophysics"

Dr. Isabel Fabregat-Romero (IDIBELL, CIBEREHD, UB, Barcelona).

In this antagonistic scenario, Biophysics has often offered an elegant synthesis, by bringing in the quantitative tools for sophisticated experiments, together with the mathematical approach for precise modeling and falsifiable predictions. Interestingly, Cell Biology has been one of the disciplines that has benefited the most from this union. Just think about the quantitative description of many cellular processes, such as the membrane potential, ion channels and the diffusion across the membrane, the mechanisms of intracellular transport and sorting of molecules, to name a few… The strong link between these fields is clearly demonstrated by a brief internet search, showing that several universities worldwide offer courses, graduate programs, workshops or have departments of "Cell Biology and Biophysics". Citing the editorial team of the homonym journal "In all, cell biology and biophysics has become an integrative hub of much modern biological research to address biological questions" [2].

To discuss about this liaison, I met with Isabel Fabregat Romero, principal investigator of the research group "TGF-beta and cancer" at IDIBELL and CIBEREHD, associate professor at the Universitat de Barcelona and president of the Spanish Society for Cell Biology – SEBC.

CM: It is still rather rare to find a woman at the top of a scientific institution.

IF: Indeed, men continue to outnumber women in management positions at the university and research institutes. Sometimes, women are less ambitious and are afraid to get top position that would rob a lot of time from their private life. My situation was slightly simplified by the fact that I gave birth to my daughter at a relatively young age, so when I started as an independent researcher, she did not need the care of a newborn and I could dedicate myself to building up my research group. As a scientist and as president of the SEBC, I am trying to push young female researchers to pursue their careers. I try to convince them that both professional and personal life can be compatible if the time is well distributed. Something is moving, see e.g. the fellowship programs favoring mothers, but more efforts are needed.

CM: you have been president of the SEBC for almost 8 years. What has been the main focus of your term? What's the balance?

IF: As a small society, we preferred not to take part in big actions. We have rather attempted to build up a society of loyal and active members, providing financial support – mainly directed to young fellows – for participation to conferences and for doctoral studies. We have been working to improve the scientific level of our annual congress that in recent years has reached the international stage. We have incorporated sponsoring companies and, overall, we have been able to increase the number of members by about 25% during my two terms.

CM: Scientific research becomes every day more interdisciplinary.

IF: It is definitively true, producing and publishing relevant research requires the fusion of elements coming from several disciplines. Classifying most of the modern publications among cell biology, molecular biology,

biochemistry and biophysics has become rather tricky due to the intermingling of these subjects. In the last years, in my research field (cell biology of cancer), I have also noticed that clinicians are increasingly appreciating the contributions from basic sciences. This is happening in spite of differences in language and jargon and the passive resistance of some old school mindset that can sometimes make communicating with each other difficult. I see this contamination very positively: in this way, we can genuinely link basic and applied research to obtain the so coveted translational research, besides the promises of research proposals. Moreover, this is the way to go to enable in a near future personalized treatments, taking into account the patients' variability and cancer mutations.

CM: In this interdisciplinary scenario, what is the role of a society focused on a single discipline?

IF: I think that one of the roles of scientific societies is to provide a stratification of scientists based on expertise. Let us imagine you want to explore a new field and you are looking for an expert to ask for advice or collaborate with, the affiliation to a society works like the indexing for a search engine, making it easier to find the expert you are looking for. However, at the same time, a person or a research group can be found under different categories.

It would be exciting to put together biophysicists and cell biology, to foster collaborations by matching the demand for solving biological problems with the supply of biophysical tools and methods

Another point is to favor contacts and interactions among members through the organization of annual meetings and other activities. A small society like the SEBC gives the possibility of having "Gordon conference-sized" congresses, without parallel sessions and with plenty of networking, thus allowing us to create a community. With respect to congresses organized by bigger societies, I guess this is a main reason of attraction, in particular for students and early career researchers. Of course, this does not exclude the organization of shared meetings and workshops with companion societies. As an example, in 2017 we organized a joined congress with the Spanish Society of Genetics and the Spanish Society of Developmental Biology. It was a great success and – in spite of the difference in the number of members – we registered a larger participation of SEBC affiliates. We were impressed and we think that is due to the fact that we have been able to earn the loyalty of our members.

I would have loved to organize more joint workshops. For example, it would be exciting to put together biophysicists and cell biology, to foster collaborations by matching the demand for solving biological problems with the supply of biophysical tools and methods. Unfortunately, often it is difficult due to time constraints and logistic. In this sense, we also miss support from institutions.

CM: How do you think biophysicists are helping or can help the cell biologists?

IF: If I think about biophysics, microscopy is the first thing that comes to mind, due the massive use that biologists make of it. The recent advances in super-resolution techniques are providing a new view on many cellular processes. However, I find that many biologists are not fully aware of the potential of these novel techniques. Moreover, the fact that they are still evolving and thus often require the support of experts is probably preventing a wider application in our field.

Along the line of my research, concerning signaling in liver cancer through clinical and animal model studies, it would be extremely informative to apply the new tools of cell mechano-transduction, to get more insights on collective migration, cell contractility, cell-cell interactions and its relation to cancer. I would really love to start a collaboration on this topic.

CM: Earlier, you mentioned the use of personalized medicine and the differences found in patients with same conditions/treatments. This somehow connects to the current discussion on data reproducibility, p-hacking, …

IF: Besides fraudulent cases of misuse of data analysis, which I think will be highly reduced by the public sharing of the raw data required by many journals, there are other aspects that I consider important in relation to

the use of statistics. In particular in clinical studies, it is not rare to find highly heterogeneous datasets. The heterogeneity reflects significant characteristics of the sample and, as such, should be taken into account. Just to keep it simple, if we find differences of up to two orders of magnitude when measuring the level of a marker in cancer patients, by summarizing the data through their average we throw away a lot of useful information. Methods to properly condense and represent these data without washing out their heterogeneity must be definitively popularized and diffused among experimentalists.
More generally, we often deal with data that require advanced statistical treatment, beyond the classical methods. However, sometimes they are treated by means of textbook statistical analysis, just because the journal demands for a p-value and one does not know what else to apply. This is partly caused by the lack of training in statistics provided to biology students. Considering the importance of quantitative experiments and data analysis, the teaching of statistics must be definitively potentiated.

Before the interview, I had prepared a list of questions, but I could not ask them all. Actually, I only asked the firsts two or three of the list. From that, the chat flew naturally: more and more hints for further discussion were popping up. I was noting down Isabel's answers and, at the same time, using a corner of the page to quickly log reminders of new topics, about which I would have liked to know her thinking. Stepping down the stairs of IDIBELL, I was recalling all the questions I did not ask, while trying to figure out the punch line of the interview. All in all, forcing a bit the definitions, I felt like embedded in a hypothetical fractal structure: science itself – as well as many of the systems it studies – can be analyzed in a reductionist fashion, one discipline at the time. It is up to us to contaminate the disciplines, so that emergent properties can arise.

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Biofísica Magazine

COOL BIOPHYSICS

How do membrane proteins fold?

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Membrane-spanning proteins account for 23% of all human genes [1], and numbers are similar for most other organisms [2]. They serve many essential roles in the cell, including solute transport, signal transduction and energy generation. However, our knowledge on how they achieve their functional structure is still scarce. In fact, the biophysical tools used for characterizing the folding and assembly of transmembrane (TM) proteins are limited in comparison to those available for studying soluble proteins. Many experimental assays designed for the study of protein folding are not straightforwardly applicable to membrane proteins because these proteins require the presence of a lipid bilayer, or at least some membrane-mimicking environment (like detergent micelles) to maintain their native structure. This is in contrast to water soluble proteins, for which a generous set of biophysical tools has in many cases allowed the definition of the molecular mechanisms governing their folding and has permitted, in parallel, a better understanding of their function. Thus, there is increasing interest in achieving a similar level of knowledge about the molecular mechanisms that drive the folding of proteins in the membrane environment, and in particular the rules that explain the stability and assembly of TM segments.

The free energy of transferring hydrophobic TM segments from an aqueous environment into the lipid bilayer provides most of the thermodynamic stability of membrane proteins. In addition, TM segment hydrophobicity is the main factor for driving membrane partitioning. However, hydrophobicity does not rely only on the amino acid composition of the TM segments, but also on structure formation, which in turn depends upon non-trivial atomic-detail interactions with the polypeptide environment. TM segments fold as either α-helices or β-strands, due to the biophysical constraints imposed by the membrane environment [3]. Nevertheless, in biological membranes α-helical membrane proteins are most abundant, and thus they will be the focus of the current text.

The membrane milieu

The chemical and physical properties of the lipid bilayer make it clear that biological membranes provide a very special milieu for proteins. The basic unit of these membranes are lipids, organized in two monolayers with their polar headgroups exposed on the two surfaces and their acyl chains forming a central hydrophobic core. Then, biological membranes are highly heterogeneous along the normal direction, with a large gradient of environmental polarity over a short distance because of steep changes in chemical composition [4]. Additionally, natural membranes have usually a diverse mixture of lipids with different properties, which are asymmetrically distributed between the two bilayer leaflets. The hydrophobicity and thickness of the hydrocarbon core of the membrane bilayer leads to the expectation that membrane-spanning segments minimize the cost of harboring a polar polypeptide backbone by engaging their polar carbonyl and amide groups into a regular pattern of hydrogen bonds. In fact, in order to integrate into the membrane milieu the TM regions adopt extensive secondary structure, most often α-helical conformation.

The road to the membrane

As they do for all other proteins in living organisms, ribosomes translate membrane proteins from their encoding mRNAs. However, the high hydrophobicity of the TM segments present in membrane proteins prevents their synthesis by soluble ribosomes. Instead, the vast majority of membrane proteins are synthesized by membrane-bound ribosomes. When translating an mRNA encoding a membrane protein, the ribosome early synthesizes an N-terminal hydrophobic stretch of amino acid residues (either a true signal sequence or a non-cleavable TM segment) that must navigate through the ribosomal tunnel toward the exit site (**Fig. 1**). As the nascent polypeptide grows, the signal sequence emerges from the ribosomal exit tunnel and, if it is sufficiently hydrophobic, is recognized by the signal recognition particle (SRP). The SRP binds to the ribosome-nascent polypeptide chain complex, accommodating the signal sequence in an α-helical conformation and slowing down or halting translation (**Fig. 1**).

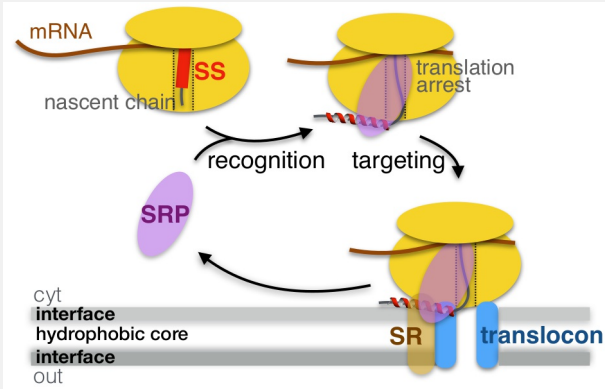

Figure 1. Targeting of membrane proteins to the translocon. A ribosome (*yellow*) translating the mRNA of a membrane protein is targeted to the membrane through the SRP (*purple*). SRP recognizes the emerging hydrophobic sequence (*red* helix), binds to the ribosome and arrests nascent polypeptide elongation. The ribosome/nascent polypeptide/SRP complex binds to the membrane resident SRP receptor (SR, *brown*), which is associated to the translocon (*blue*). SRP dissociation from the SR causes the transfer of the hydrophobic sequence to the translocon and the elongation of the nascent polypeptide resumes.

Presumably, this gives the SRP some time to find and dock to its partner, the SRP receptor (SR), which is associated to the translocon (a protein-conducting channel). At the docking site, the SR interacts with both the ribosome and the SRP, leading to conformational changes in the SRP that allow the transfer of the ribosome-nascent chain to the translocon [5]. Subsequently, SRP disassembly leads to resumption of translation and, once in the translocon, the nascent chain will deal with membrane insertion.

Protein synthesis by a membrane-bound ribosome

A ribosome bound to the Endoplasmic reticulum (ER) membrane is more than a mere decoding and synthesizing machine. It is endowed with an exit tunnel through which a newborn membrane protein, constantly growing, navigates toward the translocon to eventually reach its final destination within the bilayer. This *molecular corridor* creates a specialized microenvironment that allows the ribosome to distinguish TM from secretory segments and direct TM segment integration into the bilayer [6]. One of the features that can modulate the ribosome triage between TM and non-TM segments might be the folding of tethered nascent chains. In fact, folding of TM segments into an α-helical conformation inside the ribosomal exit tunnel has been demonstrated [7–9].

Recently, using in vitro translation of truncated nascent chains trapped within the ribosome tunnel and molecular dynamics simulations, it has been shown that folding within the ribosome is attained for TM, but not for soluble (polar) helices (**Fig. 2**). The overall hydrophobicity, helicity and length of a given segment have been found to be the major determinants for the identification of TM segments and their eventual adoption of an α-helical structure within the ribosomal exit tunnel [10]. Thus, the ribosome recognizes the TM regions and facilitates a proper environment for their folding, acting in a chaperone-like manner. From the biophysical point of view, preadoption of α-helical conformation could facilitate membrane integration of TM segments upon entering the translocon, which is well positioned below the ribosome to receive the exiting polypeptide chain (**Fig. 3**).

Membrane insertion

Once within the translocon channel, TM helices have to be transferred laterally to the surrounding lipid bilayer. Insights into the mechanism of membrane insertion have come from both structural studies [11, 12] and molecular dynamics simulations [13]. It is generally accepted that hydrophobicity is the overriding characteristic of TM segments recognized by the translocon to trigger nascent chain insertion [14]. The central component of the translocon, Sec61α in eukaryotes and SecY in prokaryotes and archaea, is itself a membrane protein formed by 10 TM helices arranged around a central pore with a lateral gate for membrane access of polypeptide nascent chains. Upon ribosome binding, lateral gate contacts are weakened and, if the nascent polypeptide sequence allocated in the central pore is sufficiently hydrophobic, the translocon opens laterally allowing access to the lipid bilayer [15].

In this scenario, integration of the first TM segment of a membrane protein into the ER membrane in the correct orientation is considered important in defining the overall topology of an integral membrane protein (**Fig. 3**). However, the sequential insertion into the membrane of TM segments (one after another) for multi-spanning membrane proteins does not explain the insertion mechanism of all membrane proteins. For instance, it has been demonstrated that poorly hydrophobic sequences insert into the lipid bilayer in a concerted manner as helical hairpins or bundles, as recently reviewed elsewhere [16].

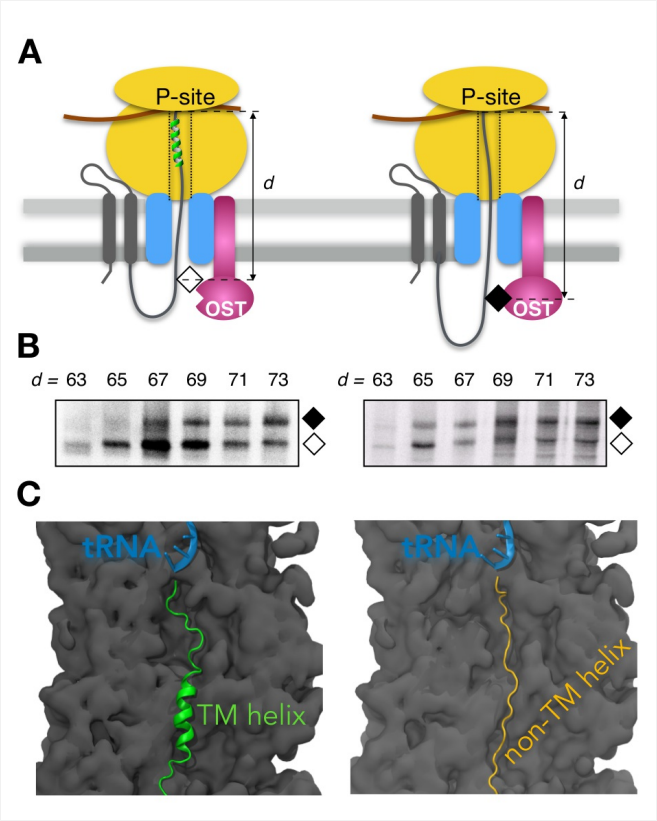

Figure 2. Folding of TM helices inside the ribosome exit tunnel. **(A)** During the translation of a membrane protein, the physical distance between the P-site of the ribosome and the active site of the ER oligosaccharyl transferase (OST), located nearby the lumenal end of the translocon central pore, sets a minimum distance (*d*, in number of residues) for nascent polypeptide chain efficient glycosylation. Such a sequence length can be investigated in a glycosylation mapping assays using test sequences in the framework of the model membrane protein Lep from *E. coli* (see ref. [20] for details about this type of experiment). **(B)** SDS-PAGE of in vitro translated samples using test sequences of different length (*d*, values indicated on the top). The test cases shown are based on two native helix fragments of similar length: one hydrophobic (the TM segment of the membrane protein gp41, *left*) and one hydrophilic (from N-acetylglutamate kinase NAGK, *right*). The results show that the minimal sequence length for efficient glycosylation (≥50%, i.e., upper bands in the gel with at least equal intensity compared to the lower bands) is larger for the case of the TM segment (at least 71 residues) than for the polar segment (67 residues), indicating that the first one is folded as a helix within the ribosome tunnel while the second adopts likely an extended conformation. **(C)** Models of characteristic structures obtained upon MD simulations of complexes of the ribosome (in *gray*) with a nascent chain harboring the TM gp41 sequence (*left*, *green* color) or the NAGK sequence (*right*, *orange* color). For a complete study with more cases of TM and polar fragments, please see ref. [10].

Membrane protein assembly

Once TM helices are established and inserted across the lipid bilayer they interact to form functional tertiary structures (in the case of multi-spanning membrane proteins) (**Fig. 3**), and in some cases quaternary membrane-spanning structures (not shown). The clues of such complex TM protein-protein interactions are crucial for understanding the biogenesis of membrane proteins, that has been historically neglected due to the difficulties in studying this process experimentally.

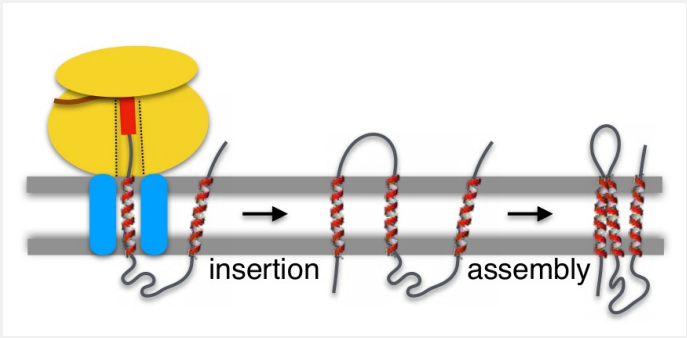

Figure 3. Insertion and assembly of membrane proteins into the membrane. The Insertion of TM segments (*red* helices) facilitates membrane integration of the newly synthesized protein, which has to be assembled in its native conformation. Monomeric membrane proteins can subsequently associate to form homo- or heteromeric complexes (not shown) to allow the broad variety of key membrane protein activities.

The forces behind TM helix-helix packing are essentially the same as those driving helix packing interactions in soluble proteins. However, their contribution to the folding/packing of the protein is significantly different due to the modified environment (aqueous *vs* lipidic). In soluble proteins, tertiary and quaternary foldings are mainly driven by the hydrophobic effect and electrostatic interactions. In contrast, in membrane proteins van der Waals interactions have been identified as the primary force behind helix-helix packing. By their nature, van der Waals forces require a large contact area between the associating protein segments. Interestingly, in helical TM segments amino acids with small side chains (like Gly or Ala) are frequently found in helix-helix contact interfaces, while bulky non-polar side chains are located mostly on lipid exposed surfaces. The role of Gly in helix-helix association has been vastly documented in the context of Glycophorin A (GpA), both in membrane-like environments [**17**, **18**] and in cells [**19**]. The abundance of small residues rather than larger hydrophobic side chains in TM interactions likely reflects the bilayer effect [**3**] in membranes and the minimal entropic requirements for packing small side chains with few rotatable bonds.

Finally, it remains to be determined whether specific chaperones and/or translocon accessory components facilitate insertion of poorly hydrophobic TM sequences and/or large topological rearrangements needed for the assembly of particular membrane proteins. Considerably more effort will need to be invested in studying the processes underlying membrane protein folding, both in vitro and in vivo, but the way towards our complete understanding starts to be paved.

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Biofísica Magazine

Germán Rivas winner of the Bruker prize 2019

The Executive Council of SBE has awarded the 2019 *"Manuel Rico" – Bruker* prize to:

Dr. Germán Rivas, *Centro de Investigaciones Biológicas -CIB, CSIC (Madrid, Spain)* ,

> *For his outstanding scientific trajectory in the study of interactions, reactivity and structural organization of supramolecular systems in crowded cell-like environments.*

ABOUT DR. GERMÁN RIVAS

CSIC Research Professor at the Centro de Investigaciones Biológicas – CIB (Madrid, Spain).

Scientific Trajectory

Dr. Germán Rivas is a CSIC Research Professor at the CIB, Madrid. He obtained his Ph. D. in Chemistry at the Autónoma University, Madrid, in 1989. He has been a Predoctoral fellow at the Instituto de Química Física Rosasolano (1985-1989), Postdoctoral fellow at the National Institutes of Health – NIH (1990-1992) and the Biocenter of the Univ. Basel (1993) and visiting scholar at the NIH (2007) and the Max Planck Institute of Biochemistry (2018). Since 1994, he works at the CIB, where he assembled the Molecular Interactions Facility and currently coordinates the CSIC-UIMP Master on Molecular and Cellular Integrative Biology.

The research program of his laboratory has three main areas of interest: 1) Biochemistry, biophysics and bottom-up synthetic biology of bacterial division: biochemical organization and reconstruction from the bottom up of minimal divisomes in cell-like test tubes. 2) Intracellular biochemistry: reactivity and organization of macromolecular systems in crowded-phase-separated cell-like environments. 3) Physical biochemistry of macromolecular interactions.

More information

Please, visit the website of the Systems Biochemistry of Bacterial Division group at CIB.

ABOUT THE *"MANUEL RICO" – BRUKER* PRIZE

> *Awarded in memory of Professor Manuel Rico , who was a leading biophysicist, member of the SBE, and a Research Professor at the Institute of Chemical Physics 'Rocasolano', CSIC (Madrid). He was a pioneer using NMR technologies to study protein structure, stability, dynamics and interactions.*

Sponsored by

Bruker Española S.A..

Addressed to

Biophysicist who develope their main activity in Spain. **Preference** is given to members of the SBE working on Structure/Function problems from a Biophisics perspective.

Award

3000 € and a talk scheduled within the programme of the EBSA 10th ICBP – IUPAP Biophysics Congress (Madrid, 20 – 24 July 2019).

Past winners of this prize

- 2018: F. Javier Luque (Madrid).
- 2017: Alicia Alonso (Leioa-Bizkaia) and María García-Parajo (Barcelona).
- 2016: Xavier Gomis-Rüth (Barcelona).
- 2015: Juan A. Hermoso (Madrid).
- 2014: Óscar Llorca (Madrid).
- 2013: José Manuel Sánchez Ruiz (Granada) and Félix Ritort (Barcelona).
- 2012: Antonio V. Ferrer Montiel (Elche) and Marta Bruix (Madrid).
- 2011: Ignacio Fita (Barcelona).
- 2010: Modesto Orozco (Barcelona) and José Luis Rodríguez Arrondo (Bilbao).
- 2008: José García de la Torre (Murcia).
- 2006: Jesús Pérez Gil (Madrid).
- 2004: Javier Sancho (Zaragoza).
- 2002: José María Valpuesta (Madrid).
- 2000: Miquel Pons (Barcelona).
- 1998: Rafael Picorel (Zaragoza).

More information

Please, visit the SBE website.

Biofísica Magazine

Iván López-Montero winner of the SBE-40 prize 2019

The Executive Council of SBE has awarded the 2019 *"Enrique Pérez-Payá" – SBE-40* prize to:

Dr. Iván López-Montero, *Universidad Complutense de Madrid – UCM (Madrid, Spain)* ,

> *For his exceptional research to disentangle vital molecular processes occurring at mitochondrial membranes with a biophysical perspective.*

ABOUT DR. IVÁN LÓPEZ-MONTERO

Associate Professor at the Department of Physical Chemistry, UCM (Madrid, Spain).

Scientific Trajectory

Dr. López-Montero completed his B.Sc. in Condensed Matter Physics at Universidad Autónoma de Madrid – UAM in 2001. Supervised by Prof. Philippe F. Devaux at Institut de Biologie Physico-Chimique, CNRS and Dr. Marisela Vélez (UAM); his PhD thesis (2006, Université Paris 7) focused on lipid asymmetry, the flip-flop of ceramides as well as the biological implications of the enzymatic conversion of sphingomyelin into ceramide. Dr. López-Montero joined the group of Prof. Francisco Monroy at the UCM with the reintegration program "Juan de la Cierva". During this time, his research contratrated on the mechanics of model lipid membranes under the action of different proteins involved in biological processes such as apoptosis or bacterial cell division. In 2013, he was awarded with an ERC Starting Grant from the European Research Council. Since 2014, Dr. López-Montero leads the Mitochondrial Membranes Lab at UCM and Hospital 12 de Octubre; first as a tenure-track "Ramón y Cajal" fellow and then as an Associate Professor at the Department of Physical Chemistry, UCM. Currently, his research focuses on mitochondrial membrane biophysics and its implications to identify new therapeutic targets against mitochondrial diseases.

ABOUT THE *"ENRIQUE PÉREZ-PAYÁ" – SBE-40* PRIZE

> *Awarded in memory of Dr. Enrique Pérez-Payá, SBE member who contributed to the development, translation and internationalization of Biophysics in Spain. He worked on peptide-membrane interactions and apoptosis and was a pioneer in the use of combinatorial chemistry to expand the chemical space for basic research and to develop peptide-based therapeutics. He was also an entrepreneur and always supportive of young biophysicists.*

Sponsored by

BCN Peptides and Prima – Derm.

Addressed to

Biophysicist under 40 who develope their main activity in Spain. **Preference** is given to members of the SBE and to achievements from the last 10 years.

Award

1500 € and a talk scheduled within the programme of the EBSA 10th ICBP – IUPAP Biophysics Congress (Madrid, 20 – 24 July 2019).

Past winners of this prize

- 2018: Pere Roca-Cusachs (Madrid).
- 2017: Carlo Manzo (Vic-Barcelona) and Emilio J. Cocinero (Leioa-Bizkaia).
- 2016: Raúl Pérez-Jiménez (San Sebastián).
- 2015: Irene Diaz Moreno (Sevilla).
- 2014: Fernando Moreno (Madrid).
- 2013: Xavier Salvatella (Barcelona).
- 2012: José Manuel Gómez Vilar (Leioa-Bizkaia).
- 2011: Teresa Giráldez (La Laguna).
- 2010: Pau Bernardó (Barcelona).

More information

Please, visit the SBE website.

Biofísica Magazine

Anna Alemany winner of the SBE-33 prize 2019

The Executive Council of SBE has awarded the 2019 *AntalGenics – SBE-33* prize to:

Dr. Anna Alemany, *Hubrecht Institute (Utrecht, The Netherlands)*,

> *For her studies on fluctuations and kinetic states in diverse biological processes such as nucleic acid folding or cell differentiation during embryo development, and the development of CRISPR/Cas9 genome editing tools to characterize the lineage of individual cells.*

ABOUT DR. ANNA ALEMANY

Postdoctoral Researcher at the Hubrecht Institute for Developmental Biology and Stem Cell Research (Utrecht, The Netherlands).

Scientific Trajectory

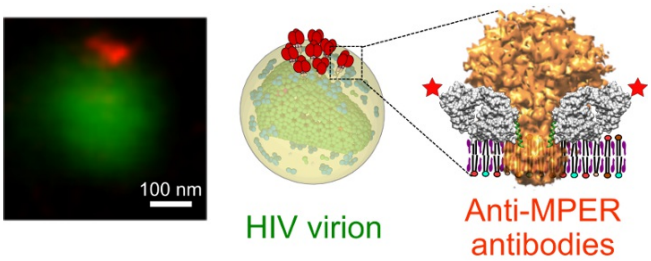
Dr. Alemany obtained her B.Sc. in Physics and her M. Sc. in Biophysics in the University of Barcelona. In 2014, she obtained her PhD under the supervision of Prof. Felix Ritort in the University of Barcelona. Her research was focused on the study of molecular fluctuations to extract information about the molecular free energy landscape, using experimental single-molecule force-spectroscopy techniques (optical tweezers) and different theoretical approaches (fluctuation theorems and transition state theory). Together with her colleagues, she extended the use of fluctuation relations to determine the thermodynamic properties of molecular kinetic states from non-equilibrium experiments for the first time.

During her postdoc in Alexander van Oudenaarden lab (Hubrecht Institute), Anna Alemany is investigating cellular differentiation as a non-equilibrium process involving sequential kinetic states. There, she developed a novel technique using Cas9-genome editing to perform lineage tracing on single cells during embryo development. Combined with scRNA-seq, this is essential to quantitatively investigate the trajectories involved in cellular processes and cell-fate commitment from a biophysical point of view.

Biofísica Magazine

HIGHLIGHTED PUBLICATIONS: JANUARY - APRIL 2019

Papers of the month by SBE members



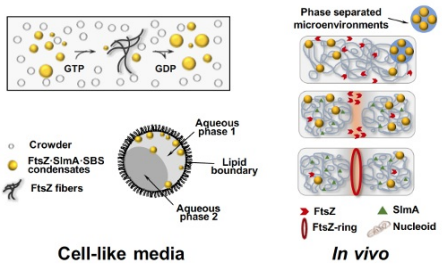
Carravilla...Nieva {*Nat Commun* 10: 78}

HIGHLIGHTS 2019 | JAN.

Molecular recognition of the native HIV-1 MPER revealed by STED microscopy of single virions

Carravilla P, Chojnacki J, Rujas E, Insausti S, Largo E, Waithe D, Apellaniz B, Sicard T, Julien J-P, Eggeling C, Nieva JL

Nat Commun **2019** (Jan), 10:



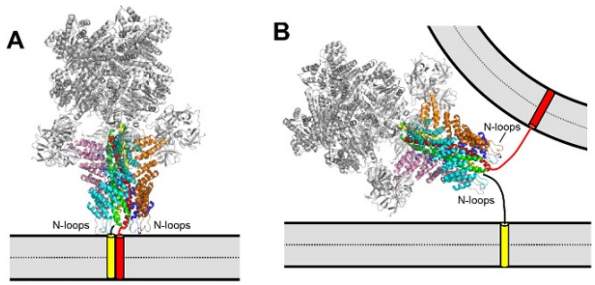
Monterroso...Rivas {*EMBO Rep* 20: e45946}

HIGHLIGHTS 2018 | JAN.

Bacterial FtsZ protein forms phase-separated condensates with its nucleoid-associated inhibitor SlmA

Monterroso B, Zorrilla S, Sobrinos-Sanguino M, Robles-Ramos MA, López-Álvarez M, Margolin W, Keating CD, Rivas G

EMBO Rep **2018** (Jan), 20: e45946



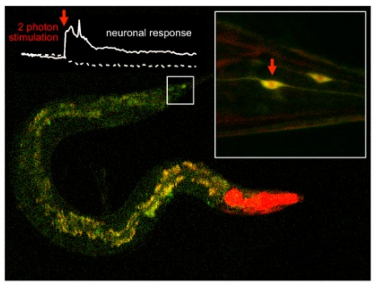
Prinslow...Rizo {*eLife* 8: e38880}

HIGHLIGHTS 2019 | JAN.

Multiple factors maintain assembled trans-SNARE complexes in the presence of NSF and upalphaSNAP

Prinslow EA, Stepien KP, Pan Y-Z, Xu J, Rizo J

eLife **2019** (Jan), 8:



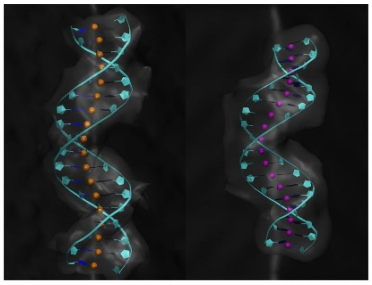
Cabre...Gorostiza, Alibes {*Nat Commun* 10: 907}

HIGHLIGHTS 2019 | FEB.

Rationally designed azobenzene photoswitches for efficient two-photon neuronal excitation

Cabré G, Garrido-Charles A, Moreno M, Bosch M, la-Riva MP-d, Krieg M, Gascón-Moya M, Camarero N, Gelabert R, Lluch JM, Busqué F, Hernando J, et al

Nat Commun **2019** (Feb), 10:



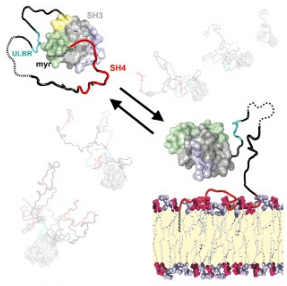
Marin-Gonzalez...Moreno-Herrero, Perez {*Phys Rev Lett* 122: 048102}

HIGHLIGHTS 2019 | FEB.

DNA Crookedness Regulates DNA Mechanical Properties at Short Length Scales

Marin-Gonzalez A, Vilhena J, Moreno-Herrero F, Perez R

Phys Rev Lett **2019** (Feb), 122:



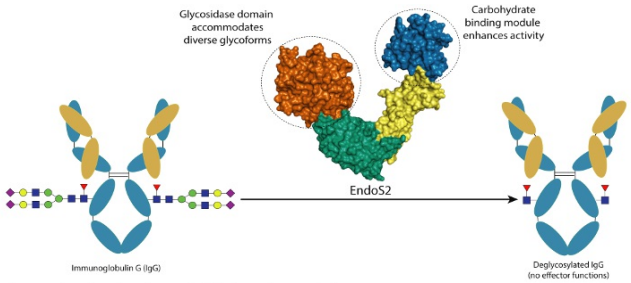
Le Roux...Pons {*iScience* 12: 194}

HIGHLIGHTS 2019 | FEB.

A Myristoyl-Binding Site in the SH3 Domain Modulates c-Src Membrane Anchoring

Roux A-LL, Mohammad I-L, Mateos B, Arbesú M, Gairí M, Khan FA, Teixeira JM, Pons M

iScience **2019** (Feb), 12: 194



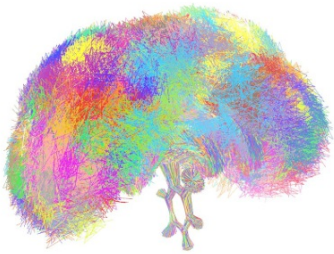
Klontz...Guerin, Sundberg {*ACS Cent Sci* 5: 524}

HIGHLIGHTS 2019 | MAR.

Molecular Basis of Broad Spectrum N-Glycan Specificity and Processing of Therapeutic IgG Monoclonal Antibodies by Endoglycosidase S2

Klontz EH, Trastoy B, Deredge D, Fields JK, Li C, Orwenyo J, Marina A, Beadenkopf R, Günther S, Flores J, Wintrode PL, Wang L-X, et al

ACS Cent Sci **2019** (Mar), 5: 524



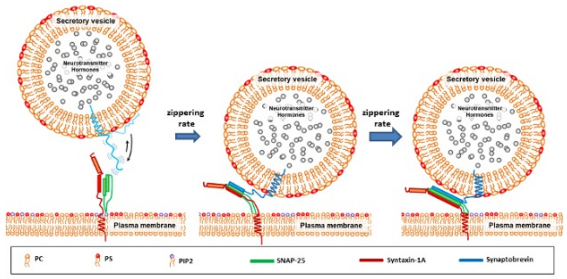
Colizzi...Orozco {*Angew Chem Int Ed Engl* 58: 3759}

HIGHLIGHTS 2019 | MAR.

Predicting the Limit of Intramolecular Hydrogen Bonding with Classical Molecular Dynamics

Colizzi F, Hospital A, Zivanovic S, Orozco M

Angew Chem Int Ed **2019** (Mar), 58: 3759



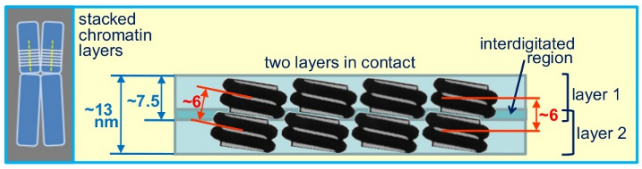
Lakomek...Perez-Lara {*Proc Natl Acad Sci USA* 116: 8699}

HIGHLIGHTS 2019 | APR.

Structural dynamics and transient lipid binding of synaptobrevin-2 tune SNARE assembly and membrane fusion

Lakomek N-A, Yavuz H, Jahn R, Pérez-Lara Á

Proc Natl Acad Sci USA **2019** (Apr), 116: 8699



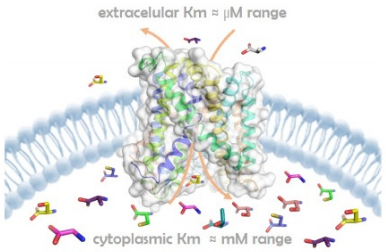
Chicano...Daban {*EMBO J* 38: e99769}

HIGHLIGHTS 2019 | APR.

Frozen-hydrated chromatin from metaphase chromosomes has an interdigitated multilayer structure

Chicano A, Crosas E, Otón J, Melero R, Engel BD, Daban J-R

EMBO J **2019** (Apr), 38: e99769



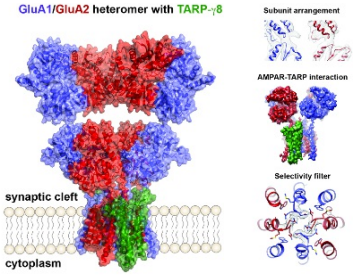
Errasti-Murugarren...Fita, Palacin {*Nat Commun* 10: 1807}

HIGHLIGHTS 2019 | APR.

L amino acid transporter structure and molecular bases for the asymmetry of substrate interaction

Errasti-Murugarren E, Fort J, Bartoccioni P, Díaz L, Pardon E, Carpena X, Espino-Guarch M, Zorzano A, Ziegler C, Steyaert J, Fernández-Recio J, Fita I, Palacín M

Nat Commun **2019** (Apr), 10:



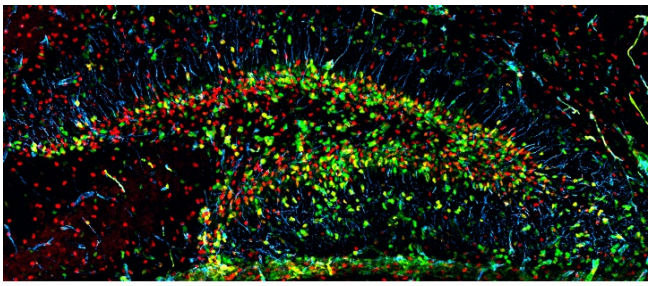
Herguedas...Greger {*Science* 364: eaav9011}

HIGHLIGHTS 2019 | APR.

Architecture of the heteromeric GluA1/2 AMPA receptor in complex with the auxiliary subunit TARP upgamma8

Herguedas B, Watson JF, Ho H, Cais O, García-Nafría J, Greger IH

Science **2019** (Apr), 364: eaav9011



Nieto-Gonzalez...Fernandez-Chacon {*Proc Natl Acad Sci USA* 116: 8000}

HIGHLIGHTS 2019 | APR.

Loss of postnatal quiescence of neural stem cells through mTOR activation upon genetic removal of cysteine string protein-upalpha

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