Transition Metal Binding Site Predictions for Drug Design Applications

A. Levy[1], S. L. Dürr[1], U. Röthlisberger[1]*

[1]Laboratory of Computational Chemistry and Biochemistry, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Transition metal-based drugs represent promising candidates for cancer treatment. In the field of computational chemistry, hybrid quantum mechanics/molecular mechanics (QM/MM) is often the method of choice for this type of system, allowing an accurate description of metal species and the formation or breaking of covalent bonds. However, QM/MM is computationally expensive, limiting its applications to drug design, where the ability to study multiple drug candidates binding to diverse sites is crucial.

In this context, we present Metal3D [1], an accurate metal site predictor recently developed in our group showing promising applications: it employs 3D convolutional neural networks and, despite being initially designed for predicting the location of zinc ion binding sites, it shows accurate predictions for other transition metal ions and, more interestingly for drug design applications, also for transition metal-based drugs. We assessed Metal3D's ability to predict binding sites for different transition metal-based compounds complexed with nucleosome core particles. Remarkably, Metal3D accurately identifies the experimentally located sites in the majority of cases.

Metal3D's ability to accurately identify binding sites for transition metal-based drugs in biological systems makes it a promising tool for drug design applications. By efficiently identifying putative binding sites, Metal3D can be a valid asset for drug design, providing a limited number of likely starting points for QM/MM simulations.

[1] Simon L. Dürr, Andrea Levy, and Ursula Rothlisberger, *Nature Communications*, **2023**, 14(1), 2713.