Prediction of the Interaction of Metallic Moieties with Proteins: An Update for Protein-Ligand Docking Techniques

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In this article, we present a new approach to expand the range of application of protein-ligand docking methods in the prediction of the interaction of coordination complexes (i.e., metallodrugs, natural and artificial cofactors, etc.) with proteins. To do so, we assume that, from a pure computational point of view, hydrogen bond functions could be an adequate model for the coordination bonds as both share directionality and polarity aspects. In this model, docking of metalloligands can be performed without using any geometrical constraints or energy restraints. The hard work consists in generating the convenient atom types and scoring functions. To test this approach, we applied our model to 39 high-quality X-ray structures with transition and main group metal complexes bound via a unique coordination bond to a protein. This concept was implemented in the protein-ligand docking program GOLD. The results are in very good agreement with the experimental structures: the percentage for which the RMSD of the simulated pose is smaller than the X-ray spectra resolution is 92.3% and the mean value of RMSD is < 1.0 Å. Such results also show the viability of the method to predict metal complexes–proteins interactions when the X-ray structure is not available. This work could be the first step for novel applicability of docking techniques in medicinal and bioinorganic chemistry and appears generalizable enough to be implemented in most protein-ligand docking programs nowadays available. © 2017 Wiley Periodicals, Inc.

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Introduction

Since the appearance of *cis*-platinum in the pharmaceutical landscape in the 1970s,[1] the interest in designing drugs based on coordination complexes has drastically increased. Over the last years, metal salts and/or metal complexes have been proposed in the therapy and diagnosis of many diseases and a large series of textbooks and reviews have been published on medicinal inorganic chemistry.[2–9] Gold, iridium, and rhodium complexes are now only few examples of central atoms in drug design.[10] Novel breakthroughs in the development of new metallodrugs are surely awaiting.

To highlight the specificity of metallodrugs in the drug design landscape, at least three aspects related to their molecular properties need to be discussed. First, transition metals provide geometric and isomeric complexity absent in organic systems, hence allowing regiospecific and enantiospecific molecular interactions. Second, the binding of the metallodrugs to biological targets can involve different degrees of chemical changes in the first coordination sphere of the metal, ranging from no exchange at all to multiple ligand exchanges (here the word ligand has the usual meaning in the coordination chemistry and it refers to the chemical species that binds the metal throughout a direct coordination bond). The third point to be mentioned is the difficulty to reach experimental resolution of structures of metallodrugs with X-ray (i.e., lability of the drug-protein interaction under crystal conditions and electron beaming) and NMR (i.e., open shell systems) approaches. Therefore, despite their potential, metallodrugs still represent a narrow field of research when compared with the amazing number of projects devoted by academia and companies to identify drug candidates based on organic species.

Computation has become a major asset in drug design projects. Either based on combinatorial, pseudo-rational or rational approaches, the use of molecular modelling is now a fundamental tool in the drug design pipeline. Protein-*ligand* docking is generally the approach used at its early stage so to reach fast and accurate enough predictions of binding energies and geometries of drug-receptor complexes (here the italic writing of *ligand* refers to the docking terminology and corresponds to any molecular species that interact with a protein). Unfortunately, valid predictions of the binding involving metal-containing *ligands* or changes in the chemical state of the *ligand* are still an open battle. In the case of metallodrugs, this represents the nexus of a major computational challenge.

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