Ions have an essential role in many biological processes. In particular when the charge density is high (Mg, Ca, Zn) and when ionic charge changes according to microenvironmental conditions (Fe, Cu, Mn). Metal ions often interact with disordered proteins, with effects yet to be understood. The affinity is high enough to compete with structured proteins, but the structural and catalytic activity of the metal center is often out of control and, therefore, potentially dangerous for cells.

Copper, for instance, is an essential element for cell life. It is the active site for many chemical reactions related to cell respiration (energy supply) and for keeping the cell at a proper oxidation potential (antioxidant effect). In neurons, copper participates to signal transmission at the level of the synapsis and it is involved in neuron plasticity, a process that is fundamental for a healthy brain. In the human brain (that is about 2% of body weight) it is concentrated 8% of the total amount of copper circulating in the body.

Despite copper be required by cells, it is toxic. When it is a free ion, it allows a fast production of aggressive radicals that can damage membranes, nucleic acids and proteins. To keep a correct copper balance in the body, organisms adapted to its presence in their environment using many macromolecules that keep the copper ions bound and apart from the water medium characteristic of cells. As an example, in many neurodegenerative diseases, like Alzheimer’s disease, the oxidative pathway induced by sporadic copper catalysts triggers cell death and these oxidative events are potential early biomarkers of the disease.

During neurodegeneration, the first stage of neuronal death, abnormal concentrations of particular proteins are measured in the synapses. Some of them, like amyloid-beta peptides, form, in the Alzheimer's disease, stable and visible aggregates that are characteristic of the irreversible pathway towards death. When such conditions occur in the synapses, the chemical species formed by copper and amyloid peptides produce levels of radicals comparable with the free copper ions. In our projects we have extensively modeled the interactions between copper ions and amyloid-beta peptides in a water environment. The models explain why these weak interactions, specific of amyloid beta peptides, make copper more aggressive [1,2].

We simulated about 100 walkers starting from different configurations for one or two copper ions in contact with one or two amyloid-beta peptides, on the basis of empirical models. Each of these configurations is refined with explicit electrons, thus modeling the details of the copper-peptide interactions for all the configurations at the same time. Thousands of computing units can be efficiently used at the same time, to provide an approximate statistical view of detailed molecular models.

These models open a new venue for understanding, at an atomic level, the role of disordered biological molecules in making the chemistry of reactive centers versatile, a general feature of living cells: a step forward, beyond the structural biology ground of the second half of the past century.

1. La Penna G., Li M.S., Chemistry Eur. J., 2018, 24, 5259-5270, http://dx.doi.org/10.1002/chem.201704654.
2. Pham D.Q.H., Li M.S., La Penna G., J. Phys. Chem. B, 2018, 122, 7243-7252, http://dx.doi.org/10.1021/acs.jpcb.8b03983.