

Metal-Ligand Interactions in Biological Systems: A Review

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ABSTRACT: Several bodily functions depend on metal-ligand interactions, and these metalloenzymes, metalloproteins, and metal-based therapies need these interactions. The machine receives coordinated geometry, oxidative state, and ligand donor characteristics, and these approaches are used to study metal-ligand complex structure and electronic characteristics in this review, and describes EPR, which uses ultraviolet-visible, X-ray, and infrared methods to measure metal oxidation. Coordination geometry, bond energies, and reaction routes are studied using density functional theory and molecular dynamics simulations. Therapists examine metal-ligand complexes, including metallodrugs, such as cisplatin or ruthenium-based medicines and metalloenzyme inhibitors of zinc- or magnesium-dependent enzymes. Environmental and evolutionary factors, including metal availability and biogeochemical cycles, explain how metalloproteins originate, why they do so, and stabilize metal in the body. Combining metal and ligand complex dynamics with biological function is tricky, and especially under fluctuating pH and redox potential. The computational and systematic biology approaches must be used with electro-optical spectroscopy to understand their current relevance and hypothesize about future. This final convergence of theoretical, computational, and functional findings paves way for next generation metallodrugs, sensors, and catalysts.



Keywords: Bioinorganic chemistry, Biological activity, Coordination, Metallodrugs, Metals

1. INTRODUCTION

Bioinorganic chemistry relies on metal-ligand interactions in biological systems to sustain existence at the molecular level. Iron, copper, zinc, and magnesium are essential cofactors in catalysis, electron transport, structural stability, and metabolic pathway management. Metals' ability to coordinate with amino acids, nucleotides, porphyrins, and thiols and adopt different oxidation states enables them to form flexible complexes that fuel metabolic and enzymatic activities. The specific mechanisms of metal-ligand recognition, selectivity, and dynamics remain unknown despite their ubiquitous usage [1, 2].

In dynamic multi-metal systems with redox and ligand exchange processes, the difficulty is the poor connection between the coordination structure data and the biological reactivity or selectivity of metal centers. Previous research investigations have mostly been confined to the static structures of metalloproteins, but have not taken into account the environmental impacts, conformational changes and transitory intermediate species that define true biological activity. In an attempt to incorporate theoretical modelling, functional analysis and experimental characterization into a cohesive knowledge of metal-ligand interaction under physiological settings we try to identify a research need [3, 4].

The objectives of this review article are to provide an insight into the structural principles and the nature of bonding of metal-ligand complexes, to discuss their biological relevance in catalysis and regulation, and to evaluate the extent to which computational and spectroscopic methods provide information on their electronic and dynamic

properties. The research also addresses the effect of environmental and evolutionary parameters on the diversity of metal coordination and the application of the results for technological and medical progress, such as development of biosensors, metal-based medicines and bioinspired catalysts.

2. METAL-LIGAND COORDINATION CHEMISTRY FUNDAMENTALS

As briefly outlined in the sections that follow, the stability and specific of metal-ligand complexes are determined by the characteristics of the metal ion and the chelating agent. The development of ligands for the specific interaction of metal ions in aqueous solution has been the subject of increasingly extensive research. The context for comprehending the characteristics of the compounds discussed in this review is established by this discussion [5].

Metals' chemical characteristics have been used by biology for various functions, as seen in Table 1. This list is not complete, but serves as a primer to emphasize key ideas. Alkali and alkaline earth metals, such as Na^+ , K^+ , and Ca^{2+} , are stable in aqueous solution as cations, promoting charge balance and electrical conductivity. Metal ions play important structural roles in biomineralized tissues through metal-ligand bonding relationships, as well as in nucleic acids and proteins that are maintained in a preferred fold [6].

Table 1. - Biochemical Functions of Inorganic Elements with Sample Case Studies

Inorganic Element	Representative Examples	Function	Ref
Ca, NO, Zn	Release of Ca^{2+} , Zn^{2+} , and NO instigates diverse biochemical signaling pathways	Signaling	[7]
Ca, Si	Biomaterials in bone, teeth, and shell	Structure (macroscopic)	[8]
Fe, Cu, Mo	Iron-sulfur proteins, cytochromes, blue copper proteins	Electron transfer	[9]
Hg, Cu, Zn, Pb, As, Sb, Cd, Ni, Fe, Mn, Co, Ag	Metalloregulatory proteins regulate transcription	Signaling to DNA	[10]
Na, K, Ca	K^+ channels responsible for electrical conduction in nervous systems	Charge balance	[11]
V, Fe, Co, Ni, Cu, Mo, W	Hemoglobin, cobalamin alkyl group transfer	Atom or group transfer	[12]
V, Mn, Fe, Co, Ni, Cu, W	Oxidation, nitrogen fixation, radical formation enzymes	Redox catalysis	[13]
Zn, Fe, Ni, Mn, Mg	Hydrolysis by carboxypeptidase, purple acid phosphatase, urease, arginase, etc	Acid–base catalysis	[14]

2.1 PREFERENCE OF DONOR ATOMS

R.G. Pearson developed the hard and soft acids and bases (HSAB) concept in 1965 by expanding on Irving, Williams, Arhland, Chatt, and Davies' criteria. Because they are small and have a high charge density, nonpolarizable bases and acids are classified as "hard" based on their polarizability. Polarizable bases and acids are classified as "soft" due to their low charge density and often large size. "Borderline" describes acids and bases that have intermediate hard/soft properties. The HSAB principle states that hard acids prefer hard bases, soft acids prefer soft bases, and borderline acids prefer borderline bases [15].

Pearson's classifications of metal ions (Lewis acids) and their ligands (Lewis bases) are shown in Table 2. This offers a useful basis for predicting metal ion preference for ligands with various donor groups. For example, soft donor groups like thioethers (R_2S) and thiolates (RS^-) prefer soft metal ions like Cu^+ , whereas hard oxygen donors, including carboxylates and phenolates, are appropriate for hard metal ions like Fe^{3+} [15].

Table 2. - Sorting Donor Atoms and Certain Metal Ions Using Pearson's HSAB Theory

Materials	Types
Cu^+ , Au^+ , Ag^+ , Tl^+ , Hg^+ , Pd^{2+} , Cd^{2+} , Pt^{2+} , Hg^{2+}	Soft Lewis acids
F^- , OH^- , H_2O , ROH , Cl^- , RO^- , R_2O , CH_3CO_2^- , NH_3 , RNH_2 , NH_2NH_2 , CO_3^{2-} , NO_3^- , O_2 , SO_4^{2-} , PO_4^{3-} , ClO_4^-	Hard Lewis bases
Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Pb^{2+} , Bi^{3+} , Rh^{3+} , Ir^{3+}	Borderline acids
H^+ , Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+} , Sc^{3+} , Ti^{4+} , Zr^{4+} , Cr^{3+} , Al^{3+} , Ga^{3+} , La^{3+} , Gd^{3+} , Co^{3+} , Fe^{3+}	Hard Lewis acids

NO₂⁻, Br⁻, N₃⁻, N₂, C₆H₅NH₂, pyridine, imidazole	Borderline bases
RSH, RS⁻, R₂S, S²⁻, CN⁻, RNC, CO, I⁻, R₃As, R₃P, C₆H₅, C₂H₄, H₂S, HS⁻, H⁻, R⁻	Soft Lewis bases

It would seem clear that improving the donor's Lewis basicity would strengthen metal-ligand bonding in accordance with the Lewis acid-Lewis base explanation. Although metal-ligand affinity can be adjusted using this concept, other parameters must also be considered. For instance, raising a phenolate's basicity also raises its pKa. Such a change may actually reduce the effective metal binding at a target pH because metal ions and protons compete for ligand binding in aqueous solution. Overall stability constants do not accurately represent a ligand's affinity for a metal in physiologically relevant solution conditions due to proton competition. Using known pKa and pH values, a pH-dependent conditional binding constant may be computed. As an alternative, the equilibrium constant at the given pH and buffer component solution conditions may be directly measured as an apparent binding constant (K_{app}, also known as K_{eff} for effective binding constant). Binding constants are often described as dissociation constants (K_d) and reversed for ease [16].

2.2 STERIC STRAIN, PREORGANIZATION, AND CHELATE RINGS

Polydentate metal-binding ligands with many donor atoms have more complex stability than monodentate ones due to the chelate effect. This effect may be increased by matching the chelate rings to the cation's size to decrease steric strain upon metal binding. Polydentate ligands with neighboring six-membered rings may generate steric strain, although five- and six-membered rings reduce it. High-affinity binding favors ligands that preorganize donor atoms spatially for complexation, minimize steric strain upon coordination to the metal ion, or both. Thus, tight complexation allows macrocycles that experience little strain during metal complexation to hold onto their metal ion [17].

2.3 INTRICATE GEOMETRY

Certain binding geometries may be preferred over others by a metal ion depending on the amount of valence d electrons it has. The foundation of this choice is ligand field stabilization energy (LFSE), which is well described in textbooks on conventional inorganic chemistry [18].

Fe²⁺ and Fe³⁺, the two major physiologically significant oxidation states of iron, favor octahedral and distorted octahedral geometries. Conversely, copper is generally found as Cu⁺ and Cu²⁺, with Cu²⁺ preferring axially deformed octahedral geometries, square planar geometries, or square pyramidal geometries because to Jahn-Teller distortions of its d⁹ electron configuration [19].

Because of its filled d¹⁰ configuration and lack of affinity for LFSE-based geometry, its reduced Cu⁺ form may be found in a variety of coordination geometries, such as two-, three-, and four-coordinate sites. The ligand field's shape may affect copper's redox state [20].

3. MODERN DRUG DESIGN: ROLE OF INTERACTIONS OF METAL-LIGAND

A significant portion of the chemical space often investigated for drug design is defined by metal-ligand interactions, which also determine the mechanisms of action of two significant drug classes: metallodrugs and metalloenzyme inhibitors. Although Rosenberg discovered in 1965 that cis-diamminedichloroplatinum(II) (cisplatin) has anticancer properties, numerous platinum-based compounds have been created and employed in clinical settings, primarily for the treatment of cancer. These metallodrugs produce drug-target covalent bonds via ligand exchange processes, which result in structural alterations at specific protein residues and nucleic acids and eventually trigger cellular death [21].

Other complexes based on transition metals, including certain ruthenium compounds, have strong inhibitory effects on proteins. Metallodrugs may also use their photoactive, redox, and catalytic qualities to break down viral proteins and label proteins in vivo, for example. The metal governs ligand coordination and the metallodrug's mechanism of action from the core of the inorganic complex (Fig. 1) [22].

Small chemical compounds containing a metal-binding group (MBG), often referred to as a metal-binding pharmacophore (MBP), that exhibit strong interactions with one or more metals at the designated catalytic site, impede the activity of medicinally significant metalloenzymes. Zinc-dependent carbonic anhydrase (CA), matrix metalloproteinases (MMPs), angiotensin-converting enzyme (ACE), histone deacetylases (HDACs), and magnesium-dependent metalloenzymes such as HIV integrase (HIV-IN) have become the focus of targeting efforts. The FDA has identified, formulated, and sanctioned metalloenzyme inhibitors for the treatment of cancer, HIV/AIDS, bacterial infections, and hypertension (Fig. 1) [23].

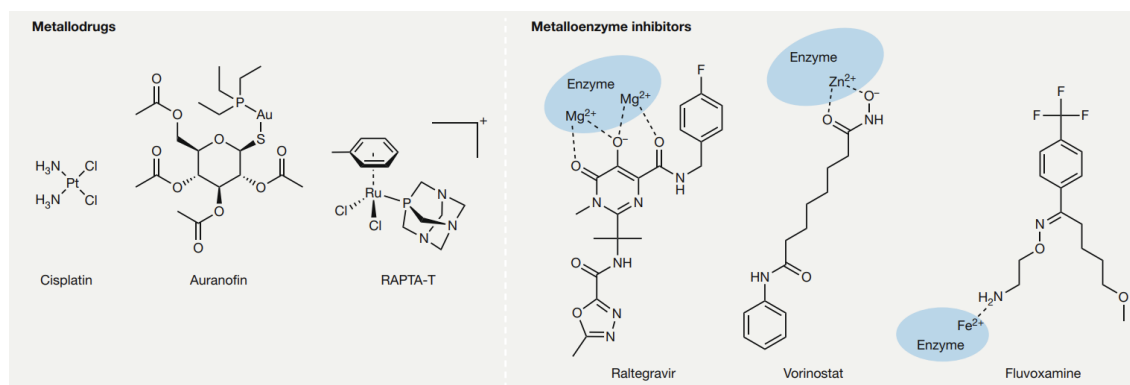


FIGURE 1. - Metal-ligand interactions in metallodrugs and metalloenzyme inhibitors [24]

Metal-ligand interactions render metallodrugs and metalloenzyme inhibitors efficacious, although their different procedures vary. Figure 2 illustrates that many structural data sets have shown metal-mediated medicines at their sites of action over time, highlighting the significance and intricacy of metal-ligand interactions and their potential implications for drug design [25].

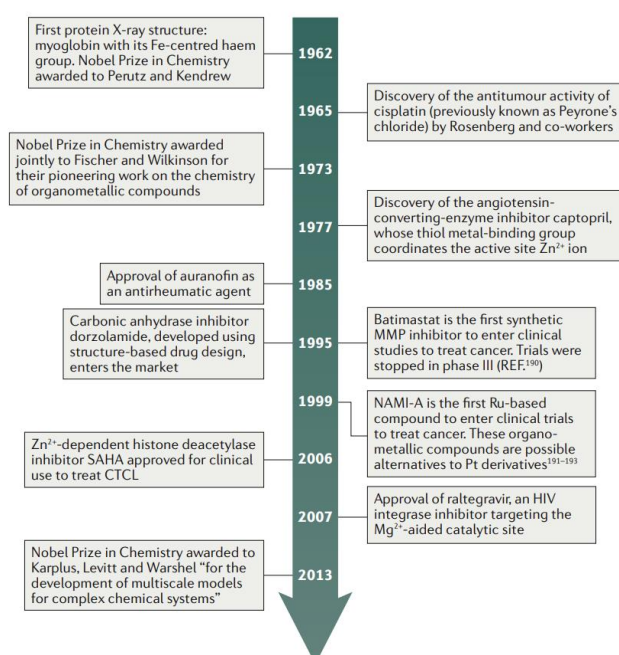


FIGURE 2. - Metal-ligand interactions in sBDD [24]

4. METAL-MEDIATED DRUG DESIGN

4.1 METALLODRUG SYNTHESIS AND DESIGN

Metallodrug design was inspired by an interest in studying the therapeutic properties of organic molecules whose chemical process was hitherto unattainable, and core of metals complexes. The development of new pharmaceuticals involves metal-centered molecules with complex structures, allowing for the exploration of novel chemistry, including unique modes of action that are inaccessible to organic small molecules. A targeted biomolecule's ability to function may be inhibited by interactions between the metal and/or ligands and amino acid residues or nucleic acids. One example of such a treatment is the nanomolar inhibition of protein kinases [26].

Potent organometallic inhibitors may also be created by coupling ferrocene derivatives to these inorganic metal-centered scaffolds. These substantial metalloids adhere to entered preclinical and clinical trials, suggesting that platinum medications may be replaced by metalloid drugs that can overcome toxicity and chemoresistance, despite their potential off-target interactions. In this case, the development of more complex metal-centered designs that are anticipated to function without serious side effects would be further stimulated by modeling and the logical design of innovative metallodrugs [26].

DFT calculations in transition-metal chemistry is constrained by electron correlation, numerous accessible spin states, and functional dependence in some metal centers, which distort projected structures, redox properties, and

reaction pathways. While the multimetallic systems, open-shell complexes, and physiologically relevant environments with dynamic solvent effects, ligand exchange, and proton-coupled processes worsen these issues, in addition many metallodrugs fail clinical translation because of poor selectivity, instability in vivo, off-target interactions, poor pharmacokinetics, and systemic toxicity, despite promising preclinical results. Thus, computational prediction and drug development in different fields, such as industry need more holistic approach that incorporates theory, experimental validation, and early translational review.

4.2 BIOLOGICAL SYSTEM METAL-LIGAND COMPLEXES: STRUCTURAL CHARACTERIZATION

Atomic-level descriptions of metal-ligand complexes in biological systems are essential for knowing why coordination geometry and bonding patterns control biochemical activity. This method determines metal-ligand bonding type, strength, and dynamics using laboratory and computational methods. UV-visible, infrared, electron paramagnetic resonance, and nuclear magnetic resonance are utilised to verify electronic transitions, metal oxidation states, and ligand environments in metalloenzymes and metalloproteins. Expect more visible-range growth. In contrast, X-ray and Mössbauer spectroscopies detect local coordination geometries and oxidation–reduction states. High-resolution X-ray crystallisation is preferred for biomacromolecule metal center placement. However, cryo-electron microscopy is increasingly used to analyze large macromolecular complexes near-atomically under functional conditions [27].

Metal binding, orbital conversation, and energy landscape are better understood by density functional theory, molecular dynamics, and quantum mechanics/molecular mechanics research. The findings show that tiny changes in coordination number, donor atoms significantly affect reductive potential, catalytic efficiency, and overall activity. Typical examples include zinc in hydrolases, iron in heme complexes, and copper enzymes that catalyze activities. Metal-ligand plasticity regulates both enzymatic activity and signal transduction from reversible binding at the active site [4]. Computational and theoretical views on ligand interaction in biological settings are needed to comprehend metals' electronic, structural, and dynamic chemical reactivity. Both computational and quantum chemistry approaches imitate metal ion coordination to biological ligands such as amino acids, nucleotides, and porphyrins. The most widely used quantum chemical technique, density functional theory, predicts bond lengths, metal-ligand charge transfer, orbital hybridisation, and reaction processes. Mechanism insights are reliably predicted by this. A molecular dynamics simulation models the time-dependent behaviour of metalloproteins and metalloenzymes in realistic solvents, temperatures, and pH environments, calculating solvent coordination number and conformational mobility by observation. Quantum/molecular mechanics hybrid approaches may properly describe massive bio-macromolecular context active sites, enabling electronic-detail biological research [4].

Through computational docking and molecular orbital analysis, the interaction of small-molecule ligands with metal centers is studied. With new machine learning and big data we can quickly and accurately assess binding affinities and selectivities for metal–ligand complexes using bioinorganic databases, accelerating discovery for new drugs that could be used in novel therapeutic agents and artificial metalloenzymes. Ultimately, when combined with DFT, MD, and data-driven modeling computational and theoretical methods present a comprehensive multi-scale picture, linking atomic-level coordination to biological function. Thanks to this work, engineers, biologists, and clinical scientists are being given the means to design warheads that study and control metal-ligand chemistry [28].

5. ENVIRONMENTAL AND EVOLUTIONARY ASPECTS

Metal-ligand interactions are central to all biological life forms not only by creating the conditions for the origins of life but also by allowing all living organisms to continue existing in their respective surroundings, and availability and distribution of metals, including iron, copper, zinc, and manganese, are determined by environmental conditions, which shape living systems and exert evolutionary pressure for the development of metal acquisition, transport systems, and detoxification, while Geochemical conditions have given rise to the abundance and scarcity of key metals on Earth [29].

The diverse environments on our planet have caused abiotic factors such as oxygen levels and redox potential to fluctuate, creating selection pressure on primitive enzymes. Hence, metalloproteins emerged as an example of convergent evolution, independently evolving in bacteria, archaea, and eukaryotes. Metallochaperones and metal-sensing regulatory proteins also emerged to facilitate homeostasis in response to environmental perturbations, with this evolutionary history shows metal binding oligomers variant design to balance availability and toxicity. Metal limitation drives the evolution of high-affinity siderophores and other ligand designs, while metal excess promotes detoxification and sequestration strategies, such as metallothioneins. In addition, global scales, biogeochemical metal cycling processes are catalyzed by microorganisms that mediate the biogeochemistry of elemental cycles in aquatic and terrestrial ecosystems [30].

6. DRUGS THAT TARGET METALLOENZYMES ARE DESIGNED USING FRAGMENTS

Metalloenzyme inhibitors have generally been designed and discovered by adding one or more MBGs to the original organic scaffold. In the metalloenzyme's specific pocket, the MBGs have the ability to chelate different catalytic ions (Fig. 3). Fragment-based drug design may find metalloenzyme inhibitors. FBDD approaches have expanded the MBG repertoire and a few near functional analogs [31].

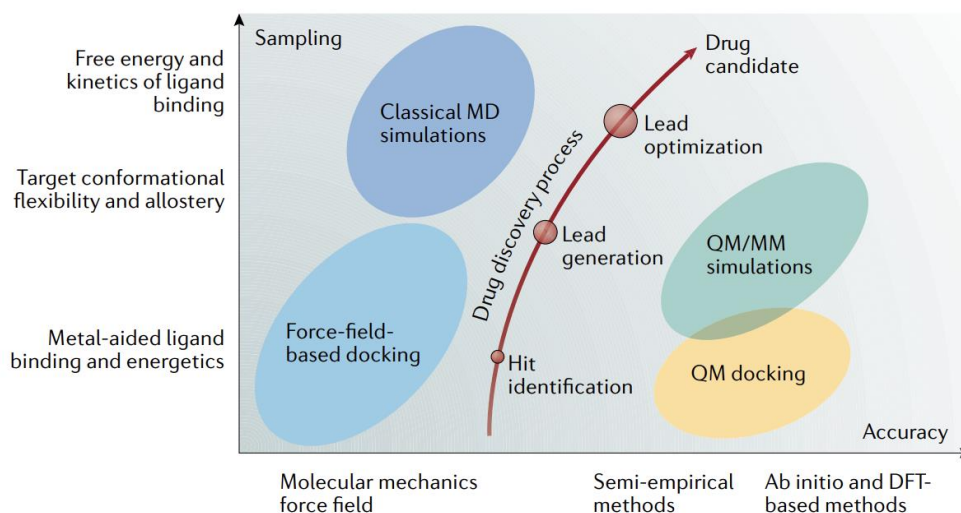


FIGURE 3. - Approaches to simulate metal-ligand interactions in structure-based pharmaceutical design [32]

Since metal coordination gives metal-ligand complexes distinctive chemical characteristics, medicinal chemistry has recently focused on them. The research identifies metallodrugs and metalloenzyme inhibitors as primary therapies. It also notes that ligand exchange and cellular target engagement make cisplatin a platinum complex with proven therapeutic use. Metal-based compounds have different coordination geometries, oxidation states, ligand exchange rates, and redox characteristics. These properties promote protein, nucleic acid, and metal-dependent enzyme interaction [4, 8].

Platinum-ruthenium complexes remain important anticancer reference systems. Metal core composition, ligand environment, stability, subcellular localization, and biological macromolecule interaction determine their activity. The publication also addresses metal-based medications that inhibit proteins and protein kinases and organometallic scaffolds that improve their therapeutic effectiveness. Similar cooperative ideas promote antibiotic use. Metal complexes interact with microbial proteins, enzymes, and membranes. Charge distribution, stability, and biological interaction alter after chelation. Limited selectivity, in vivo instability, poor pharmacokinetics, off-target interactions, and systemic toxicity hinder metallodrug development. Thus, future antibacterial and anticancer investigations should compare free ligands and their metal complexes, determine target selectivity and toxicity versus normal cells, and test, dock, DFT, molecular dynamics, and pharmacokinetics [15].

7. METAL-LIGAND INTERACTIONS FOR MEDICINAL USE SHOULD BE EXAMINED MORE THOROUGHLY

The viewpoint emphasizes structure-based metallodrug and metalloenzyme inhibitor discovery and production. However, numerous additional important types of compounds share the metal-ligand interaction interface, increasing metal-based therapy chemical space. Metal centers in contrast chemicals for magnetic resonance imaging form complexes [31]. This combination usually contains a transition metal ion like Fe or Co coupled with an organic ligand, or a lanthanide metal ion like Gd, in the therapeutic drug Gd-DTPA. The metal-ion-centered complex affects water proton relaxation time or chemical exchange saturation transfer, creating contrast. When designing metal-specific contrast agents, ligand exchange, temperature, pH, chemical self-assembly, and regiochemistry must be considered. Notably, contrast agents follow the same stringent drug design and development process as other small molecules to get clinical approval. The proton exchange systems have been investigated using quantum calculations and simulations, and use of molecular simulations will effectively depict the very dynamic responses of proton and ligand exchange events in the realm of metallodrugs. In reality, such complexes may now be fairly accurately simulated using quantum calculations incorporating an explicit solvent, greatly expanding the potential of this vibrant research area [32].

Metal nanoparticles offer applications in every possible field: catalysis, biosensors, and nanomedicine, and possibilities of monolayer-protected gold nanoparticles encoded in different ways are quite well-studied. For example, it was suggested that self-organized zinc complexes might generate metallic catalytic sites on the surfaces of modified nanoparticles. They become nanozymes that imitate the function of artificial metalloproteins: they cleave the bond in the nucleic acid model. The structural determination of these functional nanoparticles' is also best left to modeling and could once be determined by traditional MD and QM/MM simulations [33].

Coincidentally, the same multiscale computational approaches were beneficial for metal-dependent drug engineering; they are also beneficial here for metal nanoparticles. Molecular simulations, for example, should address dynamic reorganization coding in computer-aided nanoparticle production. Finally, admittedly, a significant advance stimulating the development of a model experiment circle needs to consider metal–ligand interactions. In this context, computer and experimental work in developing and finding new metalloproteins is already well-organized. Indeed, the entire computational arsenal could be useful for the rational design of new metalloproteins for drug creation. Novel artificial metalloproteins have been modeled, optimized using genetic algorithms, and integrated with docking calculations as well as classical and quantum simulations [34].

Reversible oxidation changes of physiologically relevant metals are necessary for cellular redox balance and their interaction with the ligand, and metal homeostasis is disrupted, the same redox properties might worsen oxidative damage, and recent research identifies iron and copper in electron-transfer proteins and redox enzymes, confirming their role in biological oxidation and reduction. Metal coordination with proper ligands affects geometry, redox potential, metal availability, and reactivity. Whether a metal complex is a stable biological cofactor or promotes oxidative chemistry depends on ligand composition [34]. Some ligand coordination promotes reactive metal species, whereas strong and selective coordination reduces uncontrolled metal exchange. When metal homeostasis is disrupted, metal-binding ligands should be considered. Future studies should link coordination geometry, redox behaviour, ligand exchange kinetics, and cellular oxidative responses [6, 34].

8. CHALLENGES AND FUTURE PERSPECTIVES

Despite these advances, an overarching challenge remains in the study of metal–ligand interactions in biological settings: methodologies must be integrated at the structural, dynamic, and functional levels to develop a comprehensive understanding of how metals are involved in the chemistry of life. For example, structural techniques are often unable to trap short-lived intermediates or metal binding to low-abundance proteins, and computational models cannot yet reliably predict complex electronic structure and solvent effects. Moreover, in living organisms, redox and pH fluctuate and competitive ligands abound, making the understanding of metal speciation and reactivity under biological conditions difficult. Another critical question is how metal–ligand miscoordination leads to disease, particularly in neurodegeneration, cancer, and microorganisms. An increasing focus of future research will be combining high-resolution spectroscopy with time-resolved crystallography and cryo-electron microscopy, along with modern simulations, expanding them to treat these systems in a quantitative manner. Artificial intelligence and quantum approaches will also be instrumental in speeding up the discovery of new metalloenzymes, biosensors, and metal-based drugs with improved selectivity and biocompatibility. Finally, for the next decade, the mapping of the metallome – the complete set of metal-binding species in cells, and the development of bioinspired repurposed complexes or synthetic catalysts in collaboration with chemists, biologists, and data scientists will be challenges for the next era [35].

The technique X-ray crystallography is useful for high-resolution structural data when appropriate crystals are available. However, cryo-EM can capture structures in a more natural form and does not need crystallization, making it ideal for big, flexible, or hard-to-crystallize biomolecular assemblies, therefore, these methods are complementary, not interchangeable (35).

9. CONCLUSION

Biological chemistry relies on metal-ligand interactions to link molecular coordination to life preservation catalysts, redox balance, and signal transduction, and these model systems that affect reactivity and selectivity bridge the gap between experiment and theory. The future will continue this connection between experiment and theory, which has enabled scientific knowledge of metalloproteins, metallodrugs, and artificial catalysts. Transient intermediates and how to represent them more accurately are the current emphasis, as is how to bring experimental modelling closer to nature under environmental circumstances. Most likely related to perception system issues. Rationally constructed metal-based therapies will become reality with reduced systemic toxicity and improved efficiency. Future study includes dynamic modelling of metal-ligand systems in cells and multiscale models near to molecular structure and biochemical data. Treatment highlights that a full-scale explanation of biological function requires on employing such information, not only coordination chemistry.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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