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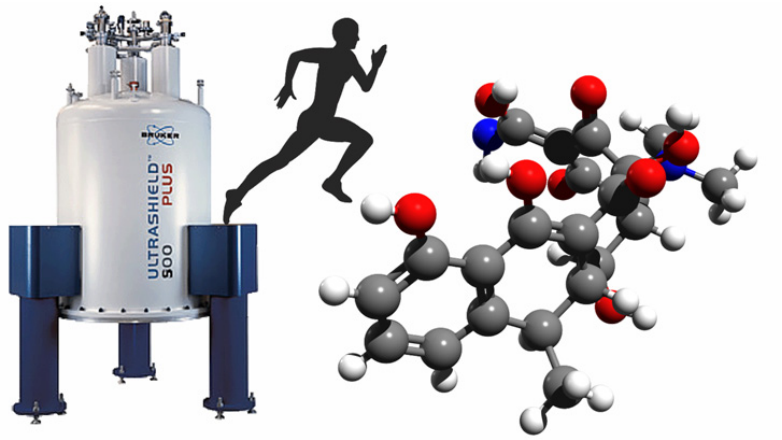
Speeding-up molecular analysis through Nuclear Magnetic Resonance (NMR)



Nuclear Magnetic Resonance (NMR) is an analytic technique which allows to determine the 3D structure of molecules in solution. One of the objectives of the investigation carried out in the UAB Nuclear Magnetic Resonance Service is to improve the scientific methodology used to obtain data in order to reduce the analysis time and thus reduce its cost. Two strategies are proposed: the Time-Sharing spectroscopy (TS) and the strategy of Multiple Free-induction-decay Acquisition (MFA) which have been successfully implemented in routine experiments.

Who has not heard about Nuclear Magnetic Resonance (NMR) technique? Although this technique is usually associated to the obtention of brain images in clinical applications, it has many other applications. In chemistry field, NMR is considered an excellent analytical technique used to determine 3D molecular structures in solution.

Concerning analysis cost, it is necessary to consider the high price of a high-resolution magnet. The most powerful currently cost between 10-20 million euros, price that can increase notably depending on accessory kits. On this base price, the not negligible, additional cost of maintenance must be added (implies cool maintenance of the magnet at He (Helium) liquid temperature, 4K). Considering these high costs, it is essential to be able to analyze the

maximum of possible samples in a certain time to get the most return on investment.

Another important point to highlight, is that to solve a structure at the molecular level is required to keep the sample in the NMR magnet a certain time. Basically, the analysis time, depends on the strength of the magnetic field generated, the sensitivity of the probe, the intrinsic molecular complexity, the amount of sample available and the scientific methodology that is used to obtain the data. It is in the improvement of this last point where our research group put their effort. Specifically, one of our most important goals is to improve the methodology of obtaining data in order to reduce the analysis time as much as possible.

The benefits are clear, obvious and instantaneous:
- Reduce the time for analysis, which is proportional to reduce their cost.
- Time to solve new samples, accelerating the research.

Recently, we have come up with new strategies and experiments that significantly reduce the analysis time of certain routine experiments. Behind this research there are two important concepts: Time-Sharing spectroscopy (TS) and the strategy of Multiple Free-induction-decay Acquisition (MFA). Below these concepts are very briefly explained.

TS experiments achieve the simultaneous acquisition of two experiments in one. Usually the experiments that can be combined with this methodology are experiments of correlation between nuclei ^{1}H-^{13}C and ^{1}H-^{15}N. Routinely these two experiments are acquired consecutively one after the other because they involve different frequencies. However, a probe with three frequency channels is available these experiments can be designed simultaneously in such a way that you get a reduction of 50% in time for analysis, and this fact has a considerable relevance. Specifically, we have published in the *Journal of Magnetic Resonance*[1] , an experiment that allows the simultaneous measurement of ^{1}H-^{13}C and ^{1}H-^{15}N coupling constants, parameters relevant to the structural elucidation of nitrogenous compounds, such as peptides. The results have been proven by using as example the Cyclosporine A, a natural product used as a medicine.

On the other hand, the MFA strategy consist in acquire different signals along a common NMR experiment (called N acquisition Windows). Each acquisition window is placed in different strategic points along an experiment in order to provide different molecular information. Briefly, it can be said that this strategy enables the acquisition of N experiments in one-shot. Without going into technical details, one of our recent contributions in the design of NMR experiments has been published in the prestigious journal *Chemical Communications*[2], where it has been shown that we can combine up to 4 experiments in 1, getting a reduced analysis time. The application has been proven effective for pattern molecules such as sucrose (common sugar), strychnine (an alkaloid used as a pesticide) and erythromycin (an antibiotic for the treatment of infections).

In summary, we have successfully implemented the concepts of TS and MFA in the experimental design of NMR experiments for small organic molecules, and have proven their benefit in reducing analysis time, and therefore, in the reduction of their cost.

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References

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[2]Motiram-Corral, Kumar & Pérez-Trujillo, Míriam & Nolis, Pau & Parella, Teodor. (2018). **Implementing one-shot multiple-FID acquisition into homonuclear and heteronuclear NMR experiments**. *Chemical Communications*. 54. DOI: 10.1039/C8CC08065H.

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