INTRODUCTION:
Friedreich ataxia (FRDA) is a neurodegenerative and hereditary disease which affects the balance, coordination and heart mainly. It is the most common autosomal recessive ataxia and it is associated with a pronounced lack of a protein named Frataxin. This protein has been associated with iron inside the mitochondria and it plays an important role in the assembly/mutation of the mitochondrial Iron-Sulfur clusters (ISCs) (see Figure 1A). It is supposed a high similarity between the human and the yeast molecular mechanisms that involve Frataxin. Moreover, in yeast it has been demonstrated experimentally that the yeast Frataxin (Yfh1, PDB code: 2GA5) interacts with the protein Isu1, and also Isu1 with both the proteins Isu2 and Nfs1, generating all together the central platform for ISC biogenesis (see Figure 1B).

METHODS:

• Sequence, structure and function for Yfh1, Isu1, Isu2 and Nfs1 were accurately studied using different bioinformatics tools. We contrasted these information with the current literature and several interacomics databases.

• Dockings were made between the proteins Yfh1/Isu1, Yfh1/Isu2 and Isu1/Nfs1. We applied the Escher NG protein-protein automatic docking system of the Vega ZZ project as a basic method for the docking experiments. The BIGGER extension of the Chemera 3.0 package was applied to validate the dockings.

• A Perl programming language script was developed to analyze the docking output-data with which we did a statistical analysis, a Principal Components Analysis (PCA) procedure and a clustering representation for each of the extracted components exploiting the Xmgrace tool.

• Tridimensional structure studies and representations were made using PyMOL and RasMol.

RESULTS:
A detailed bioinformatics study of the key proteins involved in the yeast Iron-Sulfur cluster biogenesis has been carried out. The four proteins of interest are: the yeast frataxin Yfh1 (PDB code: 2GA5), the scaffolding proteins Isu1/Isu2 and the cysteine desulfurase Nfs1. Previously, we had to model the structure for the yeast proteins Isu1, Isu2 and Nfs1 for which the tridimensional structure has not been solved yet. Docking experiments, together with an exhaustive static analysis, were made for the couples of proteins which seem to interact physically. It is reported that the interaction occur between the proteins Isu1/Yfh1, Isu1/Isu2 and Isu1/Nfs1.

The clustering graph resulting from the representation of the two extracted components of the Principal Components Analysis (PCA) of the docking output-data, and the representative docking solutions for each of the executed docking experiments, are shown in Figure 2. Owing to the accurate studied each of the proteins and an exhaustive statistic analysis of the docking output-data, we would postulate a dynamic mechanism of interaction with which these four proteins studied generate the ISCs inside the yeast mitochondria. Iron binding pockets, which presumably are the ISC linkage to the scaffolding proteins Isu1/Isu2, and individual interaction sites also on Isu1/Isu2 were identified. Moreover, the positions implicated in the iron handling on Yfh1 seems to be correctly oriented in the docking experiments and, together with its identified interaction region, fits well with our proposed model where Yfh1 is the iron donor for the ISC biogenesis. The cysteine desulfurase Nfs1 is the protein that acts as the Sulfur donor (see Figure 3).

CONCLUSION:
• We have studied bioformatically the sequence, the structure and the function of the proteins Yfh1p, Isu1, Isu2 and Isu2.

• We have applied protein-protein docking skills and developed an exhaustive statistic method to analyse the docking results with which we have postulated a dynamic mechanism of interaction among these proteins.

• We have suggested a model by which these proteins interact together to generate the ISCs inside the yeast mitochondria.

• This hypothesis would be helpful to better understand the function and molecular properties of Frataxin and be useful for a future treatment of FRDA.

FUTURE DIRECTIONS:
Yeast frataxin (Yfh1) has been shown to have a tail that seems to be very important for its functionality. We are now studying this tail in detail and demonstrating crucial implications in the ISC biogenesis model proposed here.