

## **FLEXIBLE FITTING OF PROTEIN MODELS INTO 3D-EM MAPS BY USING AN IMAGE REGISTRATION ALGORITHM**

Laura Fernández-de-Manuel<sup>1</sup>, María J. Ledesma-Carbayo<sup>1\*</sup>, Julián Atienza-Herrero<sup>2</sup>,  
Carlos O. S. Sorzano<sup>2,3</sup>, José-María Carazo<sup>2</sup>, Andrés Santos<sup>1</sup>

<sup>1</sup> ETSI Telecomunicación, Universidad Politécnica de Madrid, Spain

<sup>2</sup> Centro Nacional de Biotecnología - CSIC, Madrid, Spain

<sup>3</sup> Escuela Politécnica Superior, Univ. San Pablo – CEU, Madrid, Spain

In this work we propose an image registration algorithm to automatically fit protein atomic domain models into medium-resolution three-dimensional electron microscopy reconstructions (3D-EM map). The approach employs an image flexible registration algorithm whose optimizer controls the generation of stereo-chemically correct models from a given reference domain belonging to a super-family of proteins. Models are generated by studying the evolutionary structural variability that exists among the domains of the super-family. The proposed algorithm generates models automatically in the correct direction until the optimizer converges to the best fitted one. A local gradient optimizer is employed for this task. This optimization method seems to improve the traditional use of a grid of sampled models, since the model that best fit in the 3D-EM map could not be necessarily included in the grid. Mutual Information similarity measure is used as an alternative to Cross Correlation Coefficient that is traditionally the most widely used in the context of molecular image registration. An additional rigid registration that uses a local gradient optimization is applied between each generated model and the 3D-EM map in order to compensate small misalignments and offsets between initial images.