**Natural selection does not affect the structural evolution of proteins**

The Darwin - Wallace theory of evolution of species relates that organisms are the product of an evolutionary history that implies hereditary changes of a common ancestor and selection of favorable changes, process called natural selection. Although the role of natural selection is widely accepted regarding morphological characters, its importance at the molecular level is matter of debate.

Proteins decodify hereditary information and diverge during biological evolution. At the level of sequences, different aminoacids evolve at different rates, which is a clear evidence of natural selection. We recently found that the rate of evolution of a site depends on the stress of the protein´s active structure generated when it mutates, which is linked to the local packing density of the site. In contrast, it has been suggested that observed patterns of structural divergence are not a signature of natural selection but rather of the response of proteins structure to random mutations. Anyway, the role of natural selection in structural divergence of proteins has not been elucidated yet.

In this work, we have systematically studied whether there is any signal of natural selection in patterns of proteins structural evolution. To study this, we chose a different approach based on a mutational model and on our previous findings on sequence evolution. Firsts, we assembled our mutational model: we considered that proteins are Elastic Networks of amino acids and that a mutation at a site is a perturbation of the springs that connect it to its neighbors. Then, we selected a model of evolution: in one case we did not considered any selection, by fixing all mutations, and, in other case, we included selection by fixing mutants according to a stability-based fitness function linked to the degree of packing of the site. We analyzed the variation of structural divergence among sites and among normal modes of proteins. We compared predicted and observed patterns for several diverse protein families. We found high agreement between predicted and empirical structural divergence patterns whether natural selection is considered or not. Moreover, for all cases studied, including selection does not improve model fit. Therefore, we suggest that observed patterns can be explained in terms of mutational robustness and sensitivity. Specifically, structure is more sensitive in the direction of low-energy normal modes, which explains their higher contribution to evolutionary divergence. Also, the protein core is more structurally conserved than the surface because it is more robust with respect to random mutations.

In conclusion, we found no evidence of natural selection in patterns of structural divergence. These results are notable and go against the common belief that natural selection governs molecular evolution and are a step forward in understanding evolution.