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BEYOND BIOPHYSICS

Mathematics and Biophysics

A conversation with Paco Montero

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Mathematics is the *language of Science*. This old statement has been the moto of any mathematics professor we may have suffered, or enjoyed, in our scientific careers from the early years at high school. However, while this does not leave room for discussion in Physics, Computer Science or many branches of Chemistry, it has been somehow left aside in other scientific areas related to Life Sciences. Biophysics, being by definition well spread over all these subjects, may have developed an ambivalent feeling about the role that Mathematics has to play in this multidisciplinary topic.

In order to talk about this subject, I have met Professor Francisco ("Paco") Montero at the Chemistry Building of Complutense University in Madrid. It is the last week in July, and the building is slowly becoming more silent than it usually is. I climb three floors, from the Physical Chemistry Department, where I work, to the Biochemistry and Molecular Biology Department, where Paco has been Full Professor for many years now. His office/laboratory door reads "Biophysics" on top of the names of the people working in it. It has been that way for as long as I can remember, when Biophysics was not a trendy word. Now, it would probably be more precise to say *Bioinformatics* in order to properly refer to Paco's work, and it would still mean too many different things. However, from the very beginning he says: "I am a chemist by education, from one of the first generations who specialized in Biochemistry at this university. Nowadays, I don't know what I am". Fortunately, I add, Nature does not know what it is either, as it refuses to accommodate to the kind of compartments we are so fond of using.

We both are then chemists by education, and have used mathematical techniques to develop algorithms in different areas of Biophysics, from the times in which you needed to develop your own computer programs. It is interesting to realize that some people consider that those of us doing *theoretical* biophysics are mathematicians. Although I have met a few who really are, there are many physicists, chemists and other scientists doing this kind of work, in Spain and abroad. That is, in my opinion, one of the things that makes it so interesting.

Prof. Francisco Montero,
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Paco tells me that he has been using mathematics in his research for several decades at many different levels. Just to mention a few, he starts with *differential calculus*, as the main tool for one of his long-established research lines in metabolic networks, *algebra*, for his work in genomics, all the mathematical tools which support *statistical mechanics* and lay the basis of molecular modeling, including the development of force fields, etc. Other biophysicists may mainly consider statistics for experimental data reduction, but many parts of mathematics are interesting here. Actually, he considers as standard in the history of Science that the birth of new disciplines (as Biophysics) has also created both boundaries and synergies in the basic sciences. This has pushed the latter to evolve in order to tackle the new challenges. For example, many developments in modern mathematics where forced by the new Physics formulated in the first half of the 20th century.

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Biology has also had a role in the development of new mathematics. Many readers will be familiar with the concepts of neural networks and genetic (or, more generally, evolutionary) algorithms, just to name a couple. They have a clear biological inspiration and in the end they appear as computer algorithms which allow users from many different fields to benefit from them. However, in the middle they possess a clear mathematical formalism. Unfortunately, he says, many users do not seem to be aware of it, or even care about it. Modern science puts us all in such a rush… The availability of commercial (even free) computer packages, or web servers, for many bioinformatics developments, is able to bring useful tools to a large range of researchers, hiding the difficult mathematics under user-friendly graphical interfaces. Nevertheless, this may become *dangerous* if the users do not pay attention to the details of the method they are using. Although there are present-day programs that seem to be able to do *everything*, it is the user's responsibility to know the details of the algorithms behind, especially the limitations of the physical or mathematical models which in the end provide the basis for the computed results. This goes from apparently simple calculations, as a t-Student statistical test, to more complex cases. He mentions the flux balance analysis as a technique from his own work on metabolic networks which is today widely available, but whose results are taken in some occasions well beyond their possibilities of application. Furthermore, one can find in published scientific papers mistakes which clearly denote a lack of knowledge from careless users of the algorithms. As it used to be said some time ago, you enter the "garbage in, garbage out" risk. The computer program will provide some result in most of the cases, but if the input is wrong (or even worse, if the chosen methodology is not adequate), the results will be completely useless, and the user will not even know about it.

This brings the conversation to something that is very important to both of us. Since we work at a public university, the education of science students and the training of young scientific researchers are among our top priorities. Paco mentions that at his classes, mainly for Biochemistry undergraduate or Master's students, he tries to emphasize as much as possible how important the mathematical background is for the use of bioinformatics algorithms, but also in order to understand modern experimental biophysical techniques. However, he feels that his students are reluctant to this kind of learning (and I can say from my own experience that the very same happens with most of my Chemistry students). In the case of computer software, they seldom go beyond the default options of the graphical user interface. And the worst thing is, Paco says, that at the end they pretend they can properly understand the results they have got, when this is very far from the reality.

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As an example, he considers inconceivable the possibility that one can understand an X-ray diffraction pattern without knowing what a Fourier transform is. The same can be said from many modern biophysical techniques, as NMR or FTIR. At least the researcher in charge of the experimental technique has to know to a reasonable degree the physics and the mathematics that link the initial collection of raw data from the measured sample to the final (hopefully) useful information. Even so, the standard users must at least have a basic knowledge of the *mathematics behind* the technique (either experimental or algorithmic) if he/she has to choose which one is to be employed in order to formulate the right question. Thus, this knowledge is important for any student, and especially crucial for those that are entering scientific research. It is interesting to note (sadly, perhaps) that in the last years it seems more complicated to convince an average biochemistry or chemistry student (not to mention someone from medical disciplines) of the advantages of having this mathematical background than it is to bring the attention of an average physics or mathematics student to the beautiful complexity of biological systems. In both cases, although this may force both sides to "switch languages" to a certain extent, the required effort would clearly pay off.

Paco mentions that Biochemistry and Biophysics have had a huge development from the middle of 20th century until today. The different experimental techniques provide vast amounts of data (just as an example he mentions genome analysis, including metagenomics). In order to make it useful, it has to be adequately framed. That is the work of informatics. Although many people may take it for granted these days, informatics does not just appear from nothing, it is a certain way of using mathematics. Of course, not everybody working in computation has to be a mathematician; we have already mentioned this. But he/she has to be a user of mathematics. Moreover, he/she has to show a certain ability for abstraction, as a way of mathematical thinking, which helps to put problems in the right perspective and, again, to pose the proper questions. Unfortunately, Paco feels that this may be becoming lost among the most common *bench scientists*. He proposes, as an example, explaining his students what a loop structure is in a simple algorithm. Something incredibly useful as a way of correctly structuring the mathematical operations of many calculations, becomes difficult to grasp without a specific way of thinking which he is missing in our current young students. At a different level, from my own experience, I have the same degree of frustration when teaching Quantum Chemistry to explain the atomic/molecular behavior of chemical/biological systems, and the same could be said of Statistical Thermodynamics. In many occasions, you cannot use examples from the macroscopic world, since the laws that rule the behavior of the classic systems are different from those at the quantum scale. Mathematics takes the lead then, and the equations, and a proper way of looking at them, is what allows the systems to be understood.

Paco criticizes part of the design of the contents taught in modern university degrees related to Biophysics, at least in our university. He feels they do not leave room enough for basic mathematics, but on the other hand they are redundant in other topics, which are repeated in different years. Professors are encouraged to teach the latest scientific developments even in the early years, and that may become a mistake if it comes at the cost of suppressing basic, well-established and useful disciplines, as mathematics. Novelties may become relevant or fade off after just a few months or years. In any case, they have to be understood to be properly explored, and we may not be giving the students the proper tools for that. Mathematics is one of those important tools. A set of topics that provides a solid background for science, including of course Biophysics.

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