EXPRESIONES DE INTERÉS – BECAS PREDOCTORALES LACAIXA-INPHINIT

POSITION

1) **Analysis of macromolecular dynamics by Electron Microscopy**

2) **AREA OF KNOWLEDGE: Life Science panel**

3) **GROUP OF DISCIPLINES: Human Biology. Microbiology. Molecular Biology, Genetics, Cell Biology. Genomics and Proteomics, Biochemistry**

4) **RESEARCH PROJECT / RESEARCH GROUP DESCRIPTION (MÁXIMO 2000 CARACTERES SIN ESPACIOS)**

Since the introduction of Direct Electron Detectors (DEDs), the resolution and range of macromolecules amenable to this technique has significantly widened, generating a broad interest that explains the well over a dozen reviews in top journal in the last two years. The number of structures below 6 A has increased by an order of magnitude between 2014 and 2016, a 1000% jump, indicating the technological revolution the field is going through. Similarly, the number of job offers to lead EM groups and/or coordinate EM facilities has exploded, all over the world and with a clear shortage of qualified personnel. At the same time, FEI is doubling its production line just to accommodate an instrument waiting period of about one year. Strategic corporate movements are also happening, with very big players entering the market through key acquisitions, partly attracted by new Pharma interest in the field.

Particle flexibility and heterogeneity are at the same time the blessing and the curse of EM. On one side, flexibility reveals the macromolecule dynamics under study. On the other side, only homogeneous sets of particles can be reconstructed to atomic resolution. The compromise between a data set being as large as possible and as homogeneous as possible is still a problem, particularly so due to the low contrast and SNR of the acquired images. Advances in this regard have been made in recent years. However, the issue is far from settled, especially in those cases in which conformational changes correspond to a continuous distribution of states. This issue has been explored in some works, but this problem still needs further maturation. A particularly challenging situation occurs when studying a macromolecule of unknown structure. Indeed, most image classification algorithms are designed as local optimizers that start from a reasonably good initial map. If this map is not available, algorithms may easily find nonsensical structures. There are specific initial volume algorithms to handle this issue. However, currently, there is no algorithm specifically designed with flexibility/heterogeneity in mind.

Our group forms the Image Processing Center of the European Strategic Research Infrastructure for Structural Biology. Key Performance Figures of JMC are: Pubs: 241, Cits: 5553, h-index: 44 (source WOK as 10/24/2016)

5) JOB POSITION DESCRIPTION (MÁXIMO 2000 CARACTERES SIN ESPACIOS)

Europe has taken a lead position by enabling platforms that allow experimentalists to have access to high-end equipment and services. Instruct (https://www.structuralbiology.eu) and iNext (http://www.inext-eu.org). In this regard, Instruct Image Processing Center in Madrid (http://i2pc.cnb.csic.es) is an European and world reference center for the development of computational infrastructure as well as image processing algorithms for the elucidation of macromolecular structures.

The position offered in this proposal would tackle the heterogeneity problems in Single Particle Analysis at several levels:

1) Determination of several starting volumes solving in this way the initial volume problem in the case of highly heterogeneous datasets.
2) Elucidation of 3D continuous heterogeneity as a way to achieve high-resolution, small variations of the structure causes blurring specially for large macromolecules.
3) Development of 3D classification algorithms able to deal with strongly imbalanced classes. Macromolecular mixtures in which one of the populations is much smaller than the rest may go unnoticed and blur the final result.
4) Development of fast 2D classification algorithms capable of dealing with the increasingly larger datasets (currently in the order of several hundred thousands and rapidly growing to the millions of particles and posing a bottleneck in the processing capabilities of EM).

Collectively, this work will solve one of the major current bottlenecks in Electron Microscopy allowing this technique to become a high-resolution, high-throughput technique with the additional capability of being able to analyze the dynamics of the conformational changes taking place in the macromolecule.

GROUP LEADER

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