New 3-D method improves the study of proteins

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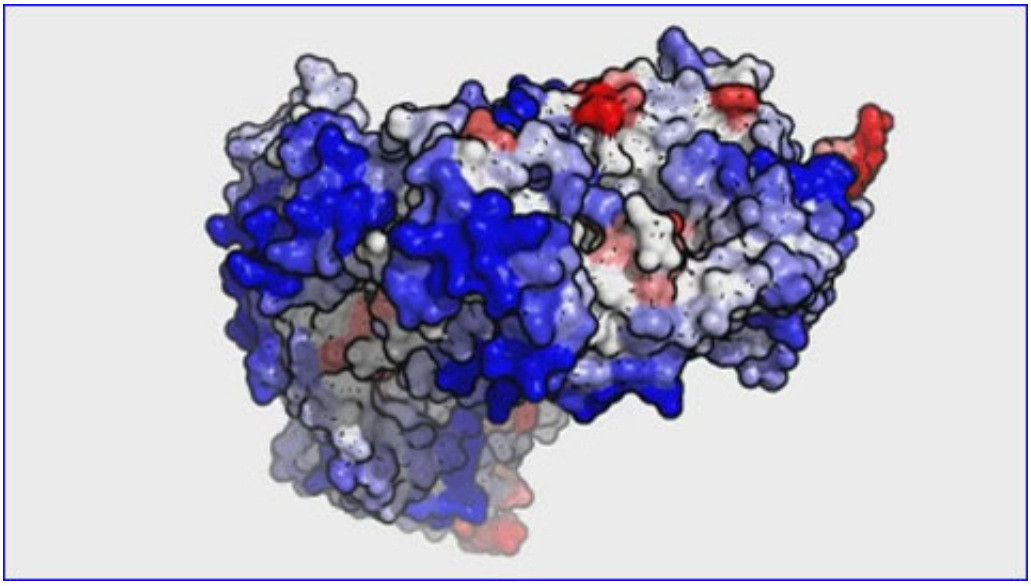

Researchers have developed a new computational method called AGGRESCAN3D which will allow studying the 3D structure of folded globular proteins and substantially improve the prediction of any propensity for forming toxic protein aggregates. With this new algorithm, proteins can also be modeled to study the pathogenic effects of the aggregation or redesign them for therapeutic means.

Current knowledge of the molecular bases of protein aggregation, the cause of several pathologies, has produced a series of algorithms to

identify the regions of the proteins with a tendency to aggregate. Among them was AGGRESCAN, one of the first computational methods created, developed eight years ago by the same IBB researchers. However, the majority of these algorithms only analyse regions in the linear sequence of proteins. That makes it more difficult to predict the aggregation properties of globular proteins, where these sequences are often protected within their native spherical structure.

The AGGRESCAN3D (A3D), which was implemented as a web server freely accessible to the academic community, surpasses these limitations with an approach based on the protein structure in a folded state. According to the article, published in *Nucleic Acids Research*, the new algorithm offers significantly higher precision than others based on linear sequences in predicting the properties of aggregation of globular proteins. It offers new and important features, such as facilitating the modelling of pathogenic mutations and the design of proteins for therapeutic means, such as antibodies, with increased solubility.

"A3D is the quickest algorithm available that can predict protein aggregation and work dynamically. In other words, it takes into account the flexibility of the protein structure. This allows us to model aggregations caused by natural fluctuations in the structure, as well as those caused by destabilising pathogenic mutations, and predict their impact on the protein's tendency to aggregate", says Salvador Ventura, IBB researcher from the UAB Department of Biochemistry and Molecular Biology and coordinator of the research team.

The new algorithm can be applied to any protein with a known structure or that can be generated by modelling. To validate the new method, researchers used proteins whose aggregation properties had already been characterised experimentally. In the static mode, it is possible to study individual proteins and protein complexes with up to 20,000 atoms and proteins with up to 400 amino acids in dynamic mode.

Protein Aggregation, a Key Issue in Biomedicine and Biotechnology

Protein aggregation has gone from being an area ignored in protein chemistry to becoming a key area of biomedicine and biotechnology.

"The incorrect folding of proteins and subsequent aggregation is the cause of a growing number of human disorders, such as Alzheimer's disease, Parkinson's and Type 2 Diabetes, and is one of the most important barriers in design and manufacturing of proteins for therapeutic means. These therapies, which imply the use of monoclonal antibodies, growth factors or enzyme replacement, have demonstrated to have an already high level of precision towards their molecular targets, and that is why continuing to study them is so significant", Salvador Ventura concludes.

More information: "AGGRESCAN3D (A3D): server for prediction of aggregation properties of protein structures." *Nucleic Acids Research*, 2015 1. DOI: 10.1093/nar/gkv359

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