The transmission of information via proteins could revolutionize drug discovery

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This image depicts Beta-sheet-rich proteins with minimal motifs that show correlations. Credit: Nature Comm/IRB Barcelona

Proteins are chains of amino acids that, when folded into certain structural patterns and also when unfolded, exert functions within cells. Proteins receive signals that are transmitted from one to the next and that are essential for life. However, within a given protein, are there "highways" along which the signals travel, like a in a relay event? That is

to say, how is the information transmitted in a given protein? "This is one of the key questions in biophysics," says Xavier Salvatella, ICREA Professor at the Institute for Research in Biomedicine (IRB Barcelona) and head of the Molecular Biophysics Lab.

The most recent study in this field published today in *Nature Communications*, in collaboration with Modesto Orozco, an expert in biocomputational simulations who also works at IRB Barcelona, shows that the transmission of information over large distances occurs within proteins. This transmission has been observed and demonstrated for all proteins containing beta sheets, one of two structural patterns that folded proteins adopt.

"We are discovering the information transmission pathways inside proteins and this concept, which we have validated for one kind of protein structural motif, allows us to speculate that proteins have many valid surfaces on which a drug can act," relates Salvatella.

The team of scientists have discovered how the motions of various parts of proteins, although physically far apart, are correlated. "The same thing happens to proteins as happens to the choreography of ballet dancers, where the movements of the participants are interconnected in spite of being physically apart. If the first one lifts an arm, the last one lifts an arm too," describes the researcher.

A gold mine for drug discovery

Drugs act on a certain site or active domain of a target protein in a given disease. In most infectious diseases and in cancer, one of the problems is that the site where the drug interacts evolves and mutates and the drug is rendered inefficient. The concept, now validated by IRB Barcelona researchers, allows one to think that the site where the drug was headed is equally as valid as any other point along the transmission pathway.

"If this were this case – which is what our data show – we would be able to find many sites within the structure of a protein that would be equally or more efficient at interacting with a drug. Sites that, although lying far from the key or functional site of the protein, would have the same effect," argues Salvatella.

The scientist goes on to explain that there are already many drugs that act at sites that are not the actives sites but that these drugs have been discovered by serendipity, through massive screenings of molecules and observing that they bound to an unexpected site. "This system is clearly not efficient. We have to be able to organise it and if we manage to do this, then we will have a potent way to discover new drugs," explains the researcher.

In addition to furthering the conceptual field, Salvatella is working with proteins of biomedical interest. "We already know enough to study in parallel the pathways of proteins of biomedical interest. If we are successful, we will have discovered a gold mine for drug discovery," affirms the scientist.

The first authors of the article are the postdoctoral fellows Bryn Fenwick, a former member of Xavier Salvatella's group, currently at the Scripps Research Institute of California, and Laura Orellana, a former member of Modesto Orozco's group, who is now at the Science for Life Laboratory at the Royal Institute of Technology in Stockholm. The work has been done within the joint programme in Computational Biology between BSC, CRG and IRB Barcelona.

More information: Correlated motions are a fundamental property of β-sheets R. Bryn Fenwick, Laura Orellana, Santi Esteban-Martín, Modesto Orozco, and Xavier Salvatella *Nature Communications* (2014) DOI: 10.1038/ncomms5070