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Molecular dynamics and computational biology studies of metalloproteins

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Introduction

The complex orchestration of life processes within living organisms requires the utilization of a variety of metal ions for their optimal functioning [1,2]. These metal ions play a significant role in numerous cellular processes, such as maintaining the three-dimensional (3D) structure of macromolecules, actively participating in enzyme catalysis, facilitating the exchange of electrons in redox reactions, and regulating various biological processes [3,4]. The pivotal role of metals in biological systems is reflected by the staggering number of structure entries, 38%, in Protein Data Bank (PDB) [5] bearing at least one metal ion [6,7]. It is estimated that no less than 40% of enzymes require metal ions for their biological function [8,9]. This extensive reliance on metal ions underscores their pivotal role in sustaining life's myriad processes. Given their potential toxicity, the cellular concentration of metals is rigorously controlled [3,4] through the coordinated action of mechanisms for transportation, delivery, storage, detoxification, and efflux [10]. The reactivity and biological significance of metal ions within metalloproteins are predominantly governed by their immediate 3D structural surroundings. These surroundings dictate the metal's position inside the active site, how it interacts with substrates, and, in the case of redox-active metals, its reduction potential [11,12].

1.1 Motivation

In the last decades, computational studies have been able to provide valuable insights into the structural and dynamic aspects of metalloprotein complexes that are challenging to determine experimentally. The advent of AlphaFold [13] and AlphaFold2 [14,15] unlocked the potential to obtain highly reliable predictions of metal-binding sites (MBS) through innovative computational tools, leading to the discover of new metalloproteins. At the same time, it is important to further our understanding of already known metalloproteins, because of their crucial role in balancing health and pathologies in living cells. So, getting a better insight into the functional role of MBSs is mandatory; this requires investigating not only their local structure and the relationship with the protein's overall structure, but also their local dynamics.

1.2 Overview of Thesis

In the first project, our aim was to develop a new methodology to identify novel MBSs using the AlphaFold predicted structures. Since these structures do not have any metal bound, it is not clear if their configuration corresponds to the holo, apo or intermediate form. To develop a tool that can be applied in all possible scenarios and especially to experimentally determined apo structures, we performed a preparatory analysis of the extent of structural rearrangement that proteins undergo upon metalation, exploiting the information stored in MetalPDB [6,7]. Leveraging the results of this analysis, we developed a predictor of metal-

binding sites. We validated the predictions of the yeast zinc(II)-proteome using the available experimental structures or those of homologous proteins. The most interesting cases are provided by AlphaFold models with no experimental structural data available.

The second project is a complementary structural analysis of the distances occurring between a metal ion and the donor atoms (DAs) in metal-binding sites as a function of the resolution of the structures. The extracted distances from the best resolution range provide a reliable reference for experimental scientists during structure determination. In addition, we observed specific patterns of metal coordination by carboxylate moieties, suggesting that this interaction differentiates among metals.

In the third project, we addressed classical molecular dynamics (MD) methods comparing two Force Fields (FFs) specifically developed for zinc(II) ion based on different modelling approaches. The main difference between the two approaches is that the more traditional one (ZAFF [16]) keeps the coordination of the metal completely fixed throughout the simulations, whereas in the more recent approach (NBFF [17,18]) the coordination can change during the trajectory, in terms of both metal-DA distances and the number of coordination bonds. A quantitative assessment of the accuracy of the two FFs was obtained by comparing the order parameter (S^2) derived from MD simulations results to ^{1}H-^{15}N nuclear Overhauser effect (Het-NOE) data.

Finally, in the last project we applied a QM/MM approach to perform MD simulations of a complex system that contains a zinc(II) ion interacting with an inhibitor. The aim of this study is to demonstrate how QM/MM studies can afford a deeper insight about the zinc(II) coordination in complex biological systems. Moreover, this will allow us to show that it is possible to harness QM/MM simulations despite the challenges they pose from a computational infrastructure perspective, thanks to a highly parallelized novel approach.

2

Methods

2.1 MetalPDB overview

MetalPDB [6,7] is a database that stores a collection of 3D templates of metal-binding sites. These are automatically extracted from the PDB [5] and describe the local environment around the metal ion(s). Any non-hydrogen atom within 3 Å from the metal ion is identified as one of its DAs, i.e. the atoms directly interacting with the ion. The metal ligands are those protein residues or small molecules that contain at least one DA, endogenous or exogenous, respectively. The full MBS contains any other residue or chemical species having at least one atom within 5.0 Å from a metal ligand.

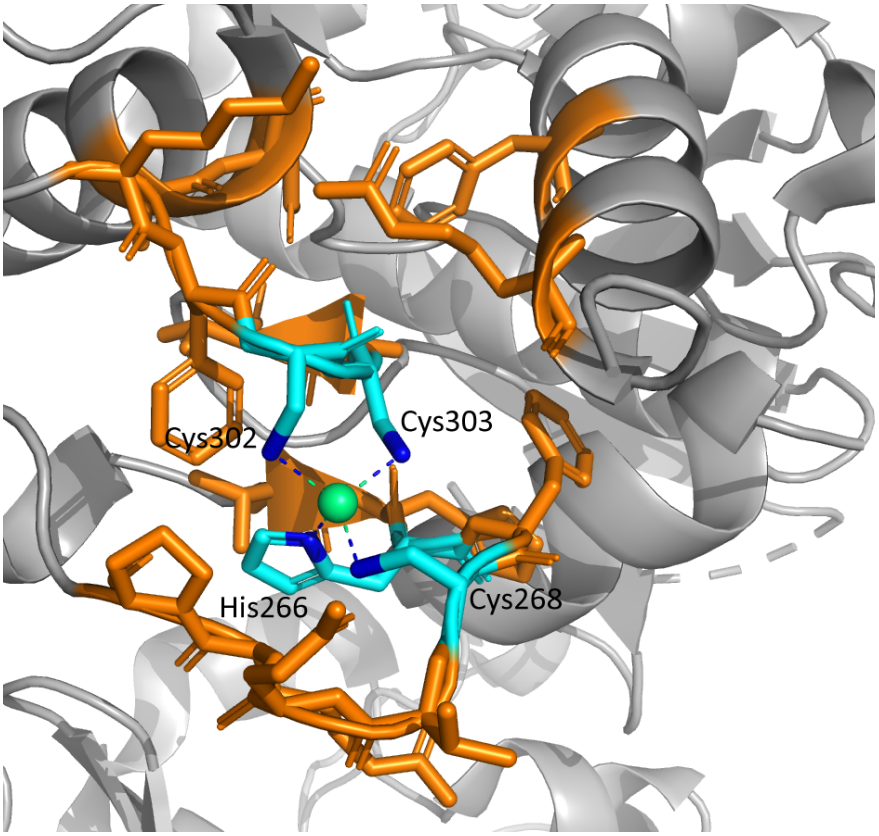


Figure 1. Metal-binding site with ligands represented in light-blue and the DAs in blu interacting with the metal, in green.

In MetalPDB all the MBSs are collected in clusters containing both “equistructural” and “equivalent” sites. Two MBSs are defined as equivalent if they satisfy all the following conditions: (i) the chains containing them have the same structure (based on Pfam domain composition or on the sequence identity between the two chains being ≥ 50%); (ii) after structural superposition of the chains, they are superimposed with the metal atoms in the

same position; (iii) they contain the same metal(s). In MetalPDB all atoms of a site are already labeled with their structural role (i.e., ligand; ligand neighbor; other). This information was propagated to the apo sites in each cluster through sequence alignment.

2.2 Structural rearrangement upon metalation

We retrieved all clusters containing mononuclear equivalent sites for all metals from MetalPDB using a SQL query. Within each cluster, associated apo structures are present. Subsequently, we employed an *in-house* Python script to parse the coordinates of each site. Prior to extracting the coordinates of Cα and donor atoms (DAs) for each ligand, the program removes exogenous ligands (i.e., non-protein, non-nucleic acid entities). For residues with multiple conformations recorded in the PDB file, only the highest occupancy conformation is retained. The list of all the MetalPDB clusters, labeled by the corresponding database identifier, together with the PDB identifiers of the holo and apo-sites in each cluster is given in the supplementary material of the corresponding article.
The extracted coordinates were then used to compute all possible distance between all possible pairs of Cα atoms and of DAs. Since all the sites in a cluster have the same ligands coordinating the metal ion and hence the same atom pairs, it was possible to average all the computed distances over all holo and over all apo sites. Then, we computed the Δ value as a subtraction of the mean holo distance from the mean apo one. For negative Δ values the sites experience a contraction after the removal of the metal ion. Instead, for positive Δ values the sites undergo expansion when the metal is not present. The absolute value of Δ quantifies the structural change occurring upon metalation. We used Pymol [19] for the visual inquiry and for the alignment of the sites to their corresponding structures. The Wilcoxon signed-rank test [20] was performed using the Python library SciPy [21]. This statistical analysis was employed to assess the statistical significance of changes in distance distributions between the Cα and DAs pairs following metalation, as well as for in their corresponding Δ values.

2.3 Metal-Donor Atom Distances

The information stored in MetalPDB was exploited also for the investigation of the metal-donor distances. We retrieved all the holo sites from the database and used another *in-house* Python script to compute the distances. The script parses each file, differentiates the residues according to the protein chain they belong to and keeps only residue conformations with the highest occupancy. In this analysis only the protein DAs were considered, according to the labeling available in MetalPDB. We imposed distance restraints to assign each DA to the correct metal ion in polynuclear sites. The side chains (SCs) of Asp and Glu contain a carboxylate group; both oxygen atoms were considered in the analysis even if only one of them was labeled as the coordinating one. This was done since in real case scenario the electrostatic charge of the second oxygen atom can be still experienced by the metal. We plotted all the computed distances for all the metal-DA pairs subdividing the measurements in 4 resolution ranges: i) 1-1.5 Å, ii) 1.5-2 Å, iii) 2-2.5 Å, and iv) 2.5-3 Å.

2.4 Classical Molecular dynamics simulations

To perform the classical MD simulations, we constructed a benchmark of six zinc-fingers (ZFs) with different secondary structures and bearing different MBSs in terms of ligand composition. The 3D structures of these ZFs were selected from PDB [5], where the NMR structures are available as bundles of conformers. We used the first deposited conformer, since it is usually the one with either the lowest conformational energy or with the best agreement with the NMR restraints [22]. For all the systems under analysis we performed MD simulations using the pmemd tool of AMBER software version 20. The ff14SB FF was used to model the protein chain, whereas for the zinc(II) and its ligands we applied the Zinc AMBER Force Field (ZAFF) [16] and the Nonbonded Force Field (NBFF) [17,18]. For four out of five of the selected ZFs (1CHC [23], 2JOX [24], 2L7X [25] and 2K9H [26]), we performed five independent simulations for each system using each zinc(II) FF. Each simulation run had a duration of 500 ns, thus we collected 2.5 μs of MD simulations data for each zinc(II) FF with each system. For the remaining ZFs (2NAX [27] and 5JPX [28]), simulations were carried out for a duration of 400 ns with each FF, resulting in a total of 2.0 μs of dynamics for each system. For all simulations an integration time step of 2 fs was used, and every 5000 steps a frame was saved. The following protocol was used for all ZFs: the system was initially placed in a truncated octahedron box with walls 10 Å away from the solute in each direction. Periodic boundary conditions were imposed, and the box was filled with TIP3P water model [29]. The minimization was carried out at 0 K in two stages. Initially only the water molecules were minimized around the protein that was kept fixed. Then, a minimization of the whole system followed. For these steps we used the Steepest Descendent and Conjugated Gradient algorithms in sequence. Then, the system underwent heating to 300 K under constant volume conditions utilizing the weak-coupling algorithm. Subsequently, equilibration was conducted in the NPT ensemble, maintaining constant pressure and temperature with a Berendsen barostat [30]. During the heating process, X-H bonds were subject to bond constraints through the SHAKE algorithm [31,32], excluding force calculations for bonds involving hydrogen. The same protocol was extended to the MD production runs, employing a greater number of integration steps. Cpptraj software [33] was used to inspect the behavior of all the systems during the trajectories. Initially, we computed the Root Mean Square Deviation (RMSD) [34] over the backbone atoms during the simulations with respect to the equilibrated structure. The RMSD measures the similarity between two superimposed 3D structures and allowed us to monitor how every protein behaved throughout the trajectories. Then, it allowed us to compute the distances between the DAs and the zinc(II) in the simulations performed applying the NBFF. Finally, we determined the secondary structures content with DSSP which employs a dictionary comprising eight distinct classes of potential structures: random coil, parallel beta-sheet, antiparallel beta-sheet, 3–10 helix, alpha-helix, Pi (3–14) helix, turn, and bend [35].

2.5 QM/MM molecular dynamics simulations

The protein selected for this study is a homodimer histone deacetylase 6 (HDAC6) with each subunit bearing a zinc(II) site (PDB ID 6MR5, at 1.85 Å resolution [36]). In our investigation we will consider only one MBS at QM level of theory. The initial phase involved both configuring and conducting classical MD simulations. This step ensured well-equilibrated trajectories at the classical level, a prerequisite for the subsequent QM/MM dynamic runs. We performed an initial modelling of few missing loop residues using the Modeller plug-in in

Chimera software [37-39]. The Amber99SBildn FF [40] was applied to the whole protein frame, whereas for the zinc(II) sites we used the NBFF since we extensively demonstrated its reliability in the previous work [41]. For the inhibitor we exploited the General AMBER Force Field (GAFF) [42,43], imposing the Zinc(II) Binding Group (ZBG), i.e. the functional group of the inhibitor interacting with the metal ion, to be in the thiolate state with a charge of -1 e on the sulfur atom. The protein was then embedded in a cubic box with 15 Å separating the system from the periodic box edge. The addition of sodium(I) and chloride followed to ensure a neutral charge of the system and the physiological salt concentration of 0.15 M. We employed the Particle Mesh Ewald (PME) method [44] with a grid spacing of 1.2 Å to compute long-range interactions. For van der Waals and short-range electrostatic interactions a distance cutoff of 1.2 Å was used. The system was minimized using the Steepest Descent algorithm, with position restraints applied to both the protein and the inhibitor. A first equilibration in NVT ensemble of the duration of 4 ns was performed utilizing Berendsen thermostat [30]. Following, a 4 ns NPT equilibration was conducted, employing the modified Berendsen thermostat and the Berendsen barostat [30]. As last step, we performed a classical production run of 200 ns with an integration step of 2 fs. GROMACS 2022 [45,46] version was used for the MD simulations. In addition, the software was used to compute the RMSD and the distances between the metal ion and the ligands throughout the trajectory to ensure that the NBFF and W45 parametrization worked properly. This project is a work in progress and so far, we performed the benchmarking of the optimal parallelization on JUWELS clusters. The multiscale QM/MM molecular dynamics will be performed using the MiMiC QM/MM framework [47-49]. MiMiC couples the GROMACS [45,46] as the MM engine, and the *ab-initio* CPMD program [50] as the QM one. In this approach both programs run on independent resources concurrently, fully exploiting their own parallelization strategies, such as multithreading and multiprocessing, to achieve maximum efficiency for the treatment of each subsystem [47-49]. The QM is 49.9 x 0.8 x 0.7 a.u. with a charge of zero and contains 106 atoms. These atoms correspond to the zinc(II) site with its endogenous ligand and with the inhibitor as well. Additionally, the QM region comprises Tyr 745, His 573, and His 574, that are supposed to interact and stabilize the inhibitor [36]. CPMD utilizes the Density Functional Theory (DFT) [51] for the electronic structure calculation.

We will use the Carr-Parrinello molecular dynamics algorithm for the propagation of electronic wavefunction and the nuclei of the QM subsystem, with B3LYP potential [52] to treat the electrons. The valence electrons will be represented explicitly with the wave function expanded in a plane-wave bases set with an energy cutoff of 90 ry. On the other hand, the core electrons will be treated via norm-conserving Trouillers-Martins pseudopotential [53]. For dangling bonds at the boundary between the QM and MM regions monovalent carbon pseudopotentials [54] will be used. The MM part will be modelled as described in preparatory MD simulation described above. The production run will be performed with and integration step of 0.12 fs, at a temperature of 300 K kept constant through coupling to a Nosé-Hoover thermostat [55]. MiMiC exploits the parallel implementation of the coupling scheme by by Laio et al. [56] to compute the electrostatic interactions between the QM and the MM subsystems. These interactions are separated into two components: i) short-range contributions occurring between the electronic density of the QM subsystem and the RESP charges of the MM portion, and ii) long-range interactions that are computed by employing the multipole expansion of the electrostatic potential arising from the QM subsystem. Multipoles allow to cut computational costs without compromising accuracy when compared to an exact treatment. We performed a first test of the best

treatment of the electrostatic interactions with a long-range cutoff of 45 a.u. and a multipole expansion of 7 being the best combination. When the requested computational time on JUWELS will be available we will perform three independent QM/MM simulations of the duration of 15 ps each followed by the results analysis.

3

Results and Discussion

3.1 Investigation of the structural rearrangement occurring upon metalation

We created a dataset of 3074 clusters of metal-binding sites (MBSs) for 30 different metals. Each group contains holo MBSs and their corresponding apo structures, all sharing the same metal-binding pattern. The amount of apo sites investigated is larger than the holo ones (Table 1) and this is because MetalPDB applies a redundancy filter only for the latter. However, the apo and holo data unevenness had no influence on the analysis outcome. As the first step, we computed the distances between all possible pairs of Cα atoms and DAs and averaged them over all apo and holo sites in each considered cluster. From 3074 clusters we computed 7042 pairs of distances for the Cα and 8607 for the DAs. The exposure of protein crystal to X-rays radiation can cause the reduction of the metal ion [57]. Consequently, the selective separation of holo sites based on their oxidation states was deemed challenging and likely to yield inaccurate data across the entire database. Hence, we opted not to implement such a step.

Metal	Holo sites	Apo sites	N° of clusters
Na	2020	28540	780
K	611	6669	179
Mg	1622	26292	539
Ca	2418	12829	486
Mn	288	1932	75
Fe	1270	577	39
Cu	341	2203	50
Zn	5440	14196	529

Table 1. Data assembled for physiological metals. Each row reports the total number of inspected clusters for the specified metal, with the corresponding number of holo- and apo- sites.

The data described in Figure 2 shows immediately that the distance distributions for Cα-Cα pairs are similar in holo and apo sites for different metals.

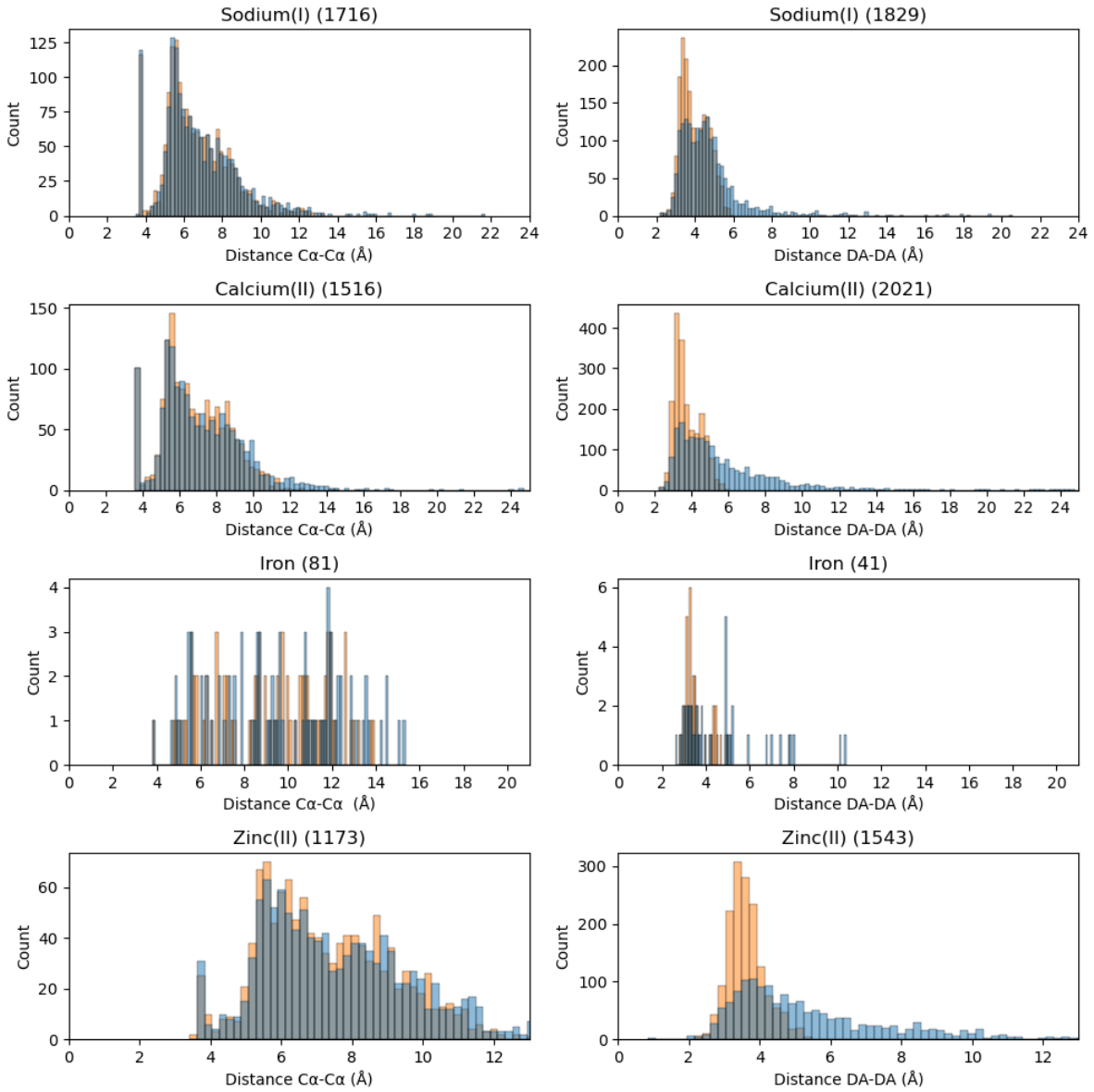


Figure. 2. Frequency counts of Cα-Cα (left) and donor atom (right) distances (orange: holo; blue: apo). The metal corresponding to each distribution is reported on the top of the panel with the number of distances. For iron we did not report the oxidation state since we did not such filtering procedure.

Instead, for the DAs we can observe much higher differences in the distance distributions passing from the apo to the holo state. This suggests that the protein backbone is less sensitive to the metal removal than the SCs of the MBS. In our dataset the SCs harboring the donor atoms commonly change their relative positions upon change of metalation state, especially for transition metals such as zinc(II). To reject the null hypothesis that the Cα-Cα and DA-DA distances are the same for the apo- and holo-sites, we computed the Wilcoxon signed-rank test [20]. In Table 2 the physiological metals for which we detected significant differences between the apo and holo sites, at the $p < 10^{-3}$ level, are reported.

Metal	p-value for the Cα-Cα distance distribution	p-value for the DA-DA distance distribution	N° of Cα-Cα distances	N° of DA-DA distances
Na	**6.03E-17**	**2.76E-120**	1716	1829
K	1.89E-02	**9.07E-43**	556	604
Mg	**3.90E-11**	**7.01E-99**	1097	1218
Ca	**2.10E-19**	**3.25E-230**	1516	2021
Mn	**1.22E-08**	**2.53E-27**	170	205
Fe	5.93E-04	**2.70E-14**	81	96
Cu	1.09E-01	**3.68E-21**	113	141
Zn	**3.30E-13**	**5.57E-173**	1173	1543

Table 2. P-values for the comparison between the distance distributions in apo- vs holo-sites in physiological metals. The p-value obtained from the Wilcoxon signed-rank test indicates the likelihood that the compared distributions are the same. The table lists all metals for which at least one of the Cα-Cα or DA-DA distance distributions differed in the comparison at a p-value threshold of 10^{-3}. The values in bold highlight the comparisons with a p-value < 10^{-5}.

The changes are more significant for the distances computed for the DAs than for the corresponding Cα atoms. Only for calcium(II), magnesium(II), sodium(I), manganese(II/III) and zinc(II) we observed a significant difference in the Cα-Cα distributions passing from apo to holo form. These result suggest that these MBSs undergo meaningful structural rearrangements also at the protein backbone. We then proceeded by analyzing how the relative position of the Cα and for DAs atoms changes upon metalation (Figure 3 and Table 3). This was done through the frequency count of their Δ values, i.e. the deviations measured for all the distances in each apo-holo pair.

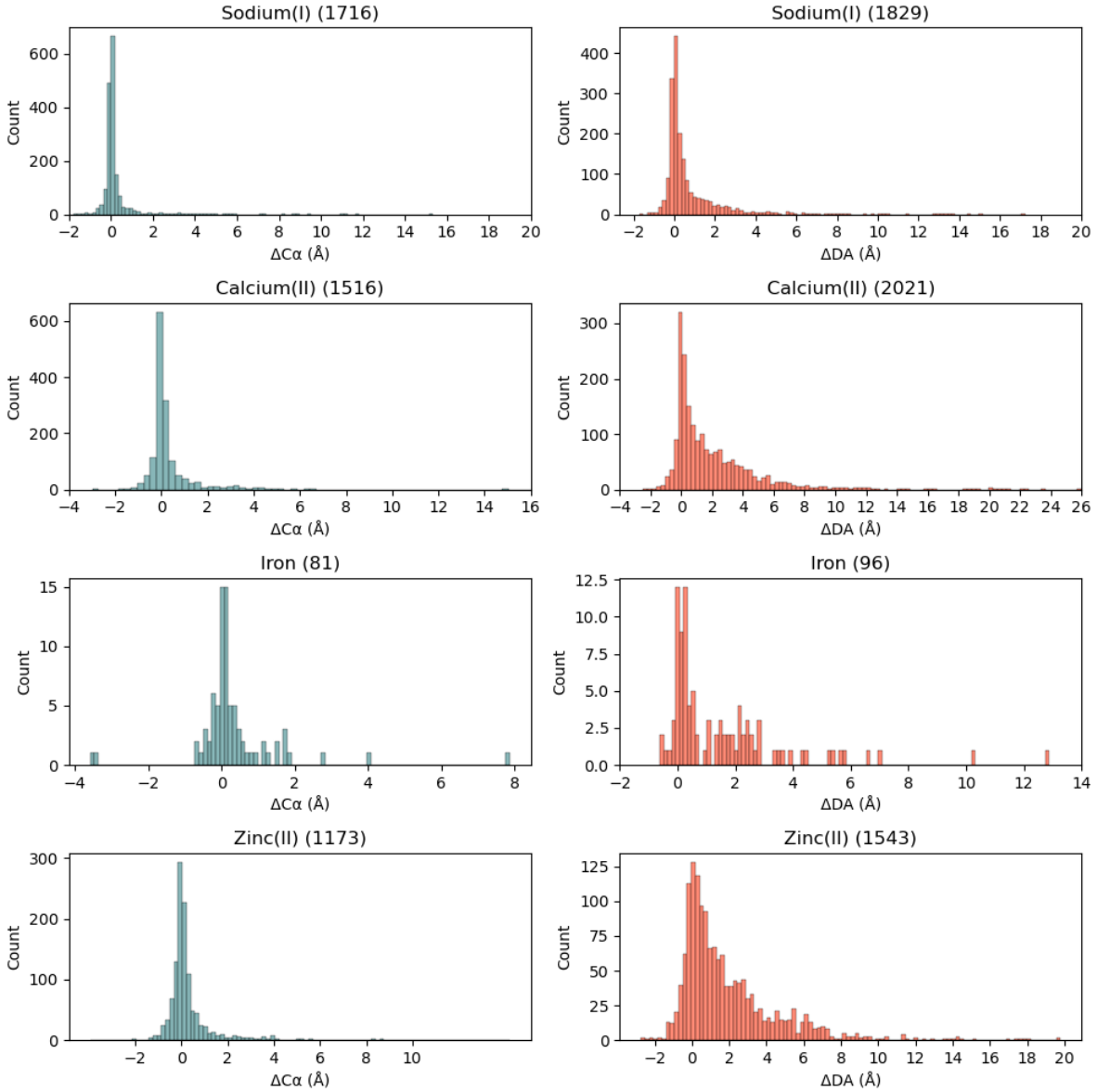


Figure 3. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in MBSs. Each row shows the overall behavior of one metal. All changes are measured as apo- minus the corresponding holo- distances.

In Figure 3 the distributions of ΔCα present a sharp peak around 0 Å with little data spread up to higher distances values. The negative values represent sites that are more compact in the absence of the metal ion. On the contrary, the positive Δ values correspond to an expansion the MBSs when the metal is missing. For the DAs, we still observe data centered at 0 Å, however these distributions are highly skewed towards positive values. At distances around 4 Å there is still a remarkable amount of data, and several rearrangements larger than 10 Å are observed. A more straightforward way to visualize the effect of metalation over the entire site is to compute the per-site average Δ values.

For the physiological metals the Wilcoxon signed-rank test pinpoints significant differences between the backbone and donor atom rearrangements (Table 3, at $p < 10-3$ level).

Metal	p-value	Median |ΔCα| (Å)	Median |ΔDA| (Å)
Na	**7.86E-52**	**0.02**	**0.18**
K	**2.62E-14**	**0.01**	**0.23**
Mg	**3.00E-51**	**0.02**	**0.38**
Ca	**4.50E-66**	**0.02**	**1.03**
Mn	**1.45E-10**	**0.07**	**1.24**
Fe	**2.81E-07**	**0.09**	**1.26**
Cu	**1.42E-08**	**0.04**	**1.54**
Zn	**1.35E-71**	**0.04**	**1.30**

Table 3. P-values for the comparison of the Cα-Cα vs the DA-DA Δ value distributions computed for averaged sites with the Wilcoxon signed-rank test for physiological metals. The median Δ values reflect the overall behavior of the site upon metalation. The table lists all metals for which at least one of the Cα-Cα or DA-DA distance distributions differed in the comparison at a p-value threshold of 10^{-3}. The most significant values ($p < 10^{-5}$) are highlighted in bold.

The behavior of each site upon metalation is showed in Figure 4, where each point corresponds to a single site and shows the correlation between distance variations of the Cα-Cα pairs and of the DAs pairs for a single MBS cluster. For values of 10 Å and more there is a linear correlation, where both the protein backbone and the SCs undergo major structural rearrangement upon metalation. The majority of our data feature negligible to small backbone rearrangement with different extent of SC orientations spanning from negligible up to 8–10 Å (Fig. 4, inset). Small rearrangements for both Cα and the DAs correspond to pre-organized MBSs, where the 3D coordination environment is set ahead of the metal binding [58]. Typically, DAs show major structural rearrangements with respect to the corresponding backbone configuration. A particular case is that of MBSs containing ligands consecutive in sequence (Figure 4, red dots), where the Cα-Cα distance is fixed, and structural rearrangements can occur only at the ligands' SCs level.

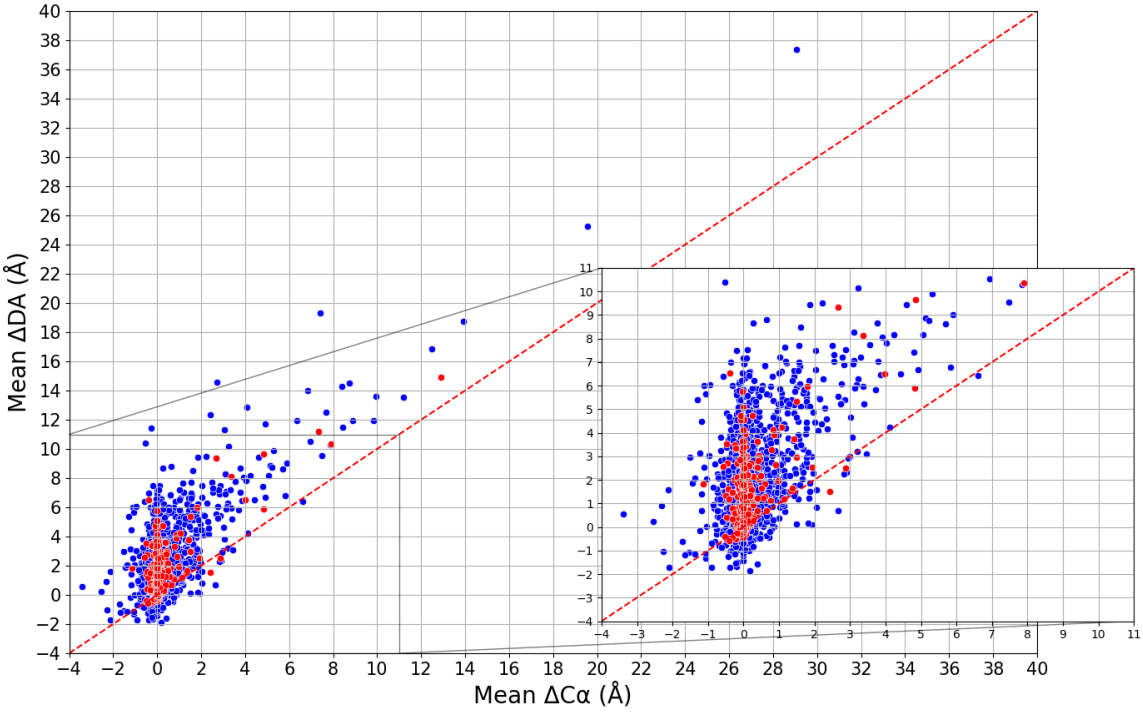


Figure 4. Mean Δ values over entire MBSs. The red line is y = x and serves only to guide the eye. Red dots correspond to sites having at least two metal ligands that are consecutive in sequence, hence featuring at least one fixed Cα-Cα distance. All changes are measured as apo- minus the corresponding holo- distances. All the metals of Table 3 are included in the plot.

Based on a Wilcoxon signed-rank test at $p < 10^{-5}$, most metals show statistically significant difference between the distributions of the DA-DA distances in the holo- vs apo-sites. In few cases Cα- Cα distances were significantly different upon metal removal. On the other hand, there were no instances in which substantial variations were detected exclusively in the Cα-Cα distances while not affecting the DAs. This observation is reasonable because backbone reconfiguration should lead to a concomitant repositioning of SCs. From our results it is evident that the DAs experience major structural rearrangements more often than the protein backbone. It is noteworthy that in our analysis the DAs comprise the main-chain oxygen and nitrogen atoms, so the conformational reorganization of the SCs is expected to be even larger than suggested by our data (Table 2 and 3).

The absolute median value of the distance variations is smaller than 0.2 Å for most considered metals at the backbone level. For physiological metals this value is almost zero, with three quarters of the sites having a backbone rearrangement smaller than 0.04 Å, except iron. We consider absolute distances in order not to worry whether the site contracts or expands upon metalation. The corresponding data for DAs show two different trends for physiological ions. On one hand, the median ΔDA of transition metals spans from 1.2 to almost 2 Å (Table 3). This is due to the preference of SC coordination which raises major conformational changes upon metalation. On the other hand, potassium(I) and sodium(I) have a median value about 0.2 Å. To address the values of these two metals, we investigated the chemical nature of the coordinating atoms. Main-chain oxygen atom coordination is preferred by both metal ions, making up the 82% and 84% of DA-DA distances for sodium(I) and potassium(I), respectively. Since the DAs structural rearrangements mainly reflects that of the backbone, we observe small median values [59]. Despite the chemical similarity, for

magnesium we computed a median ΔDA of 0.38 Å for magnesium(II) and of 1.03 Å for calcium(II). For both metals, about 60% of DAs come from the main-chain oxygen atoms since they share a preference for oxygen coordination, including Asp and Glu backbone and SC oxygen atoms. The different median ΔDA for magnesium(II) and calcium(II) may be addressed to the larger number of protein ligands coordinating the calcium(II), whereas magnesium(II) interacts with more water molecules or exogenous ligands[60]. An alternative explanation relies on the structural factors underlying the selectivity for calcium(II) over magnesium(II) ions in calcium-binding proteins. Energetic considerations indeed imply that flexible MBSs would be inclined towards calcium binding [61]. The structural dynamics of the calcium(II) sites may play a critical role in their functional relevance within signaling processes, suggesting a potential mechanism [62].

3.3 Assessment of Master of Metal performances

The data collected from the preparatory analysis reported in the previous section was used for the development of Master of Metals (MoM), an MBS predictor that relies on the structural approach. The above investigation showed that the backbone tends to undergo smaller conformational changes upon metalation than DAs. Thus, we decided to rely on the backbone information provided by the Cα. Additionally, we included the Cβ as well, since it can act as a proxy of the possible orientation of the SCs. The MoM protocol starts by scanning the whole apo protein given as input looking for groups of CHED residues whose Cα distance is within 13 Å from one another (potential sites, PSs). This step ensures that the residues in each group are at reasonable distances, but we have no information about their spatial configuration. A trained graph neural network (GNN) establishes the probability that a PS is an MBS. The PS with a probability greater than 0.6 are called Highly Probable Potential Sites (HPPSs). Each HPPS is compared with all the MBSs of the training set that share the same metal-binding pattern (i.e. the type and order of amino acids coordinating the metal ion). This comparison is performed using the distance matrices of the Cα and Cβ atoms. If the distance between the matrices of the HPPS and of the known MBS is lower than a given threshold (in this study it is of 0.35 Å), then the HPPS is regarded as a real MBS. The basis of this assumption is the existence of a real and experimentally determined MBS having a similar disposition of the Cα and Cβ atom to the HPPS.

So far, MoM was optimized to hunt down zinc(II)-binding sites starting from an apo 3D structure. We assessed the tool's performances on the entire *Saccharomyces cerevisiae* proteome predicted by Alphafold [1]. Before the actual test, we filtered the initial 6309 predicted models so to avoid bias the prediction results due to the quality of the AlphaFold models. Our final dataset contained of 1500 structures with least 90%of their residues with a plDDT >0.7 (i.e. measure indicative of the local accuracy of the prediction reported by AlphaFold itself). For 191 of these models MoM identified at least one possible zinc(II)-binding site. By mapping the UniProt codes to the PDB we searched for experimental structures that could confirm our predictions. For 77 models an experimental structure was available and their superimposition to our predictions allowed us to verify MoM's ability to find zinc(II) site(s). For 62 out of 77 cases the MBS was correctly identified. This corresponds to a precision (PPV) of 80.5% and a false discovery rate of 19.5% (Figure 5A).

Figure 5: Validation of Master of Metals against the *S. cerevisiae* proteome. A) correct (dark grey, "positive") and wrong (light grey, "negative") predictions (outer doughnut) based on yeast proteins with deposited structure (inner doughnut, yellow), or on the structures of homologous proteins as well as visual inspection (inner doughnut, light blue); B) breakdown of the validation based on the proteins in the light blue wedge of panel A, as a function of their characteristics (inner doughnut, compare to the columns of Table 4), showing correct and wrong predictions (outer doughnut; light and dark colors, respectively) for each group. The total number of positives in panel A is 145, whereas the total number of negatives is 46.

We then looked for the structurally characterized homologs of the 114 proteins with no deposited structure. Using BLASTP we retrieved close homologs with an experimental structure for 75 proteins. 46 of these structures have at least one zinc(II)-biding site, 16 (21%) have sites with different metal than zinc(II), and 13 (17%) are apo proteins. Furthermore, for 8 models we could retrieve distant homologs (i.e. the default search threshold was not respected). The remaining 31 yeast proteins did not have any kind of homologs, and for 9 of them the deposited structure lacks the region with the predicted metal site due to the presence of an additional domain or motif in the AlphaFold model. Based on the idea of same structure, same function we can expect that if a homolog bears an experimental zinc(II)-binding site, so must the model predicted by AlphaFold. For this reason, we superimposed all the available structurally determined homologs to their respective AlphaFold models to assess if the actual zinc(II) site matched the predicted one. For the apo structures we visually inspected the spatial disposition of the putative ligands in the site to verify if, under appropriate conditions, it could be occupied by zinc(II). In fact, due to shortcomings in the sample handling procedures, the MBSs of metalloproteins may not be populated by the actual metal ion [63]. However, we anticipated that the predictions linked to homologs with no metal site(s) would have the highest false positive (FP) rate. Considering a mild rearrangement of the protein backbone, we established that for 10 of these proteins (76%) the prediction is unreliable for the inappropriate disposition and/or orientation of the supposed ligands was not appropriate for the metal accommodation. For 3 proteins (23%), sites resembling the physiological ones were detected (Table 4 and Figure 6B)

	Homologs with zinc	Homologs with different metals	Apo homologs	Distant homologs	No homologs or no corresponding region	**Total**
Unreliable	7 (15%)	7 (44%)	10 (77%)	/	7 (23%)	32 (28%)
Good / Partial match	7 (15%)	4 (25%)	3 (23%)	2 (25%)	13 (42%)	28 (24%)
Perfect match	32 (70%)	5 (31%)	n.a.	6 (75%)	11 (35%)	54 (47 %)
Total	**46**	**16**	**13**	**8**	**31**	**114**

Table 4. Results of the inspection of the structural models of the 114 predicted zinc(II) proteins lacking an experimental structure. Distant homologs are the proteins identified by BLAST in the PDB with an e-value > 10^{-5} or a sequence identity to the yeast protein of interest < 30%. Partial matches occur when at least two predicted metal-binding residues overlapped properly in the structural comparison, as opposed to complete matches, which occurred when all predicted metal-binding residues overlapped correctly.

Then, we assessed the predictions for the 16 proteins whose experimentally characterized homologs bear different metals. As shown in Figure 6E-F, we obtained satisfactory results from the superimposition of the experimental structure for 9 proteins (56%). Among all the homologs for the UniProt ID Q05584, we found one protein with a dinuclear zinc(II)-binding site, and our tool found almost perfectly the ligands reported in the experimental structure. For the 8 models with only 3D structures of distant homologs we obtained a prediction rate of 100% by superimposition (Table 4 and figure 6A-B). For 32 out of the 46 (70%) near homologs structures having zinc(II) site(s) the prediction was correct with perfectly overlapped ligands. For 7 of these structure (15%) the site(s) predicted by MoM showed only partial overlap to the actual MBS, and finally for the remaining 7 models (15%) the prediction was not correct.

The 31 AlphaFold models with no related structural data from any kind of homologs represent the most interesting case, since the prediction of MBSs could reveal new zinc(II)-binding proteins. To evaluate the prediction, we relied on the superimposition with the closest sites used by MoM (Figure 2D). We observed a perfect overlap for 11 structures (35%), whereas for 13 of them (42%) we judged the outcome as satisfactory considering the arrangement of the putative ligands as compatible with the binding geometry in the refence site. The prediction for 7 proteins (23%) does not resemble to an MBS, since some of the ligands are integral part of secondary structures and this prevents their rearrangement to coordinate a metal ion (Figure 6C).

The superimposition of the predicted MBSs to the experimental ones and the visual inspection when there was not any available allowed us to evaluate MoM as a reliable tool for the prediction of zinc(II)-binding sites. We obtained satisfactory results in a real case scenario, namely the analysis of the proteome of an entire organism. With a threshold of 0.35 Å for the comparison of the distance matrices, MoM had an error rate for all its predicted MBSs of 24% and a precision of 76%.

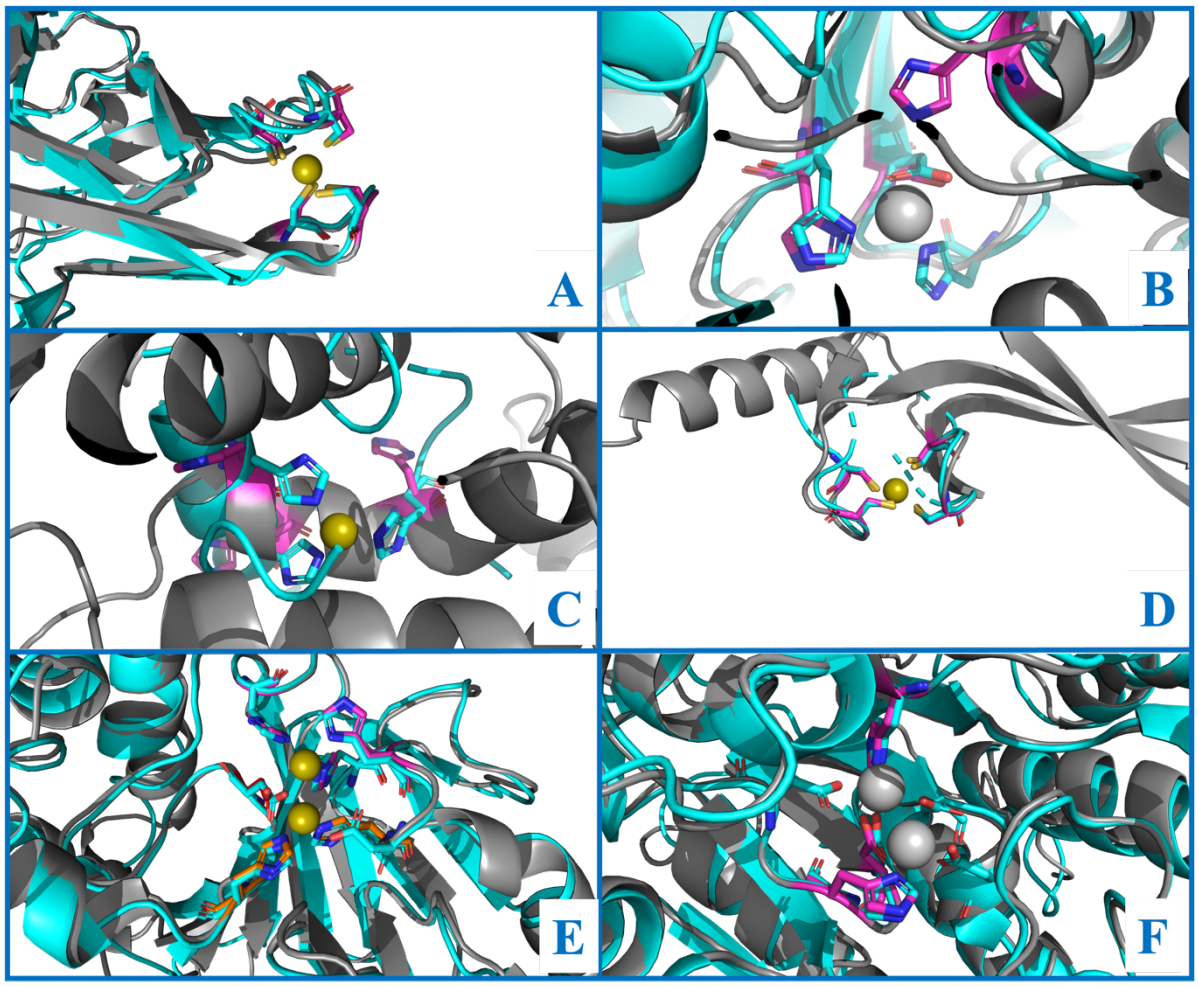


Figure 6. Examples of structure predictions by Master of Metals. A) a correct prediction, validated by superimposition to a distant homolog structure (PDB ID 5ZLQ [64]); B) a partial match, with two out of three residues correctly superimposed to the metal ligands of the manganese(II) ion of a distant homolog structure (PDB ID 5M45 [65]; C) an inaccurate prediction (superimposed to the 1BM6_2 [66] MetalPDB site), in which two of the three predicted His have a plausible spatial disposition, but the third His cannot be regarded a putative ligand since its positioning in the □-helix prevents any movement to form an MBS in the presence of the metal ion; D) a correct prediction for a protein lacking a homolog with known structure, validated by superposition of the AlphaFold structural model to the closest MetalPDB site (3BVO_1 [67]) identified by MoM; E) a correct prediction for two zinc(II) sites in spatial proximity, validated by superimposition to a homolog structure (PDB ID 2P18 [68]), which contains a dinuclear zinc(II) cluster; F) a partial match, where MoM predicted only one site containing a subset of the ligands to the two manganese(II) ions present in a homolog structure (1WVB). The color code is as follows: grey, AlphaFold structural models; fuchsia, predicted ligand residues; cyan, homolog structures or closest MetalPDB site. The zinc(II) ions are shown as olive green spheres, whereas all other metal ions are shown as grey spheres.

3.2 Metal-donor atom distances

We analyzed a total of 161601 MBSs retrieved from MetalPDB [4, 5], for all of which we computed the distances of all metal-DA pairs. In the present discussion we will address each metal singularly since it is difficult to generalize the trends of metals belonging to the same group, and it is even more challenging to generalize for all the inspected metals. All metals exhibit markedly diverse behaviors, closely tied to their electronic configuration and their oxidation states. The latter influence also the coordination and the composition of ligands interacting with a given metal. As noted earlier, the differentiation of metals based on their oxidation state is not viable due to potential alterations during X-ray crystallography data collection; indeed, there is no definitive confirmation of the reported oxidation state in the deposited metalloprotein structures. We analyzed only the metal-DA pairs with more than 500 entries for each site nuclearity.

The multinuclear sites have been subdivided into homo- and hetero-nuclear; binding the same or different metals within their sites, respectively. Unless differently stated, we will refer to the results obtained from the best resolution range (1-1.5 Å). Before proceeding, in Figure 7 we report the three typical Asp and Glu carboxylate metal coordination.

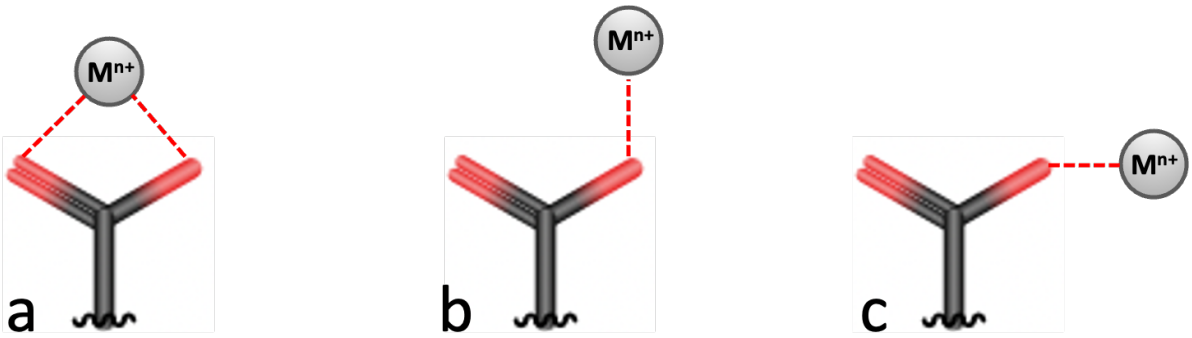


Figure 7. Typical coordination of the carboxylate group in mononuclear sites: a) bidentate coordination with both oxygen atoms interacting with the metal ion, b) monodentate coordination performed by OX1, with OX2 with *syn* orientation with respect to the metal ion, c) monodentate coordination with OX2 in disposed in *anti* fashion.

Carboxylate coordination plays a pivotal role in metalloproteins and is the only functional group interacting with all metals. Within metalloenzymes, the repositioning of the carboxylate group at the metal ion during the catalytic cycle is termed a carboxylate shift. This shift can control of the CN and the metal center reactivity. The carboxylate shift is often observed in metalloproteins involved in redox reactions, where the metal undergoes changes in its oxidation state. Additionally, carboxylate coordination is also encountered in polynuclear sites, where this group can act as a connecting bridge between two metal ions.

Alkali and alkali earth

Sodium(I) is exclusively coordinated by oxygen atoms of the backbone and of the SCs (Gln, Asn, Glu, Asp). Despite the DA is always the same, we observe different trends with different ligands. For the backbone O of some residues (Ala, Gln, Ile, Leu, Phe, Ser, and Tyr) we observe a major distance peak around 2.3 Å and a minor one around 2.9 Å (Figure 8). For Tyr-OH coordination we did not have enough distances for an appropriate analysis. Arg and Pro produce extremely broad peaks ranging from 2.3 to almost 3 Å, whereas for Cys the distribution is slightly less broad (2.2 -2.8 Å). Asn, Lys and Val have a single peak at 2.8 Å with some data skewed towards higher values. The same is observed for Thr coordinating with the main-chain O atom, however the OG1 gives a peak at 2.7 Å with the highest intensity and a second minor one at 2.4 Å. Asp and Glu interact with the metal through the backbone oxygen mainly in mononuclear sites, with a prevalent distance of 2.4 Å. The OD1 interaction spans a wider range of distances when compared with other metals, especially the transition ones, in mono- and bi-nuclear sites. The distribution of the OD2 distances in mononuclear sites is broad and skewed towards high values, covering all possible modes of carboxylate coordination. On the contrary, in binuclear sites we observe two peaks with similar intensity around 3.8 and 4.8 Å. For the Glu SC, OE1 shows two peaks with the same intensity around 2.3 and 2.7 Å. The distances for OE2 are extremely spread with growing intensities going from bidentate coordination to the monodentate *anti* one.

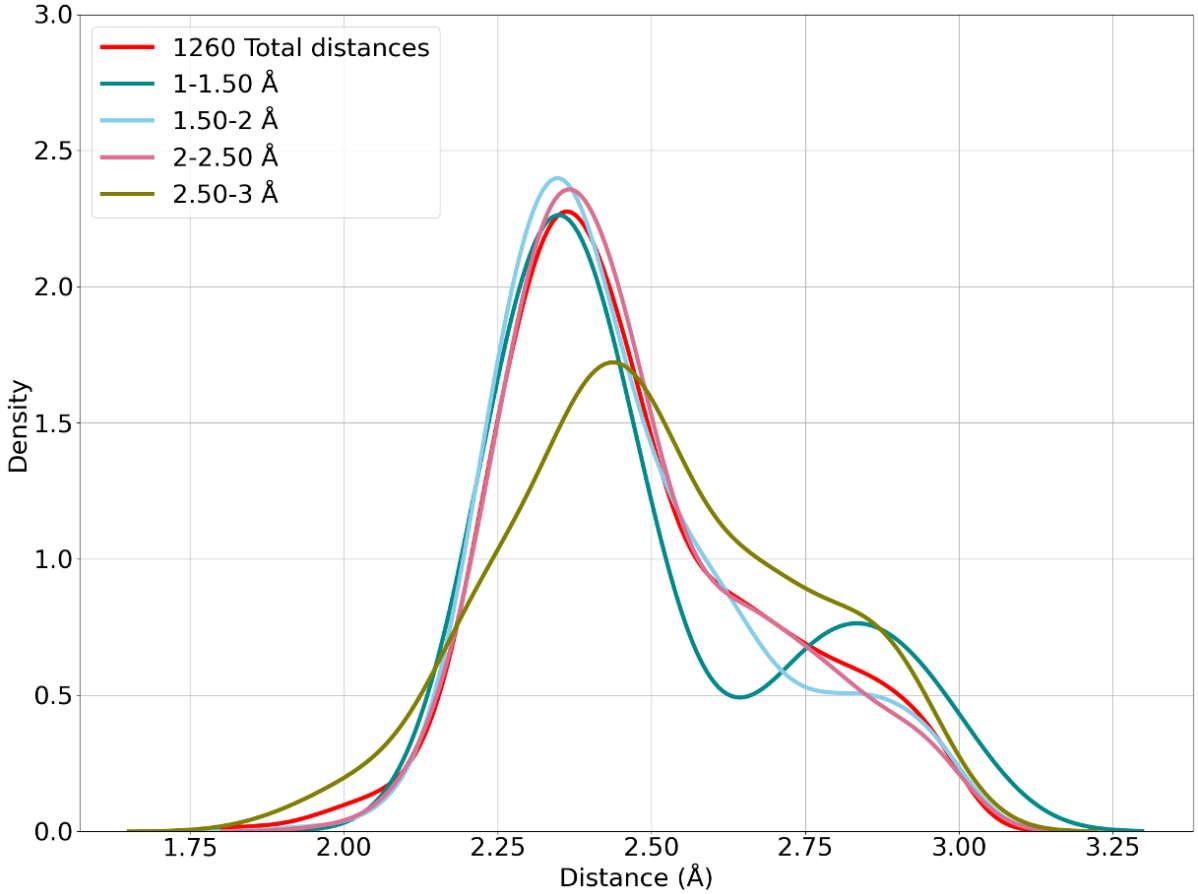


Figure 8. Distance distribution of sodium(I) coordinated by O of Ala.

Potassium(I) is coordinated by the O atom of the backbone of almost every residue (no strong evidence for Cys, His and Met). For almost every residue type the distances show

two different behaviors with either one peak around 2.7 Å followed by a minor one at around 3 Å or with a single and extremely broad peak going from 2.6 Å to 3 Å. For carboxylate distances we collected enough data only for mononuclear sites. The OD1 of Asp and the OE1 of Glu show higher data density around 2.7 Å. OD2 has distances continuously distributed from 4 to 5 Å which correspond to an exclusive monodentate *anti* interaction with the metal ion. The OE2 of Glu shows extremely spread data with continuously growing intensities from the bidentate to monodentate *anti* coordination mode.

Also for magnesium(II) we observe an absolute preference for main-chain and SC oxygen coordination. Additionally, His SC coordination is also present. For some residues coordinating with the main-chain oxygen atom (Ala, Arg, Asn, Ile, Leu, Ser) there is one major peak (around 2.3 Å), possibly followed by a minor one (around 2.8 Å). For Gln, Gly, Thr, and Val we observed broad peaks centered around 2.2 – 2.4 Å and spreading up to 3 Å. His ND1 has a peak around 2.2 Å, and a minor peak at shorter distances caused by structures containing experimental errors; His NE2 has a single peak at 2.2 Å. Asp coordinates the metal ion with the main-chain O atom at about 2.1 Å, but the data is spread up to 2.8 Å. The corresponding interaction with Glu does not have sufficient data. Both Asp and Glu show the distance for OX1 around 2.1 Å with skewed data towards higher values. On the other hand, the peaks of OX2 correspond to the *syn* and *anti* monodentate coordination with no evidence of bidentate interaction.

Calcium(II), as the previous metals, has an absolute preference for oxygen coordination which is in line with its hard nature. Excluding Met and Cys, 18 out of the 20 amino acids can participate to calcium(II) coordination through the main-chain O atom with a distance around 2.3 Å. In some cases, we observe some deviations with some minor peaks at higher distances, but these are caused by the low number of distances in the considered range. For Asp and Glu coordinating with the main-chain O and OX1 the distances are centered around 2.4 Å. OX2 has three peaks that correspond to all the three interaction modes shown in Figure 9. Both residue have good amount of SC coordination data for sites with nuclearity up to 3 where the same trends are conserved.

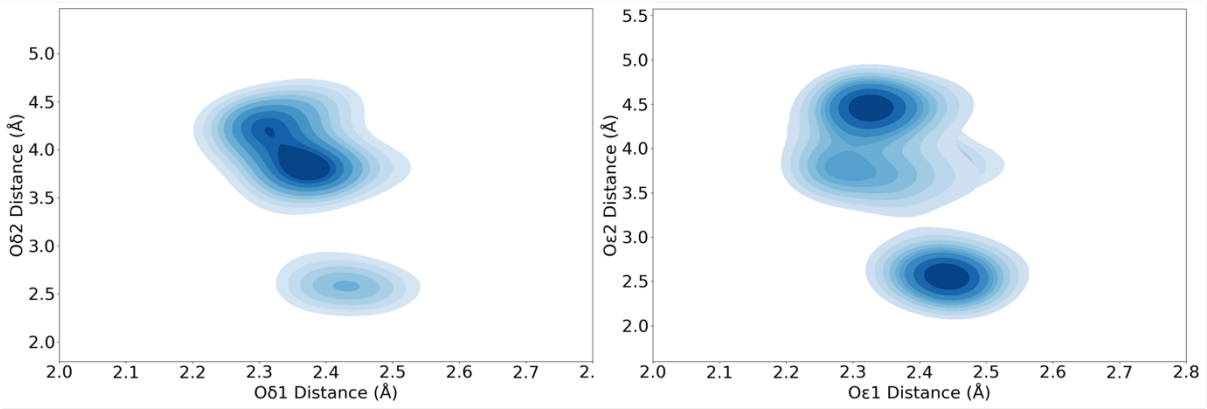


Figure 9. Calcium(II) coordination performed by carboxylate group of Asp (left panel) and Glu (right panel). The deeper the blue the more data are present in that region.

Metal	Ligand	DA	Mean distance Å	Standard deviation Å
Sodium(I)	Ala	O	2.49	0.23
Sodium(I)	Arg	O	2.4	0.15
Sodium(I)	Asn	O	2.62	0.3
Sodium(I)	Asn	OD1	2.44	0.18
Sodium(I)	Asp	O	2.46	0.19
Sodium(I)	Asp	OD1	2.44	0.17
Sodium(I)	Asp	OD2	2.49	0.23
Sodium(I)	Cys	O	3.95	0.57
Sodium(I)	Gln	O	2.46	0.11
Sodium(I)	Gln	OE1	2.52	0.26
Sodium(I)	Glu	O	2.49	0.27
Sodium(I)	Glu	OE1	2.46	0.22
Sodium(I)	Glu	OE2	2.49	0.23
Sodium(I)	Gly	O	4.04	0.71
Sodium(I)	Ile	O	2.52	0.24
Sodium(I)	Leu	O	2.5	0.36
Sodium(I)	Lys	O	2.55	0.26
Sodium(I)	Met	O	2.58	0.27
Sodium(I)	Phe	O	2.61	0.25
Sodium(I)	Pro	O	2.42	0.15
Sodium(I)	Ser	O	2.36	0.14
Sodium(I)	Ser	OG	2.55	0.23
Sodium(I)	Thr	O	2.66	0.24
Sodium(I)	Thr	OG1	2.46	0.22
Sodium(I)	Tyr	O	2.64	0.22
Sodium(I)	Val	O	2.45	0.2
Potassium(I)	Ala	O	2.74	0.19
Potassium(I)	Asn	OD1	2.7	0.15
Potassium(I)	Asp	O	2.74	0.1
Potassium(I)	Asp	OD1	2.74	0.16

Potassium(I)	Asp	OD2	4.33	0.55
Potassium(I)	Glu	O	2.8	0.15
Potassium(I)	Glu	OE1	2.59	0.34
Potassium(I)	Glu	OE2	4.1	0.84
Potassium(I)	Gly	O	2.71	0.13
Potassium(I)	Ile	O	2.75	0.11
Potassium(I)	Leu	O	2.72	0.15
Potassium(I)	Phe	O	2.67	0.13
Potassium(I)	Ser	O	2.72	0.15
Potassium(I)	Ser	OG	2.83	0.12
Potassium(I)	Thr	O	2.72	0.17
Potassium(I)	Val	O	2.67	0.12
Magnesium(II)	Ala	O	2.46	0.25
Magnesium(II)	Arg	O	2.48	0.16
Magnesium(II)	Asn	O	2.68	0.15
Magnesium(II)	Asn	OD1	2.16	0.16
Magnesium(II)	Asp	O	2.29	0.29
Magnesium(II)	Asp	OD1	2.11	0.16
Magnesium(II)	Asp	OD2	3.64	0.42
Magnesium(II)	Gln	OE1	2.24	0.24
Magnesium(II)	Glu	OE1	2.17	0.19
Magnesium(II)	Glu	OE2	3.57	0.45
Magnesium(II)	Gly	O	2.3	0.23
Magnesium(II)	His	ND1	2.08	0.23
Magnesium(II)	His	NE2	2.19	0.1
Magnesium(II)	Ile	O	2.32	0.19
Magnesium(II)	Leu	O	2.47	0.28
Magnesium(II)	Ser	O	2.45	0.28
Magnesium(II)	Ser	OG	2.18	0.22
Magnesium(II)	Thr	O	2.4	0.25
Magnesium(II)	Thr	OG1	2.21	0.23
Magnesium(II)	Val	O	2.33	0.19

Calcium(II)	Als	O	2.39	0.14
Calcium(II)	Arg	O	2.34	0.14
Calcium(II)	Asn	O	2.34	0.11
Calcium(II)	Asn	OD1	2.37	0.09
Calcium(II)	Asp	O	2.4	0.1
Calcium(II)	Asp	OD1	2.37	0.12
Calcium(II)	Asp	OD2	3.69	0.65
Calcium(II)	Gln	O	2.33	0.05
Calcium(II)	Gln	OE1	2.36	0.1
Calcium(II)	Glu	O	2.35	0.1
Calcium(II)	Glu	OE1	2.39	0.12
Calcium(II)	Glu	OE2	3.64	0.8
Calcium(II)	Gly	O	2.37	0.12
Calcium(II)	His	O	2.39	0.08
Calcium(II)	Ile	O	2.34	0.1
Calcium(II)	Leu	O	2.39	0.18
Calcium(II)	Lys	O	2.34	0.08
Calcium(II)	Phe	O	2.35	0.11
Calcium(II)	Pro	O	2.4	0.08
Calcium(II)	Ser	O	2.36	0.09
Calcium(II)	Ser	OG	2.53	0.2
Calcium(II)	Thr	O	2.41	0.12
Calcium(II)	Thr	OG1	2.46	0.12
Calcium(II)	Tyr	O	2.35	0.07
Calcium(II)	Val	O	2.33	0.14

Table 5. Mean distances and standard deviation computed for mononuclear sites bearing alkali and alkali-earth metals. The values were computed considering only the best range resolution, i.e. 1-1.5 Å.

Transition Metals

The main ligands in mononuclear manganese sites are His, Asp and Glu. For His, our data confirmed the preference for NE2 coordination (3581 distances measured) with a peak at 2.2 Å (Figure 10), despite the tautomer with an available lone pair on ND1 (408 entries) being the most abundant [69].

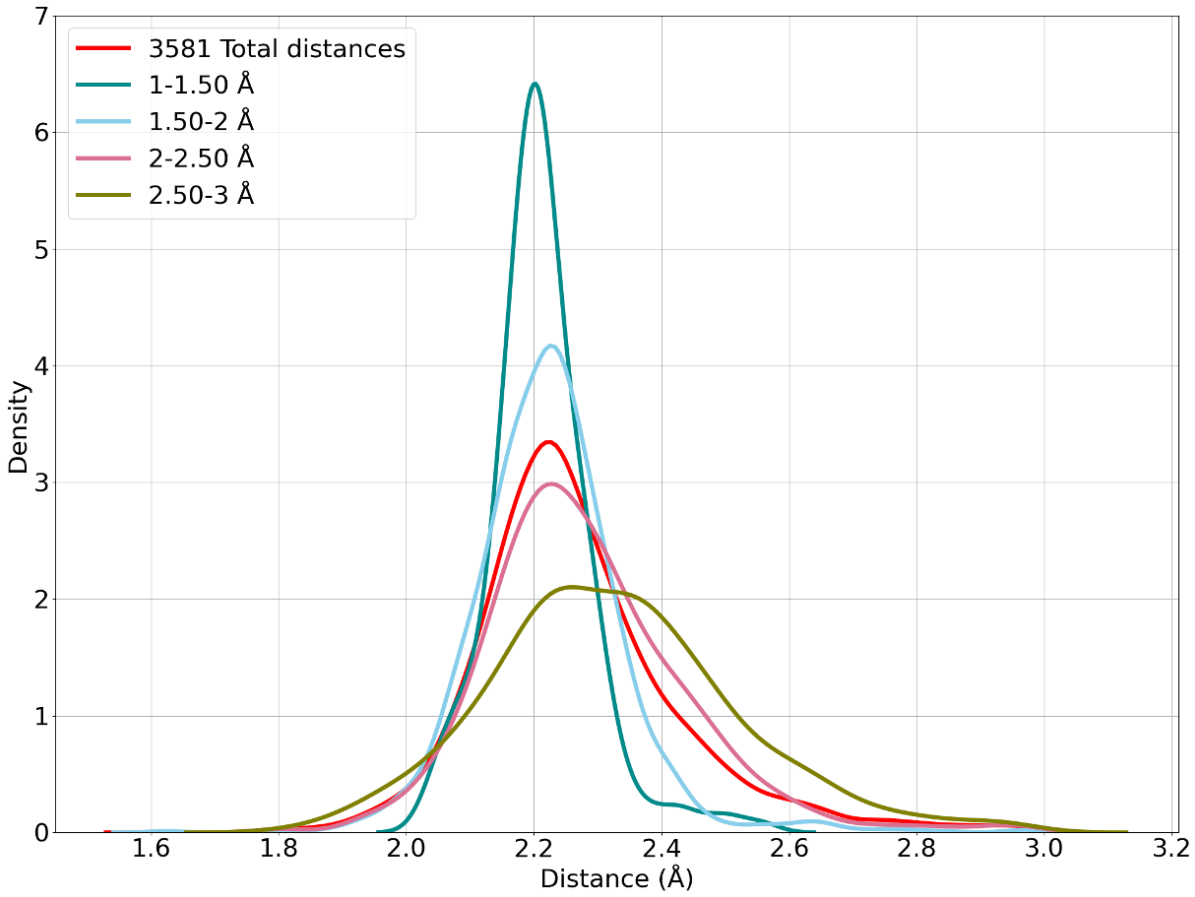


Figure 10. Manganese coordinated by His NE2 distance distributions

The carboxylate coordination of Asp and Glu is prevalently monodentate *syn* fashion, with a few cases of bidentate and *anti* coordination in mononuclear site. Asp shows the same coordination trends also in dinuclear sites, whereas in trinuclear ones the bidentate interaction is not present. Glu, on the other hand, prefers *syn* coordination [69]. This is especially clear in dinuclear sites where most of the OE2 distances are between 3 and 3.8 Å; for Glu in trinuclear sites we do not have enough data. The above observations are at variance with previous claims that the carboxylate-manganese(II) interaction is equally likely to happen with the same preference towards *syn* and *anti* stereochemistry [69]. On the other hand, manganese(III) was proposed to prefer *anti* carboxylate coordination. However, this does not imply that *syn* oriented carboxylate are completely disfavored in manganese(III) sites [69].

Iron is mainly coordinated by Met, Cys, Asp, Glu, His, and Tyr SCs. Met and His are typically found in heme proteins where they can act as axial ligands. Mononuclear sites bearing Met-SD feature a distance distribution centered at 2.3 Å. His is important also in iron-O/N proteins (neither heme nor FeS clusters) [70]. In heme proteins the iron coordination is mainly performed with NE2, as our analysis involves more than 15000 measurements for NE2 in mononuclear sites, and 534 instances for ND1. In iron-O/N proteins His seems to provide a rigid coordination framework, which is presumably due to their bulkiness, relatively low structural flexibility, and capacity in providing good second-sphere hydrogen bonding [70]. Cys shows a sharp peak around 2.3 Å in all sites regardless the nuclearity. This is because the

disposition of Cys is crucial for the enzymes bearing the iron ion(s) and extremely conserved in along all the iron site types. However, in sites with 5 or 8 metals we observe some skewed data towards higher distances and slightly broader peaks. This behavior is mainly to address to the low amount of data in the considered resolution range, since the visual inspection did not highlight any abnormality. Tyr is present only in mononuclear sites with a target distance around 2 Å. Glu and Asp carboxylate groups can stabilize high-valent iron intermediates [70] through their negative charge. For both Asp and Glu (Figure 11), in mononuclear sites the OX1 peaks are around 2.1 Å and with data skewed towards higher values. These values correspond to a bidentate binding mode that causes a distance increase for OX1. Accordingly, the distance distribution of OX2 shows peaks typical of the bidentate interaction (2.5 Å),as well as the monodentate *syn* (3.5 Å), which is actually prevalent, and *anti* (4.5 Å) fashion. The distributions are similar in dinuclear sites with slightly more data around 4.5 Å for the Asp. In iron sites the carboxylate shift is plays an important role in controlling the availability of coordinating positions in the active sites, especially of those with multiple iron ions [70]. In mononuclear sites, the change in carboxylate coordination mode can be a mechanism to control the CN of the iron and plays a crucial role in controlling the O_2 reactivity [70].

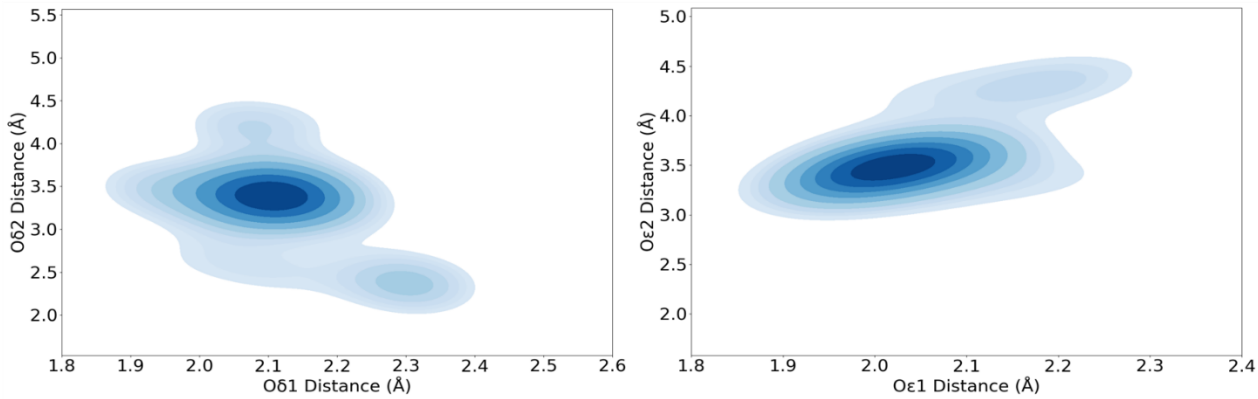


Figure 11. Iron coordination coordinated by carboxylate group of Asp (left panel) and Glu (right panel).

Nickel coordination in mononuclear sites is commonly performed by His, Asp and Glu. Cys is also known to participate to its coordination, however we collected enough data only for dinuclear sites. For His coordination we observe an initial peak around 2.0 Å for ND1, which corresponds to sites where the metal is chelated by ligands close in the protein sequence. However, the main peak is centered at 2.25 Å. These two different values could be caused by the different site geometry. The NE2 interaction shows no deviations from the already reported His optimal distance, namely 2.25 Å. Cys coordination in dinuclear sites with SG features a first peak at 2.25 Å, corresponding to the most probable distance, and a second peak around 2.5 Å. The latter originates from [NiFe]-hydrogenase sites where a Cys bridges the two metals and is closer to the iron atom. Sufficient data about Asp and Glu were collected only for mononuclear sites. Interestingly, Glu coordinates predominantly in a *syn* fashion, whereas Asp coordinates both in *syn* and in *anti* way. However, it must be noted that for the latter, most of the data are due to the deposition of multiple structures of the same protein in complex with a library of different small organic molecules.

Cys, His and Met are the main ligands of copper. Main-chain oxygen and nitrogen atoms, and the carboxylate groups of Asp and Glu are known copper ligands, but in the

present work we did not obtain sufficient data. For Cys a peak at 2.2 Å is present in mono-, di-, and tri- nuclear sites. This recurring distance through all site nuclearity arises from Cys forming a strong covalent bond to the copper ion with an extensive charge transfer from the thiolate to the metal [71]. The coordination of copper by the Met SD atom (Figure 12) is more variable with a mean value of 2.5 Å and a standard deviation of 0.2 Å.

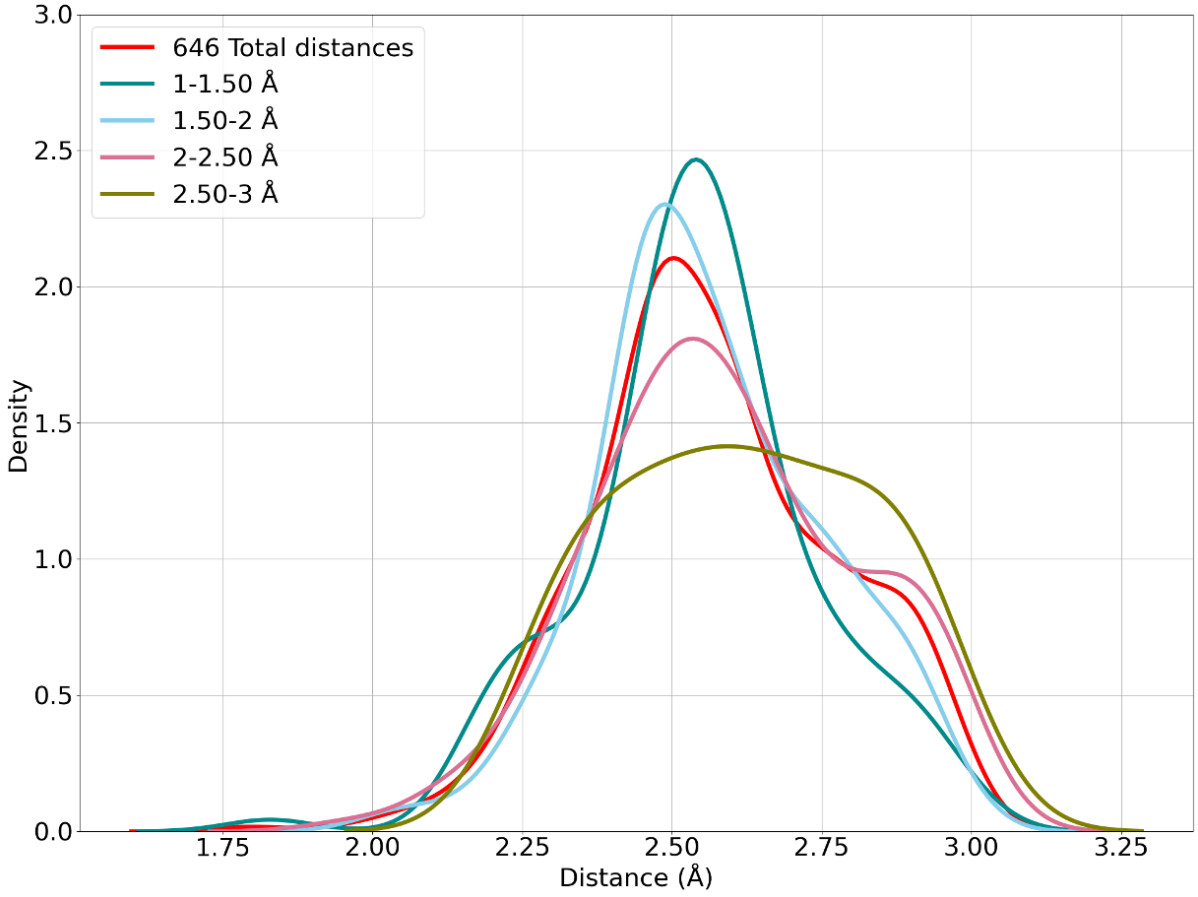


Figure 12. Copper coordination performed by the Met with SD atom.

This may be due to the weaker interaction between the Met sulfur atom, which coordinates only with its lone pairs, whereas the Cys thiolate group bears a net negative charge. Geometrical factors and site organization can also impact the interaction between the Met and the copper atom [71]. His coordination with ND1 and NE2 is equally common in mononuclear sites with both peaks at 2.0 Å. In dinuclear sites, ND1 has a sharper peak while for NE2 we observe a broader distribution, with both distance distributions having a peak around 2.1 Å. At a distance of 2.25 Å, NE2 has a tail that corresponds to heterodinuclear sites with a zinc(II) coordinated by ND1 and copper by NE2. The catalytic role of the copper in these sites can explain the higher distance, since changes of the oxidation state can cause an increase of the distance. In trinuclear sites we have only data available for NE2, with two different peaks of same intensity. From visual inspection of the sites, we can address this behavior to a typical disposition of this residue in multi His sites.

Zinc(II) coordination is performed by His, Cys, Asp and Glu. His and Cys can interact in only one possible way (i.e. a single DA coordinates the metal ion), and this produces high, sharp peaks in all sites regardless of the nuclearity (Figure 13). The main difference between Cys thiolate coordination and the His NE2 and ND1 is the distance, which is longer by about

0.2 Å for the former. However, for His-ND1 we observe some data skewed towards higher distance values even in the best resolution range. In these cases, the sterical hindrance of the near backbone plays a relevant role and also the involvement of His in catalytical zinc(II) sites must be considered. The coordination of a metal ion in catalytic sites must allow transient distortions so that the reactions can take place. Asp and Glu show the same kind of interactions with the metal ion in all sites, regardless of the nuclearity. The distances for OX2 show continuous distributions over values typical of bidentate (with lower intensity), monodentate *syn* and *anti* coordination. In dinuclear sites the best resolution range has few entries for the Glu OE2 coordination and only the bidentate coordination is observable.

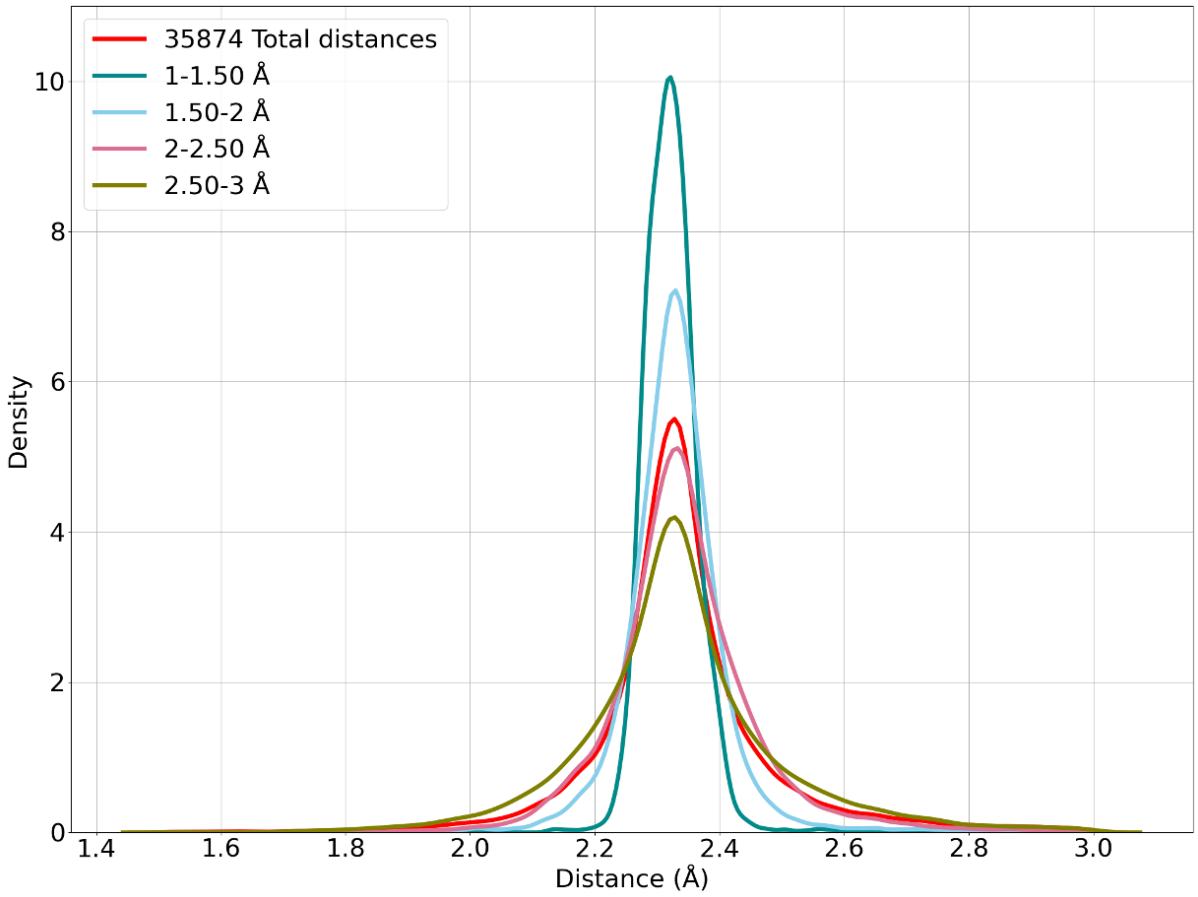


Figure 13. Zinc(II) coordinated by SG of Cys in mononuclear sites.

Metal	Ligand	DA	Mean distance Å	Standard deviation Å
Manganese	Asp	OD1	2.19	0.15
Manganese	Asp	OD2	3.44	0.61
Manganese	Glu	OE1	2.15	0.09
Manganese	Glu	OE2	3.55	0.59
Manganese	His	NE2	2.21	0.08
Iron	Asp	OD1	2.14	0.15
Iron	Asp	OD2	3.32	0.57

Iron	Cys	SG	2.32	0.07
Iron	Glu	OE1	2.06	0.15
Iron	Glu	OE2	3.6	0.44
Iron	His	ND1	2.18	0.02
Iron	His	NE2	2.1	0.11
Iron	Met	SD	2.32	0.06
Iron	Tyr	OH	2.02	0.12
Nickel	Asp	OD1	2.19	0.08
Nickel	Asp	OD2	4.26	0.33
Nickel	Glu	OE1	2.02	0.06
Nickel	Glu	OE2	3.36	0.28
Nickel	His	ND1	2.2	0.12
Nickel	His	NE2	2.2	0.09
Copper	Cys	SG	2.18	0.08
Copper	His	ND1	2.02	0.08
Copper	His	NE2	2.03	0.11
Copper	Met	SD	2.54	0.19
Zinc(II)	Asp	OD1	2.02	0.13
Zinc(II)	Asp	OD2	3.15	0.49
Zinc(II)	Cys	SG	2.32	0.05
Zinc(II)	Glu	OE1	2.04	0.16
Zinc(II)	Glu	OE2	3.01	0.49
Zinc(II)	His	ND1	2.07	0.07
Zinc(II)	His	NE2	2.06	0.08

Table 6. Mean distances and standard deviation computed for mononuclear sites bearing transition metals. The values were computed considering only the best range resolution, i.e. 1-1.5 Å. Manganese, iron, nickel and copper can have different oxidation states that are difficult to accurately identify, for this reason we did not reported them as for zinc(II).

Metalloprotein structures present somewhat different distances between any given metal ion and its DAs. This is caused by the experimental limits such as resolution, and lack of availability of good constraints for the structure refinement of the metal site. In this study, we aim to assess what are the most common distances for each metal-DA pair, and to establish reliable distance information that can be used during the structure determination of metalloproteins. We analyzed a relevant number of distances for different metal-DA pairs.

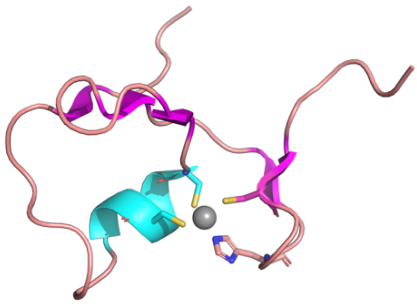
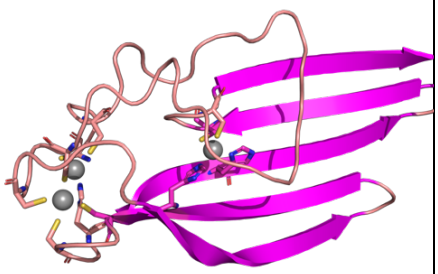
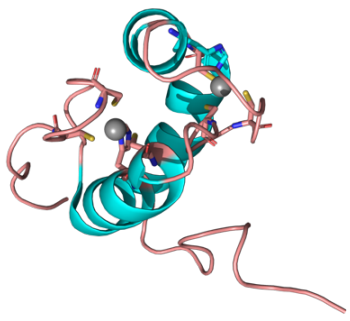
The distance distributions show different behaviors not only among metal groups but also for each metal inside a group. For alkali and alkali-earth metals all data refer to the oxygen atom as DA from the backbone as well as from the SCs, with exception of magnesium(II) for which coordination with His NE2 and ND1 was observed. We attribute this exclusive oxygen coordination to the hard nature of these metal ions. The distance distributions are spread over broad value ranges. This can be attributed to the coordination of the metal being mainly of electrostatic nature, which permits variability of the DA distances. Notably, calcium(II) coordination has more of a covalent character than magnesium(II), which is consistent with our observation of more defined peaks and less skewed data.
When compared with alkali and alkali-earth metals, the transition metals produce narrower peaks centered at a value that is mainly dependent on the identity of the DA. For Cys SG coordination this value corresponds to a mean value of 2.3 Å except for copper where it is slightly smaller. In copper sites we observed that sulfur coordination occurs at difference distances for Met and Cys. We ascribe this difference to the presence of a net negative charge on the Cys thiolate group that interacts strongly with the metal ion, whereas the Met SD is neutral producing a greater distance of about 0.2 Å. Asp and Glu carboxylate coordination shows the most diverse results for all metals. Sodium(I) and potassium(I) coordinate with carboxylate in all the three possible ways (Figure 7). Magnesium(II) is coordinated almost exclusively in a monodentate way, whereas calcium(II) features bidentate interaction as well. This different preference is to be ascribed to the higher number of coordination waters present in magnesium(II) sites which force the carboxylate interaction to be monodentate. Moreover, this different interaction is functional in enzymatic sites to distinguish between these two chemically similar metals [72]. When considering transition metals, the computed distances exclusively involve atoms within the SCs. The typical distance values are shorter and more similar for all transition metals due to more covalent nature of the coordination, in contrast with alkali and alkaline earth metals. The interaction of OD2 with manganese can occur in all the three possible ways (Figure 7), except for trinuclear sites where bidentate coordination is not present. In mononuclear sites the OE2 atom coordinates in all the three possible ways, but it also positions itself at intermediate values between the bidentate and the *syn* coordination. In binuclear sites OE2 coordinates exclusively in a monodentate *syn* fashion. In mononuclear iron sites the Asp and Glu carboxylates feature three distinct peaks. The interaction in dinuclear sites is different for Asp and Glu. The former one coordinates exclusively in both monodentate ways, whereas Glu interacts with the iron either with both oxygen atoms or in *syn* fashion. Nickel interacts with OE2 only in a monodentate syn way, OD2 additionally can place itself even further from the metal. Copper interacts with carboxylate groups only in mononuclear sites, with Glu OE2 exclusively in a *syn* fashion and the Asp OD2 in *anti*. For zinc(II) the carboxylate coordination resembles that of magnesium(II) with OX2 distances spread continuously over all the possible values with higher data density at *syn* interaction values.

The subdivision in resolution ranges allows one to appreciate how the data distributions change for all metals as the resolution worsens. In the best resolution range, the distributions show well-defined peak, and as we move to lower resolutions the data becomes more and more spread towards higher values. This is because in high resolution structures the electron density maps are more accurate and allows a better determination of the position of the atoms, including the metal ion and the ligands. This decreased uncertainty results in more reliable and well-defined metal-ligand distances. Thus, we used only measurements at the best resolution range to compute the mean distances of Tables 5-6. For

those metals with few data, we averaged the results over the first and the second resolution ranges. Indeed, in the 1.5-2 Å range the results are quite similar to the best range.

3.3 A Comparison of Bonded and Nonbonded Zinc(II) Force Fields with NMR Data

The subject of our analysis are ZFs, a group of very structurally diverse metalloprotein domains. They present diverse architecture, metal binding mode, functions, and reactivity [73,74]. We selected NMR studies where structure determination (PDB IDs: 2NAX, 5JPX, 2JOX) was complemented by the measurement of heteronuclear nuclear Overhauser effects (Het-NOE). We additionally included proteins (PDB IDs: 1CHC, 2K9H) with no available relaxation data to expand and reflect the diversity of the superfamily. Our benchmark targets different protein topologies with one or two independent zinc(II) sites, and even a binuclear site.

PDB CODE	ZF STRUCTURE	BIOLOGICAL ROLE
2NAX [27] CCHC		Pcf11's C-terminal domain that very likely acts as a platform and bridge with other protein factors involved in 3'-end processing of pre-mRNAs.
5JPX [28] CHCC		Possible functional role in regulating RING-mediated ubiquitination as well as interactions with other proteins.
2JOX [24] CCCHCCC HHCC		Probably involved in protein-interaction during embryogenesis.
2L7X [25] CCHC CCHC		Region of the tail of the Gn glycoprotein from the crimean Congo hemorrhagic fever virus. This protein is involved in host-pathogen interaction and viral assembly.

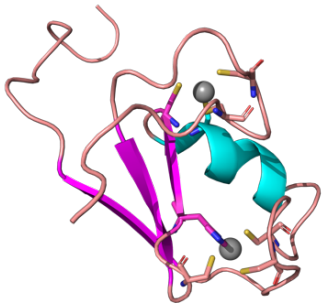
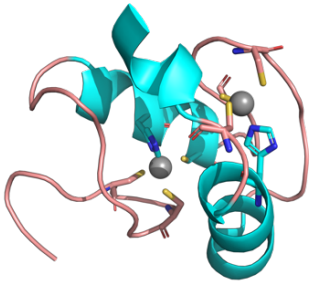
1CHC [23] CCCC CHCC		Domain of E3 ubiquitin-protein ligase that probably interacts with DNA or RNA.
2K9H [26] CCHC CCHC		Region of the transmembrane glycoprotein G1 of Hantaviruses. This protein is involved in viral assembly.

Table 7. Zinc-fingers used to test the bonded and nonbonded FF. The first column reports the PDB code of the structure together with the amino acid pattern(s) binding the zinc(II) ion(s). The third column reports information about their biological role.

Our aim was to assess the performance of the two zinc(II) FFs that rely on different modelling approaches of the metal-ligands interactions [16-18]. The agreement with experimental data is a reliable measure of the accuracy of the FFs [75-78]. NMR spectroscopy is used to obtain information about protein motions on a broad range of timescales, as nuclear spin relaxation rate reports on the internal motions on different timescales. The three commonly measured NMR relaxation rates are the spin-lattice relaxation rate (R1), the spin-spin relaxation rate (R2), and Het-NOE data for all the 1H-15N moieties in the protein. Het-NOE data are extremely sensitive to fast protein dynamics [31–33]. Except for Pro, all amino acids have one N-H moiety within the peptide bond, and ^{15}N relaxation information provides information about the flexibility of the entire protein chain. In most approaches to interpret the NMR relaxation data in proteins, the core assumption is the decoupling of the overall and of the internal motions. The local motions are obtained by fitting suitable parametric functions to the relaxation rates, as done in the model-free approach [79-81]. The latter method is called model-free since the parameters are derived without the need to invoke a specific model for the internal motion. From the application of this approach, we obtain a set of parameters for each N-H bond in the protein. The order parameter (S^2), in particular, gives information about the magnitude of the angular fluctuation of each bond vector, reflecting the flexibility of the protein at those sites with respect to the overall frame [79,80]. Since Het-NOE data can be used with no interpretation or assumption and report on the relevant timescale of dynamics (sub-ns), we decided to compare the MD-derived S^2 with the Het-NOE data instead of the NMR-derived S^2 values.

As shown by the RMSD values (Figures S1–S6 in the supplementary material of the corresponding article), for all the systems the overall protein fold remained stable during the production runs. The NBFF depicts the coordination through electrostatics and van der Waals interactions that allow transient distortions of the metal ion and may lead to its detachment from the protein site [17,82]. For this reason it was necessary to monitor the distances

between the zinc(II) ion and the DAs throughout the trajectories. During all the MD runs the distances showed a fluctuation of 0.04 Å around the equilibrium values. For the simulations performed applying ZAFF this procedure was not necessary since the metal is fixed through explicit bonds to the DAs [16]. We computed the S^2 parameter using the trajectories and averaged them for each FF. To inspect the differences in the accuracy of the protein dynamics simulated with each FF, we superimposed the mean S^2 values to the Het-NOE data. The agreement with the relaxation data is quantitatively expressed by the Pearson coefficient.

Zinc-Fingers	Pearson Coefficient for NBFF	Pearson Coefficient for ZAFF
2NAX	0.82	0.89
5JPX	0.68	0.69
2JOX	0.77	n.a.
2L7X	0.79	0.84

Table 8. Pearson coefficients computed for each zinc(II) FF with respect to the Het-NOE data. For 2JOX, it was not possible to apply the ZAFF. 1CHC and 2K9H are not reported since there are no experimental data available.

The 2NAX structures contains seven β strands, a short N-terminal 3_{10}-helix and a longer C-terminal α helix (Table 7). The zinc(II) is coordinated by Cys^{564} and Cys^{567} in the β2β3-hairpin, and His^{596} and Cys^{599} on the C-terminal α helix [27]. The averaged MD computed S^2 for both FFs superimposed to the Het-NOE data is shown in Figure 14. We obtained a Pearson coefficient of 0.82 and 0.89 for the NBFF and the ZAFF, respectively (Table 8).

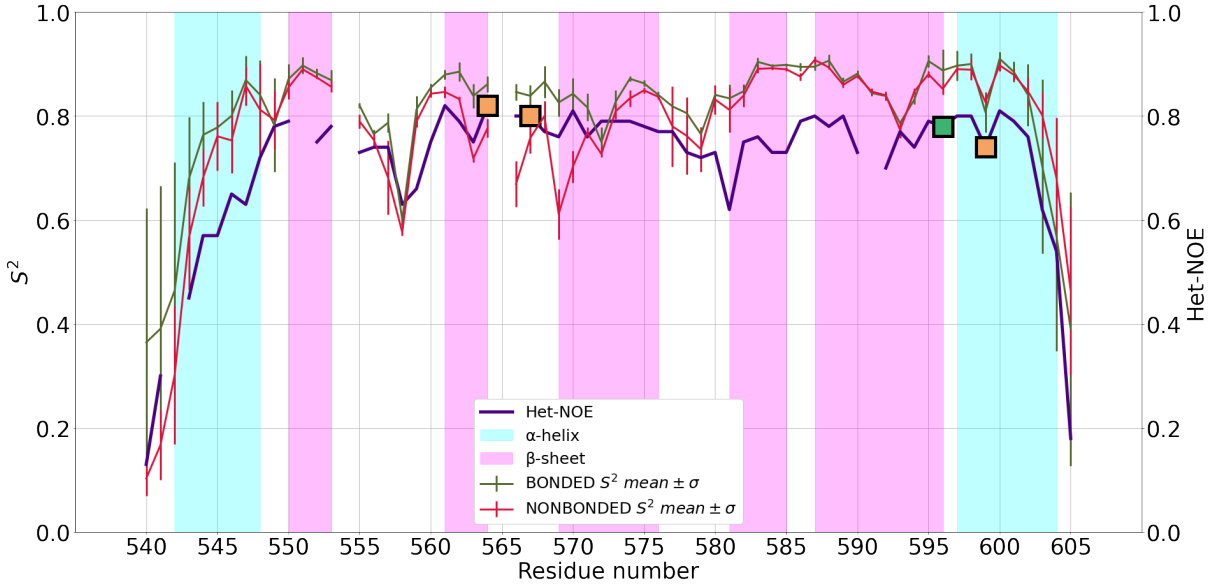


Figure 14. Mean S^2 of 2NAX and standard deviation for bonded (red) and nonbonded (green) simulations superimposed to Het-NOE data (purple). Orange squares represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green squares represent zinc(II)-binding His residues.

The mean S^2 values corresponding to the ZAFF and the NBFF are very similar to each other, and both represent well the dynamical trend of the Het-NOE data. Both S^2 show, as expected, high values (>0.7) for regions of secondary structure and lower values for loop regions. The

ligands are located in protein regions with higher stability. The Het-NOE data describe a rigid domain except around residue 558, which was well captured by our simulations. The largest deviation between the two types of simulations is the higher flexibility at residues 569-570 in the NBFF trajectories and that was not observed with ZAFF. The relaxation data reported the N-terminal helix as looser than the C-terminal one and in the corresponding paper the helix α1 was described as partially unfolding [27]. In our investigations, we considered the trajectories both including and excluding this helix to see if its presence would affect the computed S^2 values. We observed that the local dynamics of the helix α1 was effectively decoupled from whole protein. Even though we inspected different structural factors, namely: i) the distances between the donor atoms, ii) the distribution of water molecules around the metal site, and iii) the hydrogen bond patterns, we could not highlight possible causes of the high flexibility of helix α1.

The core domain of 5JPX presents a ββαβ structure, with two additional short strands and a disordered N-terminal tail (Table 7)[28]. The S^2 computed for each FF are perfectly superimposed and represent the same trends in correspondence of secondary structures, with small differences for the loop regions. Moreover, both represent the dynamical behavior of the relaxation data (Figure 15). For the NBFF we obtained a Pearson coefficient of 0.68 and for the ZAFF simulations a coefficient of 0.69 (Table 8).

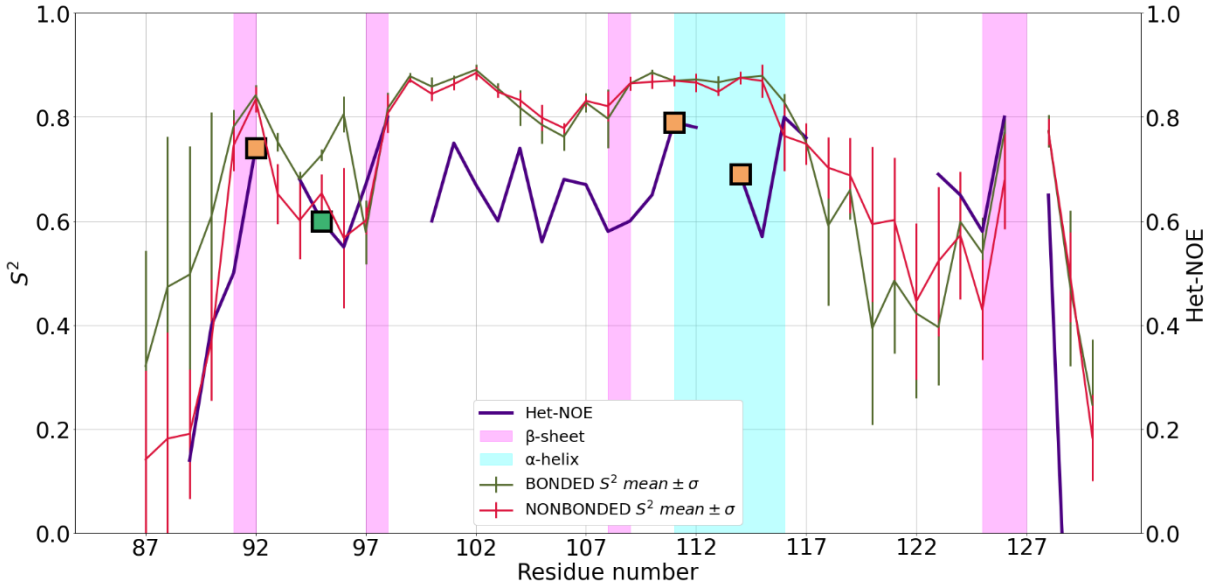


Figure 15. Mean S^2 of 5JPX and standard deviation for bonded (red) and non-bonded (green) simulations superimposed to Het-NOE data (purple). Values on y-axis were truncated at 0 because S^2 has no negative values. Orange squares represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green squares represent zinc(II)-binding His residues.

The core encompassing the ligands (Cys^{92}, His^{95}, Cys^{111} and Cys^{114}) was stable during all trajectories, with mean S^2 values around 0.8, corresponding to well folded secondary structures. The region Arg^{118}-Asp^{122} was not characterized experimentally due to signal broadening [48], so no Het-NOE data are available for these residues. The MD simulations indicated that this region is highly flexible also on the sub-ns timescale.

2JOX presents an antiparallel β-sheet with five strands, with both sides of the sheet being solvent exposed. A mononuclear zinc(II) site (His^{59}, His^{71}, Cys^{88} and Cys^{91}) stabilizes the sheet through cross strand interactions. The N-terminal region holds together an additional binuclear site (Cys^{2}, Cys^{5}, Cys^{30}, His^{66} for one zinc(II) ion, and Cys^{30}, Cys^{33}, Cys^{61}, Cys^{64} for the other one) [24]. It was not possible to investigate this system with ZAFF since it was not parametrized for peculiar sites as the binuclear cluster. However, 2JOX is particularly challenging for the NBFF as well. Through the trajectory visualization and the DA-metal distance analysis we observed that the binuclear site splits. In detail, the Cys initially acting as a bridge between the two metal ions, coordinates only the zinc(II)^{109}, with the second metal ion interacting only with three ligands. However, the coordination and the geometry of the latter metal ion was maintained during all trajectories. Despite come discrepancies of the computed mean S^2 (Figure 16) from the superimposed Het-NOE data, the overall local dynamics are well reproduced with a Pearson coefficient of 0.77 (Table 8).

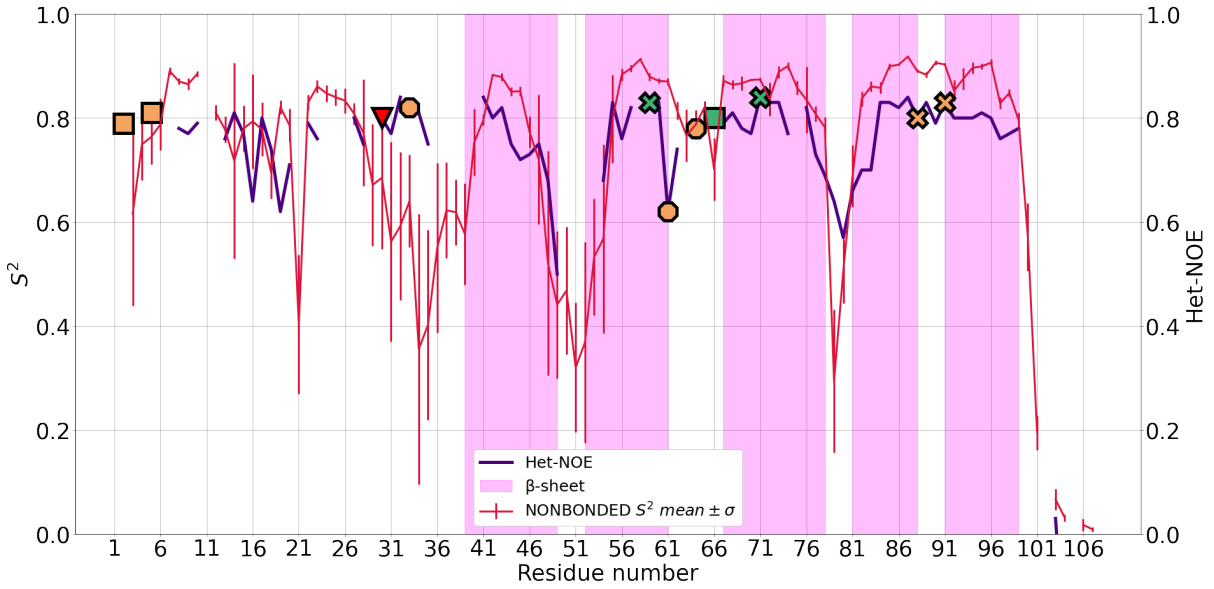


Figure 16. Mean S^2 of 2JOX and standard deviation for nonbonded (red) simulations superimposed to Het-NOE data (purple). It was not possible to apply ZAFF to the system. The y-axis was truncated at 0 because S^2 had no negative values, hence some Het-NOE data for the last protein residues were not visible. Orange markers represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green markers represent zinc(II)-binding His residues. Residues belonging to the same site are represented with the same marker shape (crosses for the mononuclear site; circles for the binuclear site except the bridging Cys^{30}, which is represented as a red triangle).

In the N-terminal tail, the loop region 29–39 shows higher mobility during the trajectories than observed in the experimental data. However, for five out of the 11 residues in this region, there are no recorded experimental Het-NOE values [24]. The flexibility enhancement is due to the splitting of the binuclear sites, which leads to the spatial displacement of this region with a resulting higher solvent exposure and a wider conformational space available. The data agreement is excellent in correspondence of the β-sheet part of the protein where the mononuclear site is embedded. Our simulations are also fully consistent with the Het-NOE data for the flexibility observed in the β1-β2 portion of the sheet, also involving the terminal regions of the two strands. The β-turns between strands β1-

β2 and β3-β4 have a higher mobility than the turns between β2-β3 and β4-β5, since they comprise some of the ligands of the zinc(II) ions (Figure 16). The role in metal coordination of these residues restricts their conformational freedom.

The 2L7X structure features two zinc fingers, with an additional α3 that packed against the dual zinc finger fold (Table 7). The N- and C-terminal regions are unstructured and flank the central part of the domain. In the first site (ZF1) the zinc(II) is coordinated by Cys^{736}, Cys^{739}, His^{752} and Cys^{756}, while in ZF2, the coordination is carried out by Cys^{761}, Cys^{764}, His^{776} and Cys^{780} [25]. The S^2 values obtained from the trajectories of each FF, are almost superimposable and both reproduce a rigid and compact system (Figure 7). ZF1, ZF2 and the linker in between them behave as one entity, whereas the two tails show enhanced flexibility. For both FFs, the predicted dynamics correlate well with the experimental data.

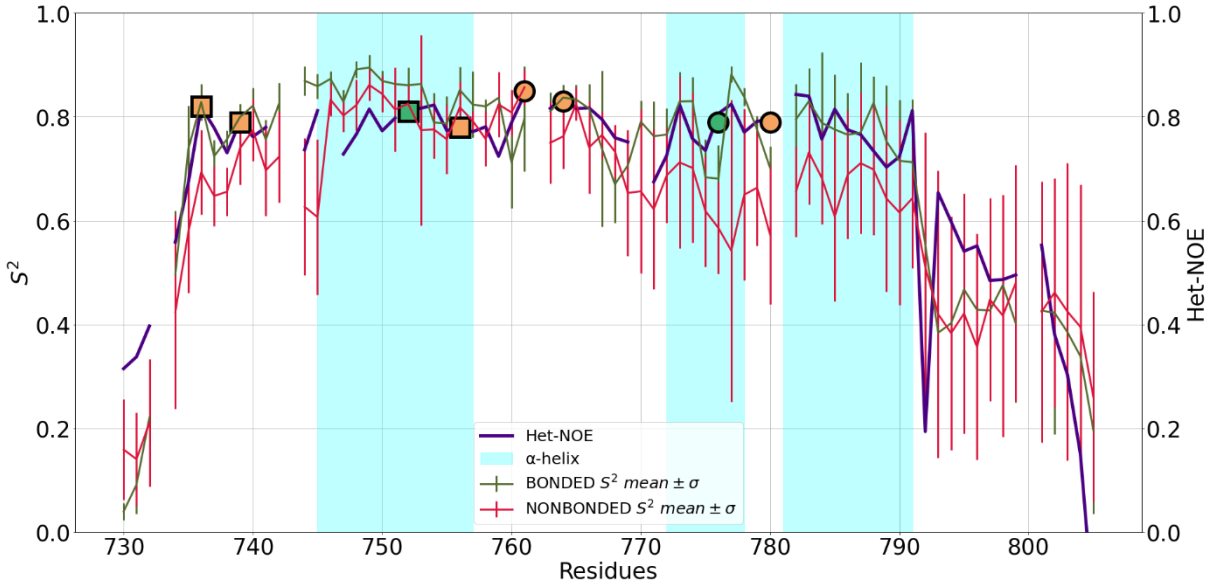


Figure 17. Mean S^2 of 2L7X and standard deviation for bonded (red) and nonbonded (green) simulations superimposed to het-NOE data (purple). Values on y-axis were truncated at 0 because S^2 had no negative values. Orange markers represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green markers represent zinc(II)-binding His residues. Residues belonging to the same site are represented with the same marker shape (squares: ZF1; circles: ZF2).

No experimental data for results validation is available for 1CHC and 2K9H. For this reason, we only inspected the similarities between the MD-derived S^2 values for each FF (Figures S8 and S9 in the supplementary material of the corresponding article). 1CHC has a split-βαβ topology with an amphipathic α-helix spanning the triple-stranded antiparallel β-sheet [23]. The computed S^2 for both FFs show high similarity and represent a stable core with values around 0.8 for secondary structures and for the loop regions containing the ligands (Figure S8 in the supplementary material of the corresponding article). Higher flexibility is observed for the N- and the C- termini that flank the core. One relevant difference between the two results is the enhanced flexibility of Cys^{32}, which was caused by the lower stability in the NBFF simulations of the secondary structure it belonged to. 2K9H features a novel CCHC dual ZF fold; the ligands of the zinc(II) ions are Cys^{548}, Cys^{551}, Cys^{568} and His^{564} for the first ZF, and Cys^{573}, Cys^{576}, His^{590} and Cys^{594} for the second one [26]. The obtained results are

extremely superimposable and represent a compact system with just some discrepancies in the loop region immediately following Cys^{576} (Figure S9 in the supplementary material of the corresponding article).

All the simulates proteins bear zinc(II) ions coordinated in a tetrahedral geometry with His and Cys as ligands. The results computed for each FF agree with the dynamics showed by the Het-NOE data. For secondary structure we observe lower mobility (characterized by S^2 > 0.8 and Het-NOE > 0.7), and for unstructured regions the flexibility is enhanced. The agreement with the experimental data is expressed quantitatively by the Pearson coefficient that we computed between the relaxation data and the mean S^2 of each FF (Table 8). The Pearson coefficient is an indicator of how accurately each FF represents the experimental trend, and the results are satisfactory for all the simulations with both FFs. For 2JOX, it was possible to perform only the NBFF simulations, as discussed above, and the Pearson coefficient of 0.77 suggests the ability of the NBFF to reproduce such complex systems. The Pearson coefficient is slightly better for ZAFF simulations than those performed with the NBFF, indicating that the two FFs had comparable accuracy. Upon closer investigation, we noticed that in certain cases, the initial regions of secondary structures are not consistently preserved throughout the NBFF trajectories as indicated by the DSSP analysis (not shown). We hypothesize that the slight destabilization may arise from the electrostatic interaction occurring between the residues of the secondary structures and the zinc(II) site. Consistent with this observation, the mean S^2 values calculated from NBFF trajectories exhibited greater variability, as indicated by higher standard deviations compared to those derived from ZAFF simulations. This implies that the individual trajectories displayed more pronounced differences when using the former force field compared to the latter. Our results demonstrate that NBFF and ZAFF are equally suitable and reliable for the zinc(II) binding proteins investigations, despite the MD runs with the former had slightly higher standard deviations.
The local protein dynamics showed in the relaxation data of all proteins are properly reproduced by both FFs. However, for the NBFF we must pinpoint one main advantage. The simple parametrization of this FF allows its extensibility to more complex zinc(II) binding sites as in 2JOX without the need to use a metal center parameter builder such as MCPB.py [83]. A recent study investigated the ability of different models to reproduce the zinc(II) coordination and the ligand binding in metalloproteins [84]. Among them, the NBFF displayed a very satisfactory performance for its ability to reproduce the geometry and to maintain the correct distances between the ligands and the metal. Moreover, the coordination by His residues was consistently kept in simulations performed the NBFF, differently from the other non-bonded models. In this study, we conducted further validation of the NBFF using experimental NMR data validate our results. A noticeable difference between the trajectories generated with both FFs is that ZAFF gives out steadier RMSD profiles and the secondary structures are more consistent if compared to the NBFF. This difference is likely attributed to the stability conferred upon the protein topology by the presence of four fixed bonds between the polypeptide chain and each zinc(II) ion. Nevertheless, the S^2 calculated from MD trajectories showed a highly satisfactory correlation with experimental Het-NOE values for both ZAFF and NBFF, with no significant deviations between the two. Overall, we judge the NBFF to be well capable of reproducing the dynamical behavior in zinc(II)-proteins, and thus constitutes a widely adoptable FF for MD simulations of such systems [17,18].

3.4 Unveiling the coordination chemistry of zinc(II) in a protein: a QM/MM study.

This project is a collaboration with Prof. Paolo Carloni (Jülich Forschungszentrum) that will allow us to be the first Italian research group to use the JUWELS clusters, the most powerful supercomputer in Europe. Our complex (PDB ID 6MR5 [36]) is a homodimer with a mononuclear zinc(II) site in each chain. We selected this metalloprotein because its coordination complexity is suitable to assess the application of the QM/MM simulations in the MiMiC framework [47-49]. The zinc(II) ion is coordinated by one His, two Asp and by an inhibitor (i.e. W45, belonging to the mercaptoacetamide inhibitors of Alzheimer disease) in a slightly distorted tetrahedral geometry. The Asp residues contribute to the coordination through their carboxylate groups, interacting with the metal ion in a monodentate *syn* fashion. Notably, both oxygen atoms of the Asp ligands can exert an influence on the metal ion even when the coordination is monodentate. The His ligand participates in the coordination, and it can contribute to charge delocalization through its imidazole ring. Furthermore, the inhibitor plays a role in the coordination, adding another negative charge to the coordination sphere (Figure 18).

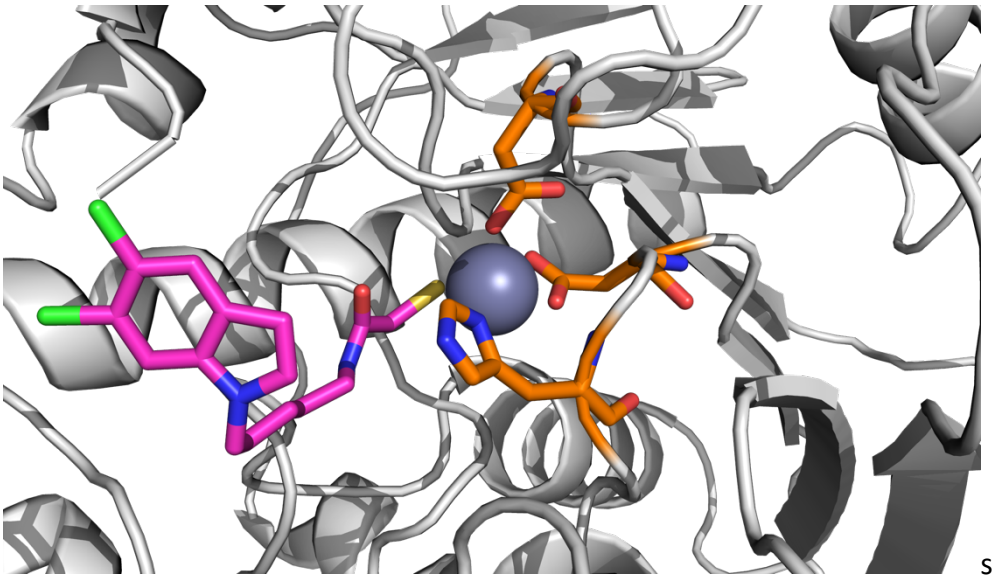


Figure 18. Close-up of the zinc(II) site in 6MR5. The endogenous ligands are represented in orange, and the inhibitor in hot pink.

This work aims to investigate how each contribution impacts the coordination of the zinc(II) ion, but also how the ligands influence each other within the site and contribute to transient geometry distortions. Moreover, we will address how the fluctuations of the overall protein framework affect the coordination in the zinc(II) site. Specifically, to investigate electron dynamics, we will compute the Maximally Localized Wannier Functions (MLWFs) [85] within the MiMiC QM/MM framework [47-49]. The MLWFs are molecular orbitals that provide a close representation of chemical concepts like electron lone pairs and covalent bonds, and they will be used to obtain detailed insights about the metal coordination, the

charge distribution and charge transfer within the zinc(II) site. Besides being of a considerable size (162311 atoms), our system also presents a not trivial coordination environment. The planned analysis will leverage the scaling efficiency of MiMiC framework in order to provide a comprehensive reference for the investigation of other closed-shell metalloproteins through QM/MM simulations. At the present time, we applied for the computational resources that will be available from November 2023, so we did not perform the three independent QM/MM simulations of 15 ps each yet. However, we performed a classical MD production run of 200 ns to assess if the system is stable. The RMSD values for both the protein and the exogenous ligand, show the system is steady during the trajectory. Moreover, we computed the evolution of the distance between the metal ion and each DA, which is necessary because we applied the NBFF [17,18], providing also an evaluation of the parametrization of the exogenous ligand. Table 9 shows that the coordination is perfectly maintained throughout the simulation by all ligands.

	Chain A (mean ± std)	**Chain B (mean ± std)**
Asp 612 OD1	0.196 ± 0.004	0.197 ± 0.004
Asp 612 OD2	0.251 ± 0.016	0.249 ± 0.016
His 614	0.205 ± 0.004	0.205 ± 0.004
Asp 705 OD1	0.196 ± 0.003	0.196 ± 0.003
Asp 705 OD2	0.334 ± 0.017	0.331 ± 0.016
W45 S04	0.221 ± 0.005	0.222 ± 0.005

Table 9. Mean distance ± standard deviation (std) for each donor atom coordinating the zinc(II) ion. All distances are in nm.

This preliminary work produced a well-equilibrated system, a prerequisite for the subsequent QM/MM dynamic runs. To obtain some starting data about the zinc(II) site at QM level, we set up a 0.5 ps simulation on JURECA clusters that is still running.

4

Final Remarks and Outlook

4.1 Conclusions

As discussed in the introduction section, metalloproteins perform extremely relevant roles in almost all biological processes. In this thesis we initially addressed the need of a reliable tool for the prediction of metal sites. For its development we needed to collect structural information about the site reorganization passing from the apo to the holo form. Our analysis highlighted that the DAs undergo major structural rearrangements upon metalation and thus are not a reliable source of structural information that can be exploited for the structure-based prediction of a metal site. On the other hand, the backbone shows minimal changes between the apo and holo states. The application of our new tool, MoM, to the entire *Saccharomyces cerevisiae* proteome modeled by Alphafold showed promising results, with an error rate for all predicted MBSs of 24% and a precision of 76%. This level of performances were not obtained with different tools, except for Metal3D **[86]**, which performs slightly better but with a more complicated approach and significantly longer analysis time. MoM enables comparative metalloproteomics for hundreds of organisms, in order to map metal usage over the entire tree of life.

From our detailed analyses of the structural features of MBSs, it became apparent that the refinement of the local structure around the metal ion is sometimes less than optimal. We partly ascribed this to the lack of appropriate restraints that crystallographers may apply during the structure determination process, especially when the resolution of the data is not excellent. Thus, we perfume an extensive analysis of metal-DA distances in the whole MetalPDB database. The study provides reliable target distances extracted from an extensive number of measurements and highlights specific aspects of metal coordination by carboxylate groups that may be of functional relevance. This kind of statistical information can be advantageously complemented by more detailed computational studies, such as QM/MM simulations. Although this is still work in progress, we have already started the implementation of a comprehensive approach to such simulations for closed-shell systems, exploiting the high scalability of the MiMiC framework as well as the availability of forefront supercomputing capabilities at Jülich Forschungszentrum.

For users lacking access to supercomputers and/or the knowledge to successfully apply QM/MM methods, classical MD simulations with a non-bonded FF are a suitable alternative option to investigate features such as the flexibility of or geometrical transitions in metal-binding sites. For this kind of studies, the validation of the FF parameters is a crucial aspect. In this thesis, we showed how to construct and apply a benchmark of zinc(II)-binding proteins whose dynamics had been experimentally characterized by NMR. This provides a reference methodology for the validation of novel FFs.

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Metal-induced structural variability of mononuclear metal-binding sites from a database perspective

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Definitions.
apo-protein: the polypeptide part of a holo-protein (i.e. the holo-protein without its prosthetic group).
donor atom: an atom that forms a direct interaction (coordination bond) with the metal ion.
holo-protein: a protein bound to its prosthetic group.
MBS: metal-binding site.

ABSTRACT

Metalloproteins are ubiquitous in all kingdoms of life. Their role and function are tightly related to the local structure of the metal-binding site. In this regard, the MetalPDB database is an invaluable tool since it stores the 3D structure of metal-binding sites and of their corresponding apo forms. In this work, we exploited MetalPDB to compute extensive statistics over >3000 clusters of mononuclear sites about the rearrangements occurring upon change in metalation state. For each cluster, we matched the holo and apo sites so that it was possible to average the distances between all possible pairs of Cα and donor atoms and thus quantitatively assess structural variations by computing the Δ values (mean apo distance – mean holo distance). For most of the structures the backbone is rigid with little to no rearrangement, while donor atoms experience significant changes of their relative position when the metal is removed. Sodium and potassium sites are an exception to this general observation. This is most likely caused by their preference for coordination by the main-chain oxygen atoms, making the rearrangement of donor atoms superimposable to that of the backbone. Magnesium and calcium show a different behavior, despite their chemical similarity: calcium sites undergo a larger reorganization upon metalation although both metals have similar percentage of backbone oxygen as donor atoms. We ascribe this observation to the structural and energetic factors regulating the selectivity for calcium over magnesium.

1. Introduction

38% of the entries in the Protein Data Bank (PDB [1]) harbor one or more metal ions [2,3]. Furthermore, it has been shown that at least 40% of enzymes need metal ions for their biological function [4,5]. Thus, it is not surprising that a variety of metals are essential for organisms in all kingdoms of life [6,7]. However, many essential metals, particularly from the d-block, are poorly available in the environment and can become cytotoxic in high amounts. Consequently, the intracellular concentration of metal ions is strictly controlled [8,9], thanks to the joint action of transport, delivery, storage, detoxification, and efflux machineries. Bacterial pathogens must acquire their required metal ions from the host organism. To counter this, the host can deploy a protective mechanism, called nutritional immunity, aimed at inhibiting the growth of pathogens by restricting the availability of crucial metal ions [10]. A similar strategy can be pursued also through pharmacological treatment [11].

The reactivity and physiological role of metal ions in metalloproteins is largely defined by the local structure environment, which determines how the metal is placed in the active site, how it interacts with the substrate and, for redox-active metals, its reduction potential [12,13]. The metal-binding site (MBS) can be thought as a substructure around the metal ion(s) that represents the macromolecular environment sensed by the metal. This substructure should correspond to the minimal environment determining the function of the metal, i.e., the "minimal functional site" [14]. The MBS can be defined in a way such that it is possible to automatically extract these sites from the 3D structures of metalloproteins available from the PDB. Atomic-level knowledge of the MBSs is crucial to understand the function of these systems. However, sometimes it is not straightforward to obtain a metalloprotein sample of sufficient quality for structural studies. This can be caused by various factors; for example, the metal ion can be lost during purification or never be incorporated into the target protein under the experimental conditions used to produce the protein. In such cases, it may still be

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possible to determine the 3D structure of the protein without its metal cofactor(s), namely of the apo-protein.

The availability of the 3D structure of the apo-protein enables structure-based prediction of the occurrence of metal-sites, by leveraging the information on the relative position in space of the potential donor atoms that coordinate the metal. In addition, the success of AlphaFold and AlphaFold2 in the CASP initiatives [15–18] has made it possible to obtain high-quality computer-generated 3D structural models for proteins not yet characterized experimentally [19–21]. In turn, this may allow novel MBSs to be discovered [22]. Initial attempts in this direction assumed that the side chains of the protein residues were already correctly placed in space. This is very likely when the cofactor is essential for folding, i.e. when in vivo the protein exists only in the holo-form. However, there are numerous cases where both the apo- and holo-proteins may exist in vivo, e.g. in the context of signaling processes or of metal storage. This can be relevant in particular for systems binding individual metal ions or small metal-containing cofactors, such as dimetallic clusters, where the hydrophobic core of the protein is sufficiently large for a compact 3D structure to form [23]. The occurrence of physiologically relevant apo- and holo-protein pairs is important for two distinct reasons. From the structural bioinformatics perspective, it poses the issue of systems where the predicted conformation may not be the correct one to dock the cofactor(s). Secondly, and perhaps more fundamentally, it corresponds to two distinct structural states that interconvert in the cell upon metal binding, with presumably different properties with respect to e.g. the recognition of molecular partners or their thermodynamic and kinetic stability (and ultimately lifetime) in the cell [24,25].

Here we took advantage of the MetalPDB database of MBSs [2,3] to create an extensive dataset of apo- and holo-pairs of mononuclear sites. We used the dataset to compute statistics of MBS rearrangements. We observed that for the majority of physiologically relevant metal ions, there are statistically significant rearrangements of the position of the donor atoms upon change of metallation state. Sodium, potassium and magnesium sites were noticeable exceptions to this general trend. Our results have implications for metalloprotein structure-based prediction, metalloprotein design and the understanding of the fundamental structural properties of metalloproteins.

2. Methods

We used a SQL query to retrieve all data from the MetalPDB database [2,3]. The latter stores a collection of 3D templates automatically extracted from the PDB describing the local environment around metal (s). In the automated procedure, for each metal atom in the structure, the non-hydrogen atoms at a distance smaller than 3.0 Å are identified as its donor atoms (DAs), i.e. the atoms that bind directly to the metal. The protein residues or small molecules that contain at least one donor atom are the metal ligands (called endogenous or exogenous, respectively). The full metal-binding site (MBS hereafter) is obtained by including any other residue or chemical species having at least one atom within 5.0 Å from a metal ligand. MetalPDB groups all MBSs in clusters containing both “equistructural” and “equivalent” sites [2,3]. For the construction of our dataset, we retrieved the clusters containing only “equivalent” sites and their corresponding apo structures. Two MBSs are defined as equivalent in MetalPDB if they satisfy all the following conditions: (i) they are found in PDB chains with the same structure (based on Pfam domain composition or on the sequence identity between the two chains being $\geq$ 50%); (ii) after structural superposition of the PDB chains, they are superimposed with the metal atoms in the same position; (iii) they contain the same metal(s). For each cluster we acquired only mononuclear sites sharing the same metal ligands.

In MetalPDB all atoms of a site are already labeled with their structural role (i.e., ligand; ligand neighbor; other). This information was propagated to the apo sites in each cluster through sequence alignment. This allowed us also to properly associate residues across all the sites in the cluster regardless of possible differences in the numbering schemes of the original structures. After assembling the dataset, we used in-house-written Python scripts to parse the coordinates of the sites. Firstly, we separated the residues based on their protein chain and removed all exogenous ligands (i.e., non-protein, non-nucleic acid). Only the conformation with the highest occupancy was retained for residues having multiple conformations in the PDB file. Subsequently, the program extracts the coordinates and B-factors of the Cα and the donor atoms (DAs) for each ligand. These coordinates are used to compute the distances between all pairs of Cα atoms and all pairs of donor atoms. The list of all the MetalPDB clusters, labeled by the corresponding database identifier, together with the PDB identifiers of the holo and apo-sites in each cluster is given in the Supplementary material (Table S1).

Since we ensured that all sites had the same ligands and consequently the same atom pairs, we could average the measured distances over all holo or apo sites for each cluster. By subtracting the mean holo distance from the mean apo distance, we computed the Δ value. Negative Δ values correspond to sites that contract upon metal removal, whereas positive Δ values correspond to sites that expand upon metal removal. The absolute value of Δ quantifies the change occurring upon metalation.

Pymol was exploited for structure visualization, as well as for the alignment of the sites to their corresponding structures [26]. The MetalS^2 tool was used for pairwise structural alignment of MBSs [27].

Finally, to assess if the changes in the distributions of the distances between the Cα and DA pairs upon metalation, and between their corresponding Δ values were statistically significant, we computed the Wilcoxon signed-rank test [28] using the Python library SciPy [29].

3. Results

Our pairing was based on the clusters of equivalent mononuclear MBSs in MetalPDB. These were further filtered in order to retain subclusters that had the same metal-binding pattern. MetalPDB associates to each cluster of MBSs the corresponding apo-structures contained in the PDB on the basis of sequence similarity (with a 50% threshold). For the present analysis we kept only apo sites where all the ligands were conserved and had the same spacing as in the corresponding cluster of holo-MBSs. In practice, we constructed groups of holo-MBSs and of the corresponding apo-sites, all sharing the same metal-binding pattern. We assembled a dataset of 3074 groups, for 30 different metals (Table 1). The number of apo-sites in Table 1 is larger than the holo-sites because MetalPDB automatically applies a redundancy filter to the latter. However, this imbalance did not affect the subsequent analysis, which were all based exclusively on the group averages. Indeed, to evaluate the structural deviations between the holo/apo pairs, we measured all intra-site distances between Cα atoms as well as between donor atoms (DAs) and averaged them for holo/apo sites within each group. Consequently, we compared 7042 pairs of distances for the Cα and 8607 for the DAs in the 3074 clusters. We did not attempt to separate MBSs on the basis of the oxidation state of the bound metal. This was motivated by the fact that the X-ray radiation applied to protein crystals may cause undetected reduction of the metal sites [30]. This makes it difficult to ascertain the metal oxidation state at the database scale.

Fig. 1 shows the distribution of distances for zinc sites, separated by the number of protein ligands in each site. The corresponding plots for all other metals are reported in the Supplementary Material.

The data of Fig. 1 readily show that the distributions of Cα-Cα distances are relatively similar for holo- and apo-sites, whereas there are strong differences in the distributions of distances between DAs. This suggests that the structural rearrangements of the protein backbone occurring upon change of the metalation state of a MBS are typically small. On the other hand, significant changes in the position of the side chains appear to be more common in our dataset.

The Wilcoxon signed-rank test was used to reject the null hypothesis

Table 1
Assembled dataset. Each row reports the total number of inspected clusters for the specified metal, with the corresponding number of holo- and apo- sites.

Metal	Holo sites	Apo sites	N° of clusters
As	2	15	1
Ba	17	181	11
Ca	2418	12,829	486
Cd	387	5739	136
Co	67	513	28
Cs	9	978	7
Cu	341	2203	50
Eu	2	7	2
Fe	1270	577	39
Gd	8	39	6
Hg	247	1986	67
K	610	6668	178
Li	11	83	6
Mg	1616	26,277	538
Mn	286	1931	74
Na	2019	28,524	779
Ni	158	1147	71
Pb	8	344	6
Pd	4	356	4
Pr	10	44	7
Pt	28	128	10
Rb	7	896	4
Sm	25	187	14
Sr	21	53	3
Tl	6	16	2
U	52	102	6
Y	10	205	8
Yb	2	54	2
Zn	5440	14,196	529

that the distributions of the Cα-Cα and DA-DA distances are the same for the apo- and holo-sites [31]. Table 2 includes all the metals for which we detected a significant difference between the apo- and holo-sites at the $p < 10^{-3}$ level. In all cases, the deviation was more significant for the distances between the DAs than between the corresponding Cα atoms. Indeed, we observed significant differences for the Cα-Cα distance distributions only for calcium, magnesium, manganese, sodium and zinc (Table 2). Thus, these five metals experience statistically meaningful rearrangements in the conformation of the backbone of the MBSs upon change of metalation state.

We selected X-ray structures with a resolution in the range 1.5–2.0 Å to investigate whether apo-structures were appreciably "floppier" than the corresponding holo sites. We focused on the 1.5–2.0 resolution range in order to avoid possible biases due to different mathematical treatment of the anisotropy of B-factors. In the selected range all B-factors are considered isotropic, which, also thanks to the relatively small range breadth, should make it possible to compare them in a meaningful way (Fig. 2). Because we requested that both the apo- and holo-structure fell in the desired resolution range, our sample contains significantly less data than the whole dataset. Eventually, we analyzed only the data for four different metals, all having >100 clusters, namely sodium, magnesium, calcium and zinc. Whereas the B-factors of Cα and DA atoms are quite similar for the former two metals in both forms, there are noticeable differences for calcium and zinc sites. For the latter, B-factors (and hence flexibility) are higher in the apo- than in the holo-sites. The effect is more pronounced for the DAs, in line with the qualitative notion that metal binding "fixes" the position of residue side chains.

We then decided to evaluate what is the relationship between the rearrangements of the relative position of the Cα atoms, which can be used as a proxy for the protein backbone rearrangements, and the corresponding donor atoms. A straightforward way to visualize the different behavior of these two groups is through the frequency count of the deviations measured for all site pairs. The example of zinc sites is displayed in Fig. 3, whereas the corresponding graphs for all other metals are reported in the Supplementary material.

The distributions of changes in the Cα-Cα distances have sharp peaks at around 0 Å and are modestly skewed towards positive values (indicating that the site is more open in the apo-structure) with a few sites experiencing rearrangements up to 10 Å. Interestingly, there are some instances of negative values, indicating compaction of the backbone upon metal removal. For the donor atom distances, the peak of the distributions is also at about 0 Å. However, these distributions are broader and highly skewed towards positive values, with changes up to 4 Å being common. Several values larger than 10 Å are observed. Furthermore, we aimed to assess the average effect of metalation over the entire site, rather than on each distance individually, to understand whether the structural rearrangements are spread over all ligands. We did this by analyzing the per-site average Δ values. The Wilcoxon signed-rank test indicated significant differences between the backbone and donor atom rearrangements for 17 metals (Table 3, at $p < 10^{-3}$ level).

Fig. 4 shows the correlation between the distance changes observed for the Cα-Cα pairs and for the donor atom pairs. For clarity, here we averaged the changes over each entire site, so that any dot in the plot corresponds to a single MBS. Qualitatively, we can identify two different behaviors. When the rearrangement of the protein backbone is very large (of the order of 10 Å or more), there is an essentially linear correlation. This is presumably due to the fact that the overall protein structure changes greatly upon metalation of the site and both the backbone and the side chain are greatly displaced. On the other hand, smaller backbone rearrangements, which are most cases in our dataset, can correspond to a very different extent of side chain rearrangements, going from negligible up to 8–10 Å (Fig. 4, inset). Sites with small rearrangements for both the Cα and the donor atoms are pre-organized MBSs, where the coordination environment for the metal ion is structurally defined ahead of metal binding [32]. However, in the majority of cases, the structural rearrangements of the donor atoms were somewhat larger than the corresponding backbone rearrangements. A peculiar case is that of MBSs containing ligands that are consecutive in sequence. In these cases, (red dots in Fig. 4), the Cα-Cα distance is fixed, and structural rearrangements can occur only for the ligand side chains.

4. Discussion

We examined 3074 clusters of MBSs by evaluating the Cα-Cα and DA-DA (donor atom) distances for all metal ligands in both holo- and apo-protein structures. Pairings between these structures were taken from the clusters stored in the MetalPDB database. For the present analysis, we took into account only mononuclear sites (i.e. MBSs harboring a single metal ion) where all the ligands as well as the metal identity were conserved in all the members of that cluster.

For most metals there is a statistically significant difference between the distributions of the DA-DA distances in the holo- vs apo-sites, based on a Wilcoxon signed-rank test at $p < 10^{-5}$. These included all biologically relevant metal ions. For some metals (Table 2), also the Cα- Cα distances were significantly different upon change of metalation state. Instead, there were no metals for which a significant variation was observed only for the Cα- Cα distances but not for the donor atoms. This is reasonable because a backbone rearrangement almost inevitably causes the side chains to reposition as well. In a previous analysis based on 210 sites, it was observed, in line with our findings here, that rearrangements of the MBSs were relatively common (occurring in about 40% of the dataset) and that such rearrangements typically occurred at the level of the side chains of the metal ligands, even when the backbone conformation was preserved upon metalation [33].

We then looked at the average reorganization of sites, which is possibly more relevant in the perspective of prediction/identification of MBSs from apo-protein structures. This is because sites where the majority of the metal ligands, even if not all, are already structurally predisposed for metal binding should be identifiable with relative ease. Instead, sites where all the ligands rearrange upon metalation, and hence are associated with a larger mean variation of distances, are

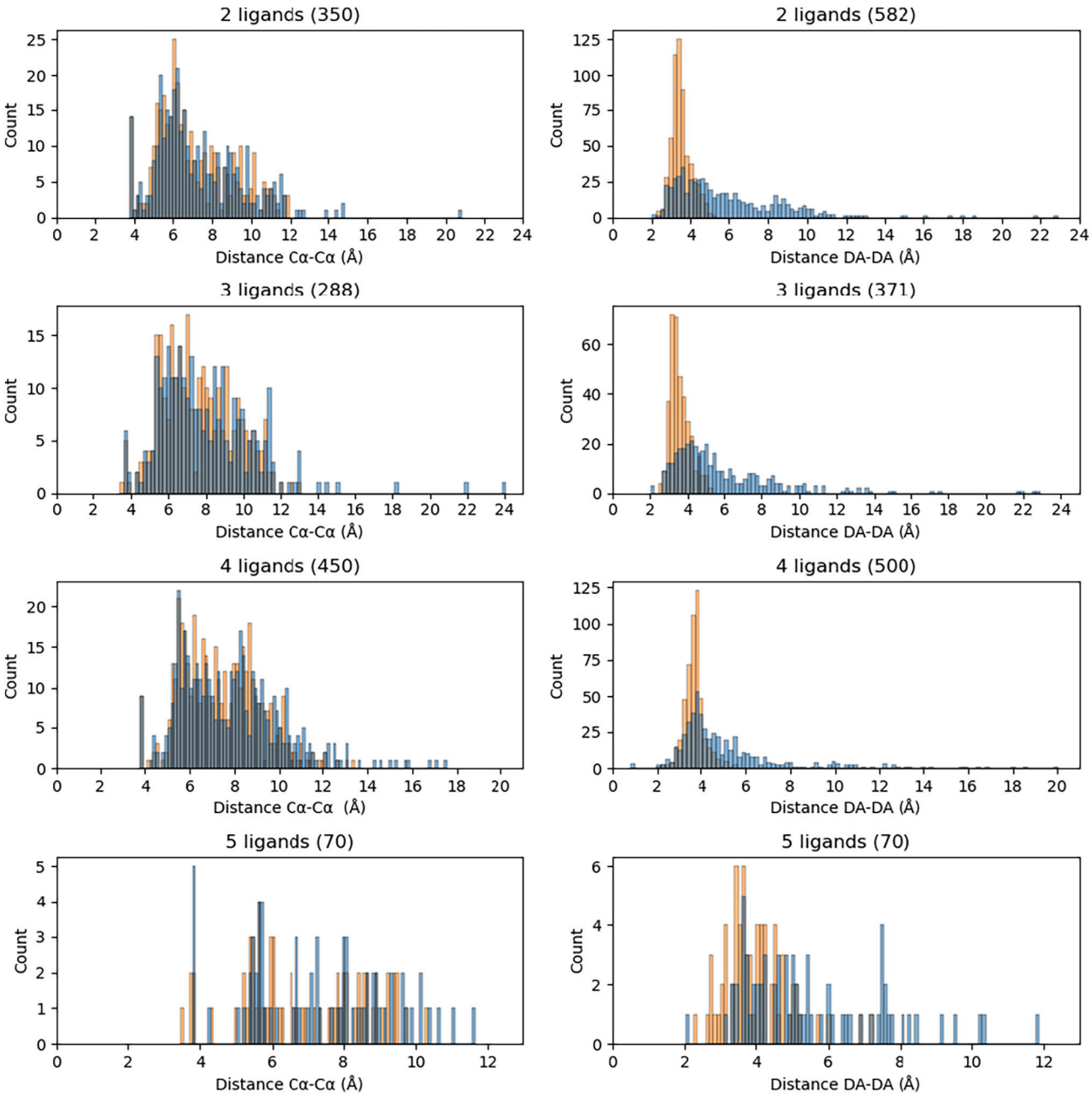

Fig. 1. Frequency counts of Cα-Cα (left) and donor atom (right) distances in zinc sites (orange: holo; blue: apo), separated by the number of endogenous metal ligands. The number of distances included in each panel is also shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

presumably harder to identify with e.g. template-based prediction methods. Our results indicate that the average displacement of donor atoms is larger than the average displacement of the backbone. In fact, because our statistics on donor atoms sometimes include backbone oxygen atoms, the conformational reorganization of the side chains of the metal ligands is presumably even larger than suggested by the data in Tables 2 and 3. For all metals the median value of the variations of absolute distance values among Cα atoms are below 0.2 Å, being practically zero for physiological metal ions. For the latter ions, three quarters of the sites have a backbone rearrangement smaller than 0.4 Å, except Fe. Note that we consider absolute distances in order not to worry whether the site contracts or expands upon metalation. Both behaviors should be similarly problematic from the site prediction perspective.

When looking at the corresponding data for donor atoms, we observed two different behaviors for physiological metal ions. The median ΔDA of transition metals goes from 1.2 to almost 2 Å (Table 3). These metals show preference for side chain coordination, thus metalation results in an appreciable conformational rearrangement of the donor atoms. Instead, the median of the distance variation for potassium and sodium is only about 0.2 Å. To explain the difference from the other metals, we investigated the nature of the donor atoms involved in the coordination of sodium and potassium. They are mainly coordinated by the main-chain oxygen atoms. 82% of the DA-DA distances for sodium sites involve at least one backbone oxygen, whereas the corresponding value for potassium is 84%. The donor atoms thus experience structural rearrangements whose extent is closely comparable to the backbone [34]. This can also justify the very small effect of the change of metallation state on the B-factors of sodium sites (Fig. 2).

Table 2
P-values for the comparison between the distance distributions in apo- vs holo-sites. The *p*-value obtained from the Wilcoxon signed-rank test indicates the likelihood that the compared distributions are the same. The table lists all metals for which at least one of the Cα-Cα or DA-DA distance distributions differed in the comparison at a *p*-value threshold of 10^{-3}. The values in bold highlight the comparisons with a p-value $<10^{-5}$.

Metal	p-value for the Cα-Cα distance distribution	p-value for the DA-DA distance distribution	N° of Cα-Cα distances	N° of DA-DA distances
Ca	**2.10E-19**	**3.25E-230**	1516	2021
Cd	1.48E-04	**8.48E-49**	182	344
Co	5.70E-02	**2.31E-13**	63	89
Cu	1.09E-01	**3.68E-21**	113	141
Fe	5.93E-04	**2.70E-14**	81	96
Hg	5.58E-01	8.95E-05	103	121
K	3.03E-02	**1.47E-43**	553	603
Mg	**5.22E-11**	**1.91E-98**	1096	1216
Mn	**4.46E-08**	**9.96E-27**	167	202
Na	**1.27E-16**	**4.55E-120**	1713	1828
Ni	2.53E-04	**3.33E-25**	133	164
Pb	1.20E-01	2.94E-04	17	28
Pr	1.29E-01	1.49E-05	9	26
Pt	1.37E-02	9.77E-04	10	11
Sm	2.11E-01	**9.09E-08**	16	38
Y	5.19E-01	**2.38E-07**	12	23
Zn	**3.30E-13**	**5.57E-173**	1173	1543

The median ΔDA of magnesium (0.38 Å) is like that of sodium and potassium and is quite different from that of calcium (1.03 Å), despite their chemical similarity. Both metal ions have a similar percentage of backbone oxygens acting as donor atoms (about 60%), and in general share a preference for having oxygen atoms in their first coordination spheres, also from Glx/Asx side chains. A major difference, as already noted in the literature, is that calcium typically involves a larger number of protein residues in its coordination sphere, whereas magnesium involves more water molecules or other exogenous ligands (such as ATP) [35]. However, these considerations do not provide a rationale for the larger extent of DA reorganization in calcium vs magnesium sites. It is possible that this is linked to structural factors underlying the selectivity for calcium over magnesium ions in calcium-binding proteins. Energetic considerations indeed suggest that flexible MBSs should favor calcium binding [36]. In line with this, we indeed observed that the B-factors of calcium sites featured somewhat higher values in the apo-form, indicating that metal binding reduces the flexibility of the site, at variance with what happens for magnesium where the B-factors of apo- and holo-sites are similar (and close to the value for calcium holo-sites). We can speculate that the structural behavior of the calcium sites is instrumental for their functional role in signaling processes [37].

We inspected a selection of structures representing typical patterns of structural changes in our dataset (Figs. 5-7). Cases associated to negative displacements of the Cα atoms upon metal removal (i.e. negative values along the x-axis of Fig. 4) feature either rearrangements of at least one of the fragments harboring a metal ligand, leading the backbone in the apo-structure to occupy the position of the metal, or the rigid shift of one structural element closer to the others. In the latter case, it is likely that the distance among the side chains is also shorter in the apo- vs the holo-structure. An example is the formation of disulfide bridges in the absence of the zinc ion seen in PDB entry 5ax2 (Fig. 5B)

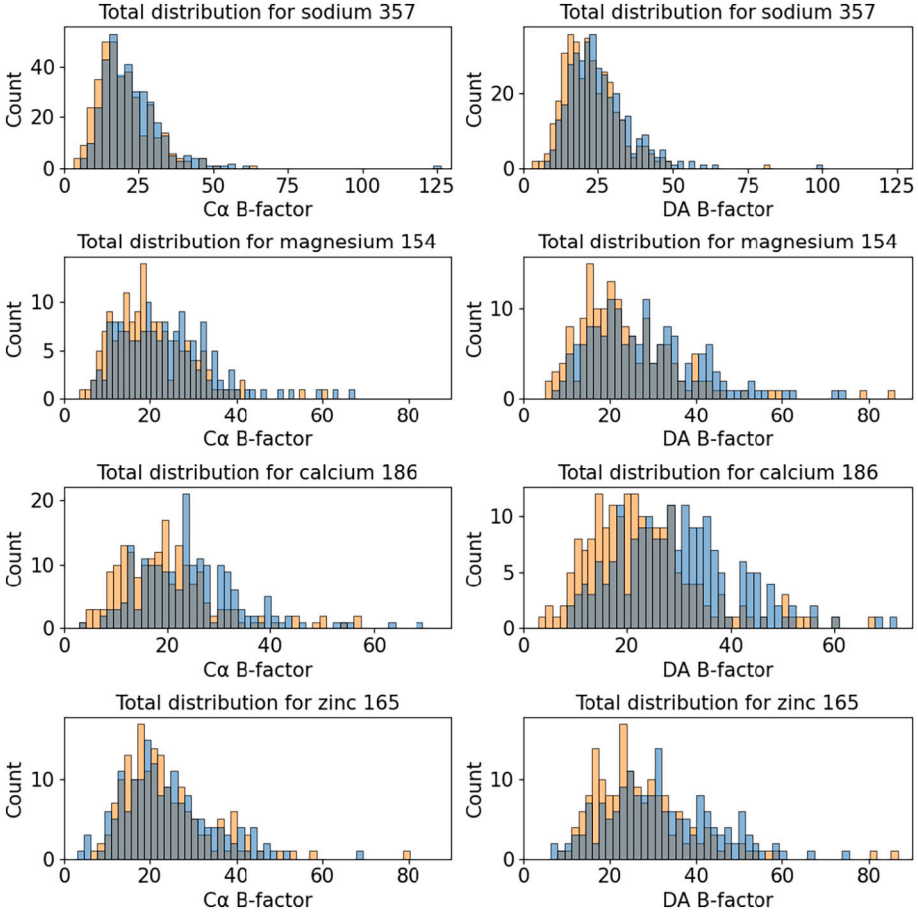

Fig. 2. Frequency count of B-factors for Cα (left) and donor atoms (right). The values were extracted for each atom and averaged over all sites of a cluster. Each panel shows the holo (orange) and apo (blue) distribution for the four metals having >100 clusters with both apo- and holo-sites in the 1.5–2.0 resolution range. In the panel of each metal is reported the count. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

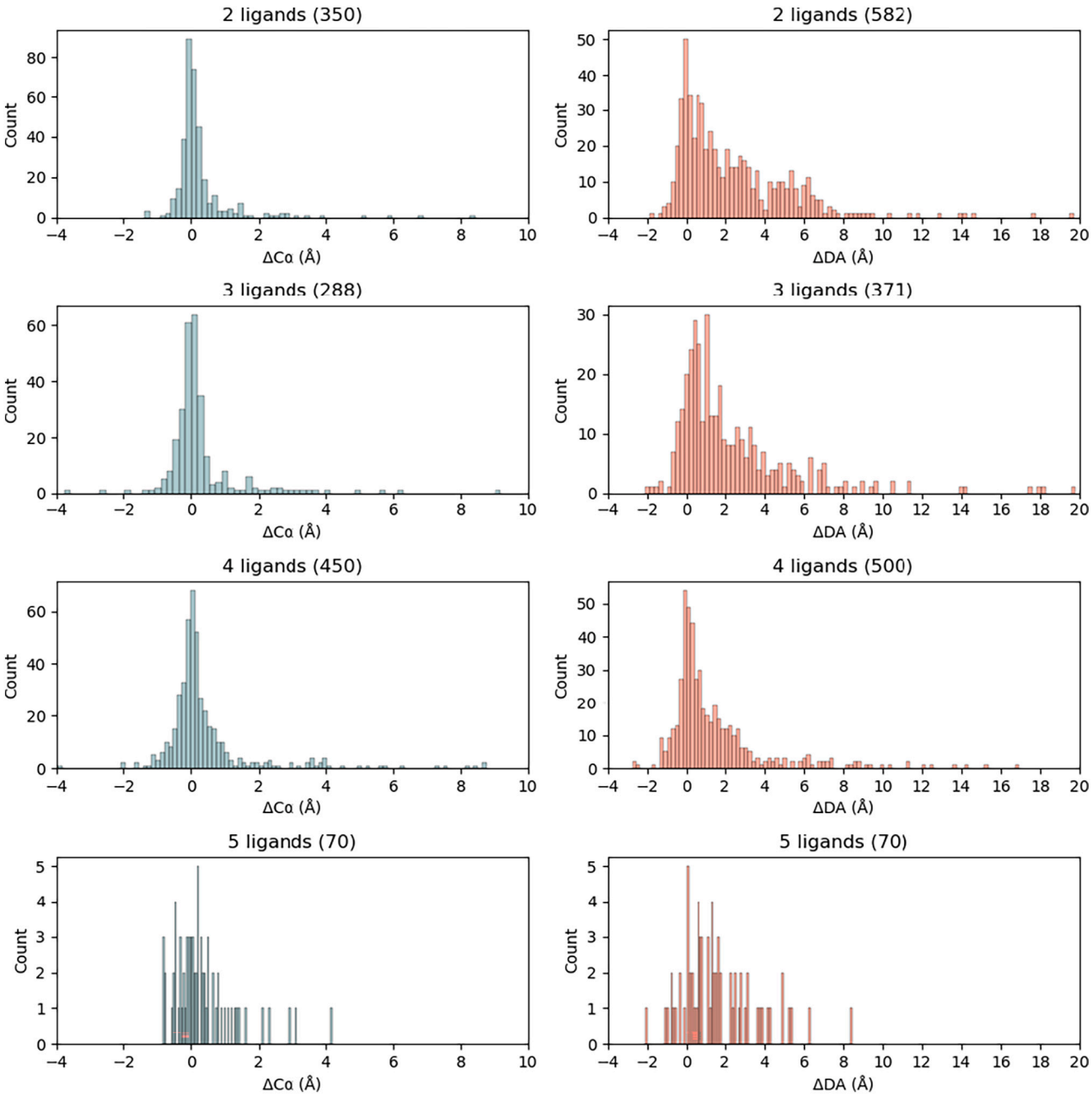

Fig. 3. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in zinc sites, separated by number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances.

[38]. In a few cases the displacement of the DAs is larger than the Cα atoms. For example, in the HypBA1 hydrolase two of the four ligands of the MBS are displaced in the apo-structure (Fig. 5A), causing a partial unwinding of a helix [39].

Instead, when the ΔCα values are close to zero and the ΔDA values are of the order of a few Å, it is likely that the local backbone structure, especially when having a high secondary structure content, is maintained and only the rotameric state of the ligand side chains is perturbed (Fig. 6A). Alternatively, sites containing ligands that are consecutive along the sequence or separated by just one residue, tend to have small or null ΔCα values because of the constraints imposed by the covalent chemical structure of the polypeptide chain, even when the local 3D structure undergoes relevant changes upon change of metallation state (Fig. 6B).

Only in a handful of cases we observed large-scale rearrangements of the whole protein backbone (Fig. 7). These correspond to cases where the MBS is located at a domain-domain interface, so that metal removal causes the two structural domains to reorient with respect to one another. This is not a general property of interfacial sites, as there are known cases where the interface is stable even in the absence of metal [40].

5. Concluding remarks

This work provides an extensive overview of the structural rearrangements taking place in clusters of mononuclear metal-binding sites. To assemble our dataset we took all metalloprotein clusters already stored in MetalPDB and filtered them to ensure that the apo−/holo-protein pairs analyzed here maintained all the residues in the metal-binding pattern. In this way, we could obtain information also from

Table 3
P-values computed for averaged sites with the Wilcoxon signed-rank test. The median data are computed over the absolute Δ values to reflect the overall behavior of the site upon metalation. The table lists all metals for which at least one of the Cα-Cα or DA-DA distance distributions differed in the comparison at a *p*-value threshold of 10^{-3}. The most significant values ($p < 10^{-5}$) are highlighted in bold.

Metal	p-value	Median |ΔCα| (Å)	Median |ΔDA| (Å)
Ca	**4.50E-66**	**0.02**	**1.03**
Cd	**7.38E-19**	**0.04**	**1.62**
Co	1.08E-04	0.02	1.68
Cu	**1.42E-08**	**0.04**	**1.54**
Fe	**2.81E-07**	**0.09**	**1.26**
Hg	1.87E-03	0.00	0.19
K	**5.87E-15**	**0.01**	**0.22**
Mg	**4.92E-51**	**0.02**	**0.38**
Mn	**2.33E-10**	**0.07**	**1.22**
Na	**2.05E-52**	**0.02**	**0.18**
Ni	**1.67E-11**	**0.04**	**2.54**
Pb	6.25E-02	0.15	3.01
Pr	1.56E-02	0.05	1.91
Pt	3.91E-03	0.16	2.05
Sm	3.66E-04	0.03	2.97
Y	7.81E-03	0.12	3.10
Zn	**1.35E-71**	**0.04**	**1.30**

apo−/holo-protein pairs of homologous proteins from different organisms.

The distributions of Cα and DA distances for the metal ligands were statistically different for most metals, and in particular for all the physiological metals. Nevertheless, 75% of the MBSs harboring physiological metals had Cα distance variations within 0.2 Å, which means that the backbone conformation was typically maintained upon (de) metalation. On the other hand, there were significant changes in the relative position of DA for all metals except sodium, potassium, magnesium. For the two alkaline metals, the reason can be attributed to their first coordination sphere involving mainly backbone oxygen atoms (in addition to exogenous ligands). For magnesium, this is not true and we hypothesize that the small DA rearrangements observed here are due to the surface location of magnesium-binding sites and/or to the comparatively small binding energy of the metal. In terms of template-based prediction of MBSs, our findings suggest that backbone-driven methods might perform best.

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CRediT authorship contribution statement

Milana Bazayeva: Data curation, Formal analysis, Writing – original draft. **Vincenzo Laveglia:** Data curation, Methodology. **Claudia Andreini:** Conceptualization, Writing – review & editing. **Antonio Rosato:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data are summarized in the Supplementary Table S1 and can be downloaded from the MetalPDB database (https://metalpdb.cerm.unifi.it/)

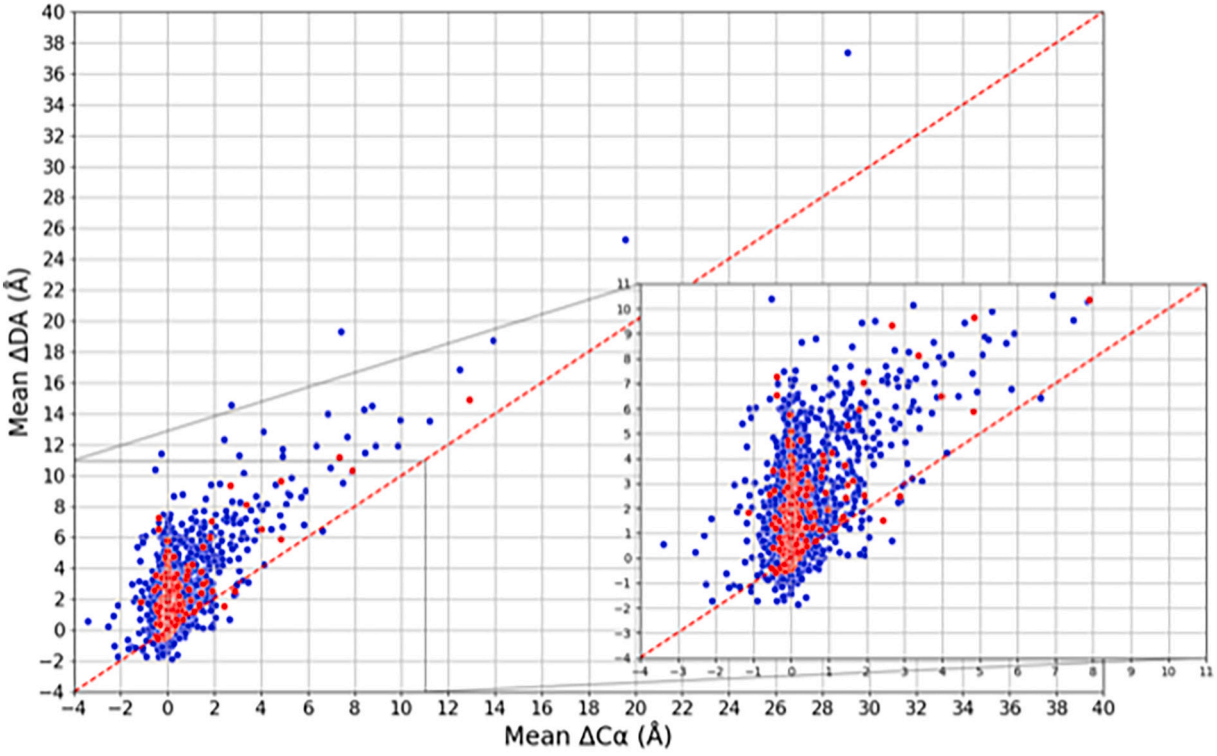

Fig. 4. Mean Δ values over entire MBSs. The red line is y = x and serves only to guide the eye. Red dots correspond to sites having at least two metal ligands that are consecutive in sequence, hence featuring at least one fixed Cα-Cα distance. All changes are measured as apo- minus the corresponding holo- distances. All the metals of Table 3 are included in the plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

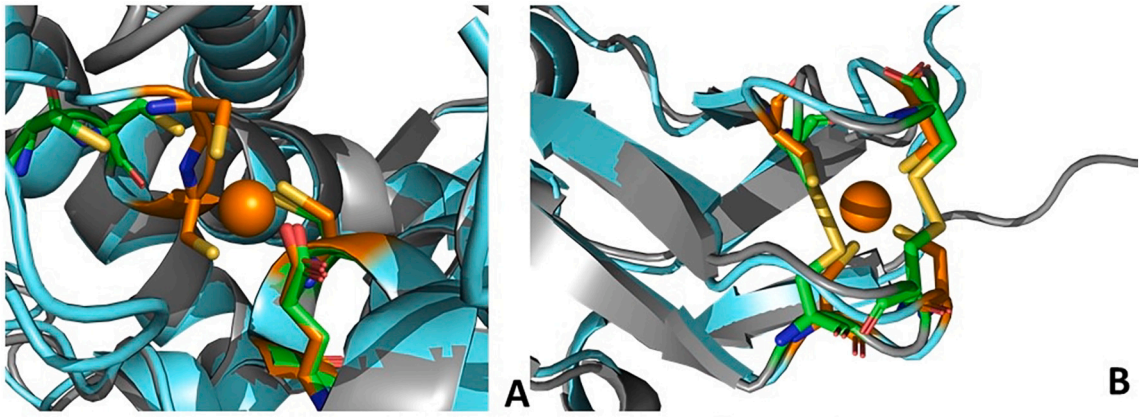

Fig. 5. Representation of selected patterns of structural rearrangements. A. Apo: 3wrf and Holo: 3wkx (2.42, 1.52). *B. Apo*: 5ax2 and Holo: 1wge (−0.24, −0.32). The holo-structure (cyan, metal ligands in orange) is superimposed to the corresponding apo (gray, metal ligands in green). In parenthesis we reported for each panel the coordinates of the corresponding point in Fig. 4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

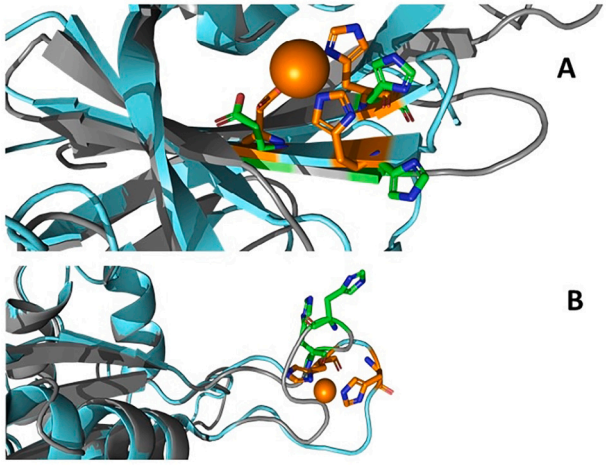

Fig. 6. Examples of large-scale structural rearrangements. A. Apo: 1lj6 and Holo: 3n9b (0.292, 7.07). *B. Apo*: 3e1u and Holo: 3ir2 (0.40, 5.69) The colour code is as in Fig. 4.

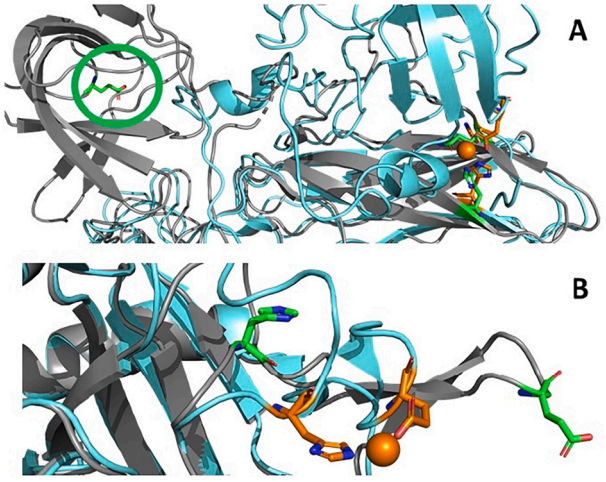

Fig. 7. Examples of large-scale structural rearrangements. A. Apo: 5i5k and Holo: 3cu7 (29.1, 37.4). *B. Apo*: 2jig and Holo: 3gze (13.9, 18.72) The colour code is as in Fig. 4.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2022.112025.

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289 cles_1755 1e1a_2 2iao_1 3hlh_3 3hlh_1 2ias_2 3hli_4 3byc_2 2iaw_2
290 cles_2356 3iov_11
291 cles_2592 3de1_1 3dvq_1 3dvr_1 3de2_1
292 cles_3524 4yis_3
293 cles_2592 3p5b_1 3p5c_4
294 cles_1650 3q2j_2 3q2j_1
295 cles_2268 2p5r_2
296 cles_2014 3pz0_1
297 cles_2149 3cv1_2
298 cles_2616 3s55_4 3s55_1
299 cles_1948 4ex8_1
300 cles_1900 1nwk_4
301 cles_3908 4uyq_3
302 cles_1803 1jb0_21 3pcq_83 4fe1_50
303 cles_2278 4yx6_1 4yx6_2
304 cles_2577 3q7q_2
305 cles_1870 3njn_1
306 cles_2264 1j0n_1 1x1j_1
307 cles_2563 2htv_1 2htv_2
308 cles_1804 3fcs_3 3fcs_1
309 cles_2614 4gkb_2 4gkb_1 4gkb_3 4ijk_1
310 cles_2592 3vyv_2 1ndq_1 1st3_1 1tm3_1 3wiv_7 2z2x_4 1c9j_1 1tm7
311 cles_2212 2wvx_3 2wvx_2 2wvx_4 2wvx_1
312 cles_3465 5tj6_5
313 cles_1686 1uz0_2 1uy0_2 1uyz_2 1uyz_4 1uyx_4 1uy0_5 1uyy_3 1uyy
314 cles_2150 1rrq_2 1vrl_2 3fsq_2 1rrs_2 3fsp_2 5dpk_3 3g0q_2
315 cles_2565 2wm4_2
316 cles_1825 2qub_10 2zvd_5 2zvd_8 2qub_18 2qub_29 2qub_4 3a6z_1
317 cles_1621 3c3y_1
318 cles_1936 1mu5_2
319 cles_3434 1y1a_1 1y1a_4
320 cles_1681 2w1w_1 2w1w_2
321 cles_1616 3lyb_2
322 cles_2512 2y5p_1
323 cles_3879 4ktp_2
324 cles_3435 2r2i_2
325 cles_1690 1uww_1
326 cles_3496 3wmm_6
327 cles_1882 2e1q_19 2e1q_16 2e1q_15
328 cles_2563 3ti4_1 3beq_5 3ti6_3 3ti3_1 3ti3_3 4b7r_1 4b7r_5 3b7e_5

329 cles_3887(4q4x_5 4q4w_3 4q4y_4
330 cles_3783(4zmz_1
331 cles_2595(1bjr_2
332 cles_2087(3jxs_2 5dpn_1 2y6h_2 2y6g_1 2y64_1 4bj0_1 2y6l_2 3jxs_4
333 cles_2043(5kn0_1 5kn1_28 5kn0_9 3v1w_4 5crg_46 5crg_26 5kn1_29
334 cles_2454(2pqy_1 2z70_1 2pqx_1
335 cles_2072(2d00_3
336 cles_2126(3axd_6
337 cles_2549(1lhv_2 1lhu_1 1f5f_2 1lhw_1 1lhn_1 1d2s_1 1lho_1 1kdm_
338 cles_2371(2es2_1
339 cles_2561(1a4v_2
340 cles_4129(5ue1_2
341 cles_2212(3goe_1
342 cles_2214(4rbm_1
343 cles_2196(4wff_4 4wfg_4 4i9w_2 4wfh_5 4wfe_4
344 cles_2082(1g9j_2
345 cles_2553(4a0p_2
346 cles_4077(4ghg_1 2ig9_4 4z6m_5 3ojn_2 4ghe_5 3ecj_3 4ghh_5 4z6v_
347 cles_2385(1snn_1 1pvy_3
348 cles_3837(4wk1_1
349 cles_2592(1r0r_3
350 cles_1689(3h6h_1 3h6h_2
351 cles_2516(3qhq_1 3toc_2 3v7f_2
352 cles_3775(5c6c_9
353 cles_2670(4jbe_2
354 cles_2448(3dss_1
355 cles_2448(4gtt_1 3dsu_1 3pz1_1 3hxc_1 3dsx_1 3pz2_1 3c72_1 3dsv_
356 cles_1722(2bfn_1
357 cles_2592(1yu6_2 1bh6_1 1c3l_2 1cse_2 1scn_2 1scd_1 1scb_1 2wuv_
358 cles_2015(2por_3
359 cles_1798(2e85_2
360 cles_2215(2whk_3
361 cles_1773(2np0_1
362 cles_2288(4n2c_4
363 cles_2044(3uom_39 3uom_51 5crg_55 3uom_26 3uom_48 3uom_45
364 cles_3470(5er7_2
365 cles_2600(1rfn_1
366 cles_2309(4haq_3
367 cles_1738(4tnk_57 4tnj_73 4ixq_55 3prr_21 4tni_70 4ixr_68 4ixr_7 4i
368 cles_2685(3brx_3
369 cles_2563(4mww_1 4mwl_1 1nnb_1 2qwi_1 5jyy_1 4mx0_1 4mwy_1
370 cles_3634(4bwe_1 4bwe_6 4bwe_7 4bwe_8 4ywt_2 4ywt_1 4ywt_9 4
371 cles_2278(2z6i_6 2z6i_4
372 cles_2575(4dlz_1 3rs4_4 1lf0_1 3rso_1 4dlr_3 5b30_2 3k9n_1 3rsl_4 5
373 cles_4001(5cpo_1 5cpl_1
374 cles_2650(2jhm_1 2jhh_1 2jhi_1 2d39_1 2d39_2 2jhl_1 2jhh_2 2wnp_
375 cles_3530(5fk0_2

376 cles_1681(1uy0_4 1uyz_1 1uyy_4 1uyx_1 1uyy_1 1uyx_2 1uyz_5 1uy0
377 cles_2643(1dhk_1
378 cles_2155(1c8d_1
379 cles_2088(1te2_1
380 cles_2372(3gwz_3
381 cles_1660(3gv5_4
382 cles_2270(6std_2 7std_4 6std_3 5std_3 3std_1 3std_2
383 cles_2127(2vn7_1
384 cles_1899(1j6z_6
385 cles_3696(4n6f_5
386 cles_2516(3qhq_4
387 cles_1873(4i9x_3
388 cles_2387(2ivz_5 2ivz_4 2ivz_6
389 cles_2446(1e8t_1
390 cles_2525(1nub_5 1nub_1
391 cles_2587(4dy7_3
392 cles_2436(2ozn_2
393 cles_1791(1svy_2
394 cles_2616(4h15_3 4h15_8
395 cles_3433(2kbm_1 2kbm_3
396 cles_1672(2uvp_2 2uvp_3
397 cles_2525(1nub_6 1nub_3 1bmo_1 1bmo_3
398 cles_1891(3c63_6 3c62_12
399 cles_2022(4m93_1
400 cles_2506(2w27_2 2w27_1
401 cles_3982(5iju_1
402 cles_2563(1b9t_2 1ivb_1 1inf_2 1b9v_2 1b9s_1
403 cles_1720(1g42_3 1iz7_3 1iz8_1 2bfn_2
404 cles_1783(2obm_1 2obl_1
405 cles_3687(3gri_5
406 cles_3909(5tgf_2
407 cles_3650(4n3o_1
408 cles_3912(4n95_2
409 cles_1755(2dso_12 2dso_3 2dg1_1 2dg1_6 2dso_4 2dg1_8 2dso_5 2d
410 cles_3415(3hx5_10 3hx7_7 3hx5_9 3hx5_6 3hx5_12 3hx7_11 3hx5_11
411 cles_2506(4fou_2
412 cles_1675(3n1r_2
413 cles_2685(3brx_1
414 cles_2654(1qi0_2 1qhz_2 1qi2_1 1h5v_4 1e5j_2
415 cles_2684(4evh_1
416 cles_1910(1f4n_3
417 cles_1692(3om7_1 3om6_3 1pt2_1 3om4_4 3om5_1 3om5_4 3om6_
418 cles_3899(5i0f_5
419 cles_3541(5kzm_1
420 cles_1812(1xzo_3 1xzo_11
421 cles_2563(3san_1 2hty_5 4mju_1 2hty_4 2hty_7 4qn5_1 5hun_1 2hty
422 cles_2598(2xc2_1

423 cles_3844{ 4pqi_1
424 cles_3865{ 5duv_1 5duv_4 4xzp_1 5duv_2 5duv_3
425 cles_3541{ 4y28_85
426 cles_1811{ 1w0p_1 1w0o_3
427 cles_2442{ 1qic_11
428 cles_3634{ 4ywt_3 4bwe_4 4ywt_6 4bwe_5 4bwe_9 4ywt_7 4bwe_2 4
429 cles_1923{ 2kid_1
430 cles_2351{ 1kwh_1 1y3q_1
431 cles_2657{ 2oxe_2 2oxe_1 1lpa_1 1eth_2 1gpl_1 2pvs_1 1hpl_1 1rp1_
432 cles_2485{ 1w3b_1
433 cles_2232{ 2r1b_1 2r1b_2
434 cles_2155{ 5etk_2 4m5l_1 5ett_3 4m5k_1 5etn_1 5ett_2 5etr_3 4m5i_
435 cles_3433{ 2f8p_3 2f8p_2 4mry_1 2f8p_1 1f4o_1 4mry_2 4mry_3
436 cles_4115{ 5bn2_1
437 cles_1856{ 5f2i_10 5f2l_6 5f4s_3 5f2i_7 5f2g_2 5f2m_7 3mhg_4
438 cles_4035{ 5d9o_3
439 cles_2332{ 5m1p_1 5m1p_2
440 cles_3536{ 4by6_2 4by6_1
441 cles_2447{ 5fws_1 5fwt_1
442 cles_2262{ 5fre_8 5fre_7 5fre_5 2v73_2
443 cles_1928{ 1nud_6 1nud_1
444 cles_2054{ 4kc8_2 4kc8_1 4kc8_3
445 cles_3433{ 2n8y_1
446 cles_2611{ 2b50_2 2b50_1
447 cles_3810{ 4pib_8
448 cles_2074{ 3iqe_3 3iqz_3 3iqf_2
449 cles_1778{ 3eki_2
450 cles_1984{ 4aal_2 2c1u_5 3o5c_6 1zzh_17 2c1u_6 1zzh_15 1iqc_10 3o
451 cles_1958{ 3k5s_1
452 cles_4126{ 4hro_3 4hro_5
453 cles_1651{ 3kpt_1
454 cles_2636{ 3bcd_1
455 cles_2638{ 1v3w_3 1v67_1
456 cles_1638{ 3c5i_10 3mes_3 3c5i_9 1nw1_1 1nw1_2 3c5i_6 3c5i_2 3m
457 cles_2075{ 3iqf_4
458 cles_2545{ 5dcg_1 3kmo_2 5jcw_6 3km6_2 3hkr_4 3csh_1 2a2s_1 3n9
459 cles_1826{ 3iuc_2 3ay9_1
460 cles_1867{ 2b1o_3
461 cles_2270{ 5std_2 5std_1
462 cles_1748{ 3fia_1
463 cles_3657{ 5e5o_2
464 cles_3781{ 4bxo_3
465 cles_2652{ 4h2g_2 4h2i_2 4h1y_2 4h2f_2 4h2b_2
466 cles_2684{ 3chk_4
467 cles_3671{ 5j04_4 5j04_3
468 cles_2668{ 3u4j_1
469 cles_1985{ 4ngr_2 4p4d_2 3bi0_1 2c6c_2 2jbj_2 4oc0_2 5d29_1 4p45_

470 cles_1672(3lor_1
471 cles_2578- 2wkp_1
472 cles_2420: 2l51_2 2l51_4
473 cles_2635] 4j3u_3 4j3u_2 4cvw_1 2y5e_2 4aio_2 2y4s_2 4cvw_3
474 cles_2226] 1c1y_2 3kuc_2 1gua_1
475 cles_1739] 1h80_10 1ktw_5 1h80_7 1ktw_9
476 cles_2620[2wbf_1
477 cles_3697(4n6f_4
478 cles_3440: 1gn1_2
479 cles_2205[1s0f_2 3v0b_1 2np0_3 1s0e_3 3v0a_1 1s0b_2 1s0d_1 1s0c
480 cles_3743[4bxo_4
481 cles_2370[2es2_2
482 cles_3966] 5jdj_1 5jdj_6 5jdj_4
483 cles_4097[4wp9_2
484 cles_2614] 3s55_2 3s55_6
485 cles_2026(4i9x_1
486 cles_2658(3jtx_1
487 cles_2042[3trq_6 3trp_3
488 cles_1826[1s3x_2
489 cles_2273: 2xgp_2
490 cles_1815[3hdb_6
491 cles_3840] 1gxr_1
492 cles_2554[2e3x_6
493 cles_2561[3b0k_2 2fyd_4 1f6s_5 1nqi_1 2fyd_1 1el1_2 1o23_3 1hfz_2
494 cles_2447[3poe_2
495 cles_1985[3s9m_2 1de4_3 3s9n_2 3s9l_1 1de4_1 3s9n_4 3s9m_1 1de
496 cles_1804(4ief_14 4ief_13 4ief_1 4ief_19
497 cles_2469- 1g5c_7
498 cles_1689(5c5c_2
499 cles_1953] 4zxl_14 2ydq_15 2ydr_8 2yds_11
500 cles_1953[2ydq_4 2yds_3 4zxl_8 2ydr_5
501 cles_2378[1mwt_8
502 cles_2307[2fu4_5
503 cles_4051] 3wzo_2 3wzo_6 3wzo_4
504 cles_2205: 3h1u_4 3h1u_5 2fcs_3 2fcq_7 2fcs_2 2jf5_3 2fcq_1 2jf5_2
505 cles_1801- 3po0_2
506 cles_3696: 4kb4_1
507 cles_2426] 3her_2 3hes_2 1i4m_1 3heq_1 3heq_2 3her_1 3hjx_1
508 cles_2045] 2zgg_1
509 cles_3468] 4mvs_4 4mvs_2 4mvs_5 4mvs_1
510 cles_1976(1ihf_1
511 cles_4074[4v0k_4
512 cles_1728- 1gyn_2
513 cles_2315[1zww_8 1zww_4
514 cles_2091[4o84_1 3u54_5 4o82_5 4o81_2 3u54_10 4o81_7 4o82_8 4
515 cles_1794] 1jed_15 1g8f_4 1g8h_28 1jee_19 1jee_12 1g8g_31 1jec_12
516 cles_1692(3nqi_19 3nqi_9

517 cles_2603{ 1gl0_2 1gl1_3 1gl1_1 1gl1_5
518 cles_2265: 2eik_8
519 cles_3461: 4v0k_7
520 cles_3777: 4o83_1 4o83_15
521 cles_1791: 3umk_3 3umi_8
522 cles_2080: 4b7b_10
523 cles_1647- 1ii0_14 1ii9_5 1f48_9 1ihu_6
524 cles_3766- 3wtn_2 3wtn_48 3wtn_40
525 cles_1881: 4e57_28
526 cles_1954(2ydr_14 2ydq_11 2yds_10
527 cles_1807: 2r1f_5
528 cles_1826: 4kc6_2
529 cles_2473: 1dpe_5
530 cles_2300: 4h3o_5
531 cles_2347: 4gsx_4 4gt0_1
532 cles_3419: 4evd_5 4evc_7
533 cles_3738{ 4jc6_23 4jc6_24 4jc6_10 4jc6_25 4jc6_45 4jc6_4 4jc6_27 4
534 cles_1798: 1cfz_1 1cfz_2 1cfz_3 1cfz_6 1cfz_4 1cfz_5
535 cles_2392: 1m1k_16 1yij_75 1vqk_109 1vq5_102 1jj2_101 1q7y_146 3
536 cles_2455: 4az3_2
537 cles_2142: 2x05_18
538 cles_4027: 4oqp_4
539 cles_2243: 1lrn_2 1lrq_2 1lrn_1 1lro_1 1lro_2 1lrq_1
540 cles_2098: 2xgl_9 2xgl_4
541 cles_2087: 2w5f_1 2w5f_10
542 cles_3702(5h4h_1
543 cles_3887: 4zty_2
544 cles_2358: 2wxu_6
545 cles_2227: 1feu_14 1feu_22
546 cles_1906: 3m31_1
547 cles_3773: 4q9m_14
548 cles_1791: 3umh_9 3umi_2 3umk_1
549 cles_3644(5ax2_3
550 cles_2357: 2wxt_5 2wxu_4
551 cles_2148: 2x05_9
552 cles_1780- 4fvf_8 4fvf_3
553 cles_2268- 2p5q_6 2p5q_10
554 cles_1818: 3cu7_3 3kls_9
555 cles_2557: 1jv4_1
556 cles_1764- 2yc3_4 2yc5_5
557 cles_1961: 1z18_2
558 cles_1812(1xzo_8
559 cles_1681{ 3c99_1
560 cles_2243: 1rzm_3
561 cles_2655: 1g0c_7
562 cles_2557: 1gm6_1
563 cles_2260{ 1kui_8 1kuf_3 1kug_6 1kuk_2

564 cles_2679(1hk7_1
565 cles_2479: 1hsl_2
566 cles_3856(4yiv_5
567 cles_2683(1wvr_6
568 cles_2378: 1mwr_4
569 cles_3652(5an6_5
570 cles_1952: 4zxl_9 2ydq_1 2ydr_1 2yds_18
571 cles_2099(2bjd_4
572 cles_2099: 2bjd_6
573 cles_2090(2x05_16
574 cles_2473(1dpe_3
575 cles_2568(3ggf_1 3ggf_2
576 cles_1790(3umh_4 3umi_4
577 cles_2430: 1eu1_1
578 cles_2678(1hk7_3
579 cles_3637: 5cax_5 5cax_6 5cax_7 5cax_8
580 cles_2084: 4bxn_11
581 cles_2267: 2p5q_25 2p5q_17 2p5q_13
582 cles_1657(1vcf_1
583 cles_1796(1rtx_4 2hz3_2 2hz1_1 2hz2_4
584 cles_2386(2igi_6 2igi_11
585 cles_2110(1g8g_27 1jec_13 1jee_20 1g8f_2 1g8g_7 1jed_14 1g8h_27
586 cles_2321: 1n2z_17 1n2z_3
587 cles_1640: 2xdv_7
588 cles_2596(1xwb_3
589 cles_1644(4fmk_2
590 cles_2062(3r7c_1
591 cles_2661(2x7k_2
592 cles_2405(4avv_22 4avv_11 4avv_10 4avv_19
593 cles_3566: 4hmp_9 4hmp_22
594 cles_2249: 3kxd_2
595 cles_2034(1pw3_4
596 cles_2609(3d4c_3
597 cles_1981: 1m05_1 1m05_2
598 cles_1666(1oo2_2
599 cles_2560: 4lyc_9
600 cles_2311: 3cel_3
601 cles_3938: 5ac3_2
602 cles_2257: 1kui_6 1kuk_10 1kug_9 1kuf_8
603 cles_1928: 3liz_1
604 cles_1765: 2ycm_2
605 cles_2359(1ca1_4
606 cles_2090: 2x09_3 2vzs_2 2vzt_1 2vzo_9 2x05_6 2vzu_6
607 cles_2661: 2x7k_3
608 cles_3558(4qi4_9
609 cles_1961(1z16_1
610 cles_2121: 4jc6_36 1z98_1 4jc6_30 4jc6_29 4jc6_11 4jc6_33 1z98_2 3

611 cles_2637(3fqw_4 3fqt_7 3fqx_4 3fqr_5 3fqu_6 3fqn_3
612 cles_2199{ 1qjw_4 1qjw_2
613 cles_3972(5jpd_3
614 cles_2092⁴ 4o82_6 4o83_9 4o81_9
615 cles_1963: 3c7m_4
616 cles_1951: 2qp9_1
617 cles_2534: 1c6r_4
618 cles_2597⁴ 3kd0_1
619 cles_2561: 4lyc_2
620 cles_2083{ 4as7_6
621 cles_2654(1g0c_8
622 cles_2028: 1orq_7
623 cles_1779{ 4fvf_1
624 cles_2083: 3g6e_163 3cc7_192 1vq7_97 3i56_30 1vq6_48 1vqo_71 3c
625 cles_1896(2x28_4
626 cles_2268{ 2p5q_21 2p5q_15 2p5q_26 2p5q_18
627 cles_1897: 2x28_1
628 cles_2064⁴ 3cu7_9 3km9_2 3km9_3 3cu7_8
629 cles_2550: 1uxj_5
630 cles_3821(5bxa_1 5bx9_4
631 cles_2084(4b7b_12
632 cles_1879: 1rj4_5 1rj4_8 1rj4_6 1rj4_7
633 cles_1880{ 4e57_30 4e57_11
634 cles_2653: 3mmu_37 3mmu_28 3mmu_47 3mmu_43 3mmu_10 3mm
635 cles_1822(2d2x_3
636 cles_1935: 1h41_3 1h41_10
637 cles_2256⁴ 2ero_7 2erp_4
638 cles_3856: 4yiv_3
639 cles_2400{ 2amx_1
640 cles_2319{ 2eff_1
641 cles_3775{ 4ft8_1 4ft8_2
642 cles_1620⁴ 3p0f_1
643 cles_1933{ 1ukw_1
644 cles_3491: 4xyj_5
645 cles_2497: 2gz5_3
646 cles_2267: 1ugs_1
647 cles_2483: 4ekd_3
648 cles_2252{ 3qq7_1
649 cles_1670{ 4jka_4 4jk9_1 4jka_6 4jk9_6
650 cles_1620: 3p0f_2
651 cles_1717{ 2xvz_1 2xvy_3
652 cles_2035{ 3ut1_4
653 cles_1756: 1jn1_2 1jn1_1 1jn1_4
654 cles_2186: 1u8r_14 1u8r_18 1c0w_6 1c0w_3 1fx7_13 1c0w_7 1c0w_4
655 cles_3559⁴ 5e8g_3 5e8g_1 5e8g_4 5e8g_2
656 cles_2175: 1w8q_12 1w8q_17 1w8q_2 1w8q_8
657 cles_1823(2d2x_1

658 cles_3605 4y5t_2 4y5s_3 4zon_1
659 cles_2172 2wke_5 2wke_1 1w8q_3 1w8q_11 2wke_11 1w8q_14 2wk
660 cles_3856 4yiv_2
661 cles_3620 3vxm_1
662 cles_2483 4ekd_1
663 cles_2250 4ila_26 4ila_18
664 cles_4125 5cgq_2
665 cles_2413 3atf_1
666 cles_2284 3vy9_3
667 cles_1673 2ov4_1
668 cles_4125 5cgq_3
669 cles_2480 3c35_7 3c35_4
670 cles_2632 3fsv_1
671 cles_1653 1s1q_2 1s1q_4
672 cles_1898 2wq8_1 2eid_1 2eie_1 1t2x_2 2eib_2 1gof_2 2vz3_2 2eic_
673 cles_2094 4bdv_1 3j2q_2 3cdz_2
674 cles_4039 4r6d_1
675 cles_1873 1ui7_1 1ui7_2
676 cles_2581 1aqp_1
677 cles_2531 3n7d_2 3n7d_1 3n7e_1 3n7e_2
678 cles_2632 2azu_2 2idf_3 1jvo_12 2azu_1 1azn_3 2azu_3 1jvo_11 1jvo
679 cles_1663 1opm_1 3phm_2 3mig_2 3mib_3 3mih_3 3mic_1 3mie_2 3
680 cles_1953 2c9p_1
681 cles_2163 2rnb_1
682 cles_2163 1u96_1
683 cles_1983 3ciq_3 3ciq_12 3mzt_2 3ciq_2 3mzt_3 3ciq_5 3ciq_1 3mzt_
684 cles_4095 4tm7_7
685 cles_2531 3dso_1 3n7d_3
686 cles_2122 2yxw_6
687 cles_2545 3b1j_1
688 cles_2094 3x1b_3 2q9o_4 2ih9_3 3pps_6 2yar_2 3pps_7 3ta4_10 1zp
689 cles_2398 3sb8_1
690 cles_1872 2c11_2 2c11_3 2c11_19 2c11_15
691 cles_3789 5ffc_2
692 cles_1669 4zel_1
693 cles_1725 2zwd_1 2zwf_2 2ahl_1 2zwg_1 2ahk_1 1wx2_2
694 cles_3745 4hu7_1
695 cles_1952 2c9q_2
696 cles_2124 3nt0_6
697 cles_2356 3kss_1 4dnr_1 3t56_1 3k0i_2
698 cles_2286 3u52_2 3u52_5
699 cles_2531 2lel_1
700 cles_1874 2c11_34 2c11_4 2c11_28 2c11_16
701 cles_1725 2zmz_2 2zwe_2
702 cles_2094 1asq_5 1aoz_5 1asp_2 1aso_2 1asq_2 1aso_1 1asp_5 1aoz
703 cles_2531 2km0_1 2lel_2
704 cles_2211 4flm_2 4flm_1

705 cles_1952(2c9q_1 2c9p_6 2c9p_2 2c9p_3
706 cles_2034: 5jxa_1
707 cles_3874: 4lsy_1
708 cles_2581! 1aqp_2
709 cles_4094! 4tm7_8
710 cles_1728: 3ow7_2 3ow7_3
711 cles_4052! 3x1e_5 4ysq_7 4ysp_7 4yss_2 4yso_2 4ysr_7
712 cles_1966: 4hcf_1 4hcf_2
713 cles_4052: 5i0x_1
714 cles_1967! 2k70_1 1x9l_1 2k6z_1 3zja_1
715 cles_3407: 4n3u_1
716 cles_2122! 1n68_4
717 cles_1783! 2fk2_1 2fk1_1
718 cles_2063: 5emt_2 5emt_1
719 cles_2094(3ta4_7 3ta4_9
720 cles_3915: 4lp1_7
721 cles_2320(2p1x_2
722 cles_1648: 3gjb_2 3gjb_1
723 cles_1648! 2fcv_2 2fct_2 2fcv_1 3nnl_1 3nnl_2 2fct_1 3nnf_1
724 cles_2318(2xrx_23 2xrx_13 2xsh_9 2xrx_9 2xrx_6 2xrx_8 2xrx_22 2yfl_
725 cles_2233! 3pce_4 4ilv_1 3pch_2 3pcg_4 2boy_14 3pce_5 4whp_1 3pc
726 cles_2219! 2hk6_3
727 cles_1943: 4aq6_4 4aq6_5 4aq2_5 4aq2_7 3zds_12 3zds_11 4aq2_1 4a
728 cles_2320! 5a1j_1 5a5d_1 5adw_1 5adv_3 5adw_2 5ad1_1 3zk3_1 5ac
729 cles_3429: 3cxh_6 3cxh_7 2d2c_8 4d6u_3 4pd4_1 3l72_3 2qjk_24 3l7(
730 cles_2542: 4pqb_1
731 cles_2533: 1cry_1 5wve_7 1csv_1 4rsz_11 3o1y_1 2n9i_1 1cif_1 1chh_
732 cles_1944! 2fiy_4
733 cles_2158! 3rtl_7 3rtl_9 3rtl_2 4h8q_1 3rtl_4
734 cles_1770: 1j3q_1 1j3q_2
735 cles_2220! 2fyu_4 2fyn_15 2a06_2 1kb9_2 3h1h_3 3l75_1 2qjp_21 1sc
736 cles_1886: 3hni_13 3tom_1 3hni_7 2qla_6 3tol_6 3foo_21 3nmk_6 3m
737 cles_1714: 3csl_2 3csl_1
738 cles_3788! 4m25_4 4m26_1 4m25_6 4m25_1 4m25_3
739 cles_3415: 4ism_4 4zkh_8 4ism_11 4zkh_19 4ism_14 4zkh_18 4zkh_3
740 cles_2221: 2hk6_6
741 cles_2461! 3bfj_19 3bfj_18 3bfj_5 3ox4_1 3ox4_3 3bfj_3 3bfj_2 2bl4_2
742 cles_2306: 2ot4_13 3owm_1 2rf7_10 3s7w_12 1gu6_10 3gm6_11 3rkh
743 cles_3646: 3wr9_4 3wr9_2
744 cles_3514(5jy8_4
745 cles_1872: 2csg_1
746 cles_1792: 5f8p_1
747 cles_2188(3h7j_5 3h9a_1
748 cles_2220(3vsj_2 3vsh_2 3vsh_1 3vsi_1 3vsi_2 3vsj_1
749 cles_3420(4toa_117 4toa_106 4toa_9 4toe_128 4toc_54 4toc_60 3is8
750 cles_2277: 4ou9_2 2biw_1 4ryy_2 4f3d_2 4zhk_4 4rse_2 4f3a_1 5kk0_
751 cles_2672: 1icc_6 1jex_1 1blv_1 1lj0_7 1u9m_2 1m20_1 1ehb_1 1u9m

752 cles_2289{ 4wwj_2 4wwj_1 4wx0_1 4wx0_2
753 cles_2436{ 3s9n_3 3s9n_1
754 cles_2188{ 3h7j_4
755 cles_1908{ 1xvx_4
756 cles_1648{ 4mhu_1 4q5o_1 3emr_1 4mhu_2 4q5o_2
757 cles_1848{ 1gy9_1
758 cles_2542{ 3ng6_4 3nfe_2 4iro_2 1z8u_2 3ng6_1 1s5y_3 3nfe_3 1s5y_
759 cles_3429{ 1ppj_8 1ntz_3 3h1h_5 2qjk_23 3l70_6 1ntm_3 1ntk_3 2e7
760 cles_2299{ 4kvk_2
761 cles_4055{ 3vx0_6
762 cles_2524{ 4ahx_1
763 cles_2344{ 3h9v_2
764 cles_3563{ 5fbh_1 5fbh_5
765 cles_2331{ 1v8m_3
766 cles_2177{ 1b9y_5 1b9x_4
767 cles_1627{ 2z9g_1
768 cles_2076{ 1fnl_1
769 cles_1918{ 2is1_5 2is1_4
770 cles_2686{ 4jsa_1 8ca2_2 2geh_3 3v5g_1 2qp6_1 2qo8_1 2hoc_1 4q7
771 cles_3864{ 4xym_10 4xym_6
772 cles_2611{ 1hj1_2
773 cles_3768{ 5g3s_2 5g3s_14
774 cles_2393{ 3gfh_2 3gfh_1
775 cles_1738{ 1xma_3
776 cles_1764{ 1k1e_2 1k1e_16 1k1e_13 1k1e_20 1k1e_12 1k1e_24 1k1e_
777 cles_3587{ 4yix_13
778 cles_2634{ 1jfh_2
779 cles_2174{ 2jes_1 2jes_9 2jes_17 2jes_25
780 cles_2094{ 3hfx_1
781 cles_1881{ 2j0e_1 2j0e_2
782 cles_3526{ 4r20_5
783 cles_2290{ 1fo8_1
784 cles_1667{ 1lzi_5 2i7b_1 5cmh_1 1r81_3 1zi1_4 5cqm_3 2a8w_3 5cmj
785 cles_1734{ 1ixz_1
786 cles_2221{ 1sdn_1
787 cles_1926{ 1tlf_4 1tlf_1 1tlf_3
788 cles_2095{ 1plq_1
789 cles_1605{ 1e7z_1
790 cles_2377{ 1dkq_2
791 cles_1745{ 1ej0_1
792 cles_1890{ 1dbu_1
793 cles_2680{ 1dr5_1 1dr4_1
794 cles_2147{ 1is9_2
795 cles_3426{ 5awg_3 5awg_4
796 cles_1647{ 3qm0_2
797 cles_4004{ 4ihd_2 4ihd_1
798 cles_1654{ 3w1b_4

799 cles_21912 2jln_1
800 cles_16481 3qm0_1
801 cles_34691 5ko2_10 5ko2_13
802 cles_25863 1qai_1 1qai_4
803 cles_19935 1dlq_1 1dlq_3
804 cles_23768 1dkm_1 1dkq_1 1dkn_2 1dkp_3
805 cles_22021 1iub_2
806 cles_26019 2tpi_1
807 cles_20954 1plq_2
808 cles_20303 1j99_1
809 cles_18930 1jop_3 1jop_11 1jop_12 1jop_1
810 cles_21649 2cfq_4
811 cles_18927 1jop_5 1jop_9
812 cles_25181 4m1m_11 4m1m_4 4lsg_5 4lsg_9
813 cles_21648 2cfp_2
814 cles_23939 1aro_7
815 cles_24611 1igw_19 1igw_24 1igw_5 1igw_20
816 cles_23954 1vcp_1 1vcp_2 1vcp_3
817 cles_20285 1fmj_6 1fmj_3
818 cles_19715 1qz4_4
819 cles_34270 5awg_2 5awg_1
820 cles_19771 1g9u_8
821 cles_18553 3kbk_1
822 cles_21478 1is9_1
823 cles_18507 3kbk_2
824 cles_40632 4uxm_1
825 cles_16199 1fl9_1 1fl9_3 1fl9_2
826 cles_24301 1g8k_2 1g8k_29 1g8k_21 1g8k_25
827 cles_21477 1is9_4
828 cles_38799 4xym_8 4xym_9
829 cles_25237 1of5_1
830 cles_21722 2wiu_5 2wiu_2
831 cles_20946 3hfx_7
832 cles_18941 1miu_5
833 cles_18506 1n1b_1 1n1b_6
834 cles_35679 5clk_7
835 cles_26015 2sgd_1
836 cles_34405 1kp8_6 1kp8_5 1sx3_2 1sx3_16
837 cles_16050 1e12_1
838 cles_23849 3mio_2 3mio_1
839 cles_24848 3zdp_1 3zdp_2 3zdp_3
840 cles_37862 4lzb_2 4lzb_4
841 cles_40978 5ftb_3
842 cles_39164 4nai_6 4nan_4 4nal_1 4nak_8
843 cles_22274 3jzo_1 3jzp_1
844 cles_41090 2x7x_2
845 cles_38783 5t5i_24

846 cles_2670: 4l1o_4
847 cles_3722(4qcl_4
848 cles_2336(4efq_9 4efq_8
849 cles_3686- 3v7p_2
850 cles_2217(3zdd_1
851 cles_3774(5txg_2
852 cles_2026(1bw9_3 1c1d_3 1c1x_1 1c1d_1 1c1x_2
853 cles_2324(2rkb_5 2rkb_3 2rkb_1 2rkb_2 2rkb_4
854 cles_2107- 1fl1_1
855 cles_2470- 2pmu_2 2pmu_3
856 cles_4012(5cog_1 5cog_2
857 cles_2522(2qiz_1
858 cles_1626: 1xgk_4 1ti7_1
859 cles_1883- 1rm6_11
860 cles_1960: 1vph_3 1vph_1 1vph_4 1vph_2
861 cles_3770(3vd8_3
862 cles_1709: 3b0m_2 3vlx_1 3vm0_2 3vly_2 3vm1_2 3vkt_2 2gep_2 3b0
863 cles_1990- 2fhk_10
864 cles_2101(3unf_2
865 cles_1914- 2p74_2 2p74_1
866 cles_2490- 2asc_1
867 cles_3935(3zn2_2
868 cles_3661(5hv0_1 5hv0_4
869 cles_1653(4j7c_3 4j7c_1 4j7c_4 4j7c_2
870 cles_1625(1ti7_3 1xgk_3
871 cles_4036(4o5f_2 4o5f_1
872 cles_2099(2xwe_2 2xwe_1
873 cles_3497(3qe9_4 3qe9_1
874 cles_1606- 2cvi_1 2cvi_2
875 cles_2691: 1c1d_6 1bxg_1 1c1x_3 1bw9_4
876 cles_1998(4edj_1
877 cles_1855(3iv3_2
878 cles_2266: 1eex_3 1eex_6 1egv_6 1egv_5 1iwb_2 1iwb_7
879 cles_1790- 4m3p_6 4m3p_5 4m3p_3 4m3p_7
880 cles_3976(5lk2_1 5lk3_1 5ljx_1 5lk1_2
881 cles_2675: 4f7i_6 4f7i_11 4f7i_4
882 cles_1655(2fca_2 2fca_1
883 cles_1758(4dgh_1
884 cles_2466(4x3z_2
885 cles_1604(3imq_1
886 cles_2492(3ahs_1 3ahs_2
887 cles_1993- 2qki_1 2qki_2
888 cles_4046: 3x3z_5
889 cles_3761(3w7a_5 3w7a_3
890 cles_2371- 2qyo_10 2qyo_9
891 cles_2324(3ss9_1
892 cles_3924: 5cbw_2 5cbt_1 5ccq_2

893 cles_2376{ 4aro_1
894 cles_2168{ 4dxt_1
895 cles_1769{ 3ven_3
896 cles_1913{ 1m40_1 1jvj_2 1nym_1
897 cles_1755{ 3osd_1
898 cles_1640{ 2a6x_1 2a6v_2
899 cles_2296{ 4znd_1 3tr1_1
900 cles_2618{ 2ibw_4 2ib9_2 2ib9_3 2ib9_1 2ibw_1 2iby_3 2ib8_4 2ib9_4
901 cles_1774{ 2fpq_2
902 cles_2436{ 2o84_1
903 cles_2083{ 1zl0_1
904 cles_2466{ 1meh_1 1me9_1 1me8_1 1mew_1
905 cles_2285{ 3pox_6 3pox_20
906 cles_3961{ 5aeo_1
907 cles_2431{ 4x3k_3
908 cles_2564{ 3r9b_4 3r9b_5 3r9b_6
909 cles_3769{ 3vd8_2
910 cles_3936{ 4ls7_2 4ls5_4 4ls5_2 4ls6_1 4ls7_3
911 cles_3874{ 4v23_1
912 cles_1776{ 1ooz_1 1ope_5 1ooz_3 1ope_4 1ooy_3 1ooy_2
913 cles_2668{ 2xdr_7 2xdr_3 2xdr_5
914 cles_3584{ 4yu6_5 4yu6_4
915 cles_1695{ 1wjx_1
916 cles_2680{ 2w3b_2 2w3b_1
917 cles_1728{ 3llp_1
918 cles_2060{ 3i7r_4 4eou_3 4eou_2
919 cles_2642{ 2vwj_1
920 cles_3497{ 4q0w_3 4q0z_1 4q0z_2 4q10_3 4q0w_2 4q0z_4 4q10_2 4q
921 cles_3830{ 4y02_2 4y04_1
922 cles_2560{ 2g4n_3 2g4n_6
923 cles_2363{ 4jay_4 4jay_1 4jay_3 4jay_2
924 cles_2599{ 2h5f_3 2h5f_1
925 cles_3550{ 5ehh_1 5e3a_3 5e33_1
926 cles_1779{ 1lvg_1 2an9_1 2an9_2
927 cles_3924{ 4nan_5 4nak_2 4nai_2
928 cles_1789{ 4fmw_1
929 cles_2388{ 3usz_2
930 cles_2302{ 3mmx_5 3mmx_9 3mmx_6 3mmx_3 3mmx_7 3mmx_1 3m
931 cles_1625{ 1ti7_2
932 cles_2668{ 4caz_5 4caz_4
933 cles_4060{ 4nai_11
934 cles_1921{ 2yia_1 2yia_5 2yi9_2 2yia_3 3zed_5 2yia_7 2yi8_2 2yia_6 3
935 cles_3859{ 4u6c_1
936 cles_1920{ 3zed_2 3zed_4 3zed_6
937 cles_3676{ 4bva_2 4bva_1 4bv8_2 4bv8_1
938 cles_2642{ 2vwj_2
939 cles_3769{ 3vd8_4

940 cles_3868: 4qca_1
941 cles_2191! 2ycb_5 2ycb_4
942 cles_2235: 4iq0_2
943 cles_3941(5koe_5 5koe_3 5koe_7
944 cles_2548/ 4dur_2 4dur_1
945 cles_1823: 3rsf_1
946 cles_2146! 1fp7_1
947 cles_2328: 2vqm_1 2vqj_3
948 cles_2398! 1lwg_1
949 cles_2347: 4k8t_1 4k9c_2 4k8c_1 4lca_2 4lc4_1 4kad_2 4k9i_2 4kal_2
950 cles_1705/ 4ia6_4 4ia6_1 4ia5_2
951 cles_2363: 3h8f_4 3h8f_9 3h8f_11 3h8f_10 3h8f_12 3h8f_8
952 cles_3961: 4xd0_2
953 cles_3769(3vd8_1
954 cles_3984: 5evc_4 5evc_2
955 cles_2454/ 2j7p_3 2j7p_6
956 cles_1779! 2j41_1 2j41_3 2j41_2
957 cles_2054: 3nkq_2
958 cles_4029(4x6j_1
959 cles_4031/ 4qbb_1
960 cles_2405: 1kee_20 1cs0_11 1ce8_22 1c30_6 1jdb_16 1ce8_17 1t36_2
961 cles_3863: 4c13_2
962 cles_2167: 2rdg_3
963 cles_1603(1c1d_2
964 cles_3935! 4c1l_3 4c1l_1
965 cles_2526(3tfz_3 3tfz_2 3tfz_1 3tfz_4
966 cles_2629: 3i4d_3
967 cles_3819! 5lup_2
968 cles_4060: 4nai_8
969 cles_2452: 5ii2_2 4yh4_1 3p1e_1 4lyi_1 4flp_1 4pkl_1 4pkl_2 5ii2_1 4l
970 cles_2685! 1keq_1
971 cles_3554: 4tm0_8 4tm0_2 4tlz_5 4tm0_3 4tlz_3 4tlz_7 4tlx_6 4tlz_4 4
972 cles_3805: 5cjz_1
973 cles_3766(4ud8_2
974 cles_2266: 1iwb_5 1iwb_6
975 cles_2459: 3ryd_3 3ryd_1
976 cles_3746: 4w8k_1
977 cles_2012: 4g9p_1
978 cles_2105/ 4bi3_2
979 cles_3922(5tkr_2
980 cles_1933! 3cl1_3
981 cles_3722! 4nea_7 4nea_4 4u3w_1 4i26_3 4nea_13 4i26_2 4nea_5 4u
982 cles_1990(1m5h_22 1m5h_20 1m5h_13 1m5h_15 1m5h_9 1m5h_4
983 cles_2546! 3ifd_1
984 cles_2544! 1usb_1 1usb_2
985 cles_3587! 5dou_7 5dou_6
986 cles_1914: 1jwv_2 1nym_2 1m40_3 1jvj_4

987 cles_1912{ 1li0_2
988 cles_2320: 1c30_12 1kee_17 1jdb_24 1c3o_28 1cs0_23 1c3o_14 1bxr_
989 cles_2366{ 1bp6_1 1bo8_1 1bp0_1 1bpj_1
990 cles_2569- 5li1_3
991 cles_2466; 4fxs_1 1jr1_2 4mz1_1 4mz1_3 1nf7_1 4ix2_4 1nf7_2 1jr1_:
992 cles_2675{ 4f7i_5 4f7i_2 4f7i_10 4f7i_1
993 cles_1746: 2irf_1 2irf_6 2irf_3 2irf_5 2irf_2 2irf_4
994 cles_1640- 2a6v_1
995 cles_2077; 4esk_1 4esk_3
996 cles_2466{ 1mei_1 1me7_2
997 cles_2527{ 3jsr_1
998 cles_2459; 3ryd_5
999 cles_2062; 3i7q_4 3du0_3 3i7q_3 3du0_2
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1002 cles_2366; 2c97_9 2c97_12 2c94_3 2c97_14 2c94_16 2c97_16 2c94_2
1003 cles_1659- 5dkp_24 5dkp_7 5dkp_23 4ryf_1 5dkp_26 5dkp_11 5dkp_2
1004 cles_1689(3qek_2 3qek_1
1005 cles_4118: 4chi_5 4chi_3
1006 cles_2366{ 3rde_2
1007 cles_3661; 5hv4_5
1008 cles_3850(4udj_4 4udj_8
1009 cles_1990; 2fhj_11 2fhj_17 2fhk_2 2fhj_7 2fhk_4 2fhk_1 2fhk_11 2fhj_
1010 cles_1781: 3a45_1
1011 cles_2010; 4b7v_2 4ls5_3 3e60_2 4jb6_2 4ls5_1 4jb6_1 3e60_1 4b7v_
1012 cles_4120; 4p3v_1
1013 cles_2000(1knw_2
1014 cles_4113{ 4k1e_1
1015 cles_2304: 1knw_1
1016 cles_1883{ 3l4p_7
1017 cles_1922; 3f7h_1 2i3i_3 1tw6_3 3f7i_1 2i3h_2 3gta_3
1018 cles_3896{ 4ypm_1
1019 cles_2565: 3nc5_3
1020 cles_2462; 3v2f_191
1021 cles_1808- 2xzo_1
1022 cles_2102- 1iru_10 1iru_25
1023 cles_3857: 4s0m_1
1024 cles_1821: 2e89_1
1025 cles_2428{ 3i8g_960
1026 cles_3627(4ok9_1 4okq_2 4okq_1 4ok9_3
1027 cles_3504; 4gi2_1
1028 cles_1641(3n8b_1 3nm7_1 3n8b_2
1029 cles_2151- 1smy_250
1030 cles_1746(2uag_2 2uag_1
1031 cles_2322(3rmw_2 3rmv_1
1032 cles_2019{ 4ip2_1 4ip2_3 4ip2_2
1033 cles_2275: 4av3_4 4av3_2

1034 cles_20927 1obd_2
1035 cles_39609 4usx_3
1036 cles_23729 3i8h_1142
1037 cles_37405 4nyz_1
1038 cles_41299 5dgd_5
1039 cles_39505 4zze_4 4zze_3
1040 cles_17840 1xpu_5 1xpu_1 1xpu_2 1xpu_4 1xpu_6 1xpu_3
1041 cles_22794 4i45_1
1042 cles_19169 3t1o_2
1043 cles_39532 5dx6_3 5dx6_4
1044 cles_22548 3pyo_18
1045 cles_23974 3w6n_3 3zyc_1 3w6o_2 3w6n_2 3w6o_1 3zyc_2 4p4s_2 4p
1046 cles_18576 2qdf_1
1047 cles_26639 4khp_62
1048 cles_17242 4bix_1
1049 cles_16648 1i94_41
1050 cles_39510 4kfj_1
1051 cles_38110 5bn3_3
1052 cles_16217 2xrf_3 2xrf_2 2xrf_1
1053 cles_26772 3v2d_224 3v27_582
1054 cles_24113 1smy_2
1055 cles_21128 1g8h_3 1jee_31 1jee_1 1g8h_19
1056 cles_18911 4fmm_2
1057 cles_16076 2zy9_2 2zy9_8 2yvy_1
1058 cles_25209 2a68_334
1059 cles_18776 1vr0_2 1vr0_1
1060 cles_25730 3ll6_2
1061 cles_35520 4qox_1
1062 cles_24608 1f61_2 1f61_1
1063 cles_35139 5eiy_1 5ejz_1 4p02_1
1064 cles_24583 3lpl_2 3lpl_1
1065 cles_39603 5byr_13
1066 cles_38652 4ktz_3 4ktz_1
1067 cles_19708 3d5b_173
1068 cles_25012 1smy_128
1069 cles_23242 1ze1_1 1ze1_2 1ze1_4 1ze1_3
1070 cles_35202 5l5u_9
1071 cles_24831 3cx6_1
1072 cles_21547 4yqf_2 4z54_2 5cyp_1 4z54_1 5cyp_2 5cyo_1 5cyo_2 3ftq_
1073 cles_20137 1shk_3 1shk_2 2shk_2 2shk_3
1074 cles_35207 4xco_10
1075 cles_21723 5f9c_1 5f9c_2
1076 cles_25061 2r6o_3
1077 cles_22484 3eyw_1
1078 cles_20057 1smy_109
1079 cles_20868 3quq_2 3qut_1
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1081 cles_2332 1pus_1 1ppx_1 1pun_1 1puq_1
1082 cles_1921 2yi9_6 2yi9_3 2yi9_1 2yi9_5 2yi9_8
1083 cles_2689 2x9t_122
1084 cles_1772 2a69_429
1085 cles_2570 3dls_11 3dls_10 3dls_13
1086 cles_1831 4fma_15
1087 cles_1942 3tiq_1
1088 cles_1634 1e3m_2
1089 cles_2565 3nc3_2
1090 cles_1628 4g6h_4
1091 cles_2235 3dty_2 3dty_1
1092 cles_2464 2ae8_12
1093 cles_2466 2kfn_3 2kfz_2 1d9d_4
1094 cles_2586 4dg1_2
1095 cles_2152 3kb4_2 3kb4_1
1096 cles_2520 1iw7_287
1097 cles_2108 2a68_398
1098 cles_3652 4p2x_1
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1101 cles_4023 4toq_10
1102 cles_2292 2hv6_1
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1104 cles_3685 5ee5_13
1105 cles_2204 2vu9_1
1106 cles_2382 3vmt_1 3vmq_1
1107 cles_3416 2c2j_1
1108 cles_3598 4ktt_1
1109 cles_3651 5c5h_2
1110 cles_2110 2a69_44
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1112 cles_2223 5g5t_1
1113 cles_1665 1i94_46
1114 cles_2238 1g3u_1 1mrn_1 1n5j_1 1mrs_1 1gsi_1
1115 cles_1777 1smy_229
1116 cles_2062 4dxv_1
1117 cles_2500 2a68_13 1iw7_292
1118 cles_2014 4ari_2
1119 cles_2607 2b2x_2 2b2x_1
1120 cles_2440 3f1e_124
1121 cles_1736 2vp0_1 1zm7_1 2jcs_1 1oe0_4 1oe0_1 2jcs_2 1oe0_3 2vp0
1122 cles_2244 2a07_5 3qrf_2 2a07_1 2a07_3 3qrf_1 3qrf_3 2a07_4 2a07_
1123 cles_2154 4kva_1 4kva_2
1124 cles_2573 3qfv_1
1125 cles_2168 3nl3_1 3nl3_7 3nl3_2 3nl3_6 3nl3_10 3nl3_5
1126 cles_2272 3gqc_8 3gqc_6
1127 cles_2184 1q4r_1 2q3p_1

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1130 cles_2362 2o06_3
1131 cles_2658(2x5f_1
1132 cles_1790 3c94_1
1133 cles_2658 1xmv_1
1134 cles_2228(2iuc_4 2iuc_1
1135 cles_3486 5t3r_3
1136 cles_1978 3ck5_2 4h1z_4 4dn1_1 4h1z_1 4h1z_2 4h1z_5 3ck5_1 4dn
1137 cles_1648(3bbx_43
1138 cles_2068(4c7h_1 2ync_2 4b11_3 5a27_1 4c68_2 4c2y_2 5g1z_3 5g1
1139 cles_2411 1iw7_422
1140 cles_3771 4cn2_9
1141 cles_1916 3t1o_3
1142 cles_3593 5fr1_3
1143 cles_2501 1smy_143
1144 cles_3744 5exc_3
1145 cles_2110 1smy_68
1146 cles_1619 1htw_7 1htw_6 1htw_1
1147 cles_2616 3r3s_3 3ijr_3 5u8p_2 3ijr_7 3ijr_5 3r3s_4 3i3o_2 5u8p_1 3i
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1149 cles_3931 3wky_4
1150 cles_2082 4ex7_1 4f71_1 3cnh_2 4dfd_2 4dcc_2 3i76_3 4f71_2 4ex6_
1151 cles_1957(3vzx_1 3vzx_5 3vzy_3
1152 cles_1939 3uoa_1
1153 cles_2255 3pyo_893
1154 cles_2498 1smy_94
1155 cles_1740 3fvy_3
1156 cles_2210 3mga_2
1157 cles_2419(4pfk_1 1pfk_3 1pfk_1
1158 cles_2140 1iw7_250
1159 cles_2061 2hmc_1
1160 cles_2408 1smy_211
1161 cles_3550 5ehh_4 5e33_4 5egy_2 5e2q_2 5e3c_1
1162 cles_1687 5iit_1 5iit_2
1163 cles_4134 4uys_7
1164 cles_3639 4rwg_1
1165 cles_2340 1yw0_5
1166 cles_3550 5e3a_4 5ehh_3 5e33_3 5e3c_2
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1168 cles_1736(2a2z_5 3ipx_1 2qrn_2 1p62_1 2qrn_3 2a2z_3 2qro_2 2qrn_
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1172 cles_2319(3s5f_1 3s5e_1 3s5f_2
1173 cles_2488 2oy3_2
1174 cles_2575 3q72_4 3q7q_3 3q7q_1 3q7p_2 3q72_2 3q7p_1

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1176 cles_3744(5exc_2
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1178 cles_2204: 4dxp_1
1179 cles_2568(1x8b_2
1180 cles_4013(4nbm_4
1181 cles_2575: 1kmq_1
1182 cles_1983(1qs0_1
1183 cles_2576(4f38_1
1184 cles_1615(4dsc_1 4dsc_2
1185 cles_2281(3kgx_1
1186 cles_3525: 5hr6_2 5hr6_6
1187 cles_1996(4f0q_3 4f0q_2 4f0p_2 4f0p_1 4f0q_1
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1191 cles_1644: 3c8c_2
1192 cles_3838(4i5q_1
1193 cles_1965(3dc7_1
1194 cles_2295: 2j0q_2 2j0q_1
1195 cles_2306: 2e5a_1
1196 cles_2034(1smy_151
1197 cles_2242(3n6q_9
1198 cles_1891(4fmm_3
1199 cles_2039(2a69_149
1200 cles_1921: 3lgy_1
1201 cles_2012: 2shk_1 1shk_1
1202 cles_2205: 1jbz_1
1203 cles_4108(1rzr_1 5hko_4 1rzr_2
1204 cles_2511(2fh5_1 5ck3_2 5ck3_1 5ck3_3
1205 cles_1976(2ag1_2 4qpz_5 4qq8_4 4qpz_3 4qq8_2 2ag0_3 4qpz_2 2ag
1206 cles_2386(1n32_55
1207 cles_2042: 1smy_121
1208 cles_1976(3oe1_1 4cok_2 2vbi_1 2wva_3 2wva_8 2wva_6 2vbi_2 2w
1209 cles_2153(3q6j_2 3q6j_1
1210 cles_2382(3vmt_2
1211 cles_1837: 3mmh_7
1212 cles_1746(4c12_2 4c12_1
1213 cles_4047(5x5h_2
1214 cles_1658(1qr0_1
1215 cles_2229(2w5x_4 2w5v_3 2iuc_5 2w5x_1 2iuc_6 2w5v_4
1216 cles_3840: 4bl0_2 4bl0_1
1217 cles_1647(3uzr_1
1218 cles_2284: 4lse_1
1219 cles_3771: 4cn2_6
1220 cles_2681: 4kfj_3
1221 cles_2032: 3lkm_3

1222 cles_1965: 2hsj_2 2hsj_4 2hsj_1
1223 cles_2230: 2wcj_1
1224 cles_2110(1iw7_383
1225 cles_2084: 3h4s_3
1226 cles_2041: 1iw7_166
1227 cles_3967: 5d5g_4
1228 cles_1783(2a84_1
1229 cles_2146: 2a68_482
1230 cles_1627(5c0y_1
1231 cles_1685: 1xd3_5
1232 cles_2042: 1smy_207
1233 cles_2129(4hhl_1
1234 cles_3743: 5exc_8 5exc_10
1235 cles_2211: 3fcx_2
1236 cles_1715: 3bsu_1 3bsu_2
1237 cles_1696: 3qku_1 3qku_2
1238 cles_1917(4v0o_4 4v0o_6 4v0o_9 4v0o_8
1239 cles_1991: 3bs1_1
1240 cles_2175: 2wda_1
1241 cles_2313: 1i94_27
1242 cles_2145: 2a69_412
1243 cles_2481: 3day_1 3c5e_1 3gpc_2
1244 cles_2566(3nc7_4 3nc7_2
1245 cles_3827: 5acp_2
1246 cles_2627: 3b9b_1 5a3r_1
1247 cles_4052: 4ied_5 4ied_8
1248 cles_2298: 4dha_472 4dhc_299
1249 cles_4014: 4toq_12
1250 cles_2407: 2a69_186
1251 cles_2603: 1c2e_3 1c2f_1
1252 cles_2149: 5cc3_1 5cc5_1 4ex4_5 5c9r_1 5t8g_1 5cc6_1 3cv2_1 3sb0_
1253 cles_1971(3v2d_153 3v27_330
1254 cles_2489: 1h7q_1
1255 cles_2034: 1smy_5
1256 cles_2108: 1smy_13
1257 cles_1984(3cfx_5 3cfx_3
1258 cles_2586: 3kyl_1
1259 cles_2345(3d1r_1
1260 cles_1808(3t9f_1
1261 cles_1674: 2azx_1
1262 cles_1880: 1jue_1 1jqv_2 1ovd_1 1jub_1 1jue_2 1ovd_2 2bx7_2 1jqv_
1263 cles_2108: 2a68_83
1264 cles_2103: 1juy_1 1qf4_1 1cib_1 1cg0_1 1cg1_1 1lon_1 2gcq_1 1lny_1
1265 cles_2006: 1smy_168
1266 cles_1819(2fco_1 2fco_2
1267 cles_3988: 4ygr_1 4ygs_1
1268 cles_3744: 5exc_1

1269 cles_2619[illegible]2alm_2
1270 cles_1863[illegible]2xo6_4
1271 cles_2447[illegible]3ksq_2 1o1t_2
1272 cles_3771[illegible]5f2t_1
1273 cles_2301[illegible]3d5b_144
1274 cles_1759[illegible]1twy_1
1275 cles_4069[illegible]4hvy_6
1276 cles_1732[illegible]3lcb_2 3eps_1 3lcb_1 3eps_2
1277 cles_2108[illegible]1smy_247
1278 cles_2295[illegible]3ly5_1
1279 cles_3643[illegible]5ayr_4 5ayr_2
1280 cles_1975[illegible]4a0g_1 4a0g_2
1281 cles_1624[illegible]1muh_2
1282 cles_3659[illegible]5tw7_1 5tw7_2
1283 cles_1660[illegible]4nwi_2
1284 cles_2031[illegible]3lkm_1
1285 cles_4019[illegible]4s1h_2 4s1h_3
1286 cles_2683[illegible]3sfs_3
1287 cles_2110[illegible]2a69_224
1288 cles_2440[illegible]3f1e_329
1289 cles_3711[illegible]4yb7_11 4yb7_4 4yb7_5 4yb7_6 4yb7_2 4yb7_1 4yb7_9 4y
1290 cles_3958[illegible]5aqu_1
1291 cles_3644[illegible]5ayr_1 5ayr_3
1292 cles_3569[illegible]5wq5_2
1293 cles_2332[illegible]2dsc_1 2dsc_2
1294 cles_3654[illegible]4qql_8
1295 cles_2419[illegible]1i94_63
1296 cles_2174[illegible]2qyl_2
1297 cles_1734[illegible]2ps4_2 2aek_1 2ps7_1
1298 cles_1729[illegible]5jm8_5 2x3j_1 5jm8_7 5jm8_3 5jm8_2 2w02_1 3to3_1 5jm
1299 cles_2368[illegible]1i94_61
1300 cles_2166[illegible]2xja_2
1301 cles_2376[illegible]3fnb_2
1302 cles_2112[illegible]1smy_129
1303 cles_2370[illegible]3v22_17
1304 cles_1633[illegible]5i0d_6 5f7u_2 5hxm_1 5i0d_10 4kmq_8 4kwu_6
1305 cles_1903[illegible]1tt4_1 1tt4_2
1306 cles_1997[illegible]4lq3_1 4lq9_1
1307 cles_1638[illegible]1z3h_1
1308 cles_2113[illegible]1iw7_304
1309 cles_2346[illegible]1dgm_1
1310 cles_2470[illegible]1xrj_1 1xrj_2
1311 cles_4091[illegible]5u2i_3
1312 cles_2446[illegible]3hwo_3 3hwo_1
1313 cles_2412[illegible]2a69_421
1314 cles_2380[illegible]2x6v_1
1315 cles_2040[illegible]1iw7_235

1316 cles_1997{ 3sfg_1 4nru_5 3sfu_1 4nru_2 3sfg_2 4nru_4 4nru_3 4nru_1
1317 cles_1920{ 1h56_2
1318 cles_1997[4gzk_5
1319 cles_2247[3mwb_1
1320 cles_2405(3t7d_10
1321 cles_1998[2a69_257
1322 cles_1665{ 1i94_71
1323 cles_1974[3s5m_3
1324 cles_1837{ 3mmh_8
1325 cles_2156(1eqm_1
1326 cles_2404(3t7d_7
1327 cles_2264{ 1mus_2
1328 cles_2470[1esn_2 1esn_4 1esn_3 1esn_1
1329 cles_3782[4kg0_1
1330 cles_2092(1obg_1
1331 cles_3676{ 5kw9_1
1332 cles_2410[1iw7_384
1333 cles_1757[4ag5_3 4ag5_1
1334 cles_3829{ 4hzc_1 4hzc_5
1335 cles_2573[3dls_4
1336 cles_2315[4fvu_2
1337 cles_2382[2zl6_1 2zl5_2 2zl7_2 2zl6_2 2zl5_3 2zl7_3
1338 cles_2580(2a9r_1
1339 cles_1694[3b2s_2
1340 cles_2458[2qtc_1 2g25_2 1l8a_2 1l8a_1 2iea_1 2g28_1 1rp7_1 3lq2_1
1341 cles_2435[4a48_2
1342 cles_2008{ 1iw7_28
1343 cles_2117[1smy_210
1344 cles_2523{ 4f24_1
1345 cles_2361[3v2d_491
1346 cles_2565(3nc5_5
1347 cles_3935[5g3t_5
1348 cles_2017[2qf7_1 4mfd_5 4jx6_5 4jx5_2 4mfe_8 4mfd_3 3tw7_3 4mi
1349 cles_2676[3f1f_251
1350 cles_1971(1mji_5 1mji_6
1351 cles_2389[2xg1_665
1352 cles_2362(1nr9_2 1nr9_3 1nr9_1 1nr9_4
1353 cles_2523[4f24_5
1354 cles_2199[1cmc_2 1cmc_1
1355 cles_2068[2j7q_1
1356 cles_2381{ 3rdk_1
1357 cles_1725{ 2vpn_3 2vpo_1
1358 cles_3520[5fgf_4
1359 cles_1881(3hrd_1
1360 cles_2575{ 2mse_1 2msd_1
1361 cles_1632[1rep_1
1362 cles_2578{ 1mb3_1

1363 cles_3890⁴ 4hzd_1
1364 cles_1627⁹ 4g6h_3
1365 cles_2499⁴ 2a69_324
1366 cles_2006⁰ 1zno_2
1367 cles_2115⁷ 1smy_260
1368 cles_2306⁰ 3a7r_1
1369 cles_1902⁷ 3ozy_3 3ozy_4
1370 cles_1734⁵ 3eih_1 3eih_2 3eih_3
1371 cles_2689⁵ 3i8h_849
1372 cles_2336⁷ 3t1r_5 3t1r_4 3t1r_2 3t1r_1
1373 cles_1676⁰ 3tah_1
1374 cles_2304⁷ 3lac_1
1375 cles_1933⁷ 3hzt_1
1376 cles_2363⁷ 5d8n_4 5d8n_1 5d8n_3
1377 cles_3929⁹ 5ez6_2
1378 cles_1655⁷ 1p4n_2 1ne9_1 1xf8_1 3gkr_1
1379 cles_2500⁸ 2a69_112
1380 cles_4047⁸ 5x5h_1
1381 cles_1957⁷ 3vkb_3 3vkd_1 3vkb_2
1382 cles_2432⁹ 1n70_4 1mzy_2 2a3t_3 1zv2_5
1383 cles_1628⁹ 4g6h_1
1384 cles_2634⁴ 3wy2_2 3wy1_2 3wy2_1 3wy4_1 3wy1_1
1385 cles_3832⁴ 4u3w_5
1386 cles_2306⁸ 1kvk_1
1387 cles_3726⁷ 4cfu_1
1388 cles_2072⁷ 2p0c_1
1389 cles_1701⁷ 4lps_2 2hf9_1 2hf8_2 2hf8_1 2hf9_4 4lps_3
1390 cles_2008⁰ 1iw7_409
1391 cles_2229⁸ 2wcj_2
1392 cles_4036⁷ 4s35_3
1393 cles_2341⁷ 3v8e_2 3v8e_10 3v8e_11 3v8e_5 3v8e_13 3v8e_1 3v8e_12
1394 cles_4081⁷ 1rdd_1
1395 cles_1854⁶ 3kdn_5 2v63_1 1ir2_11 3kdn_6 3axm_7 1uzh_4 1bwv_3 1i
1396 cles_3743⁸ 5exc_11
1397 cles_1975⁸ 3fpa_3 3fpa_2 3fpa_4 3fpa_1
1398 cles_2410⁸ 5d4c_2 5d4c_12 4oip_1
1399 cles_1905⁸ 2xj9_2 2xj9_1
1400 cles_2404⁷ 3t5t_2
1401 cles_3521⁰ 4b3m_94
1402 cles_2665⁵ 1i94_87
1403 cles_2576⁵ 1cf4_1
1404 cles_2082⁸ 1g9g_2
1405 cles_3549⁷ 5gri_2 5grl_2 5gre_2
1406 cles_2575⁹ 1zbd_3
1407 cles_3533⁷ 4zwe_2
1408 cles_1978⁷ 2gge_8 2gge_3 2gge_2 2gge_7 2gge_5 2gge_6 2gge_1 2gge
1409 cles_4097⁵ 4wp9_3

1410 cles_3464(4oo1_1
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1412 cles_2617(3osu_1
1413 cles_1655(3bbx_47
1414 cles_1826(3d2f_4 3d2f_1
1415 cles_2027(2a68_313
1416 cles_2684(2d5h_6 1od5_1 1od5_2 2d5h_2 2d5h_3 2d5h_1 2d5h_4
1417 cles_3599(4u45_2
1418 cles_2397(1jwy_1
1419 cles_2358(3f1f_507
1420 cles_3923(5ez6_3
1421 cles_2409(2a68_28
1422 cles_2295(4ddw_3
1423 cles_2674(2ztw_1
1424 cles_1836(3l6t_1
1425 cles_3902(4kbn_4
1426 cles_2186(3htw_7
1427 cles_1988(4k9m_4
1428 cles_1606(2oux_8
1429 cles_1628(4g73_7 4g73_3
1430 cles_2420(1i94_50
1431 cles_1817(3crc_1
1432 cles_2019(2hpm_3 2hpi_3
1433 cles_2289(1z72_1
1434 cles_2082(3l8f_2
1435 cles_2404(3t5t_4
1436 cles_3865(5dxo_2 5dxn_1 5dxo_1
1437 cles_1715(2h28_2
1438 cles_1658(2c43_1
1439 cles_3549(4ng4_2 4ng4_1 4ng4_3
1440 cles_1697(4h2u_4 4h2u_2
1441 cles_2036(2a69_56
1442 cles_2022(2a69_17
1443 cles_1972(4dmz_2
1444 cles_2002(1smy_103
1445 cles_3697(4d4g_1
1446 cles_2458(3v2d_231
1447 cles_3556(4s2u_1
1448 cles_2407(2xi3_4
1449 cles_2568(3krw_1
1450 cles_2403(3t5t_3 3t5t_5 3t7d_13
1451 cles_1996(2w35_2 2w35_1 4b20_2 4b20_1
1452 cles_2510(2hvq_1
1453 cles_2523(1n67_3
1454 cles_2304(3d5d_234
1455 cles_2011(2vrn_1
1456 cles_2368(3i8h_1366

1457 cles_2195[illegible] 4twk_2
1458 cles_2316[illegible] 3tii_4 3tii_6
1459 cles_4121[illegible] 5hob_1
1460 cles_2523[illegible] 3au0_2
1461 cles_2363[illegible] 1mms_15
1462 cles_3716[illegible] 4tyw_1
1463 cles_2503[illegible] 1smy_288
1464 cles_2119[illegible] 1iw7_401
1465 cles_1787[illegible] 4hut_2 1g64_2 1g5t_1 4hut_3 1g64_1
1466 cles_1771[illegible] 1ymq_2
1467 cles_2325[illegible] 1wyw_1
1468 cles_1629[illegible] 4g73_9 4g6g_4
1469 cles_2255[illegible] 3d5b_119
1470 cles_1848[illegible] 4j5i_3
1471 cles_1742[illegible] 3dkx_2
1472 cles_2238[illegible] 2v54_1
1473 cles_2322[illegible] 4ffr_2
1474 cles_4110[illegible] 5j1s_2
1475 cles_2137[illegible] 2a69_249
1476 cles_2431[illegible] 5e4x_1
1477 cles_3900[illegible] 5ecl_1
1478 cles_1936[illegible] 1z5b_2
1479 cles_1832[illegible] 4fma_4
1480 cles_3949[illegible] 4kfj_5
1481 cles_2463[illegible] 3bbx_15
1482 cles_1711[illegible] 2p4p_2
1483 cles_2412[illegible] 2a68_53
1484 cles_1734[illegible] 2ps7_2 2aek_2 2ps4_1
1485 cles_1998[illegible] 1smy_40
1486 cles_3757[illegible] 3wbh_2 3wbh_4
1487 cles_3967[illegible] 5d5g_1
1488 cles_2172[illegible] 1s2o_1 3gyg_4 3gyg_1 3gyg_3 3gyg_2
1489 cles_1831[illegible] 4fma_12 4fma_13 4fma_18 4fma_19 4fma_16 4fma_3 4fm
1490 cles_2372[illegible] 2uuc_119 3t1y_4 2uua_142 2uub_207
1491 cles_2575[illegible] 4c0l_3
1492 cles_2243[illegible] 1hbn_19
1493 cles_1777[illegible] 1iw7_17
1494 cles_2346[illegible] 1bx4_3
1495 cles_2102[illegible] 1g0u_16 1g0u_7
1496 cles_1616[illegible] 2qlx_2 2qlw_2 2qlx_1 2qlw_1
1497 cles_2296[illegible] 3nvs_1
1498 cles_2404[illegible] 3t5t_6
1499 cles_2626[illegible] 2uu7_14 2uu7_5 2uu7_6 2uu7_13 2uu7_7 2uu7_2 2uu7_1[illegible]
1500 cles_1689[illegible] 1ewk_1 3lmk_2 3ks9_1 3lmk_1 3ks9_2 1ewk_2 5c5c_1
1501 cles_2406[illegible] 4wxw_1 3qyy_1 3qyy_2
1502 cles_2495[illegible] 3da8_1
1503 cles_2171[illegible] 2h5n_2 2h5n_1 2h5n_3

1504 cles_2133: 2yl5_1 4azc_1
1505 cles_1682: 3dlz_1
1506 cles_1686: 2hs4_2
1507 cles_2140: 2a68_409
1508 cles_2501: 2a69_70
1509 cles_2146(4jjz_1 4jjz_2 4iok_2 4iok_1
1510 cles_3806(4cfv_4 4cfv_1
1511 cles_2015(3prn_1 2prn_1
1512 cles_2136 2a68_224
1513 cles_3748: 3wad_1 3wag_1
1514 cles_3547: 5d8h_12
1515 cles_2191: 2y8a_2 2y87_2
1516 cles_3829: 5cx7_13 5cx7_12
1517 cles_2409: 1smy_238
1518 cles_1929: 3wnw_15 3wnw_4
1519 cles_1763: 2dsy_1
1520 cles_3935: 4q57_3
1521 cles_3791: 4o2w_2 4o2w_1 4o2w_3
1522 cles_1659 3p2l_5 3q7h_11 1y7o_2 3q7h_13 3q7h_5 3q7h_12 3q7h_1
1523 cles_2032: 3u56_6
1524 cles_2660: 2alf_1
1525 cles_1904: 2oqy_5 2oqy_8 3fyy_3 2oqy_13 3es8_6 3es8_8 3es7_1 3es
1526 cles_2428: 2vqf_228
1527 cles_2506 4afy_3 4afy_1
1528 cles_2569(2f49_2 2f49_1
1529 cles_2464: 3d5a_185
1530 cles_2033 2a68_369
1531 cles_1673(2qui_1
1532 cles_2181(2j7o_1 2j7n_1 2j7n_2
1533 cles_2302: 1yun_1
1534 cles_4038: 4u9u_2 4u9u_4
1535 cles_2411(2a69_125
1536 cles_2129: 2zox_1
1537 cles_2575: 3sea_2 3sea_1
1538 cles_1784(5bn4_1
1539 cles_3488(5fbs_1 5hv3_1
1540 cles_2689: 4dr7_118 4x66_281 4x62_234
1541 cles_2316: 3tii_5 3tin_3 3tii_2
1542 cles_3885: 5d8g_5
1543 cles_1655(3gkr_2 1xe4_1 1p4n_3 1ne9_2
1544 cles_3973: 5hq8_7 5hq8_5
1545 cles_2433: 1gs6_3
1546 cles_2627: 4h1w_4
1547 cles_3883: 5d8g_3
1548 cles_3655: 4kjg_3 4kjg_6
1549 cles_1646: 3ir2_5 3v4k_2 3v4k_5
1550 cles_2482: 3gpc_1

1551 cles_1723{ 3h80_1
1552 cles_2499{ 1iw7_261
1553 cles_2440{ 3uzl_278 3uzi_380 4g5v_640 3uzg_380
1554 cles_2628{ 4uas_1 4uas_2
1555 cles_1784{ 1xpo_5 1xpo_3 1xpo_4 1xpo_1 1xpo_6
1556 cles_2330{ 1yd4_2
1557 cles_2060{ 2qgi_1 2qgi_2
1558 cles_2660{ 1ecc_4
1559 cles_2003{ 3n0y_1 3n0y_2 3n0z_2 3n0z_1
1560 cles_3517{ 4wtk_1 4wte_2 4wtg_2 4wtm_2 4wtf_2 4wtc_1 4wta_1 4w
1561 cles_1763{ 5b4c_1 5b4c_2
1562 cles_4081{ 1wsf_2 1wsf_3 1wsg_2 1wsg_1 1wsf_1
1563 cles_2280{ 2faf_2 2faf_1
1564 cles_3801{ 4zb0_8
1565 cles_2101{ 5c3m_2 5c3m_1 5c3m_4 5c3m_3
1566 cles_1866{ 1pzy_3 1pzy_4
1567 cles_2187{ 4xww_2 4xww_4 4xwt_4 4xwt_3
1568 cles_2323{ 3pif_4 3pif_3 3pif_1 3pif_2
1569 cles_2004{ 3bso_2 3bsn_2 3h5y_1 3h5x_3 4qpx_2
1570 cles_2017{ 3bg9_3 3ho8_3 5ks8_3 4hnt_4 3bg5_2 3bg9_1 4hnv_3 3hb
1571 cles_3858{ 5ktl_2
1572 cles_1948{ 1vkm_12
1573 cles_1833{ 2v8j_1
1574 cles_4081{ 2g8i_1
1575 cles_2159{ 2py7_1
1576 cles_2106{ 1ips_4 1ips_3
1577 cles_2497{ 4juq_6
1578 cles_2313{ 2jgu_2
1579 cles_3456{ 5m95_2 4wgw_2 5m95_1 4wgw_1
1580 cles_1679{ 3ilm_4 3ilm_1 3ilm_2
1581 cles_1826{ 4gpu_1
1582 cles_2307{ 4rb1_4 2xig_10 4raz_3 4rb2_1 4raz_2 2xig_8 4rb2_2 4rb3_
1583 cles_1931{ 1stx_4
1584 cles_2261{ 4c20_1 1fui_1 1fui_2 1fui_3 3a9r_4 3a9r_1 1fui_4 3a9r_6 4
1585 cles_3800{ 4zb0_7
1586 cles_2465{ 3py8_3
1587 cles_2571{ 3cqw_1 3mvh_1
1588 cles_2468{ 2pom_1
1589 cles_2507{ 2ygk_2 2ygk_1 3taz_1 3taz_2
1590 cles_2223{ 1z25_1
1591 cles_2201{ 1mwh_1
1592 cles_4081{ 2g8i_3
1593 cles_2579{ 1mav_2
1594 cles_1769{ 3gme_2
1595 cles_2307{ 3f8n_4 3f8n_2
1596 cles_2280{ 2g38_2 2g38_1
1597 cles_1854{ 2qvw_10

1598 cles_1859 5a07_2 5a07_1 1s4o_2 1s4o_1 1s4p_1 1s4p_2
1599 cles_3806 4zbc_8
1600 cles_2305 5ckx_1 5ckx_2
1601 cles_2262 1qps_1
1602 cles_2322 1bxr_7
1603 cles_2578 1mav_1 1mb0_2
1604 cles_2331 2dho_9
1605 cles_2489 4d0z_5 4d0z_3 4d0t_2 4d0z_4 4d11_6 4d0t_6 4d11_4 5fv9
1606 cles_1771 4dwq_2 4dwq_1 4isj_2 4isj_1
1607 cles_3627 4yvz_2 4yvz_1
1608 cles_2352 3csb_4
1609 cles_1864 2f4f_1 2f4f_2
1610 cles_4081 1wse_2 1wse_1
1611 cles_2243 3fyp_2 3fyo_2
1612 cles_2100 1up6_2 1up6_3 1up6_4
1613 cles_2464 4lom_2 4mu1_1 4gqu_4 4lpf_3
1614 cles_2280 2qf1_2 4yw8_1 2rke_2 4ywb_2 4ywd_1 4ywb_4 5fh4_2 2rk
1615 cles_1948 1vkm_1
1616 cles_1802 1r2m_1 2b97_1
1617 cles_2293 1kgp_3
1618 cles_1922 1xhv_10 1xhv_8 1xhv_6 1xhv_7
1619 cles_2322 3u2u_1 3u2w_2 3v91_1 3v8z_1 3t7m_1 1ga8_1 1zdf_1 3t7
1620 cles_2314 3r3l_7 3r3l_2 3mwt_3 3r3l_8 3mwt_5 3mwt_2
1621 cles_2567 3r0l_1
1622 cles_1805 3dbn_1 3dbn_2 4eay_1 4eay_4 4eac_3 4eac_2 4eay_2 4ea
1623 cles_3608 4wzm_1
1624 cles_2617 3lf1_2
1625 cles_2258 1d8h_1 1d8h_3 1d8h_2
1626 cles_1820 3bzj_1 3c0q_1
1627 cles_1762 3psn_1 3psn_4
1628 cles_2652 3rl4_3 3rl3_6
1629 cles_2332 2dho_2
1630 cles_1841 3od2_2 3od2_3
1631 cles_1639 2xdv_5 4bu2_1
1632 cles_1819 1y1o_2 1y1o_1
1633 cles_1891 3de9_1
1634 cles_1842 2bj8_1 3pht_2 2hza_1 2cad_3 3od2_1 2bj9_3 3qsi_7 2bj1_
1635 cles_2093 3t9w_3
1636 cles_2180 3gor_1 2qe9_1 2qe9_2 3di5_1 3gor_4 2f22_3 2f22_1 3gor_
1637 cles_3662 3wd7_1 3wd7_9
1638 cles_3832 5bu6_4
1639 cles_2571 2wqm_1 2wqn_2
1640 cles_1817 3fwv_4
1641 cles_2026 4ppt_1
1642 cles_1842 2x27_3
1643 cles_1832 3s0k_1
1644 cles_2613 1h9u_3 1h9u_1 1h9u_2 1h9u_4

1645 cles_3924: 5aun_2 5auo_2
1646 cles_1702! 1h9r_2
1647 cles_1995: 1e0o_2 1e0o_4
1648 cles_2361! 1qco_3 1qco_5 2hzy_3 2hzy_10
1649 cles_2186(2isy_2 2isy_3
1650 cles_1840! 3lgh_1 2cad_2 2cad_1 3lgh_2 3lgh_4
1651 cles_2353! 1ziu_2
1652 cles_3734' 4ufh_3
1653 cles_3528! 4zf8_3 4zfb_5 4zf6_1 4zfa_1
1654 cles_2491: 1qy7_3 1qy7_1 1qy7_2
1655 cles_2055: 2qj3_3
1656 cles_2356: 4zjq_2 4zjq_3 4ziw_2 4c48_1 4ziw_1 4ziw_3 4zit_2 3d9b_1
1657 cles_1814(2fwe_1
1658 cles_1640(2xdv_2
1659 cles_2479! 3kbr_1
1660 cles_4007! 4uwx_1
1661 cles_1609(3pgu_1
1662 cles_3575: 4k8o_2
1663 cles_3658! 4q7l_1
1664 cles_1873(2arp_2
1665 cles_2486: 3fwv_2 3esk_1
1666 cles_2687: 2qyi_2
1667 cles_2345(2bmr_2 2bmq_3 2bmo_2
1668 cles_2610! 2cfv_1
1669 cles_4076! 4mtq_2
1670 cles_1739' 2uve_4 2uvf_4
1671 cles_2658! 1ynu_1
1672 cles_2014: 3skd_1
1673 cles_1703: 1b9m_1 1b9n_1
1674 cles_2223! 1w9h_5
1675 cles_1774' 3nf3_1 3ds9_1 3dse_1
1676 cles_2573: 2vuw_1 3e7v_1 3fmd_1
1677 cles_3696' 4lvn_1
1678 cles_1797: 1xi3_1
1679 cles_1946: 2hje_3
1680 cles_1637' 3ii2_1
1681 cles_3652! 5bue_1
1682 cles_3858(5d27_1
1683 cles_3769! 4tsr_1
1684 cles_2348! 2uve_6 2uvf_3
1685 cles_2658: 1ynu_2
1686 cles_2234: 2bj8_6
1687 cles_3674: 4rzx_1
1688 cles_2319: 4gfs_3
1689 cles_1880: 1uuo_2
1690 cles_1637! 3ii2_4
1691 cles_2678! 1sf8_1 1sf8_3 1sf8_2

1692 cles_1813(2gqk_1
1693 cles_3691(5fsh_2
1694 cles_3660: 3wd7_4 3wd7_6
1695 cles_2223' 1w9h_3
1696 cles_1753: 2v24_1
1697 cles_2473: 2noo_1
1698 cles_2189(1xm5_2 1xm5_4 1xm5_3 1xm5_1
1699 cles_3687' 5mle_1 5mle_2
1700 cles_2569(1q99_1 1q99_2
1701 cles_3435: 1n0y_2
1702 cles_2156! 1xxa_4 1xxa_1
1703 cles_1911' 2fp1_2
1704 cles_3433! 3qjk_1
1705 cles_2069: 1zhz_2 1zhy_1
1706 cles_1911(2fp1_1
1707 cles_3866' 4q9x_5
1708 cles_3866! 4q9x_6
1709 cles_3866' 4q9x_8
1710 cles_1695: 1ks4_3
1711 cles_2414' 3fou_7
1712 cles_2455(4bd8_1 4bd7_1 4bd8_2
1713 cles_2414: 3fou_5
1714 cles_1921(1k0z_1 1k0z_2
1715 cles_1962(3ukj_1
1716 cles_2417: 3fou_8
1717 cles_2417: 3fou_11
1718 cles_2596(1ok9_1 1ok9_2
1719 cles_3630! 4pke_4
1720 cles_1977' 1qj8_1
1721 cles_2077! 2ch8_10 2ch8_2 2ch8_6 2ch8_3
1722 cles_3995! 4lq6_3
1723 cles_3626' 4pke_1
1724 cles_1705(2hux_1
1725 cles_1635(1bix_3
1726 cles_2077: 2ch8_12 2ch8_9 2ch8_11 2ch8_5
1727 cles_3868! 4lw9_59 4lw9_32 4lw9_46 4lw9_45 4lw9_25 4lw9_47 4lw9
1728 cles_2629(3mgr_10
1729 cles_2635(1ud5_2
1730 cles_3906' 4ngi_1
1731 cles_2397(1swy_5 1swz_1 1sx7_2 1sx2_3
1732 cles_1955' 1cx8_19 1cx8_6 1cx8_9 1cx8_13 1cx8_11 1cx8_3 1cx8_18 1
1733 cles_3768: 5g3s_4
1734 cles_1630: 1bix_4 2o3h_2
1735 cles_1636: 1bix_1
1736 cles_1937(4afp_1
1737 cles_2336: 1soi_1
1738 cles_2565: 1dt6_2

1739 cles_2398 2anv_3 2anx_3
1740 cles_2398 2anx_2 2anv_1
1741 cles_1764 2x3l_6
1742 cles_3582 4p1j_1
1743 cles_2416 2e0y_1 2e0y_2
1744 cles_1754 1dkh_3
1745 cles_2398 2anv_4
1746 cles_2360 3ccm_110 1vqk_177 1vql_93 3ow2_112 3cd6_115 1yhq_1
1747 cles_2052 1dd9_1
1748 cles_2003 1oo0_1
1749 cles_3798 5c9f_2 5c9f_1
1750 cles_3958 4igu_1
1751 cles_2025 2gsi_4
1752 cles_3855 5agv_5
1753 cles_2646 3x16_1 4pae_2 3wnu_2 3wxo_3
1754 cles_1639 4j9x_2 4j9x_1 4j9w_2 4k7x_1 4jci_1 4j9w_1
1755 cles_4027 4hiz_18
1756 cles_2221 4ekf_1
1757 cles_1938 4af8_1
1758 cles_2324 5ey5_3 5ey5_1
1759 cles_2142 1yq2_10 3ob8_11 1yq2_16 1yq2_18 3ob8_2 1yq2_14 3ob8
1760 cles_1755 4b1m_2 4b1m_1 4b1m_4 4b1l_1
1761 cles_2506 3ahe_1 3ahd_2 3ahi_2 3ahh_1 3ahc_2 3ahg_2
1762 cles_2371 1e7p_2 1e7p_22 1e7p_23 1e7p_1
1763 cles_3622 4n3p_13 4n3p_5
1764 cles_1717 2jin_1
1765 cles_1944 3lwl_4
1766 cles_1901 3a07_6 3a07_3
1767 cles_1649 3ov9_1
1768 cles_1823 3cqx_4
1769 cles_1967 2bz8_1 2bz8_2
1770 cles_3661 4wnv_1
1771 cles_2185 3gsh_4
1772 cles_2297 2bjb_1
1773 cles_3419 4tog_4 4e6k_10 4tof_3 4tog_1 4tog_5 4e6k_7 4tog_6 4e6k
1774 cles_2547 2omg_2 2omh_1
1775 cles_1629 4imq_1
1776 cles_2335 3o52_6 3o52_1
1777 cles_2426 3o79_4
1778 cles_3876 4ubh_7 4ubg_2
1779 cles_3782 4wxg_1 4wxb_6 4wxb_5 4wxg_2 4wxb_4
1780 cles_2156 2fqg_4
1781 cles_2243 3fyo_1 4jtf_1 3stf_1 3fyp_1 4jtg_1 3ste_1 4jte_1 3qpz_1 3s
1782 cles_1688 3jpw_1 3jpy_5
1783 cles_1996 4kxy_4 3mos_1 4kxu_2 4kxx_1 4kxy_2 4kxw_1
1784 cles_2653 2y8k_4
1785 cles_1718 4hry_1

1786 cles_1709: 3qm1_5
1787 cles_2624: 2iwf_12 2iwk_45
1788 cles_4071: 4mkk_1
1789 cles_2661(4eyv_7
1790 cles_2223: 2a5g_1 2a5f_2
1791 cles_1705: 3c17_9 3c17_10
1792 cles_3527: 4mvj_11
1793 cles_3752: 5h3q_1
1794 cles_3615: 4ovz_3
1795 cles_2432: 2fqe_3
1796 cles_3551: 4oua_8 4oua_4
1797 cles_1864(4adn_6
1798 cles_2204: 1q6x_1 1q6x_2
1799 cles_2605: 3p6z_5
1800 cles_2419: 2wcf_2 2wce_2 2wc8_7 2wcf_1 2wcb_2 2wc8_6 2wce_1 2
1801 cles_2496(3nrb_3
1802 cles_2010(3mqd_1
1803 cles_2059: 1w37_1
1804 cles_2187: 5b15_7
1805 cles_2390: 3ff1_1
1806 cles_2685: 2xo2_3
1807 cles_3761: 5f8a_2 5f8a_4
1808 cles_3936: 3zn2_4 3zn2_1
1809 cles_4112: 5hdk_7
1810 cles_3883: 5fay_1 5faw_2 5fav_3
1811 cles_3615: 4n3p_3
1812 cles_2230: 3d77_1 3d76_1
1813 cles_2605(1xxf_2
1814 cles_1680: 1gmm_2
1815 cles_3617: 4n3p_7
1816 cles_2257: 4dj4_3
1817 cles_1698(4gbj_1 4gbj_4 4gbj_2
1818 cles_1972: 3h7c_2
1819 cles_2249(4zzc_4 4hfd_5 4zzb_5 4hfd_3 3igq_9 4hfc_6 4hfe_6 4ila_7
1820 cles_2617: 3o38_1
1821 cles_1679: 3ipp_1 3ipo_2 3ipp_2 3ipo_1
1822 cles_3962: 4kkx_3
1823 cles_1717: 2wm2_2 2wm2_9
1824 cles_3760: 5t26_3
1825 cles_2042: 3hhq_8 3hhq_7 3hhq_13
1826 cles_3942: 4l1f_1
1827 cles_2674: 1z2u_1
1828 cles_2447(3sit_2 2i2s_2 3sis_2 2i2s_1 3tay_1 3sit_1 3tay_2 3sis_1
1829 cles_1612: 3b8x_4
1830 cles_1679: 3abr_9
1831 cles_2663: 1v6s_1 1v6s_2
1832 cles_1614: 2b9w_1

1833 cles_4072[illegible]4jqa_1
1834 cles_2610[illegible]2h4v_1
1835 cles_1804[illegible]4g1m_2
1836 cles_3569[illegible]5iak_1
1837 cles_4108[illegible]2qw1_2 2fw0_4
1838 cles_2662[illegible]1r4p_5 2ga4_4
1839 cles_2555[illegible]4alo_1
1840 cles_2245[illegible]3rwk_1
1841 cles_4010[illegible]3zpi_3
1842 cles_2033[illegible]3mj6_1
1843 cles_4110[illegible]3gbv_1
1844 cles_3785[illegible]3x2f_2
1845 cles_3730[illegible]4xn4_1 4xo4_5
1846 cles_1719[illegible]5dnu_2
1847 cles_1704[illegible]4ia6_2
1848 cles_2234[illegible]4ma5_1 3q2o_1 3q2o_2 3v4s_1 4m9u_2
1849 cles_2447[illegible]3osj_3
1850 cles_2026[illegible]4ofi_4 4ofi_3 4ofi_1 4ofi_2
1851 cles_3603[illegible]4q3m_1
1852 cles_2615[illegible]2z1n_1
1853 cles_2569[illegible]4iz7_1
1854 cles_2655[illegible]2osx_4
1855 cles_1918[illegible]3lqc_1
1856 cles_3865[illegible]4ubh_8 4ubg_6
1857 cles_2030[illegible]1t8u_2 1t8u_1
1858 cles_1746[illegible]1wnw_1
1859 cles_2075[illegible]3iqe_1
1860 cles_2364[illegible]3oi7_6
1861 cles_1816[illegible]1oa8_2 4apt_1 4aqp_2 4aqp_3 1oa8_3 1oa8_1 4aqp_1
1862 cles_3825[illegible]4qrv_2
1863 cles_3405[illegible]2vpb_3
1864 cles_2419[illegible]2rgi_3
1865 cles_2010[illegible]4jga_1
1866 cles_2255[illegible]2ga4_2 1r4p_1 2ga4_3 1r4p_4
1867 cles_2150[illegible]1diz_2 1diz_1
1868 cles_2651[illegible]3c9f_1
1869 cles_2243[illegible]1gv2_1
1870 cles_1619[illegible]1htw_3 1htw_2 1htw_4
1871 cles_2519[illegible]4fmt_1 4qpj_3 4fmt_3 4fmt_2 4qpj_5 4fmt_4
1872 cles_3877[illegible]4lh7_1 4lh6_2
1873 cles_2633[illegible]3ply_1
1874 cles_2324[illegible]3dki_1 3tbh_1 5iw8_1
1875 cles_2550[illegible]4tvo_14
1876 cles_1665[illegible]3epz_3
1877 cles_1718[illegible]4kyv_4 4kyv_1
1878 cles_1978[illegible]2d4d_1 1lds_1 2d4f_1
1879 cles_4040[illegible]5i96_3 5i96_1

1880 cles_2551(3dl2_2 3dl2_1
1881 cles_4041(4v0s_1
1882 cles_2070(2xyn_2
1883 cles_1716(3pdv_1
1884 cles_3599(4lss_1
1885 cles_3862(4ije_3 4ije_4 4ije_6
1886 cles_2145(2oln_1
1887 cles_2661(4eyv_13 4eyv_11
1888 cles_2470(2zsa_2
1889 cles_1924(4l5r_1
1890 cles_1634(3hup_1
1891 cles_1885(3h8j_1
1892 cles_3942(4csh_1 4csh_10 4csh_9 4csh_4
1893 cles_2602(2bdg_4
1894 cles_3715(5lbv_1
1895 cles_2279(3b37_1
1896 cles_2480(4gvo_1 4gvo_2
1897 cles_2188(2dct_1
1898 cles_2601(1s82_1
1899 cles_2017(4jn6_1
1900 cles_2224(4f8d_2
1901 cles_2098(2xgl_16
1902 cles_3804(5cvy_13
1903 cles_2026(4pj8_1
1904 cles_2262(2j56_3 2j56_4
1905 cles_2620(3iv2_1
1906 cles_2592(3bx1_5
1907 cles_2276(1wx5_1
1908 cles_3510(4l73_10 4l73_2 4l76_5
1909 cles_3607(4o1q_6
1910 cles_2094(2j5w_9
1911 cles_4015(4uug_1
1912 cles_1885(3u18_2 3u18_1
1913 cles_2295(4kbf_1
1914 cles_1697(4gbj_3
1915 cles_2201(3uet_2 3uet_1 3ues_1 3ues_2
1916 cles_4023(4jjd_1
1917 cles_1992(3m1h_4 3m1h_10
1918 cles_2640(3be8_1
1919 cles_1937(4r5h_1 3pwk_2 4r3w_2 4r3n_2 4r4j_2 4r54_3 4r41_3 3pws
1920 cles_3600(4c2u_4 4c2u_2
1921 cles_3833(5dmy_1
1922 cles_3979(4s0n_3 5bnh_2 4s0n_4 4s0n_2 4s0n_1
1923 cles_2235(4hkt_1 4hkt_2
1924 cles_3796(5e1i_1
1925 cles_4127(4q5k_1 4q68_3
1926 cles_4113(4yuc_1

1927 cles_4009⁴ 5faj_2
1928 cles_3753⁻ 5t0a_3 5t05_6 5t03_1
1929 cles_2241⁹ 3ob8_13 3ob8_18 3ob8_3 3ob8_5
1930 cles_2187⁻ 1p9e_3
1931 cles_2336⁵ 3gz5_2 3gz5_1
1932 cles_3616⁶ 4n3p_12
1933 cles_2070⁶ 3s95_2 3s95_1
1934 cles_2206⁰ 3ned_3
1935 cles_2519⁶ 2ynq_1 2ynq_3 2ynq_4
1936 cles_2605⁻ 4ag2_5
1937 cles_3864⁶ 4ubg_7
1938 cles_3514⁵ 4xmz_4 4xmv_2 4xmu_2
1939 cles_2093⁵ 2xyb_10
1940 cles_1875⁹ 1hx6_5 1hx6_4
1941 cles_2236⁴ 2p1r_8 2p1r_2
1942 cles_1649⁰ 3ov9_2
1943 cles_2433⁶ 2fqg_3
1944 cles_3903⁻ 4pu5_1
1945 cles_2570⁹ 3k2l_1
1946 cles_2617⁻ 3tl3_1
1947 cles_3760⁻ 5t26_5 5t26_2
1948 cles_2103⁸ 3lrl_1 3lrk_1
1949 cles_1610⁷ 3b8x_2
1950 cles_1814⁻ 3o8q_2
1951 cles_3674⁹ 5j6h_2
1952 cles_2603⁷ 3p70_3
1953 cles_3805⁻ 4xo3_4
1954 cles_2569⁴ 4z7g_1 4z7g_2
1955 cles_4058⁻ 4qm6_7
1956 cles_2657⁻ 2ppl_1
1957 cles_3877⁷ 4lh6_1 4lh7_2
1958 cles_4074⁰ 4pp4_3 3wrn_3
1959 cles_3721⁻ 4yhf_3
1960 cles_3523⁴ 4l37_1
1961 cles_2597⁰ 2yj7_1
1962 cles_2363⁻ 3kzw_16 3kzw_7 3kzw_3 3kzw_8 3kzw_14 3kzw_10 3kzw_
1963 cles_3898⁸ 4yf1_1 4yf1_2
1964 cles_1700⁵ 3otk_2 3otk_1
1965 cles_3694⁹ 4py9_4
1966 cles_2062⁻ 1h17_7 2pfl_2 1cm5_1 1h16_3 1h18_5 2pfl_1 1h18_6 1cm
1967 cles_3840⁷ 5tee_1
1968 cles_2086⁰ 4dcc_1
1969 cles_1740⁰ 1h80_8 1ktw_8 1ktw_2 1h80_1
1970 cles_2143⁵ 2o11_2
1971 cles_2132⁻ 3cmj_5
1972 cles_2170⁻ 3peb_1
1973 cles_4111⁰ 5eld_1

1974 cles_3708[illegible] 4txo_2
1975 cles_2587[illegible] 2vdx_2
1976 cles_1809[illegible] 3zq5_2
1977 cles_3624[illegible] 4udu_1
1978 cles_1685[illegible] 3ihr_1
1979 cles_2406[illegible] 2vv8_2 1xj6_2 2vv6_3 1xj4_2 2vv7_4
1980 cles_2152[illegible] 1et1_1 1et1_2
1981 cles_3846[illegible] 5cgm_2
1982 cles_4059[illegible] 4tvo_10
1983 cles_2153[illegible] 2wpc_4 2wpc_5 2wov_7 2wpc_1 2wp5_2 2wov_3 2wpe_3
1984 cles_2279[illegible] 4ywd_3 3dtb_3 2qew_3 2rk7_3 4ox2_5 2rkd_1 4gnm_2 3d
1985 cles_1881[illegible] 2ri0_2
1986 cles_2326[illegible] 1sk4_1
1987 cles_2355[illegible] 1x9j_1
1988 cles_2221[illegible] 2oz9_1
1989 cles_2034[illegible] 1hnf_1
1990 cles_2438[illegible] 4a81_1
1991 cles_2438[illegible] 4a87_1
1992 cles_2265[illegible] 4odn_1
1993 cles_2340[illegible] 3io1_3 3io1_2
1994 cles_3878[illegible] 5t5i_39 5t5i_29
1995 cles_4124[illegible] 4us6_1
1996 cles_3887[illegible] 4xgw_1 4xgv_2 4xgw_7 4xgw_4 4xgv_3
1997 cles_3894[illegible] 4mkj_1
1998 cles_2422[illegible] 3qae_3
1999 cles_2130[illegible] 4a3u_5
2000 cles_2357[illegible] 3u1o_2
2001 cles_2112[illegible] 3bga_6 3bga_5
2002 cles_3660[illegible] 4wnv_7
2003 cles_1856[illegible] 2okq_2
2004 cles_2026[illegible] 3u0a_1
2005 cles_3959[illegible] 5com_1
2006 cles_1936[illegible] 3pzr_2 3pzr_1
2007 cles_4074[illegible] 4pp4_2
2008 cles_1609[illegible] 3gjc_1 3gjc_2
2009 cles_1726[illegible] 4bvn_1 2y04_1 2vt4_2 2y03_1 2y02_1 3zpq_3 4amj_1 4am
2010 cles_2560[illegible] 1yl1_1
2011 cles_1861[illegible] 1gq2_40 1gq2_34
2012 cles_2611[illegible] 2p7g_1
2013 cles_2541[illegible] 4bqc_1 4bqc_2
2014 cles_1866[illegible] 3ov1_1
2015 cles_1617[illegible] 4eib_5
2016 cles_1870[illegible] 2o9s_1
2017 cles_1717[illegible] 2opg_1
2018 cles_3975[illegible] 4rt1_1
2019 cles_2199[illegible] 4rmj_3
2020 cles_1687[illegible] 3v45_2

2021 cles_1740: 3meq_9
2022 cles_4079: 4xin_1
2023 cles_2394(4dwg_2
2024 cles_2657 2ppl_3
2025 cles_2226 3rdq_1
2026 cles_3882: 4ook_3
2027 cles_3824: 5t25_10
2028 cles_1822 3okf_1
2029 cles_2691 1gq2_2 1gq2_39
2030 cles_4025: 4piu_1
2031 cles_1904 2bdr_1
2032 cles_3592 5hay_1
2033 cles_2419: 2rgi_1 2rgi_2
2034 cles_3999 4zac_7 4zac_3 4zac_4
2035 cles_1679 3zu2_1
2036 cles_2037 4jrx_1
2037 cles_1609 2qz7_1 2qz7_2
2038 cles_1937(4af8_4
2039 cles_3850 5d3d_1
2040 cles_3926: 5ce9_4
2041 cles_2394 3cc9_1
2042 cles_2561 3ru5_5 5fek_1 1gwd_3 5idd_2
2043 cles_2257 4dd8_13 4dd8_10 4dd8_8 4dd8_17
2044 cles_3709 4z7c_1
2045 cles_3710 4xmw_1 4xn1_1 3qjx_1
2046 cles_2070(3f66_1
2047 cles_1733: 3zwf_2
2048 cles_3584(5fob_1
2049 cles_2627 5bmx_3 5bnk_1 5bmx_1 4zz9_1 5bmx_4 5bmw_1 5bmw_2
2050 cles_2375: 3szs_11
2051 cles_2205(3ffz_4 3ffz_5
2052 cles_1666 2wsj_2
2053 cles_4006 5tee_2
2054 cles_1879 3blj_1 3blj_2
2055 cles_3839: 4qop_6 4qor_4 4qom_6 4qoo_6 4qoq_2 4qon_3 4qor_6 4c
2056 cles_2669: 2j6l_6 2j6l_1 2j6l_8 2j6l_7 2j6l_3 2j6l_2 2j6l_4 2j6l_5
2057 cles_2290 1xk8_1
2058 cles_2104(2yfo_5
2059 cles_3997(4qpk_1
2060 cles_1833 3hyj_1
2061 cles_3960 4pmr_1
2062 cles_3578 5jea_4
2063 cles_2232(2xge_1
2064 cles_4130: 4pf4_1
2065 cles_1678: 1omo_1 1omo_2
2066 cles_2560 1lzs_1 1yam_1 1eq4_1 1ip3_1 1yaq_1 1eqe_1 1yap_1 1wq
2067 cles_2435 2xmj_1 2xmk_1 2xmm_1

2068 cles_2480 2v3u_1 5dtb_1
2069 cles_2142(2ciq_1
2070 cles_2614 2wyv_2 2wyv_1 2wyu_3 2wyu_1 2wyu_2 2wyv_3
2071 cles_1666 2wsj_4
2072 cles_1867 2cfd_1 2cfw_3 2cg1_3 2cfg_4 3x3x_5 3kii_4 3x42_2 3amo_
2073 cles_1976 3of5_5
2074 cles_2026 2gsi_6
2075 cles_1970 2p7h_2 2p7h_1
2076 cles_1952 2c9r_1
2077 cles_2372 1zud_2 1zud_4
2078 cles_2369(3bos_1
2079 cles_1706 3igy_2 3igz_2
2080 cles_3894(4ohc_3 4ohc_4 4ohc_1 4ohc_2
2081 cles_3835 4xnb_2 4xnd_9
2082 cles_2104 2yfo_4
2083 cles_3785 4gy9_2
2084 cles_3707 4yaj_2
2085 cles_2041 4ao5_4
2086 cles_3785 3x2f_1
2087 cles_2572(2wnt_2
2088 cles_3723(3k9g_1
2089 cles_4121 4tvt_7 4zg3_3
2090 cles_3972 4s2l_2
2091 cles_1723(4kyv_3 4kyv_2
2092 cles_3972 4s2l_3
2093 cles_1860 1gq2_6 1gq2_15
2094 cles_4089 4c1e_1 4bz3_2 4bz3_6 4c1e_3 4c1d_5 4c1d_6
2095 cles_1732(3cmb_5
2096 cles_1965 3l8m_2
2097 cles_2558 2frs_3
2098 cles_2674 1zdn_2
2099 cles_2614(4zju_1
2100 cles_2519 2ynq_5
2101 cles_4088 4irw_5
2102 cles_1887 3n0p_1 3mzg_1 3n06_3 3nce_2 3ncc_2 3ncb_3
2103 cles_2660 4eyv_5 4eyv_4
2104 cles_1720 2wm2_6 2wm2_11
2105 cles_1786 4e71_1
2106 cles_3903 4r60_3
2107 cles_1902 4gdk_1 4naw_4 4naw_2 4naw_3 4naw_1 4gdl_1 4gdk_2
2108 cles_1746 2z68_2
2109 cles_1706 3c17_6
2110 cles_4120 4hil_3
2111 cles_4077 4gym_1
2112 cles_3920 4pcg_2 4pcg_4
2113 cles_1989(1rtq_2 3vh9_1
2114 cles_2602 3po1_1 1riw_2 2pks_1

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2116 cles_3614{ 5k8r_4
2117 cles_3487{ 4mmz_4
2118 cles_3886{ 4xn8_12
2119 cles_4123{ 3vwn_2
2120 cles_2588{ 2vdx_3 2vdx_4
2121 cles_3667{ 4jra_2
2122 cles_3731{ 4tvc_1 4ttu_2
2123 cles_2188{ 3gti_3
2124 cles_2691{ 1gq2_18
2125 cles_4120{ 5ack_2
2126 cles_3792{ 5jxj_7 5jxi_7 5jxg_6 5jxh_5
2127 cles_2364{ 3oi7_4
2128 cles_2001{ 3ddk_6
2129 cles_1936{ 3god_7 3god_8
2130 cles_3949{ 5lx8_3
2131 cles_2061{ 3s5n_2
2132 cles_2380{ 1us3_2
2133 cles_4121{ 4uu5_1
2134 cles_1901{ 3a07_5 3a07_4
2135 cles_3874{ 4ubh_9
2136 cles_1631{ 3nnb_1
2137 cles_1857{ 2qzi_7 2qzi_6 2qzi_5
2138 cles_1697{ 3dsq_1
2139 cles_2604{ 3p6z_7
2140 cles_2155{ 4g0r_3
2141 cles_4103{ 5imv_2 5imd_2 5imf_2 5ima_1 5io0_1 5iiz_3 5im9_3 5imc_
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2143 cles_2427{ 3moy_1
2144 cles_2652{ 3e7b_3
2145 cles_3861{ 4hr0_2
2146 cles_2167{ 3l27_2
2147 cles_2169{ 2rdh_1
2148 cles_1861{ 1gq2_12
2149 cles_2662{ 1r4p_3 2ga4_5
2150 cles_3623{ 4n3p_11
2151 cles_2601{ 2bdg_3
2152 cles_2379{ 1bg4_6
2153 cles_2205{ 3ffz_3
2154 cles_2223{ 2puv_2 2poc_2 2puv_3 2poc_4 2puv_4 2poc_1 2put_1 2pu
2155 cles_3803{ 4k70_10
2156 cles_2579{ 2r25_2
2157 cles_2342{ 4ntx_1 4ntw_3
2158 cles_2083{ 4fus_2
2159 cles_3808{ 4znm_2 4znm_3
2160 cles_2633{ 3ply_5
2161 cles_3878{ 5dgq_1 5dgq_2 5dgr_1 5dgr_2

2162 cles_2583 3v4m_1
2163 cles_2623 3aso_5 2ein_19 2eim_3 3wg7_11 1ocr_7 1ocz_4 3ag3_5 1c
2164 cles_2560 3txk_2
2165 cles_2373 1vi6_6 1vi6_5 1vi6_10 1vi6_1
2166 cles_1846 2oni_1
2167 cles_2330 2c3a_2 2c3a_1
2168 cles_3451 5lzq_1 5lzq_4
2169 cles_1717 3b76_1
2170 cles_1869 5ih2_3
2171 cles_2060 5t25_1 5t25_2
2172 cles_1823 3cqx_2
2173 cles_3655 5chc_14
2174 cles_3803 4k70_4
2175 cles_2376 2wnh_1
2176 cles_1758 2xyq_5 2xyv_6
2177 cles_2274 5t9c_1 5t9b_2 3qvq_14 5t91_2 3qvq_2
2178 cles_2170 5cnx_4
2179 cles_1707 4h0c_1
2180 cles_1861 1gq2_44
2181 cles_2603 1doj_2
2182 cles_2556 4alo_3
2183 cles_1635 4iem_8
2184 cles_2561 1jtt_3
2185 cles_1618 4eib_6
2186 cles_1773 1o68_4 1o68_2 1o68_3 1o68_1
2187 cles_3550 4zxs_2
2188 cles_2621 4qrg_1
2189 cles_3957 5fcc_1
2190 cles_3417 1dps_4 1dps_5 1dps_6 1dps_12 1dps_9 1dps_7 1dps_10 1c
2191 cles_2438 3e85_2
2192 cles_1988 3hww_26
2193 cles_2134 3cmj_2
2194 cles_2278 3fph_1 3fph_2
2195 cles_2264 1rwc_1 1rwh_1 1rw9_1 1rwf_1 1rwg_1
2196 cles_2214 1gvy_2 4cd4_2 1odz_1 1odz_2 1gw1_2 2whm_2 4cd5_1 2v
2197 cles_2078 4gaf_1
2198 cles_4078 5drh_1 5c6x_1
2199 cles_4058 4tvo_1
2200 cles_2470 3aez_1 2zsa_3
2201 cles_4139 4wee_3
2202 cles_3406 2vpb_2
2203 cles_3589 4on3_8 4on3_6
2204 cles_1612 3bn1_1
2205 cles_2550 4jco_21
2206 cles_3711 4cta_3
2207 cles_3433 5ibw_1
2208 cles_2675 5hn3_1

2209 cles_1726? 4ldl_1 4lde_1 4ldo_1 4qkx_1
2210 cles_1973? 3h7k_3
2211 cles_3751? 5t26_7 5t26_1
2212 cles_2660? 3hvu_3 3hvu_2 3hvu_4 3hvu_1
2213 cles_2056? 2x8f_5 2x8f_6
2214 cles_3949? 5lx8_2
2215 cles_3828? 4i6u_1
2216 cles_3932? 5kay_2
2217 cles_2244? 1ewn_1 1f4r_1 1f6o_1
2218 cles_3848? 4xhq_2
2219 cles_2024? 4tqe_4
2220 cles_2486? 4jzz_4
2221 cles_4062? 4oki_3
2222 cles_1740? 2fcw_3
2223 cles_1719? 4kaj_4
2224 cles_3747? 4xmt_1 4xn2_10 4xo5_4 4xn8_11 4xn4_8 4xnb_5 4xo3_3
2225 cles_2020? 1m65_2
2226 cles_4132? 5b8d_3 5kh9_1
2227 cles_2054? 3nkr_1 5ijs_4 3wav_3 4zg9_8 4zg6_2 4zg7_1 5dlv_6 3nkn_?
2228 cles_2103? 2yfo_17
2229 cles_3646? 4xo4_4 4xna_5 4xn2_2 4xn8_5 4xmx_2 4xmz_6
2230 cles_2520? 3scy_2
2231 cles_2224? 2xcj_2 2xcj_1
2232 cles_1636? 2wfx_4
2233 cles_2011? 3ot1_1
2234 cles_2459? 3akr_1 3aks_1
2235 cles_1754? 4jer_1
2236 cles_2527? 3m92_1
2237 cles_3780? 4h7o_1
2238 cles_2054? 2x8f_1 2x8f_2
2239 cles_1987? 3hww_20
2240 cles_2592? 2xrm_3
2241 cles_1801? 3abr_2
2242 cles_4047? 5fag_5
2243 cles_3618? 4j3g_2 4j3g_1
2244 cles_3942? 4l1f_3
2245 cles_1964? 3dc7_3
2246 cles_3587? 4yu6_1
2247 cles_4134? 5iiz_2
2248 cles_2438? 4gy9_5 4jhg_1
2249 cles_1865? 1x27_3 1x27_6 1x27_4 3uf4_1 1x27_1 1x27_5 1x27_2
2250 cles_4122? 5dnu_3
2251 cles_2026? 5e56_1
2252 cles_2201? 4a45_2 4a44_1
2253 cles_2648? 3vwn_3 3a66_1 3a65_1 3vwp_1
2254 cles_2239? 4h0c_2
2255 cles_1749? 4a1r_1

2256 cles_1937: 3dr3_2
2257 cles_1699: 3grd_1
2258 cles_3617 5bpf_3 4zqi_2 5c1o_1 5bph_2 5bph_5 5c1p_4 4zqi_5 5c1p_
2259 cles_2247 2qmw_1
2260 cles_3658 4o54_2 4o52_2 4o53_1 4o50_3 4o4w_2
2261 cles_1622 3ow2_103
2262 cles_2661 4eyv_8
2263 cles_2355 1saz_1
2264 cles_2310 4khs_2 4ki4_1
2265 cles_4124 4tvt_4 4zg3_6
2266 cles_2371 2ws3_12 2wp9_12 2wdr_14 2wu2_11 2wp9_9 2ws3_11 2w
2267 cles_3959 4o66_1
2268 cles_2382 3ur7_1
2269 cles_2189 3pui_1
2270 cles_3589 4on3_7 4on3_5
2271 cles_3573 4xn5_3
2272 cles_1858 2qzi_2 2qzi_1 2qzi_3
2273 cles_3822 5kn7_1
2274 cles_2423 3qae_6
2275 cles_2607 4hqo_1
2276 cles_2290 3opk_2
2277 cles_4128 4cnp_2 4cnn_2 4cnn_6 4cnp_3
2278 cles_2290 1nza_2
2279 cles_2039 3hhq_5
2280 cles_2497 2zsg_2
2281 cles_2546 3c7x_1
2282 cles_4059 4tvo_15
2283 cles_2347 4u7x_2
2284 cles_1780 4lc9_1
2285 cles_2614 3svt_1
2286 cles_2517 3zqs_2
2287 cles_1708 3qm1_33
2288 cles_2170 2c0g_1
2289 cles_4061 4crq_2
2290 cles_1781 3gzh_1 4efc_3
2291 cles_2190 5b1u_9
2292 cles_2689 3gzh_2
2293 cles_3917 4fdz_2 4tme_1
2294 cles_1987 3hww_17
2295 cles_2587 2vdx_1
2296 cles_1684 4i6n_1
2297 cles_3844 5cgm_9
2298 cles_2371 3pf4_1
2299 cles_2692 1gq2_16
2300 cles_1611 3b8x_6 3b8x_5
2301 cles_4110 3ga5_1 3ga5_3
2302 cles_2433 5ue6_6 5ue6_23 5ue6_7 5ue6_5 5ue6_8 5ue6_21 5ue6_1

2303 cles_2371(1knp_1 1knr_1
2304 cles_2104: 2yfo_20
2305 cles_2458: 2vgd_1
2306 cles_2181(4f3y_3
2307 cles_3711(4jii_1
2308 cles_2247(2ija_1
2309 cles_2254! 1m1k_110
2310 cles_2422(3qau_17
2311 cles_4058(4qm6_2
2312 cles_1679! 4euh_1
2313 cles_1938(4af8_2
2314 cles_3670: 5e76_1
2315 cles_2546: 3v6n_1 3v6n_3
2316 cles_2352: 3u1o_3
2317 cles_3656: 4x5l_1
2318 cles_2426: 4hls_2 4hmr_1 3o79_3 3o79_2 4hmm_3
2319 cles_3913(4us5_18 4us5_4
2320 cles_1613(2ba9_1
2321 cles_1689! 5ewl_5 5ewm_4
2322 cles_4050: 4lov_3
2323 cles_2371: 1hzb_1 1i5f_1 1c9o_2 1c9o_1 1hzc_1
2324 cles_3715: 4c75_1
2325 cles_1744: 2q16_3
2326 cles_3711: 4xn1_5
2327 cles_3523: 4l37_2
2328 cles_2691: 1gq2_13
2329 cles_3955: 4qnk_8 4qnk_14 4qnk_10 4qnk_16 4qnk_22 4qnk_6 4qnk_
2330 cles_3514(4xmz_1 4xmw_5
2331 cles_1914! 3cbt_3
2332 cles_3708(4xn1_7 4xn4_5 4xmz_5
2333 cles_1658(3mjf_1
2334 cles_4028! 4hiz_12
2335 cles_3891(4huc_1 4huc_2
2336 cles_2506: 4afy_2
2337 cles_1732: 3cmb_10 3cmb_4
2338 cles_2364: 2ekb_1 2owd_1 2p9y_1 2p2z_1 2p9z_1 2p75_1 2p78_1 2p
2339 cles_3617: 4n3p_10
2340 cles_3833: 5dmy_4
2341 cles_3776: 4q05_2
2342 cles_2682(2epf_6 2epf_8 2epf_1
2343 cles_2253(2jih_10
2344 cles_2560: 1lzn_1
2345 cles_1869: 2v1q_1
2346 cles_3680(4jra_1
2347 cles_4050: 4lov_1
2348 cles_1749(4inb_1
2349 cles_2191(4d1d_1 4d1c_1 2jln_2 2jlo_1 4d1b_1 4d1a_1

2350 cles_1664: 4e0u_1 4e0t_2 4e0t_3 4e0t_4 4e0t_1
2351 cles_1869: 4ag2_3
2352 cles_1869 3ua6_2
2353 cles_3948 4kkx_2
2354 cles_3609 4zm9_3 4zm9_6
2355 cles_3757 5t26_4
2356 cles_3777 4jvn_1 4jvm_1 4jvl_3 4jvm_2 4jvl_1 4jvn_2
2357 cles_4022 5ffl_1
2358 cles_4021 4lcy_1
2359 cles_2210 3mga_1
2360 cles_1711 2f6p_1
2361 cles_2422 3qau_10
2362 cles_2191 4znb_1 4znb_3
2363 cles_3675 5j6h_1
2364 cles_4125 4plg_4
2365 cles_2592 3h42_1
2366 cles_2569 4d9u_1 2wnt_3 3rny_2 4d9t_1 2qr8_1 2qr7_1 4m8t_1 2wr
2367 cles_2187 5axo_1 5b15_2 5b1u_10
2368 cles_2094 4ain_1 4llh_3 4llh_5
2369 cles_1944 3t3f_4
2370 cles_1985 3vh9_6 3b3s_3
2371 cles_2415 4n9m_1
2372 cles_1925 1avf_1
2373 cles_3907 4wfx_2
2374 cles_2055 2x8s_2
2375 cles_1713 1fi1_3
2376 cles_2688 4a6u_1 4a6u_2
2377 cles_3714 4qxk_1
2378 cles_1825 3cqx_3
2379 cles_2271 3d32_1
2380 cles_2560 3t6u_6
2381 cles_1609 3usk_5 3usk_1 3f48_2 4fxz_2 3usi_2 2a65_1 4us4_2 2q72_
2382 cles_1703 3klb_1
2383 cles_4096 4zh5_1 4zg8_7
2384 cles_3551 5h9v_1 5h9v_4 5h9v_2 5h9v_3
2385 cles_4057 4tvo_19
2386 cles_1734 1t6b_2
2387 cles_2615 1so8_2 3ppi_8 3ppi_6 3ppi_5 3ppi_3
2388 cles_4134 5iqx_4
2389 cles_3855 5agv_9
2390 cles_2524 1tg7_2
2391 cles_2272 3qvq_19
2392 cles_2004 2ilz_4
2393 cles_3874 4ka8_1 4ka7_1
2394 cles_3627 4udu_2
2395 cles_2345 2a9z_1 2ab8_1 2a9y_1 2aa0_2
2396 cles_1936 4r3w_1 4r3n_1 3pwk_1 4r54_1 4r41_2 4r51_2

2397 cles_3443 5ckq_1
2398 cles_2103 3ob8_17 3ob8_10 3ob8_19 3ob8_21
2399 cles_2601 4ag2_2
2400 cles_3719 4yhf_13
2401 cles_1699 3d9r_1
2402 cles_4035 4z5y_2
2403 cles_1720 5dnw_1
2404 cles_3928 4cte_2
2405 cles_4052 4xcz_4 4xd1_2
2406 cles_2103 1jz5_22 3muy_13 1jz6_10 1jyz_11 3t08_9 3i3d_27 3i3b_1 1
2407 cles_3681 4c7a_2
2408 cles_3895 5eua_2 5eua_1
2409 cles_2573 4f6u_1 4aw1_2
2410 cles_1846 3g1n_2 3g1n_1
2411 cles_3747 5ccu_1 5j14_1 5j14_2
2412 cles_2569 2a2a_1 2a2a_8 2a2a_5 2a2a_3
2413 cles_2425 5cfy_3 4izm_6 5cfy_12 5cfy_1 4izm_9 5cfy_6 5cfy_9 5cfy_7
2414 cles_2104 2yfo_16
2415 cles_1723 4kaf_6 4kaf_2
2416 cles_2016 3pj0_2
2417 cles_2569 2wnt_3 3rny_2 2wnt_1 3rny_1
2418 cles_2480 2xxu_1 2xxu_2
2419 cles_1872 4eik_1 3ua6_1 3ua6_3
2420 cles_3408 2xjl_5
2421 cles_2026 1c1x_5
2422 cles_3796 5inb_1 5j28_1
2423 cles_2582 2p6z_2
2424 cles_1632 3qi6_1
2425 cles_2691 1gq2_36
2426 cles_3991 5tdw_1
2427 cles_3653 4ccg_5
2428 cles_4108 5hdk_5 5hdk_10 5hdk_4 5hdk_12
2429 cles_3532 4q4b_1
2430 cles_2447 3pru_1
2431 cles_1621 3myv_1
2432 cles_3985 4kuf_3
2433 cles_2336 3o52_2
2434 cles_1661 1mx0_2
2435 cles_4071 4mkk_3
2436 cles_2313 2i9f_1
2437 cles_2690 4efc_2
2438 cles_1610 2ofi_2
2439 cles_2615 5en4_1
2440 cles_3654 5tbb_2
2441 cles_2026 3b5g_1
2442 cles_2025 5u17_1 4nqc_1 4pji_1 4pje_2 5u16_3 4pje_1 4pjh_1 4pjh_4
2443 cles_2198 3g13_1

2444 cles_1781? 3cx4_2
2445 cles_2547? 3exx_2
2446 cles_4079? 4mdx_1
2447 cles_4072? 4xtl_1
2448 cles_1700? 3grd_2
2449 cles_1820? 3oo2_1 3oo2_2
2450 cles_1916? 3jtz_1
2451 cles_1916? 1sa3_2 1sa3_1
2452 cles_4122? 4zg3_5
2453 cles_3886? 4g5h_1
2454 cles_2104? 2yfo_14
2455 cles_2656? 2oyl_3 2oyk_2 2oyk_1 2osw_4 2osx_3 2oyl_2 2osw_3
2456 cles_2382? 1yy6_6
2457 cles_1748? 3tif_2 3tif_1
2458 cles_2549? 2x0r_3
2459 cles_3875? 4q4e_2
2460 cles_1618? 3bpx_5
2461 cles_1810? 4m4v_1
2462 cles_3874? 4ubh_10 4ubg_5
2463 cles_3896? 5dpg_1
2464 cles_2019? 4gyf_3
2465 cles_1705? 4ia5_3
2466 cles_4073? 5bqf_1
2467 cles_3869? 4ubh_1 4ubg_8
2468 cles_2235? 3g8q_5
2469 cles_2451? 2nxb_1
2470 cles_2406? 3rfq_2 3rfq_1
2471 cles_1866? 3gxw_4 3gxw_2 3gxw_1 3gxw_3
2472 cles_1802? 3abo_3
2473 cles_4112? 5hdk_11
2474 cles_3897? 5i3l_1
2475 cles_3484? 5l3g_1
2476 cles_3929? 4nt1_1
2477 cles_2630? 3m1e_1
2478 cles_2169? 1rm6_4 1rm6_10
2479 cles_4046? 5fag_2
2480 cles_2212? 2ww2_2
2481 cles_2418? 3zq5_1
2482 cles_4111? 5hdk_2
2483 cles_2041? 4ao5_5
2484 cles_2062? 5fay_2 5kdp_1 5fay_3 5faw_1 5fav_1 5kdp_2 5fav_2
2485 cles_4079? 4uzq_1
2486 cles_3578? 5jea_1
2487 cles_2433? 2j5w_2 4enz_4
2488 cles_4132? 4p5r_2
2489 cles_3868? 4lw9_1 4lw9_62 4lw9_21
2490 cles_3787? 5p8w_1

2491 cles_2282[illegible] 3cqb_1
2492 cles_2065[illegible] 3o1x_1
2493 cles_2419[illegible] 3f5m_6
2494 cles_2402[illegible] 2y85_2 2y85_8
2495 cles_2329[illegible] 2c3a_7
2496 cles_3982[illegible] 5tt0_1
2497 cles_1828[illegible] 2r85_2 2r84_1 2r85_1 2r84_2
2498 cles_1719[illegible] 4lxh_1 4lxi_1
2499 cles_1724[illegible] 5iu4_1 4eiy_1 5iu8_1 5k2d_1 5k2c_1 5iub_1 5k2a_1 5iu7_1
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2501 cles_4038[illegible] 4u9u_1 4u9u_3
2502 cles_2660[illegible] 4eyv_6
2503 cles_2659[illegible] 2e7u_1
2504 cles_1913[illegible] 4eqi_3 4euz_1
2505 cles_3769[illegible] 4ymq_1 5g44_1 5g46_1 5apj_1 5g42_1 5g45_1
2506 cles_2691[illegible] 1gq2_38
2507 cles_2561[illegible] 3sp3_1
2508 cles_4129[illegible] 4bk7_1
2509 cles_2206[illegible] 5drg_1 5dqb_1 5drf_1
2510 cles_2481[illegible] 5ups_2 5jrh_2 5ups_1 2wd9_1 1pg4_2 5jrh_1 2vze_1 1pg4_1
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2512 cles_2315[illegible] 3mmo_6
2513 cles_2493[illegible] 3sji_1
2514 cles_3758[illegible] 4ciy_2
2515 cles_1731[illegible] 3cmb_2
2516 cles_3664[illegible] 4imm_2
2517 cles_2054[illegible] 1zm8_1
2518 cles_2325[illegible] 4d99_1
2519 cles_1828[illegible] 3ahh_2
2520 cles_3618[illegible] 4ncz_1 4k4l_2 4ncz_3 4ncz_2 4k4l_1
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2523 cles_2661[illegible] 4eyv_12
2524 cles_2180[illegible] 2xe4_2
2525 cles_2383[illegible] 3hjz_2
2526 cles_1817[illegible] 3tgo_1
2527 cles_3753[illegible] 5t26_6 5t25_6
2528 cles_3475[illegible] 4cza_2 4cza_1
2529 cles_3495[illegible] 4wfh_7 4wfh_2 4wfg_8 4wfg_3
2530 cles_2473[illegible] 1b3g_6 1b1h_3 1b32_6 1b4h_2 1b2h_1 1b51_3 1qka_2 1q[illegible]
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2532 cles_2474[illegible] 1b5j_2 1b9j_6 1qkb_3 1b5i_6 1b5h_4 1jet_3 1olc_6 1b3l_1
2533 cles_4116[illegible] 4fzp_2
2534 cles_2607[illegible] 1auq_1
2535 cles_2473[illegible] 1qka_5
2536 cles_2555[illegible] 3ph5_4 3ph6_2
2537 cles_2444[illegible] 3bfw_1

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2539 cles_3649: 4wfd_15
2540 cles_3650: 4wfd_12 4wfd_9
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2542 cles_1626: 3sag_4
2543 cles_2312(3bng_7
2544 cles_1726: 1z1y_4
2545 cles_2280(3u9w_7
2546 cles_2674: 3r3q_7
2547 cles_3788: 5lyd_4
2548 cles_2675: 2iv0_9
2549 cles_2192: 3m8t_1
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2551 cles_2471(4gsz_3 4gsz_4
2552 cles_3769(3wub_1
2553 cles_1951: 2ek0_2 2ek0_3
2554 cles_1816: 3l1e_1
2555 cles_2553: 1uv0_1 4mth_3
2556 cles_1922(1m4m_2
2557 cles_1610: 4aia_2 4ai4_1 4aia_4 2jg6_1 4aia_5 2ofi_1 1nku_1 4ai5_3 4
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2561 cles_2416(4a1b_3 3u5e_4 4a1d_2 4b6a_2 4a19_2 3u5i_4 4a18_2
2562 cles_1707(4ao7_2
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2564 cles_2384: 1k4p_2
2565 cles_3683: 5c22_2
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2567 cles_3721(3woj_1 3woj_2
2568 cles_1605: 2z45_1 2z45_9
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2572 cles_2374: 4gat_1 2vuu_7 5gat_1 2vuu_5 2vus_5 7gat_1 2vut_4 2vus_
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2576 cles_2635(1mwo_6
2577 cles_2436(3ci8_1
2578 cles_3573: 5hez_2
2579 cles_4095: 4tzh_8
2580 cles_3822: 4qc1_4 4qc1_1
2581 cles_2624(3r75_2 3r75_1
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2586 cles_2646 3fmu_7 3fkg_6 3fm1_7 3fm6_1 3fm4_6 4bll_6 2boq_2
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2588 cles_2613 5cc1_7 1hcq_2 5cc0_2 4hn5_2 2gda_1 1kb6_3 1hlz_1 5e6a
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2591 cles_2318 1k2f_3
2592 cles_2109 3hq2_2
2593 cles_3758 3won_3 3wop_2 3wor_1 3woq_2 3wom_2 3woq_4 3wom_
2594 cles_1982 2pdo_4
2595 cles_1966 4hcg_2 4hcg_3
2596 cles_2242 3nty_1 3gug_1
2597 cles_2594 3ee6_10 3ee6_4
2598 cles_2418 1f3z_1
2599 cles_2167 1pwu_1 1zxv_2 1pwp_1 4dv8_1 4pkq_1 5d1u_1 1j7n_2 1p
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2604 cles_2448 1n94_1 3q7a_1 3e37_1 3pz4_1 3sfy_1 3sfx_1 1n4s_1 1n9a_
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2609 cles_2456 3sp7_2
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2613 cles_1923 1xb1_22 1xb1_9 1xb0_21 1xb1_12 1xb1_11 1xb1_4 1xb0_9
2614 cles_2215 1cvr_1
2615 cles_2408 3hov_6 2nvy_6 4a3e_4 2yu9_6 3hoy_4 3i4n_4 1twc_6 2nv
2616 cles_2437 2rgx_3
2617 cles_2618 2d8a_3
2618 cles_3723 4lmg_5 4lmg_3
2619 cles_1792 1xaf_5 1xaf_2
2620 cles_1732 4puj_1 4gg9_1 3blo_1 5i06_1 1s38_1 2nqz_1 3c2n_1 2z1x_
2621 cles_1701 4ixm_3 4ixm_5
2622 cles_3691 5c22_4
2623 cles_4018 4xqb_4
2624 cles_1723 3gyy_11 3gyy_25
2625 cles_2248 1a7w_1
2626 cles_4048 4pxy_1 4pxy_8
2627 cles_2382 3ivb_3 3hqh_1
2628 cles_2317 3phx_2
2629 cles_1646 3ir2_3 3v4j_2 3v4k_3 3ir2_4 3v4k_6 3v4j_3
2630 cles_2244 1jml_2 1k51_3
2631 cles_2481 3poa_1

2632 cles_4005(4z9k_1 4lgr_1
2633 cles_3431: 5iyd_10
2634 cles_1661: 2wyh_1 2f1b_1 1r34_1 3ejt_1 3blb_1 2f7o_1 1qx1_1 3d51_
2635 cles_4111! 5hwa_3
2636 cles_2478: 3u93_2
2637 cles_3645(4ybh_9 4p2y_4
2638 cles_2350(3u1y_1
2639 cles_2062! 3mbg_10 3mbg_9
2640 cles_2605: 2psy_1
2641 cles_3574! 4k1t_7 4k1t_5 4k1t_1
2642 cles_2193- 1l3e_1 3p57_1 3io2_3 5hp0_1 2ka4_2 5hou_3 1p4q_2 2ka(
2643 cles_2569- 4wb7_9
2644 cles_1808: 1mwq_2
2645 cles_2494! 2qnw_3
2646 cles_2563(4fvk_8 4fvk_3
2647 cles_2350- 1yh8_4 2o3z_4
2648 cles_3880! 5chj_2 5chm_3 5cgx_2 5cgw_5 5cgs_1
2649 cles_2652- 2ush_3
2650 cles_3712(4p6s_2
2651 cles_1701- 4ixn_2 4ixm_1
2652 cles_2103: 3anv_1 3anu_1
2653 cles_3620(4ne7_3
2654 cles_1741! 3ppc_1 1u1h_2 4l6o_1 3bq5_2 4l5z_1 3bq5_1 1u1j_2 4l61_
2655 cles_1834! 3n3u_1
2656 cles_1647: 3ug7_7 3ug7_2 3ug7_4 3sja_3 3ug7_8 3sjd_4 3io3_1
2657 cles_1752! 2p1h_2 1cy5_1
2658 cles_2525: 1y8r_4 3dbl_1 1tt5_1 1r4m_3 3gzn_2 1y8q_4 1y8r_3 3dbl_
2659 cles_3691: 4lqf_4
2660 cles_1837(2vh9_2 2vh9_1
2661 cles_3941: 5a7m_11
2662 cles_2294: 1vec_1
2663 cles_1716: 3gj9_4 3gj9_3
2664 cles_3405(2fsa_5 3qzv_2 2f6n_4 2f6j_6 3kv6_2 2fuu_2 3kv6_4 2fsa_2
2665 cles_2324: 2ab4_1
2666 cles_2391(2zjs_1
2667 cles_3591! 3gze_8 3gze_5
2668 cles_2059: 1fbx_13 1fbx_5 1wpl_8 1fbx_7 1wm9_3 1fb1_2 1wm9_2 1f
2669 cles_1791(3umi_1
2670 cles_3635! 4u9g_3 4u99_3 4u9g_1 4u9b_2 4u9j_2 4u9k_3 4u9k_4 4u9
2671 cles_2072- 4aoj_6 4aoj_1
2672 cles_2532: 2p9x_4
2673 cles_2559: 1xki_1
2674 cles_2604: 1pjp_1
2675 cles_1711: 2pli_13 2pli_12 2pli_4
2676 cles_3911! 5a89_4 5a89_2 5a8a_3 5a8a_1
2677 cles_2279! 4l2l_4 4q4i_2 3ked_3 4pvb_1 4pj6_2 3ftv_1 3u9w_6 3fh7_:
2678 cles_2198! 2h2g_2

2679 cles_1920⁴ 4e2f_3 1raf_2 1rag_2 5at1_2 1rai_1 4e2f_2 7at1_1 2ipo_2
2680 cles_2165(3kzy_1 1eh8_1 1yfh_2 1eh7_1 3kzz_1 1eh6_1 3l00_1 1yfh_
2681 cles_2602(2a2q_3 2aer_3 2fir_5
2682 cles_4000: 5t7j_5 5lsv_4 5t7n_2 5t7k_1
2683 cles_3616! 5dor_1
2684 cles_1761(5brm_5 2hjn_1 5b5w_1 5brm_1 4jiz_1 5b6b_7 5b5v_2 5brl
2685 cles_3703: 4z40_15 4z3z_13 4z3z_16 4z3z_21 4z3z_7 4z40_12 4z40_2(
2686 cles_1656⁴ 1vyk_2
2687 cles_2597: 2xc2_2 2xbq_1
2688 cles_2188: 2o4m_15 2o4m_3 2o4m_12 2o4m_14
2689 cles_4015(4jjj_18
2690 cles_2253! 1e08_2
2691 cles_2351! 2xwc_2
2692 cles_3406! 3asl_2 3sox_8 3shb_1 3t6r_9 3zvy_1 3zvy_5 3sox_2
2693 cles_1789: 2ze7_1
2694 cles_1657(2j6x_1
2695 cles_1643: 4ebb_2
2696 cles_1963⁴ 2yr2_1
2697 cles_3407(1xtl_3 1xtm_1 1xtl_2
2698 cles_3564: 5imt_8
2699 cles_1692⁴ 4esj_2
2700 cles_2480⁴ 2yjp_7
2701 cles_2656: 2zum_2
2702 cles_2549⁴ 7mdh_5
2703 cles_1831! 2fe8_3 4m0w_1 3e9s_1 4wur_1 3mj5_2 3mj5_1 5ko3_1 4r
2704 cles_2691! 2hae_1
2705 cles_1733(1uns_1
2706 cles_2471(5mhb_3 1b4e_1
2707 cles_1775: 4nt9_1 4nt9_2 4nt9_3
2708 cles_2325: 3d2z_2 4knk_3 4bpa_2 2y2e_2 4knk_1 2y28_1 4ivv_1 2y2d
2709 cles_3690: 4l8h_4
2710 cles_3407(3mnd_1
2711 cles_4107(5kzz_3
2712 cles_1992: 1irx_1
2713 cles_2686! 4mdl_2 2ca2_1 2it4_1 4cnr_4 5e2s_1 2hd6_1 3b4f_1 5ezt_
2714 cles_1921: 1wcz_1
2715 cles_1726! 2ped_2 2ped_4
2716 cles_3553: 4nef_1
2717 cles_2600: 4d9q_6
2718 cles_2472! 1uqw_5
2719 cles_2576(2p2l_2 2p2l_1 2p2l_7
2720 cles_3469! 4wwu_12 4wwu_4
2721 cles_2686! 3da2_1 2hfw_1 3da2_2
2722 cles_1803: 2y6i_1 4ar9_2 4ar9_1 4arf_2 4ar8_2 2y50_1 4ar8_3 4are_1
2723 cles_2069(4aoj_3
2724 cles_3944(5dmm_2
2725 cles_2019⁴ 4gk8_2 4gyf_2

2726 cles_3618 4lx9_1
2727 cles_3408 2c9s_5 2c9s_2
2728 cles_1729 3s1l_2 4eez_3 3s2g_12 1nto_3 3s2i_5 5h83_1 3s2g_6 3s2f_
2729 cles_3948 5ioa_4
2730 cles_2193 3p57_2 1f81_1 3t92_3 2ka6_1 2kje_1 5hpd_3 5hp0_2 3io2
2731 cles_1750 5gpy_1 5iy9_8 5iy9_9 5iyb_5 5iya_7 1vd4_1 5iy6_2 5iy6_6
2732 cles_2331 3b8y_1 3b90_2 3b90_3
2733 cles_3602 5ij5_12
2734 cles_2023 2vh5_3 2uzi_2
2735 cles_1756 4c8e_3 4c8e_2 3fba_1 1yqn_2 3jvh_3 1w57_1 3ern_2 3k2x
2736 cles_3968 5g5y_13 5g5y_7
2737 cles_3971 5g5y_3
2738 cles_1861 2zc2_5
2739 cles_2602 1tq7_3 1z8i_2
2740 cles_2262 3j7a_5
2741 cles_1737 1iwl_2
2742 cles_2333 3nvo_7
2743 cles_2473 3o9p_4
2744 cles_1864 2hf1_1 2hf1_2
2745 cles_2210 3r0d_2 3rn6_2 3o7u_1
2746 cles_2208 2vad_2
2747 cles_2482 1cjv_3
2748 cles_1730 2g87_2 2ped_3 2hpy_13
2749 cles_2046 2vrs_5 2vrs_2 2vrs_4
2750 cles_1955 3ux3_2 3ux3_1
2751 cles_1863 2ptz_1 2pu0_1 2pu1_2
2752 cles_2564 2j1m_7
2753 cles_3636 5eu8_1
2754 cles_1649 1u10_6 1u10_3 1u10_4 1u10_5 1u10_1 1u10_2
2755 cles_1775 2g7n_2
2756 cles_1927 3udp_1 4i1c_2 4i12_2 3udk_2 4i0z_4 4i10_2
2757 cles_2062 3mbg_8 3mbg_12 3mbg_13
2758 cles_2337 3h90_1 3h90_11 3h90_4 3h90_19
2759 cles_2010 4a19_4 4a1d_3 4a1b_4 4a18_4
2760 cles_3514 3jpy_4
2761 cles_2437 1z83_4
2762 cles_2437 2rgx_4
2763 cles_2325 2ar3_1 2ar3_3 2l47_1 1yb0_2 2ar3_2 1yb0_3 1yb0_1
2764 cles_1958 3ubf_3
2765 cles_2258 4j4m_4 4j4m_1
2766 cles_2656 2cks_9 2ckr_1
2767 cles_3816 4d0y_3
2768 cles_1856 3kao_2
2769 cles_1823 3glf_11 1a5t_1 3glg_3 3glg_10 1njf_1 1jr3_1 1xxi_4 3gli_13
2770 cles_2153 2hba_2 2hba_7
2771 cles_1688 3fav_4
2772 cles_1623 3u5c_4 4bpp_63 4uer_3 4bpn_80 2xzn_24 2xzm_41 4bpo_

2773 cles_2341: 2h0r_5 3v8e_14 3v8e_6 2h0r_1 2h0r_6 3v8e_3 2h0r_4 3v8
2774 cles_2453: 3kno_159
2775 cles_1798: 3sjp_5
2776 cles_2639: 1gax_4 1gax_2 1jzs_1 1jzq_2 1ile_2
2777 cles_3416: 2ux1_13 2ux1_21 2ux1_16 2ux1_11 2ux1_14 2ux1_23 2ux1
2778 cles_2587: 1hp7_1
2779 cles_1614: 3wqz_1 2zzg_1 2zzf_2 2zzg_3 3wqz_2
2780 cles_3927: 4myp_6 4myp_2
2781 cles_3817: 4bf7_10
2782 cles_1946: 3af5_1
2783 cles_2484: 4a3n_1
2784 cles_2298: 3ql6_1 3q9k_2 3sxv_3 3ogw_1 3r55_3 3nyh_2 3tuw_2 3r4x
2785 cles_2088: 4dnm_1 4dlf_2
2786 cles_2598: 2ppt_1
2787 cles_2204: 4q7r_14
2788 cles_1725: 3gyy_26
2789 cles_1941: 4fum_1 4fup_1 4fun_1 4fup_2
2790 cles_2275: 3nq1_9
2791 cles_2587: 4zk0_1
2792 cles_2631: 2q5b_9
2793 cles_3461: 4r7p_6 4r7p_3
2794 cles_2023: 2ajy_5 3qg6_10 2ak1_3
2795 cles_3569: 5imt_2
2796 cles_2564: 2oo4_6
2797 cles_3687: 4b92_2 4b92_1
2798 cles_3461: 4r7p_5
2799 cles_1831: 2g7z_14
2800 cles_3461: 4r7p_2
2801 cles_1605: 2djw_1 2djw_4 2djw_3 2djw_2
2802 cles_2459: 1k9z_7
2803 cles_3686: 3dug_24 3dug_21 3dug_10 3dug_11 3dug_4 3dug_6 3dug_
2804 cles_2168: 1ty2_3 1ewc_1 1ty2_1 1i4h_2 1i4g_1 1i4h_1 1ty2_2
2805 cles_1924: 1gl4_1
2806 cles_4011: 5kas_2
2807 cles_2646: 3fm4_8 4bll_2
2808 cles_2193: 3io2_2 1f81_3 3p57_3 3t92_1 5hp0_3 2ka6_2 5hpd_2 2kje
2809 cles_1940: 2dcu_2 1k81_1 2qmu_1 2d74_1
2810 cles_2010: 3v23_230 3v25_168 3v2d_601 3v29_229 3v27_178 4dha_1
2811 cles_1857: 1k24_2
2812 cles_2058: 1jcc_1 1jcc_2 1jcc_3
2813 cles_1716: 3gj9_2
2814 cles_2354: 3ser_2
2815 cles_3721: 4kfv_1
2816 cles_1775: 3a1z_16 3a1z_7 3a1z_9
2817 cles_3679: 5ih5_1 5ih4_1 5ih6_1
2818 cles_4072: 5m1q_2
2819 cles_3620: 4ne7_4

2820 cles_2489 2f44_3 2f44_1 2f44_2
2821 cles_3426 4rvw_3
2822 cles_2384 1pvw_2
2823 cles_2190 1jjt_3 1jje_4 1jjt_4 1jje_1
2824 cles_1873 1iuj_3
2825 cles_3603 5iiu_10 5ije_5 5ij5_15 5iix_2
2826 cles_2518 3fid_5
2827 cles_2153 3u5g_4 4bpe_46 3jam_77 2xzm_30 2xzn_9 4bpo_80 4bpp_
2828 cles_2062 3mbg_7
2829 cles_3854 4odr_2
2830 cles_2581 4qfj_2 4qfi_2 3zbv_1 4qfj_1 4qfi_1 3zbw_1
2831 cles_3709 5ldz_8 5ldz_1 5ldz_9
2832 cles_1928 4i0j_2
2833 cles_2562 4fvk_7 4fvk_2
2834 cles_2322 1zzh_6
2835 cles_2465 1krp_1 1d8y_1 1ksp_1 1kfs_2 2kfz_3 2kfn_4 1d9d_3
2836 cles_1870 3ua7_1 3ua7_2
2837 cles_1673 2gyq_8
2838 cles_3420 4evb_1
2839 cles_1884 3rf5_2 3rf4_6 3rf4_5 3rf5_1
2840 cles_2199 1yc2_6 1s7g_9 1yc2_3 1s7g_1
2841 cles_2225 3sp7_1
2842 cles_2228 2eh9_2
2843 cles_2603 4nix_1
2844 cles_2122 4fc5_7 4dwz_22 4dwz_14 4dwz_17 4fc5_13 4dwz_8 4fc5_2
2845 cles_2453 2qp1_62 2qbe_13 4dha_259 5gad_283 3oat_16 2qam_47 2
2846 cles_1694 3u5c_1 4uer_2
2847 cles_1677 3fgg_3 3fgg_4
2848 cles_2494 2fad_1
2849 cles_2484 2vir_2 2vis_1 2vit_3
2850 cles_1656 1vyk_1
2851 cles_2231 4owp_1 4msm_3 5cw4_1 4zd4_4 3rzu_11 4msj_5 4msj_1 5
2852 cles_1800 3dfm_3
2853 cles_3723 3kji_2 3kjh_1 3kji_1
2854 cles_2492 1brj_1 1b2z_1 1a2p_3 1a2p_2 1b20_2 1brh_1 1brg_1 1brk_
2855 cles_2487 3l4k_2
2856 cles_1728 3q94_10
2857 cles_2085 4dlm_5 4dlf_1
2858 cles_2155 1mbx_3 1mbx_6 1r6o_6 1r6o_2
2859 cles_3952 5iqk_4
2860 cles_2161 2xqv_1
2861 cles_1780 1z7h_1
2862 cles_3518 5f1c_5 5f1c_6
2863 cles_2587 1hp7_4
2864 cles_1755 3s1r_3 4a93_3 3gtj_2 5m5x_2 4a3d_5 1twa_2 3cqz_8 4a3c
2865 cles_2678 4dyg_5 4dwx_2 4dwx_3 4dyg_2
2866 cles_2577 2p2l_5

2867 cles_1802[illegible] 2gvm_1 2fz6_1
2868 cles_3407[illegible] 3h2q_3 3h2q_4 3h2q_2 3h2q_1
2869 cles_2431[illegible] 3ea1_2 3ea2_5 3ea2_6 3ea1_6
2870 cles_2618[illegible] 1agn_14
2871 cles_3406[illegible] 1xtl_8 1xtl_1 1xtl_10 1xtl_9
2872 cles_3409[illegible] 3mnd_2 3mnd_5
2873 cles_2356[illegible] 4r9g_2 4r9g_3
2874 cles_1944[illegible] 3ee6_7 3ee6_3
2875 cles_3687[illegible] 1v51_3
2876 cles_3602[illegible] 5iix_1 5ij5_1
2877 cles_1646[illegible] 5k82_2 2kem_1 5k82_4 5k82_1 5k82_3
2878 cles_2622[illegible] 1oep_2
2879 cles_2171[illegible] 2ou3_5
2880 cles_2333[illegible] 3f07_1
2881 cles_2209[illegible] 1v51_5
2882 cles_2548[illegible] 1f5f_1
2883 cles_1782[illegible] 2ejc_8
2884 cles_3703[illegible] 4y7o_3
2885 cles_1698[illegible] 2yx1_10
2886 cles_2675[illegible] 2iv0_8
2887 cles_2263[illegible] 2agz_1 2agz_2
2888 cles_3461[illegible] 4r7p_4
2889 cles_2509[illegible] 3e1z_1
2890 cles_2493[illegible] 1euc_1
2891 cles_3750[illegible] 3woi_2
2892 cles_2214[illegible] 2qha_2 2whk_1 2qha_1
2893 cles_2608[illegible] 1u86_1 1va2_1 2ab3_1 1sp1_1 1are_1 1llm_2 1va3_1 1xf7_
2894 cles_1792[illegible] 1xaf_3 1u05_1 1xaf_6 1u05_2
2895 cles_1636[illegible] 1a0b_1 2a0b_1
2896 cles_1969[illegible] 2y20_1 2y20_3 2y20_8 2y20_9 2y20_6 2y20_4
2897 cles_3592[illegible] 3wre_1 3wrg_1 3wkx_1
2898 cles_2459[illegible] 1k9z_3
2899 cles_2245[illegible] 2qqu_3
2900 cles_3602[illegible] 5ije_11 5iiu_6 5ij5_13 5iix_6
2901 cles_2604[illegible] 1c2l_1
2902 cles_1793[illegible] 2q1z_2 3o14_2 2q1z_1 3o14_1
2903 cles_3997[illegible] 5abx_3
2904 cles_2528[illegible] 3af5_2
2905 cles_3730[illegible] 3woi_4 3woi_6
2906 cles_2456[illegible] 2ims_1 2imt_1
2907 cles_3688[illegible] 5ax7_1
2908 cles_1753[illegible] 2p1h_4
2909 cles_1731[illegible] 4pxy_10 4pxy_9
2910 cles_4107[illegible] 5k4p_3
2911 cles_4077[illegible] 5f6q_3 4naz_1 5f6q_4 4nay_1
2912 cles_2209[illegible] 1v51_8
2913 cles_3740[illegible] 4zk0_2

2914 cles_2392 4a1b_2 4a1d_1 4a19_3 4b6a_4 3u5i_3 3u5e_1
2915 cles_2392 4a18_3
2916 cles_4069 5bvr_2
2917 cles_3511 4bwz_2
2918 cles_3406 3gl6_3
2919 cles_2555 1xki_3
2920 cles_2671 2hap_2
2921 cles_1808 3s7d_2 3qwp_1 5hda_3 5mq4_8 3s7j_1 3rib_3 5mq4_12 5
2922 cles_2480 3u93_5
2923 cles_1722 3gyy_16 3gyy_7 3gyy_9 3gyy_8
2924 cles_1695 4a93_6 2e2h_6 3gtj_6 1r9s_4 4x67_4 4c2m_5 4a3i_1 3gtp_
2925 cles_2023 3na9_5
2926 cles_3407 1kmg_1
2927 cles_2201 3ggl_1
2928 cles_2238 4uib_3 3wc5_2 2jew_1 5lyl_3 4z65_2 3wc6_2 5lyd_2 3wab
2929 cles_2262 4dr4_84 3uzi_477 2wdm_330 2uua_1 4x62_153 2y10_1 1j
2930 cles_2091 1hkk_1
2931 cles_2014 1h2b_1
2932 cles_1775 3a1z_4 3a1z_15 3a1z_3 3a1z_8
2933 cles_3480 5ceh_1
2934 cles_2121 4dwz_20
2935 cles_2616 3gdf_2 3gdf_1
2936 cles_2401 2xnj_12
2937 cles_1965 1vpy_4
2938 cles_2547 3tn1_1
2939 cles_1767 2wae_1
2940 cles_2551 7mdh_14 7mdh_1
2941 cles_2622 2hh5_5 2hh5_3
2942 cles_1944 3ee6_2 3ee6_6
2943 cles_2604 1iau_5
2944 cles_3672 5iiu_3
2945 cles_1622 2gpy_6
2946 cles_2215 1j9y_1 1r7o_4
2947 cles_2092 1c8y_1
2948 cles_3657 4r2j_1
2949 cles_2402 4mtp_7 2hcs_1 4hdh_2 4mtp_4 2hcn_2 4hdh_4 4hdg_4 4m
2950 cles_1843 3j7y_50 2zjp_7 4v19_135 3kni_96 3v25_282
2951 cles_3684 4w74_3 4w74_2 4w74_6 4w74_4
2952 cles_3431 5iyd_7
2953 cles_2440 2iyb_4
2954 cles_2672 2rc6_1
2955 cles_1799 3sjp_4
2956 cles_1666 2g2n_7 2g2p_3 2g2p_7 2g2n_5 2g2n_1 2g2n_10 2g2p_8 2g
2957 cles_1614 1nyr_3
2958 cles_2337 3h90_10 3h90_20 3h90_14 3h90_5
2959 cles_4019 5uu7_5
2960 cles_1908 1ud9_11 1ud9_4

2961 cles_20913 1hkk_2
2962 cles_26867 5dvx_1
2963 cles_24408 2cuq_2 1qli_2 1ibi_2 2cur_1 1wyh_1 1cxx_1 1x4k_1 1x63_1
2964 cles_24616 1jpu_2 1jqa_2 1jq5_2
2965 cles_26326 2w8c_3 3cvd_1 2w8c_4
2966 cles_25886 1hp7_3
2967 cles_18806 4l0i_2 4pns_4 4l0v_2 5aeh_2 4li6_1 3mhj_2 3kr7_1 4bs4_1
2968 cles_34042 3rcm_1
2969 cles_22119 4by1_7 1y77_9 4a3k_6 3k1f_5 1i50_9 5flm_6 3s15_2 1wcn
2970 cles_24197 3cr5_2
2971 cles_23876 4hcc_2 4hcc_1
2972 cles_22022 4d52_1 4ahb_2
2973 cles_37265 4qcl_2
2974 cles_25636 4fvk_5 4fvk_6
2975 cles_23215 2chu_3 2chu_2
2976 cles_35542 5e33_2 5egy_1 5e3a_1
2977 cles_23176 3phx_9
2978 cles_39593 4l3k_1
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2981 cles_17508 1rly_1 5iy9_8 5iy9_9 5eio_1 5ein_1 5iyb_5 5iya_7 1dl6_1 5
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2986 cles_35942 5imt_7
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2992 cles_24424 1h71_5
2993 cles_23552 4dxb_2
2994 cles_36866 1xrf_1
2995 cles_25541 2ox8_8 2ox8_12
2996 cles_22306 4u01_4 4u01_3 4tyd_8 4u01_7 4tyd_9 4tyd_4 4tyd_6 3sud
2997 cles_35913 3gze_2
2998 cles_23619 3v77_4
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3002 cles_22791 4a0x_2
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3005 cles_19398 1ro0_1 1ro2_1
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3061 cles_2594: 3co0_3
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3073 cles_1974: 4dtt_1 3n56_1 4pf9_2 2jg4_2 1hr7_1 5cjo_1 4pes_1 4nxo_
3074 cles_2013: 1ozb_1 1sx1_1 1ozb_2 1tm6_1

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5iz5_B_26670	BA
3d6n_B_37276	BA
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3lk4_Z_17094 3lk4_N_17094 3lk4_8_17094 3	BA
3b2i_A_25598 3vg2_A_25598 2l68_A_25598	BA
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3q1h_A_26811 CA
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4nhd_A_39453 CA
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2dup_B_16405 CA
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1vcf_B_16579 3dh7_A_16579 1vcg_A_16579	CD
1s69_A_17969 1mwb_A_17969 1s6a_A_1796	CD
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1oqc_A_20625 4ldk_A_20625 3o55_A_20625	CD
1xwn_A_26619	CD
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1wx5_D_17256	CU
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1eyb_A_19431	FE
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3ver_A_17691 3vf4_A_17691 3vex_A_17691	K
1fqg_A_19136 1zg6_A_19136 4ibr_A_19136	K
3nmb_A_17554	K
2a6v_B_16403 2a6w_B_16403 2a6x_B_1640	K
4gfp_A_22967 4egr_F_22967 4egr_A_22967	K
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1tfd_A_24366 1d3k_A_24366 1d4n_A_2436	K
1zrs_B_20834 2aum_B_20834 2aum_A_2083	K
1ak5_A_24664 1me7_A_24664 1mei_A_246	K
2j4u_W_22851 3fyx_A_22851 2xe5_F_22851	K
5aeo_B_39617	K
4x3u_A_24310 4x3t_A_24310 4x3k_A_2431	K
3r9c_A_25645	K
2n44_A_37695 1fqa_A_37695 5tj4_F_37695	K
3kzu_C_39363 5sxo_A_39363 4ls8_B_39363	K
2vqp_A_38747 2ykd_A_38747	K
3k6m_D_17764 1o9l_B_17764 3dlx_D_1776	K
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2fzj_A_26800 4kbn_A_26800 3nxv_A_26800	K
4goy_B_17280 3p53_A_17280 4gp0_B_1728	K
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4q0z_F_34978 4q0z_A_34978	K
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4fmw_A_17899	K
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4jki_B_21469 4jjk_B_21469 4jim_A_21469 1e	K
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4jks_A_23472 1wye_F_23472 4e3a_B_23472	K
4ia5_B_17054	K
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2bdi_P_41138 2bdi_F_41138 4kga_B_41138	LI
1ko0_A_23043	LI
4c80_A_18838 3fc4_A_18838 3fah_A_18838	LI
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4gi2_B_35047	MG
3nm7_C_16416 3nm7_D_16416 3nm7_B_16	MG
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2x5o_A_17466 1eeh_A_17466 2uuo_A_1746	MG
3u2w_B_23220 3u2x_A_23220 3u2u_A_2322	MG
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5lzr_A_22751	MG

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1i96_B_23729 2e5l_B_23729 2xqd_B_23729	MG
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4jud_X_41299 4juf_C_41299 1mcz_D_41299	MG
4zza_A_39505 4zs9_A_39505 4zza_B_39505	MG
4q4l_A_17840	MG
3r87_A_22794	MG
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2y0y_D_26639 2j00_D_26639 4yhh_D_2663	MG
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1vr0_C_18776	MG
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3i4e_B_24608 3e5b_A_24608 3e5b_C_2460	MG
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4qoy_D_24583 4qoy_B_24583	MG
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2r6o_A_25061	MG
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3tiq_A_19420	MG
1oh5_A_16345 1wbd_A_16345 1oh7_A_1634	MG
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1d9f_A_24663 1d8y_A_24663 1krp_A_24663	MG
5j2n_B_25864 1s1x_B_25864 2ykn_B_25864	MG
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1iw7_D_21082 4oir_D_21082 5e18_D_21082	MG
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2l1b_A_40426 4x3s_B_40426 4x3s_A_40426	MG
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5g5s_A_22238	MG
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2uz1_C_19760 2uz1_A_19760 2uz1_B_19760	MG
1vos_E_23864 2b64_E_23864 3uzg_H_23864	MG
4xln_C_20421 2a68_M_20421 5d4e_M_2042	MG
3flm_A_19760	MG
2c3d_B_21535 1mok_C_21535 1mok_D_215	MG
3vmr_A_23820 3vmt_B_23820 3vmq_A_238	MG
3mmh_B_18377	MG
2gc6_A_17466	MG
1n8p_C_40479 2nmp_B_40479 3qhx_D_4047	MG
4qjk_A_16584	MG
2w5w_B_22299 2w5w_A_22299	MG
2i3t_A_38403 1u4c_B_38403 2i3s_C_38403 2	MG
3hav_A_16470 3ham_A_16470 3hav_C_1647	MG
1opf_F_22842 3k1b_C_22842 3pox_A_22842	MG
4oln_A_37713 4cn5_A_37713 1glu_B_37713	MG
3drc_A_26811 3ql3_A_26811 3f91_A_26811	MG
4zs4_A_20322 5e4h_B_20322 4zmf_A_20322	MG

2hsj_C_19652	MG
2wc6_A_22303 2wck_A_22303 2wc5_A_223(	MG
5e17_D_21100 5d4e_N_21100 2a68_N_211(	MG
1sdm_A_20845 3cob_C_20845 3cnz_B_2084	MG
5i2d_C_20419 5e17_C_20419 3aoi_C_20419	MG
5t20_I_39672 5t20_C_39672 5t1x_G_39672	MG
3coy_A_17830 3coy_B_17830 3ivg_B_17830	MG
4gzz_D_21461 5e18_D_21461 4xlp_D_21461	MG
2hbj_A_16270 5c0y_A_16270	MG
1uch_A_16855 1xd3_C_16855	MG
5d4d_C_20422 2a69_C_20422 4wqs_C_2042	MG
4zb5_A_21290 2glk_A_21290 1xyl_B_21290	MG
5exc_K_37439 5exc_I_37439 5exc_L_37439	MG
3e4d_C_22115 3e4d_D_22115 3fcx_B_22115	MG
3bsu_F_17157 3bsu_H_17157 3bsu_B_17157	MG
4nch_B_16965 5f3w_D_16965 5f3w_B_1696	MG
2h17_A_19170 1zj6_A_19170 1yzg_A_19170	MG
4xxe_D_19912 4xqn_J_19912 4xqn_G_19912	MG
2wco_A_21758 2x03_B_21758 2x03_A_2175	MG
1i95_D_23135 4ej9_D_23135 1jgp_G_23135	MG
5i2d_D_21458 5tmf_D_21458 4g7o_D_2145	MG
3eq6_B_24815 2vze_A_24815 3eq6_A_2481	MG
3nc5_B_25660 3nc6_A_25660 3nc3_B_2566(	MG
5acp_B_38272 5ev8_A_38272 5ewa_C_3827	MG
4ycm_A_26277 2o9j_A_26277 3ar7_A_26277	MG
4ied_D_40529 4ied_A_40529	MG
3kno_V_22983 4kd9_V_22983 4bye_V_2298	MG
4toq_A_40149 1kqz_A_40149 1kr1_A_40149	MG
1iw7_K_24077 4q5s_A_24077 4xlp_G_24077	MG
3a8d_A_26039 2xbx_A_26039 3rxk_A_26039	MG
5h8p_A_21493 1y8b_A_21493 2jqx_A_21493	MG
4wfb_D_19710	MG
1qgq_A_24894 1qg8_A_24894 1h7l_A_2489	MG
1zyr_M_20348 3aoi_C_20348 4g7h_M_2034	MG
4g7z_N_21085 2a68_D_21085 1ynn_D_2108	MG
3cfz_A_19846	MG
5cqg_B_25862 3du5_A_25862 3du5_B_2586	MG
3big_A_23450 1ni9_A_23450 2r8t_A_23450	MG
4nzn_A_18080 4q4c_A_18080 3t9d_A_1808(	MG
2quj_B_16745 1o5t_A_16745 1r6u_A_16745	MG
1dor_A_18802 1dor_B_18802 1jrc_A_18802	MG
4xlp_D_21083 3aoh_I_21083 5d4d_D_21083	MG
5i33_A_21032 1son_A_21032 1adi_A_21032	MG
2a68_F_20068 3eql_P_20068 5d4e_F_20068	MG
1rzn_B_18190 1y1o_C_18190 1y1o_D_1819(	MG
4ygq_A_39882	MG
2gw4_A_37441 5exc_F_37441 5exc_B_3744	MG

1oxh_C_26195 2rjt_D_26195 2rjt_C_26195 2	MG
2xm3_E_18638 2xma_F_18638 2xm3_C_186	MG
3pz4_B_24478 1tn8_B_24478 1kzo_B_24478	MG
5f31_A_37719 5f2z_D_37719 5f2z_C_37719	MG
3uzk_W_23013 3uye_W_23013 4g5u_W_230	MG
1twy_B_17593 1twy_C_17593 1twy_H_1759	MG
3gg6_A_40696	MG
4p69_A_17329 3lc6_B_17329 4p69_B_17329	MG
2o5j_D_21084 5d4d_N_21084 1ynj_D_21084	MG
3ly5_B_22952	MG
3ufm_A_36438 3wdf_A_36438 4lyl_K_36438	MG
4a0h_B_19758 4a0r_B_19758 4a0r_A_19758	MG
3ecp_A_16249	MG
1gpm_B_36596 1gpm_A_36596 5tw7_A_365	MG
2cn1_A_16607 2bdu_B_16607 2q4t_B_16607	MG
5e4h_A_20318 5e4h_E_20318 5e4h_B_2031	MG
4s1i_B_40197 4s1m_B_40197 4s1m_A_4019	MG
2xqd_C_26834 3i1q_C_26834 2qnh_d_26834	MG
4xln_D_21105 2a69_D_21105 5e17_D_2110	MG
2wdm_K_24403 4adv_K_24403 3mr8_K_244	MG
4yb5_C_37117 4yb5_A_37117 1h3d_A_3711	MG
5aqi_B_39581 5aqm_B_39581 5aqs_D_3958	MG
5ays_C_36444 5ays_D_36444 3wdg_B_3644	MG
1jpu_A_35690 1jqa_A_35690 4mca_B_3569	MG
1hx3_A_23322 1hx3_B_23322	MG
4qqp_A_36545 4qql_H_36545 4qql_F_36545	MG
3tvg_T_24198 4b3s_Q_24198 2y16_Q_24198	MG
1mkd_D_21742 1y2c_B_21742 3sl6_D_21742	MG
1yyq_A_17347 2ps5_A_17347 2ael_A_17347	MG
2x3k_A_17293 2w03_B_17293 2x3k_B_1729	MG
4lf7_P_23687 4b3t_P_23687 2wdm_P_23687	MG
2xja_B_21662 2wtz_A_21662 2wtz_D_21662	MG
3fnb_B_23760	MG
2be5_D_21125 3aoi_N_21125 2cw0_N_2112	MG
3uz3_R_23707 4lfb_O_23707 3uzi_R_23707	MG
5hpo_A_16336	MG
1r8g_B_19039 1r8g_A_19039	MG
2b43_B_19979 2b43_C_19979 1sh0_B_1997	MG
1wa5_C_16382 1z3h_B_16382	MG
4g7h_N_21131 3aoi_D_21131 4oir_D_21131	MG
1lik_A_23461 2aa0_A_23461 2abs_A_23461	MG
1uej_A_24704 1udw_B_24704 1ufq_D_2470	MG
3b54_B_40918 3vgv_P_40918 5iol_C_40918	MG
5jxz_B_24467 5jy4_A_24467 5jzd_A_24467 5	MG
2be5_L_24123 4gzy_A_24123 1iw7_L_24123	MG
4s0h_A_23804 2x6u_A_23804 4s0h_E_2380	MG
5i2d_C_20403 4oip_C_20403 5tmc_C_20403	MG

3upf_A_19979 3uqs_B_19979 3nah_A_1997	MG
1k0z_B_19208 1pvi_A_19208 3pvi_B_19208	MG
4ieg_B_19977 4ieg_A_19977 4ieg_C_19977 4	MG
3mwb_A_22473	MG
4f97_A_24050 4f9f_C_24050 4f96_B_24050	MG
4xlp_K_19982 2o5j_E_19982 2a6h_E_19982	MG
1xnr_T_16655 3v24_T_16655 1ml5_W_1665	MG
3s5i_A_19741 3s5h_A_19741 3s5k_A_19741	MG
3mmh_B_18375	MG
3ill_A_21560 3ili_A_21560	MG
3t7d_B_24040 3vdm_A_24040 3vdm_B_240	MG
3ecp_A_22648 4dm0_A_22648 1muh_A_226	MG
4bfx_B_24704 2zsf_A_24704 3af0_A_24704 4	MG
2yue_A_37821	MG
2cnu_A_20920 2cnv_A_20920 1a48_A_2092(	MG
3d26_B_36769 2zl6_B_36769 4p3i_D_36769	MG
4wqt_F_24101 4g7o_L_24101 4wqs_K_2410	MG
4ag6_C_17573 4ag6_A_17573 4ag5_C_1757	MG
4hzc_B_38295 4hzc_C_38295 3mc4_B_3829	MG
3dls_E_25734 3dls_F_25734	MG
4o6h_A_23151 4o6h_F_23151 3q7b_A_2315	MG
3d26_B_23822 5kw9_A_23822 3by1_A_2382	MG
1nxs_A_25800 1nxt_A_25800 1nxx_A_25800	MG
2rkt_A_16943 3b30_A_16943 2rkv_A_16943	MG
2g67_A_24583 4qoy_C_24583 2g67_B_2458	MG
2xmw_A_24354 4a48_B_24354 4a4j_A_2435	MG
4q4z_F_20085 2a6e_P_20085 2be5_F_20085	MG
1l9u_M_21173 1l9z_D_21173 5d4d_N_2117	MG
3asw_A_25235 4f1z_A_25235 3au0_A_2523	MG
2xux_E_23611 3kir_E_23611 3knm_E_23611	MG
3nc6_B_25656 3nc6_A_25656 3nc7_B_2565	MG
5g3s_A_39354 5g3t_D_39354 5g3t_A_39354	MG
4jx4_A_20174 4jx4_C_20174 4jx4_D_20174	MG
3tvh_D_26761 5gag_C_26761 4b8g_D_2676	MG
2xux_G_19710 2rdo_F_19710 3kiw_G_1971	MG
4dr4_J_23892 4lf9_J_23892 3kix_j_23892 2u	MG
1wzo_B_23620 1wzo_C_23620 3s52_C_2362	MG
4f20_A_25231 4f1z_A_25231 3at0_A_25231	MG
1cmb_B_21992 1mjo_B_21992 1mjm_A_219	MG
2j7q_C_20682	MG
3ro8_B_23815 3ro8_E_23815 4e4p_A_2381	MG
3gyy_D_17259 3gyy_B_17259 3gyy_A_1725	MG
5l5h_W_35202 5fgh_L_35202 3un4_Z_3520	MG
3hrd_E_18810	MG
2vrw_A_25759 3b13_D_25759 1foe_H_2575	MG
2z9o_B_16324 2z9o_A_16324	MG
2pkx_A_25789 1oxk_H_25789 1oxb_B_2578	MG

1s80_A_38904 3gvd_H_38904 4n6b_F_3890	MG
4g6h_B_16279 4g73_B_16279 4g6g_B_1627	MG
4g7o_M_24994 5d4c_C_24994 2o5j_C_2499	MG
1zwy_A_20060 1zwy_C_20060 1zwy_B_2006	MG
5d4d_D_21157 2be5_N_21157 4oir_D_2115	MG
4tvw_A_23060 4tvw_B_23060 4tvw_D_2306	MG
3op2_A_19027 3ozm_F_19027 3op2_B_1902	MG
3eie_A_17345 2rko_A_17345 2qpa_B_17345	MG
3a1p_D_26895 3v2e_S_26895 4dv3_S_2689	MG
1j3w_A_23361 1j3w_C_23361 1j3w_D_2336	MG
3lx8_A_16760 4non_A_16760 3lx5_A_16760	MG
3lac_A_23041	MG
4wg3_A_19332 4yjn_A_19332 3t3v_A_1933	MG
4ksi_A_23631	MG
3sua_A_39299 1kz7_D_39299 1i4t_D_39299	MG
1xix_A_16552 4ii9_A_16552 1xe4_A_16552	MG
2cw0_C_25008 1zyr_C_25008 4g7o_C_2500	MG
3qhx_C_40478 4l0o_E_40478 4iyo_A_40478	MG
3vka_B_19572 3vk5_B_19572 3vkd_A_1957	MG
2dy2_A_24329 1mzz_B_24329 1mzz_C_2432	MG
4g6h_A_16289 4g73_A_16289 4g74_A_1628	MG
5do8_B_26344 5do8_C_26344 5do8_A_2634	MG
5klo_B_38324 5kll_C_38324 5klk_B_38324 4	MG
2r3v_A_23068 2r3v_D_23068 2r3v_C_23068	MG
1ob3_A_37267 2c6m_A_37267 1e9h_C_3726	MG
3bpr_A_20721 4m3q_B_20721 3bpr_D_2072	MG
2wsm_A_17017	MG
2cw0_F_20080 3wod_F_20080 5d4c_F_2008	MG
2wch_A_22298 2wc6_A_22298 2wcm_A_222	MG
4s2e_A_40362 2pbr_B_40362 2pbr_A_40362	MG
2h0r_B_23411 2h0r_C_23411 2h0r_F_23411	MG
2yv0_X_40817 2zqb_C_40817 2zqb_A_40817	MG
1rsc_F_18546 1rsc_C_18546 2wvw_F_18546	MG
5exc_K_37438 5exc_L_37438 5exc_J_37438 5	MG
3fgn_D_19758 3fgn_B_19758 3fmi_C_19758	MG
4g7h_A_24108 5tmc_A_24108 3aoh_A_2410	MG
2xj4_A_19058 2xit_B_19058 2xit_A_19058	MG
4f9f_D_24043 4f97_B_24043 4f9f_C_24043 3	MG
3huy_H_35210 2b9o_H_35210 4kj4_H_3521	MG
3kiq_l_26655 3kis_l_26655 3i8g_O_26655 2o	MG
2rgn_F_25765 5fi0_D_25765 1ki1_C_25765 2	MG
1g9j_A_20828 4xwl_A_20828 1l2a_A_20828	MG
5grh_B_35493	MG
3lwn_B_25759 3lwn_A_25759 2wm9_B_257	MG
4qfx_B_35333 4qfz_C_35333 4to5_A_35333	MG
4j3z_H_19782 4j3z_E_19782 4j3z_F_19782 4	MG
4wpa_A_40975 5d15_A_40975 5d0g_B_4097	MG

4ifd_E_34640 5c0x_E_34640 5k36_E_34640 5	MG
1zyr_D_21159 5d4e_D_21159 3eql_D_21159	MG
4bo0_A_26170 4bo6_A_26170 4bo1_C_2617	MG
4csu_E_16559 3i22_E_16559 3j7z_E_16559 3	MG
3atv_A_18266 5bpl_A_18266 5aqz_A_18266	MG
1i6v_C_20277 3aoh_H_20277 4wqt_H_20277	MG
2d5f_B_26843 2d5h_B_26843 2d5f_A_26843	MG
2x7f_B_35993 4zp5_B_35993 5ax9_A_35993	MG
4p4t_A_23974 4p4u_A_23974 1jx2_B_23974	MG
3d5d_E_23582 3pyo_D_23582 2y19_E_2358	MG
1x86_D_39234 3q3j_B_39234 3t06_F_39234	MG
4oin_B_24095 2a6e_L_24095 1i6v_B_24095	MG
4ddx_B_22951 4ddu_A_22951 3p4y_A_2295	MG
4wuo_A_26749 1hex_A_26749 2y42_A_2674	MG
3l57_A_18362 3l6t_B_18362 3l57_B_18362	MG
5hqy_A_39021 2w3b_B_39021 3eig_A_3902	MG
3gtx_A_21868 4j2m_A_21868 4j35_A_21868	MG
4k9n_C_19882 4jua_A_19882 1mcz_N_1988	MG
2oux_B_16063	MG
4gap_A_16287 4gap_B_16287 4g9k_A_16287	MG
4x64_Q_24200 4dr7_Q_24200 2hgi_T_24200	MG
3crc_A_18172 3cra_B_18172 3cra_A_18172	MG
3e0d_B_20199 4iqj_B_20199 4iqj_C_20199 3	MG
1z72_A_22897 2a6b_A_22897	MG
3l8e_A_20826 3l8e_B_20826	MG
4f9f_A_24049 4f97_B_24049 3vdm_A_24049	MG
5dxl_A_38653	MG
2h28_B_17151 2inw_B_17151 2inw_A_1715	MG
2cg5_A_16584 2byd_A_16584	MG
4fey_A_35495 4ehj_B_35495 4ehj_A_35495	MG
2cjb_B_16972 2cim_A_16972 4h2t_B_16972	MG
3dxj_M_20365 4g7o_C_20365 5tmc_C_2036	MG
4wqt_C_20221 4xlr_C_20221 3eql_M_20221	MG
4dn0_A_19729 4etz_B_19729 4eu0_A_1972	MG
4g7z_P_20022 1zyr_P_20022 5e18_F_20022	MG
4d56_A_36977 4d4h_A_36977 4d57_A_3697	MG
3v23_U_24580 3kit_U_24580 2zjp_N_24580	MG
1dku_B_35561 3dah_A_35561 3dah_B_3556	MG
4jty_A_24072 4mk9_B_24072 4kai_B_24072	MG
1ym7_A_25689 3uzt_A_25689 2bcj_A_25689	MG
3vdn_B_24039 4f96_B_24039 4f96_A_24039	MG
3hd0_D_19967 3hd0_B_19967 3hd0_A_1996	MG
2hvr_A_25101 2hvs_B_25101 2hvs_A_25101	MG
5jq6_A_25234 2vr3_B_25234 2vr3_A_25234	MG
3knk_G_23049 2wrj_G_23049 3oat_F_23049	MG
2vrn_B_20119	MG
4eja_P_23684 4khp_P_23684 2xqd_P_23684	MG

4xdk_D_21959 4xdl_B_21959 4bw5_C_2195	MG
4tuy_F_23165 4i4t_F_23165 4ihj_F_23165 5c	MG
5hob_C_41213 2wtt_B_41213 2wqi_A_4121	MG
3asw_A_25232 3at0_A_25232	MG
1eg0_K_23636 487d_L_23636 1oln_A_23636	MG
4tz0_A_37162 3i5y_A_37162 3i61_A_37162	MG
3aoi_C_25037 2ppb_M_25037 2o5j_C_2503	MG
2be5_D_21199 2o5i_N_21199 2a69_N_2119	MG
1g5r_A_17870	MG
2rar_A_17710 2rb5_A_17710 2rbk_A_17710	MG
2d07_A_23250	MG
4g9k_A_16291 4g74_B_16291 4gav_B_1629	MG
3d5d_Q_22558 4g5u_P_22558 2j01_Q_2255	MG
4j5i_G_18488 4j5i_H_18488 4j5i_D_18488 4j	MG
4u87_C_17424 3dky_A_17424 3dkx_A_1742	MG
4s2e_B_22388 2pbr_A_22388 4s2e_A_2238	MG
4ffp_A_23224 4ffo_A_23224 4ffl_A_23224 4f	MG
5j1t_B_41109	MG
1ynj_D_21372 1zyr_N_21372 3eql_D_21372	MG
1x3p_A_24311 2n88_A_24311	MG
5ecp_D_39000 5eck_A_39000 5ecq_D_3900	MG
1z5a_A_19366 1mx0_C_19366 1z5a_B_1936	MG
4fma_A_18321 4fmd_A_18321 4fma_G_183	MG
3fs6_A_39496 2w3a_A_39496 2w3b_A_3949	MG
5jvh_2_24630 4kj9_2_24630 3fik_2_24630 3j	MG
2p4p_A_17119	MG
1l9z_B_24125 3dxj_K_24125 5i2d_B_24125 1	MG
2ael_B_17346 2ael_A_17346 2ps8_B_17346	MG
2a6e_O_19985 5tmc_E_19985 4gzz_E_1998	MG
3e2d_B_37577 3e2d_A_37577	MG
5d9z_B_39673 5d5g_D_39673	MG
1u2t_A_21725	MG
4fme_D_18314 4fma_K_18314 4fmd_C_1831	MG
4l6m_B_23728 2uxb_B_23728 1jgq_E_2372	MG
4c0k_A_25759 4c0j_A_25759	MG
5a8w_I_22431 3m1v_F_22431 3m2r_F_2243	MG
4wqs_D_17772 4oip_D_17772 3dxj_D_1777	MG
2i6a_B_23463 2i6a_D_23463 4o1l_B_23463	MG
5l69_U_21020 4y82_G_21020 3gpt_G_2102	MG
2qlw_A_16169 2qlx_A_16169	MG
2pq9_A_22969 3fjx_A_22969 3fjz_A_22969 2	MG
4f9f_C_24046 4f9f_D_24046 3t5t_A_24046 3	MG
4is4_F_26263 4bax_G_26263 4bax_H_26263	MG
5k5t_A_16895 1iss_B_16895 4xas_B_16895 2	MG
4wxo_C_24065 4wxo_B_24065 4wxo_A_240	MG
3da8_B_24959 3dcj_B_24959	MG
2h5n_D_21715	MG

4az7_A_21331 2yla_A_21331 4azh_C_21331	MG
3iq7_A_16825 3fmd_A_16825 3f2n_A_16825	MG
3d54_E_16867 3d54_I_16867 1vk3_A_16867	MG
4g7z_N_21405 4gzy_D_21405 5e17_D_21405	MG
2ppb_C_25013 4gzy_C_25013 1ynj_C_25013	MG
4jki_A_21466 4jjk_B_21466 4jim_B_21466 1f	MG
4eom_D_38068 1urc_B_38068 4bcm_D_3806	MG
6prn_A_20158 1prn_A_20158 1bh3_A_20158	MG
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4o2w_C_37911	MG
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3gto_A_21418	ZN
1nkb_A_24656 1l3t_A_24656 4o0i_A_24656	ZN
1sn7_A_36204 1sio_B_36204 1t1i_A_36204 1	ZN
4umm_E_26140 4umm_A_26140	ZN
2cex_A_17251 2wx9_A_17251 2cex_C_17251	ZN
5eo0_A_19829 4wu5_D_19829 5euo_C_1982	ZN
2eul_B_17002 3aoi_Y_17002 4wqt_Y_17002	ZN
3p7o_A_19742 3ami_B_19742 2g49_A_1974	ZN
1sx0_A_20139	ZN

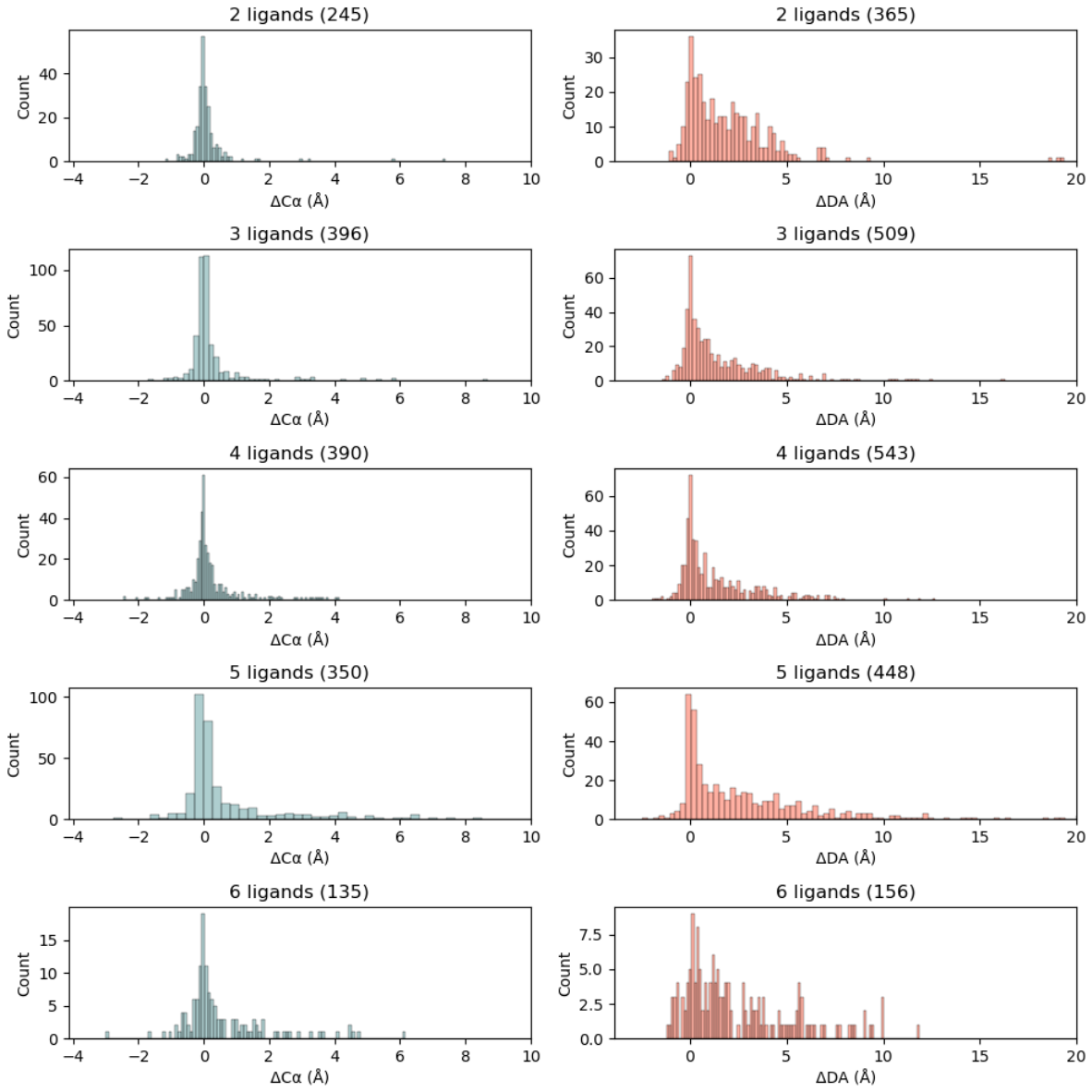

Figure S17. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in calcium sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

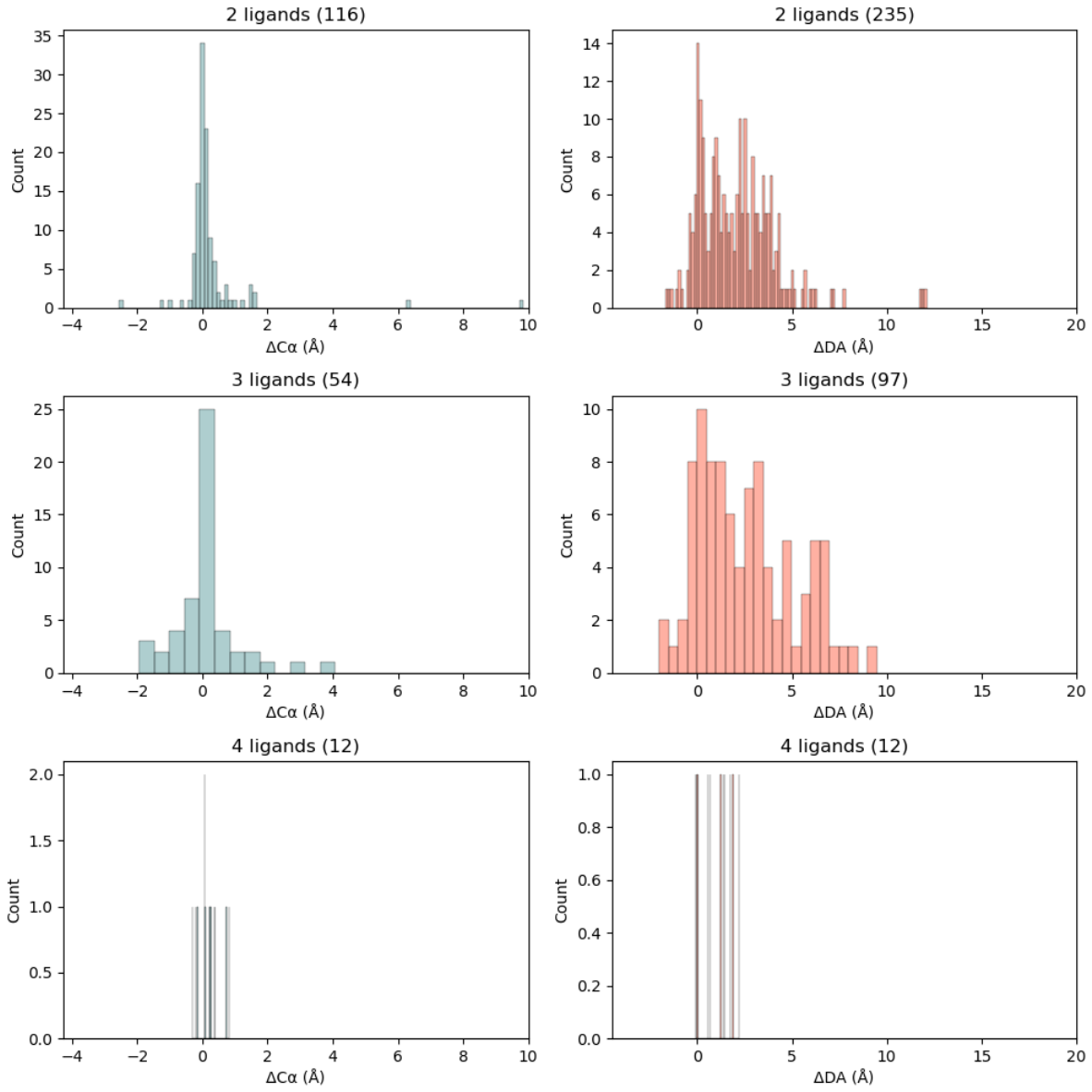

Figure S18. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in cadmium sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

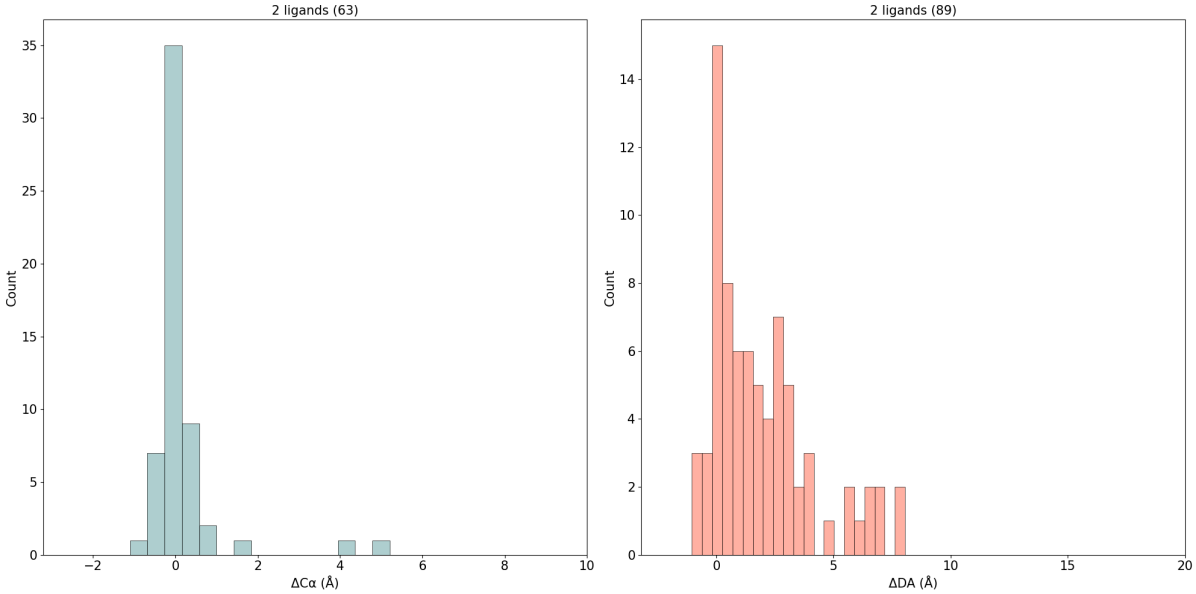

Figure S19. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in cobalt sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

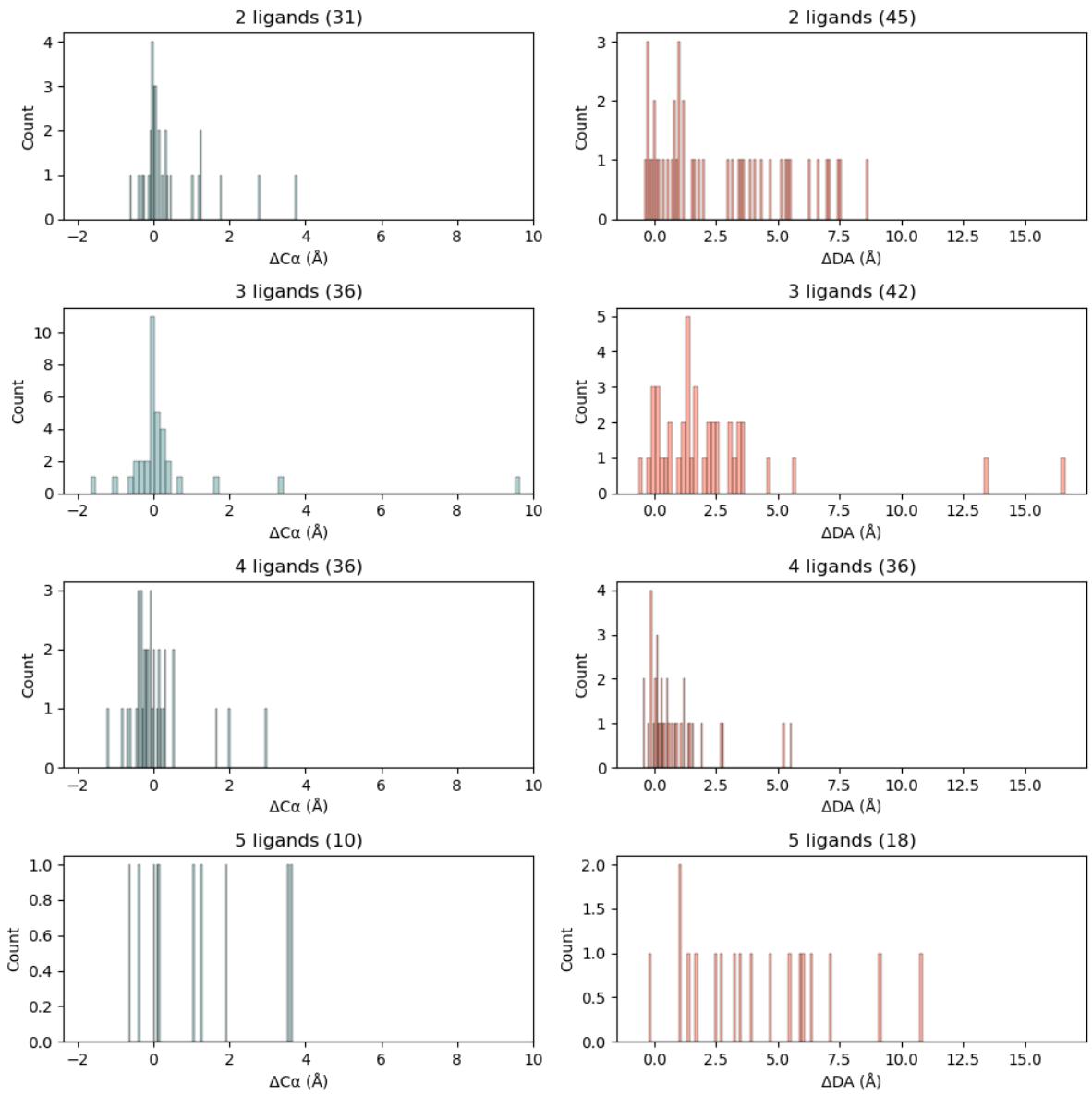

Figure S20. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in copper sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

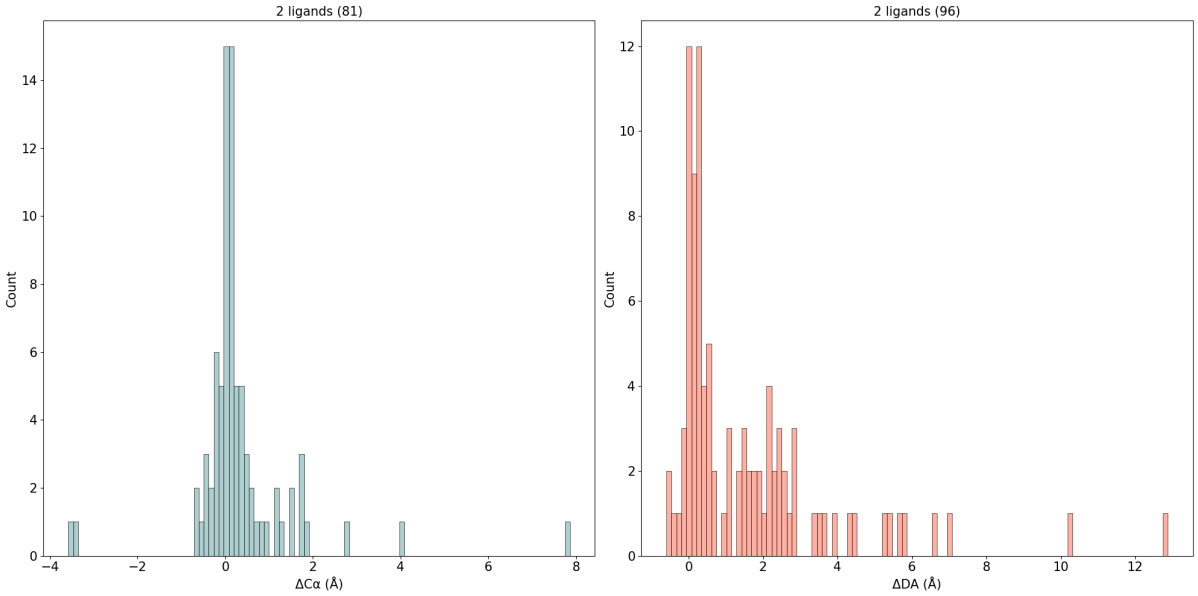

Figure S21. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in iron sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

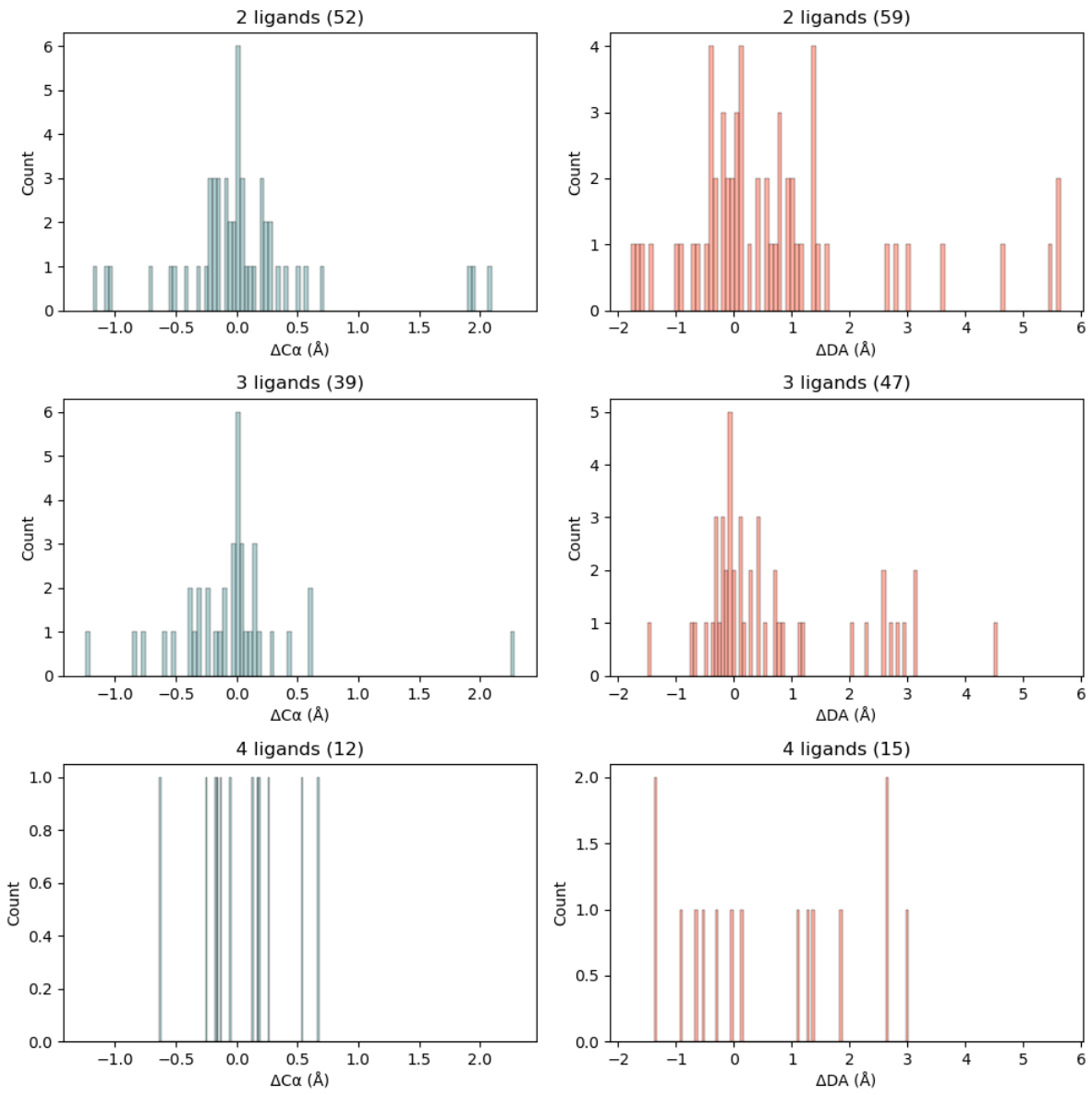

Figure S22. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in mercury sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

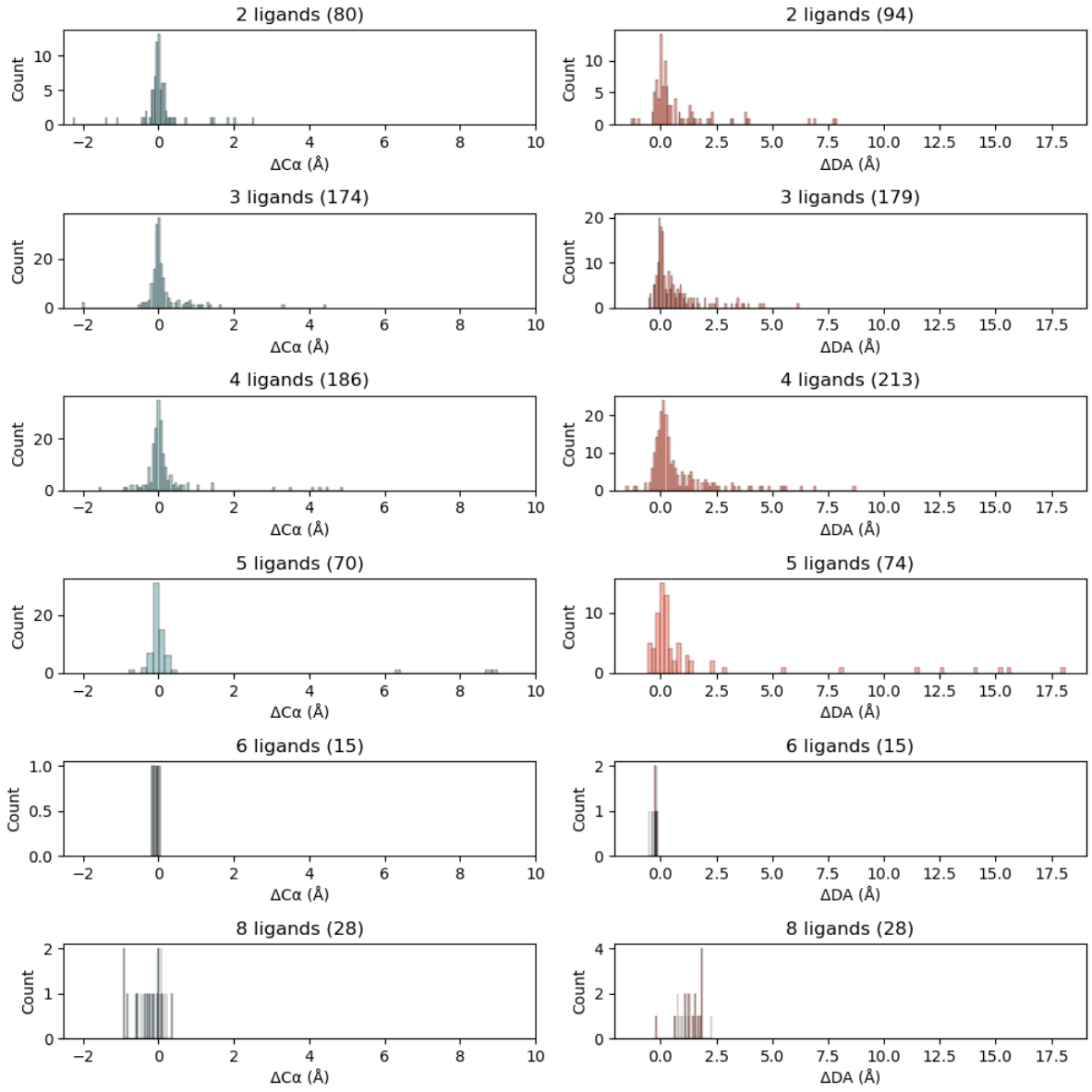

Figure S23. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in potassium sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

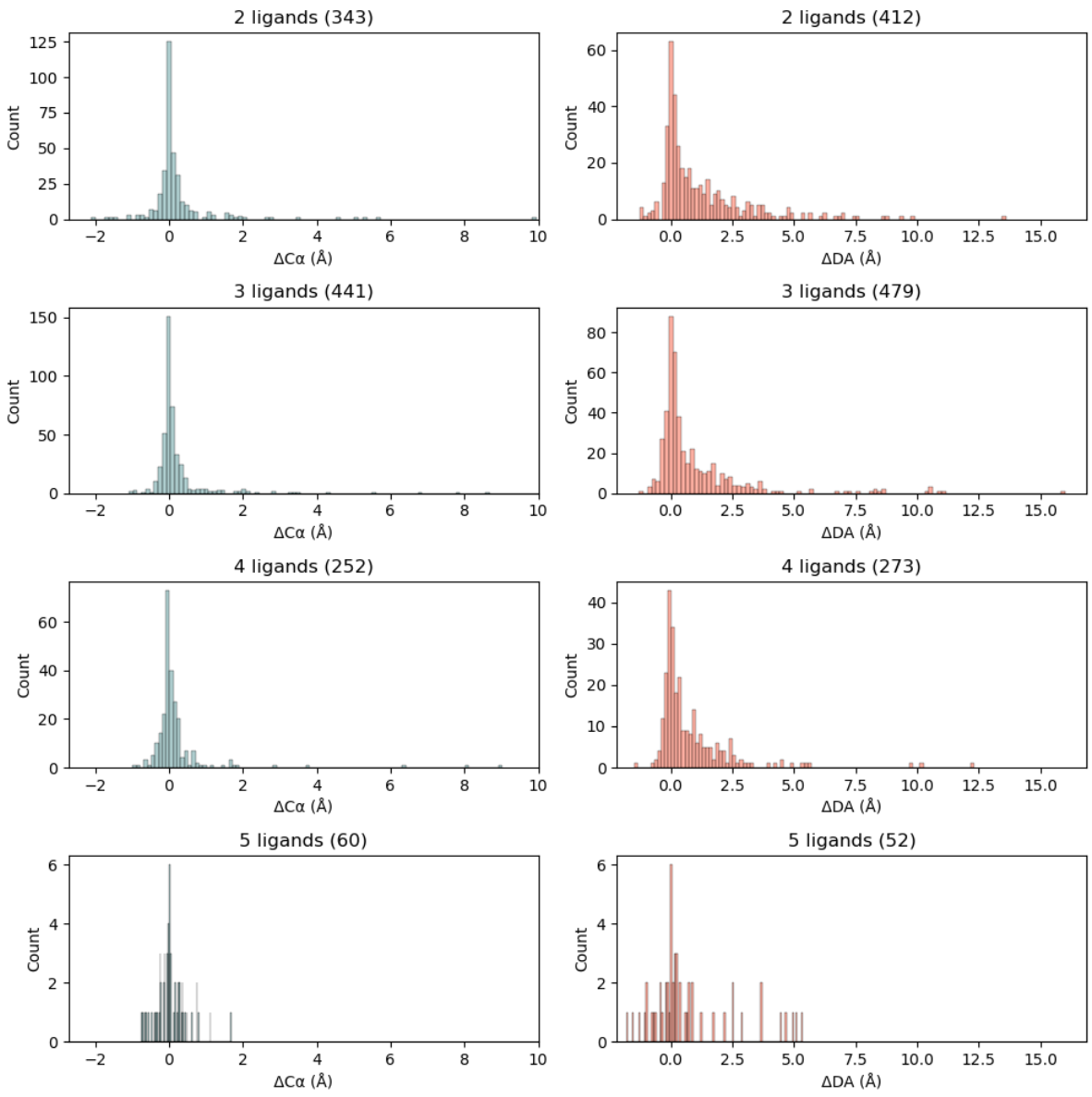

Figure S24. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in magnesium sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

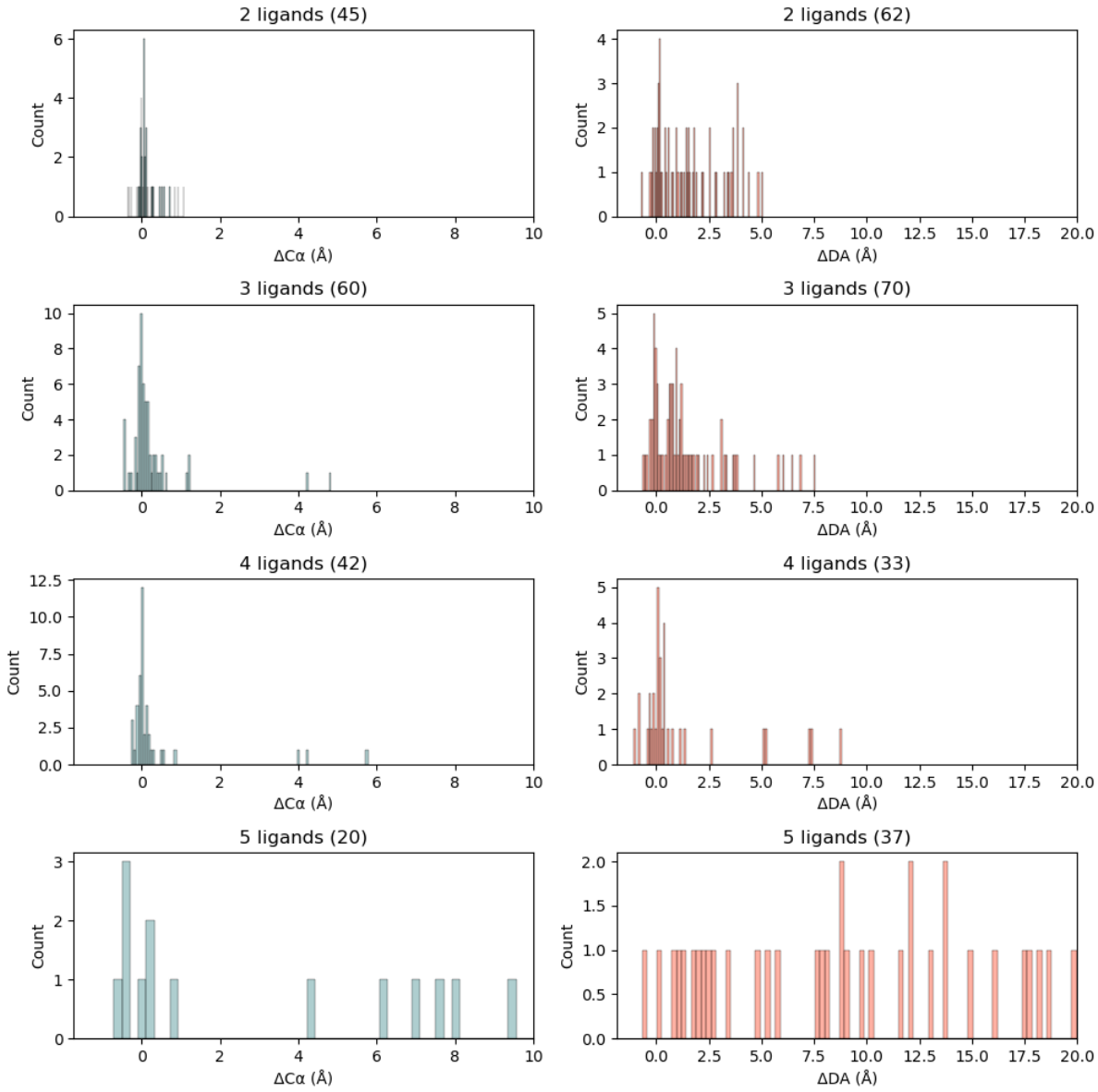

Figure S25. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in manganese sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

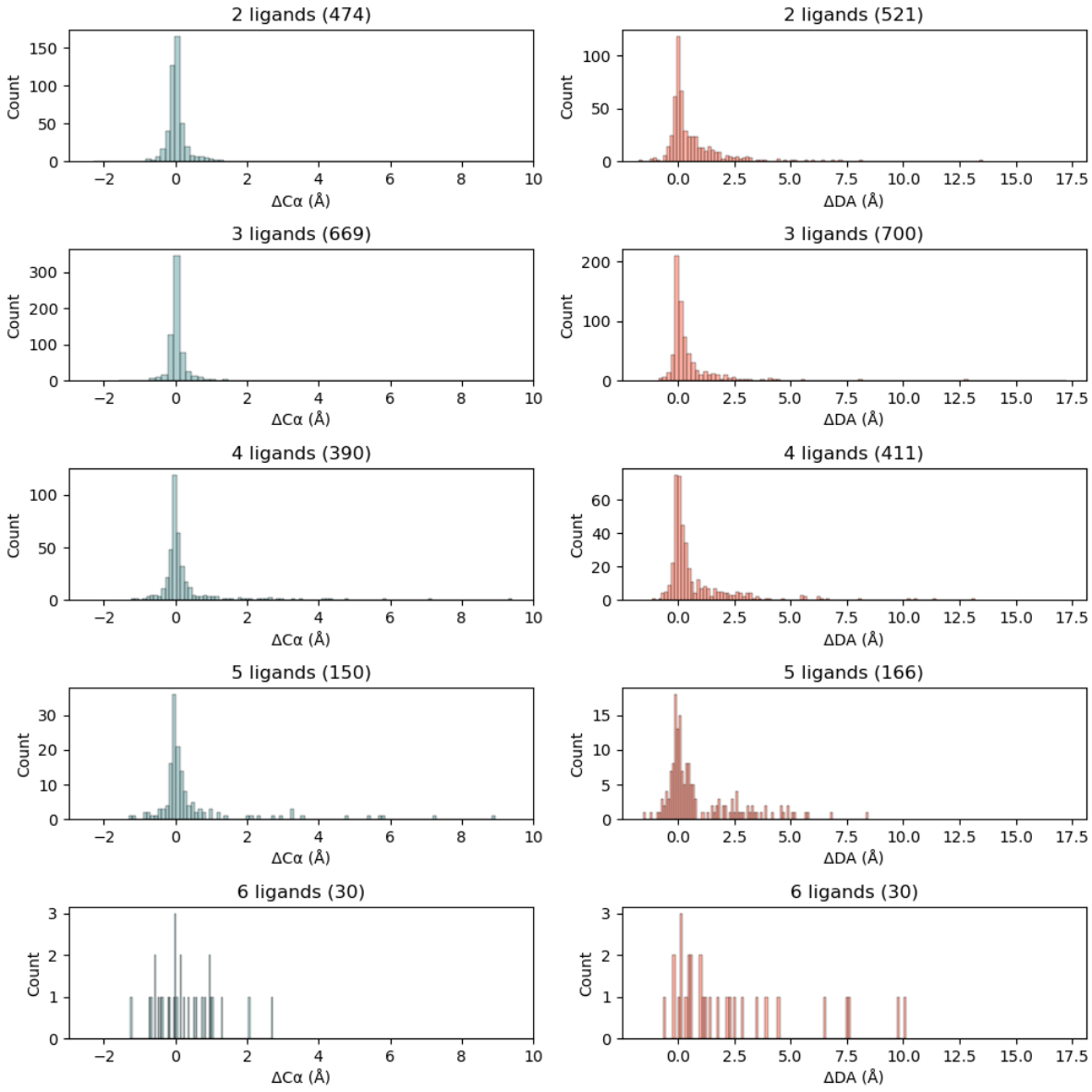

Figure S26. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in sodium sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

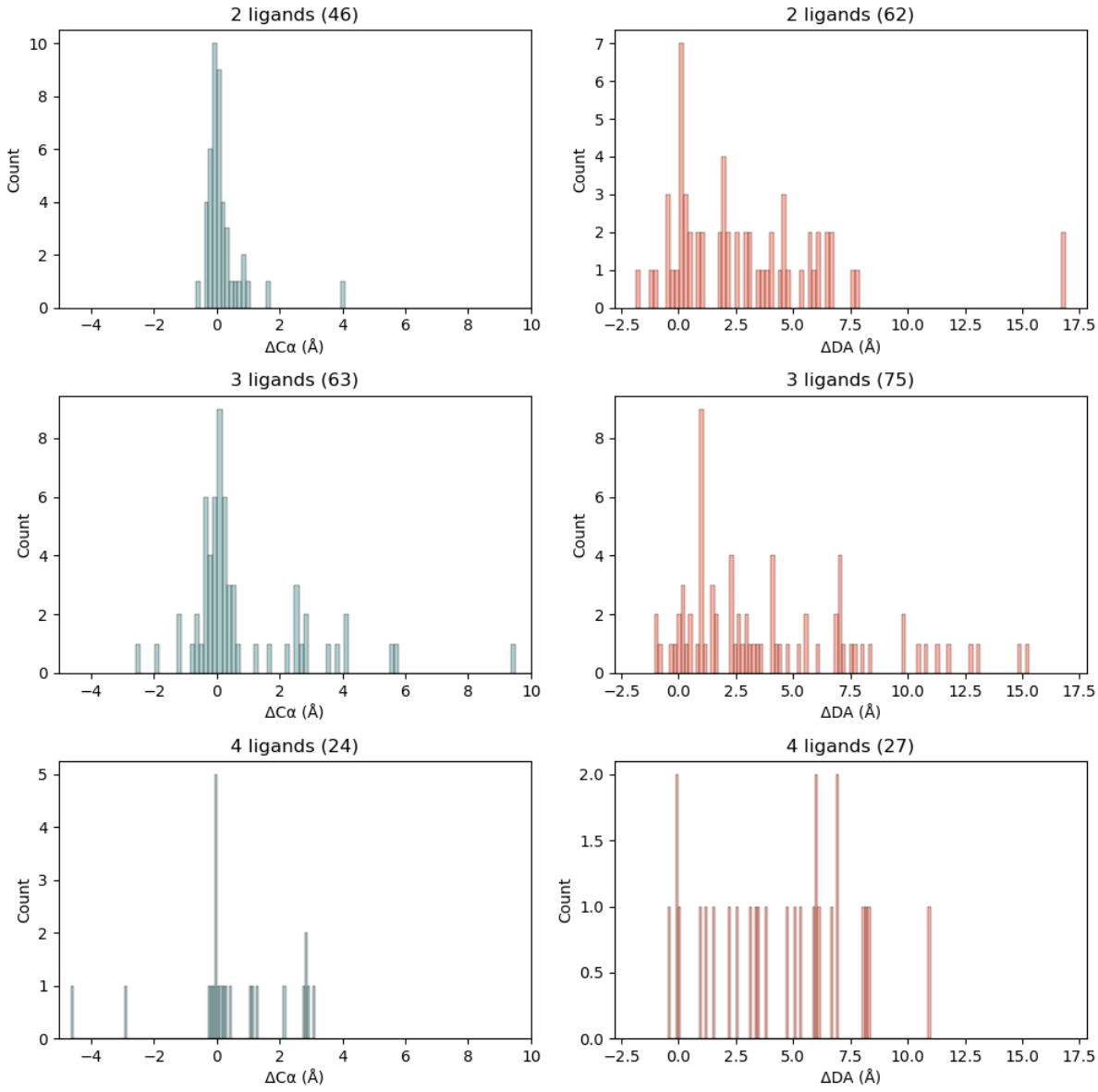

Figure S27. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in nickel sites, separated by number of endogenous metal ligands. *All changes are measured as apo- minus the corresponding holo- distances.*

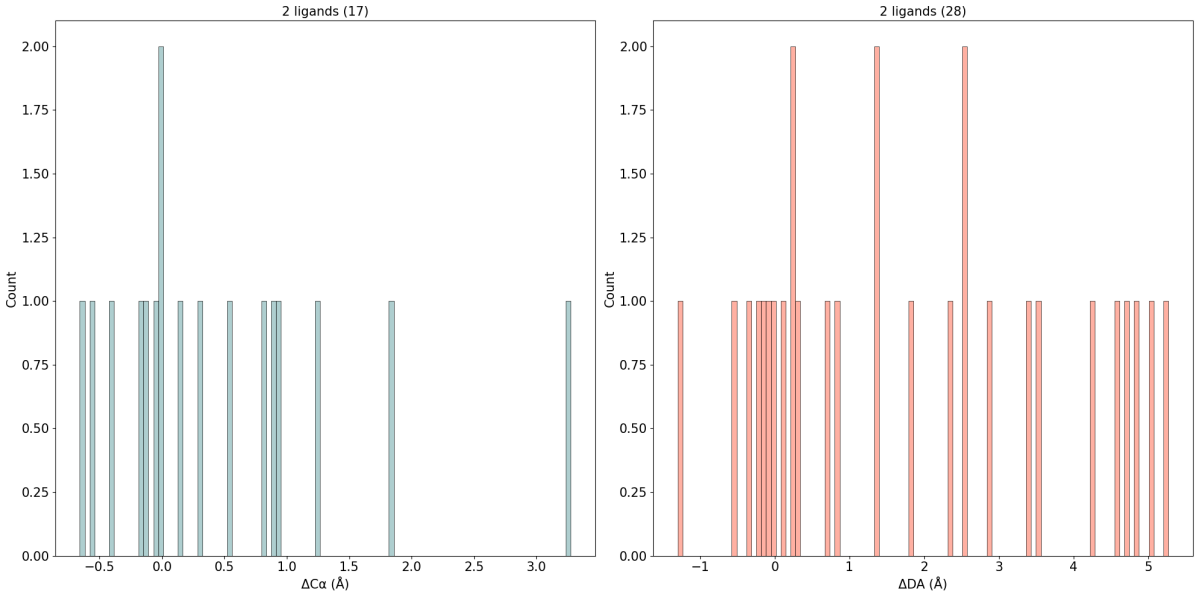

Figure S28. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in lead sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

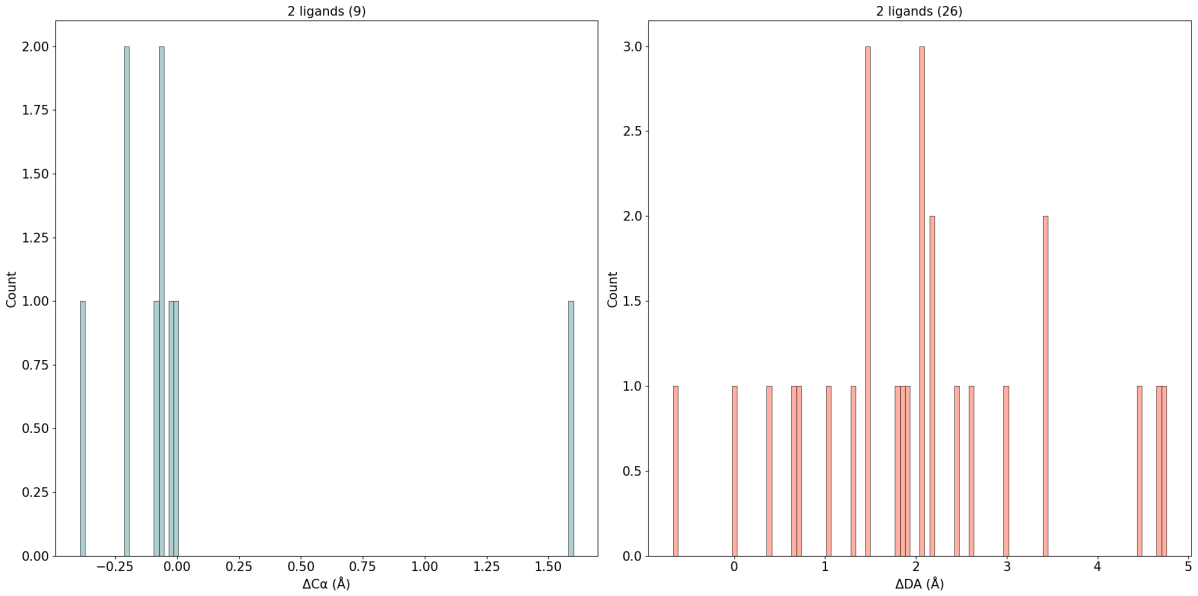

Figure S29. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in praseodymium sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

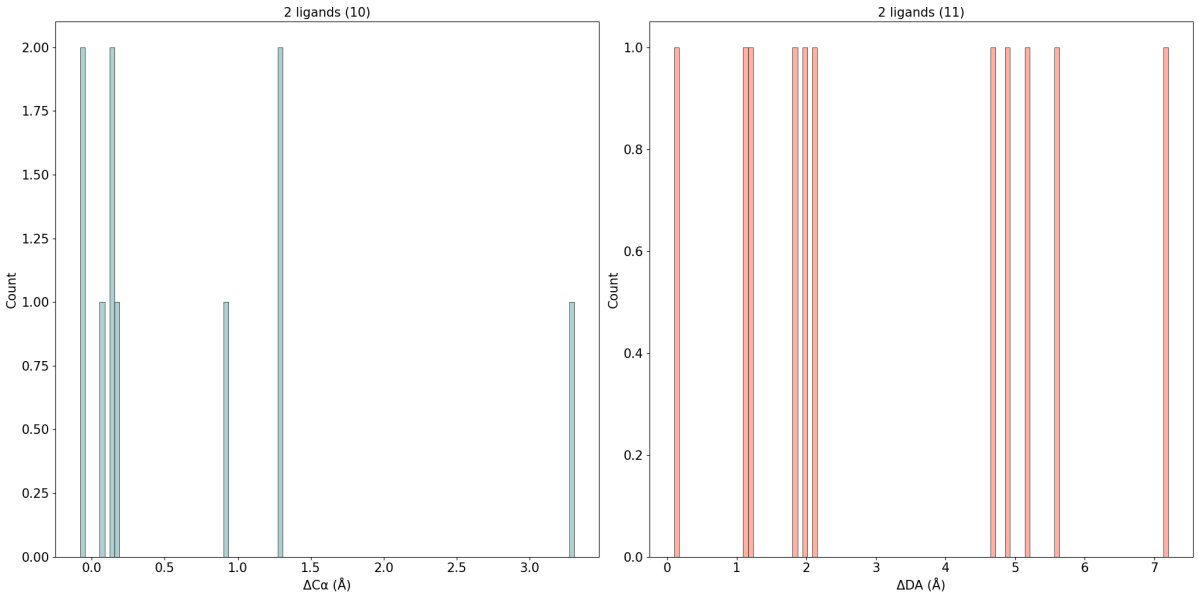

Figure S30. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in platinum sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

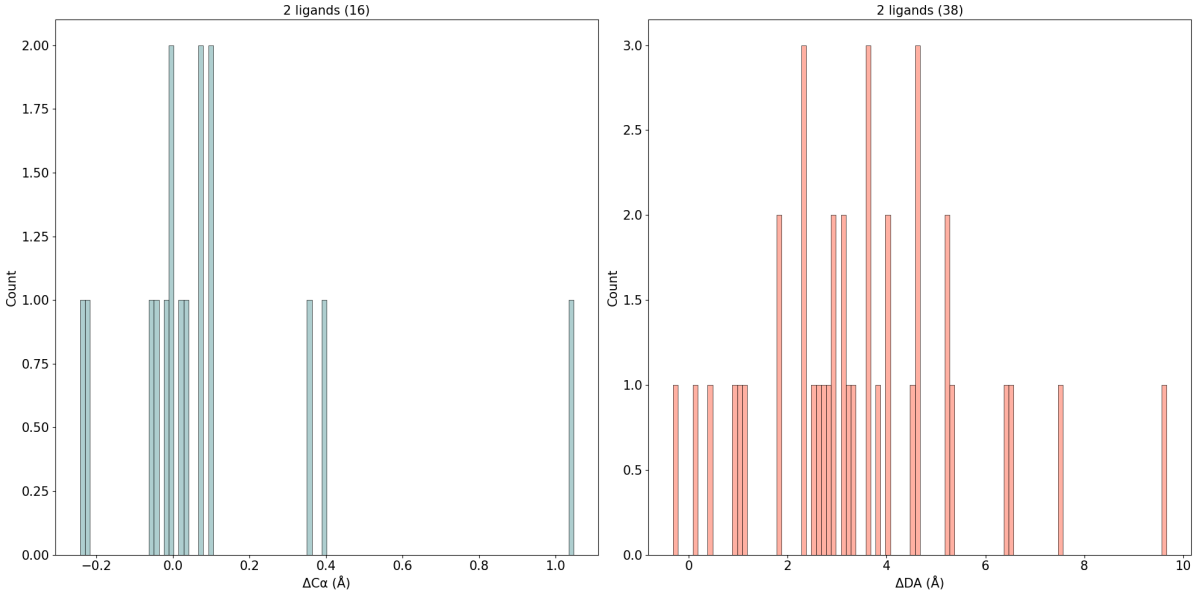

Figure S31. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in samarium sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

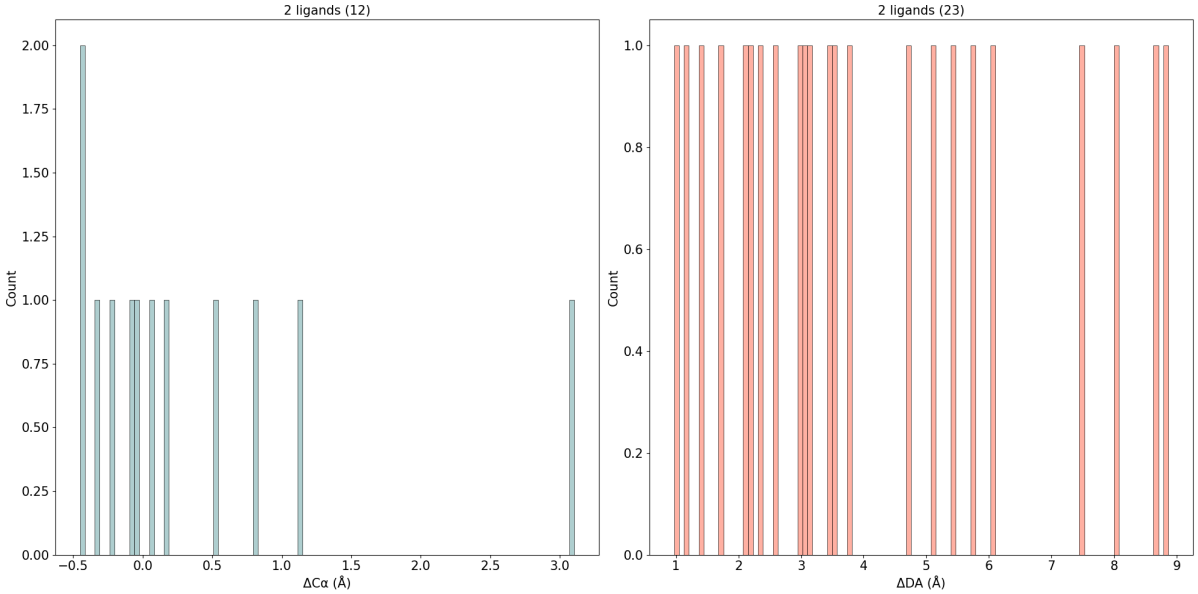

Figure S32. Frequency counts of apo vs holo structural changes measured for Cα-Cα (left) and donor atom (right) distances in yttrium sites. *There were not enough data to meaningfully separate by the number of endogenous metal ligands. All changes are measured as apo- minus the corresponding holo- distances*.

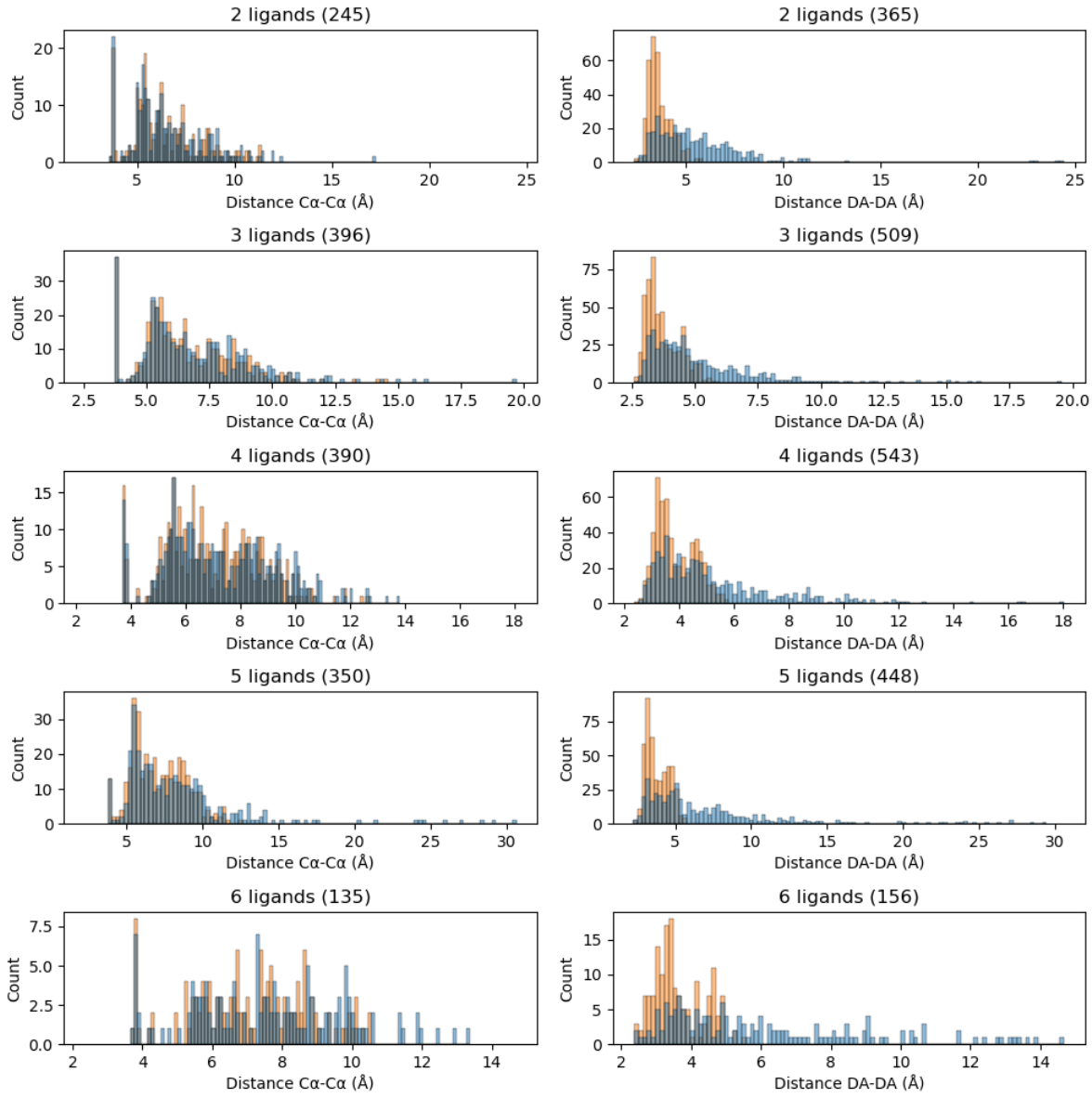

Figure S1. Frequency counts of Cα-Cα (left) and donor atom (right) distances in calcium sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

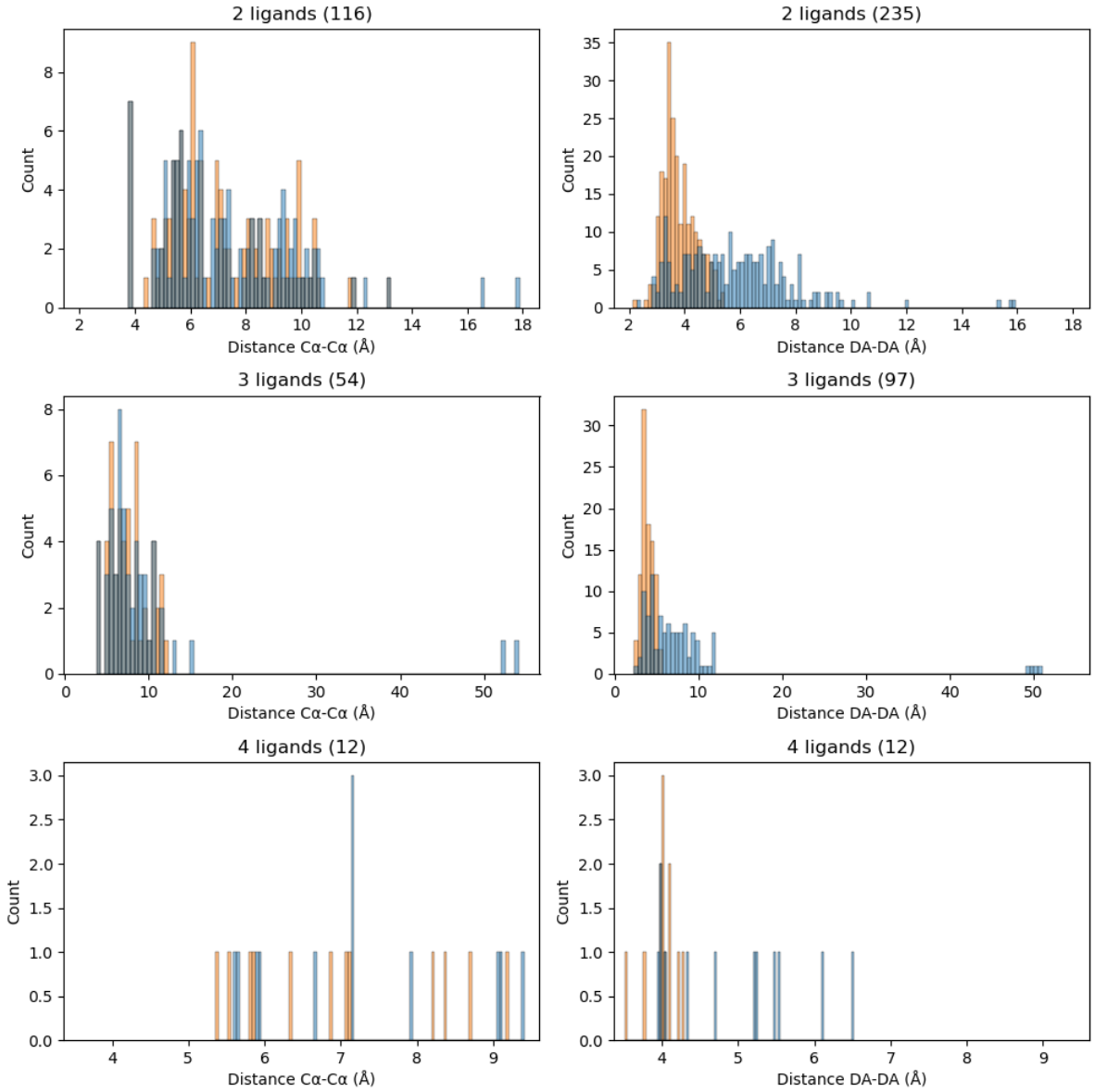

Figure S2. Frequency counts of Cα-Cα (left) and donor atom (right) distances in cadmium sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

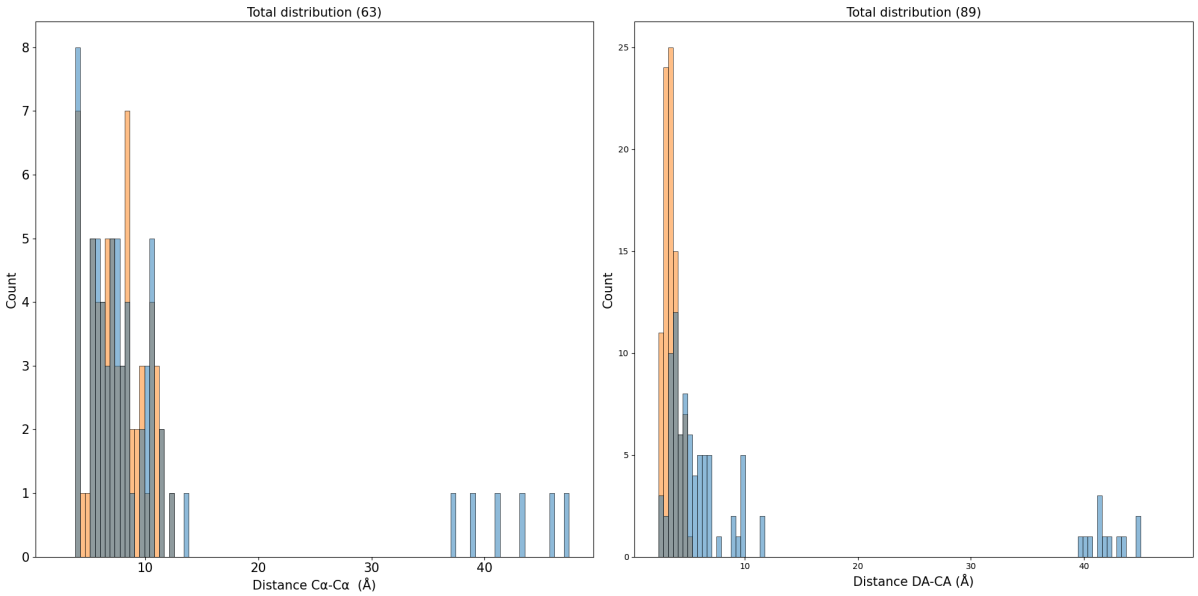

Figure S3. Frequency counts of Cα-Cα (left) and donor atom (right) distances in cobalt sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

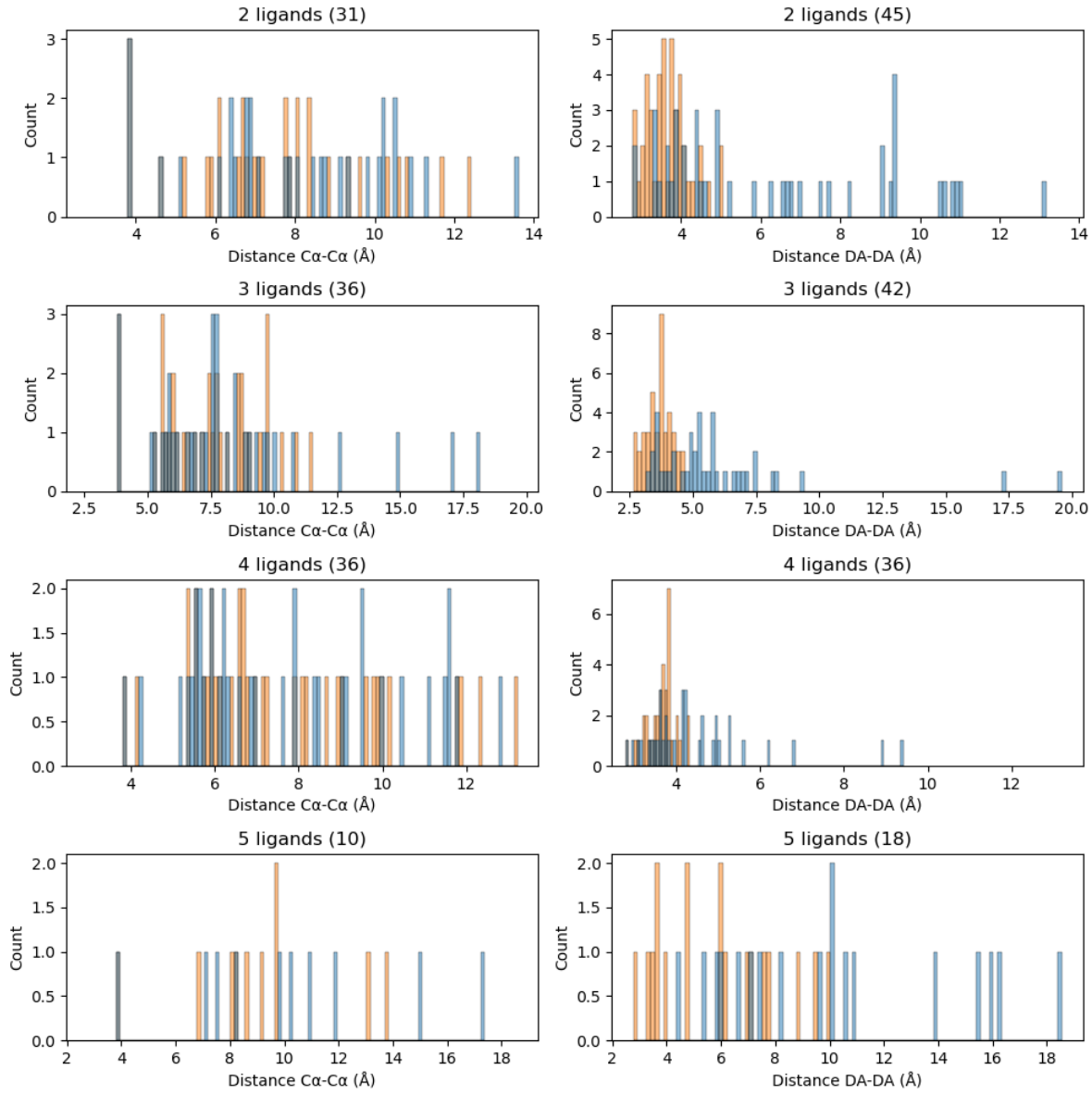

Figure* S4. *Frequency counts of Cα-Cα (left) and donor atom (right) distances in copper sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

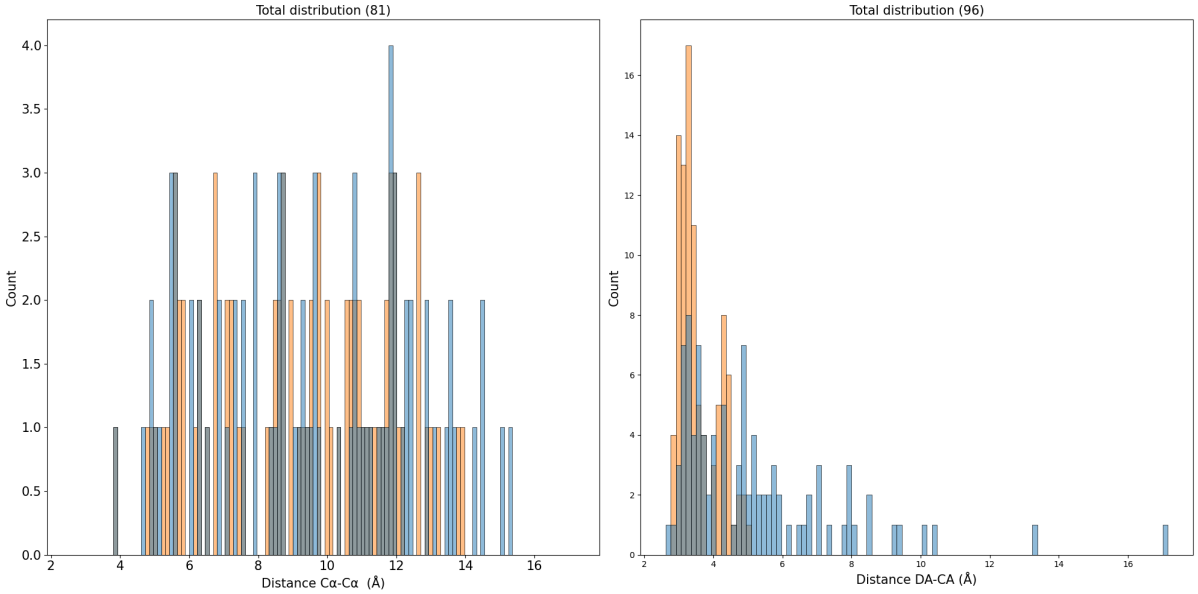

Figure S5. Frequency counts of Cα-Cα (left) and donor atom (right) distances in iron sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

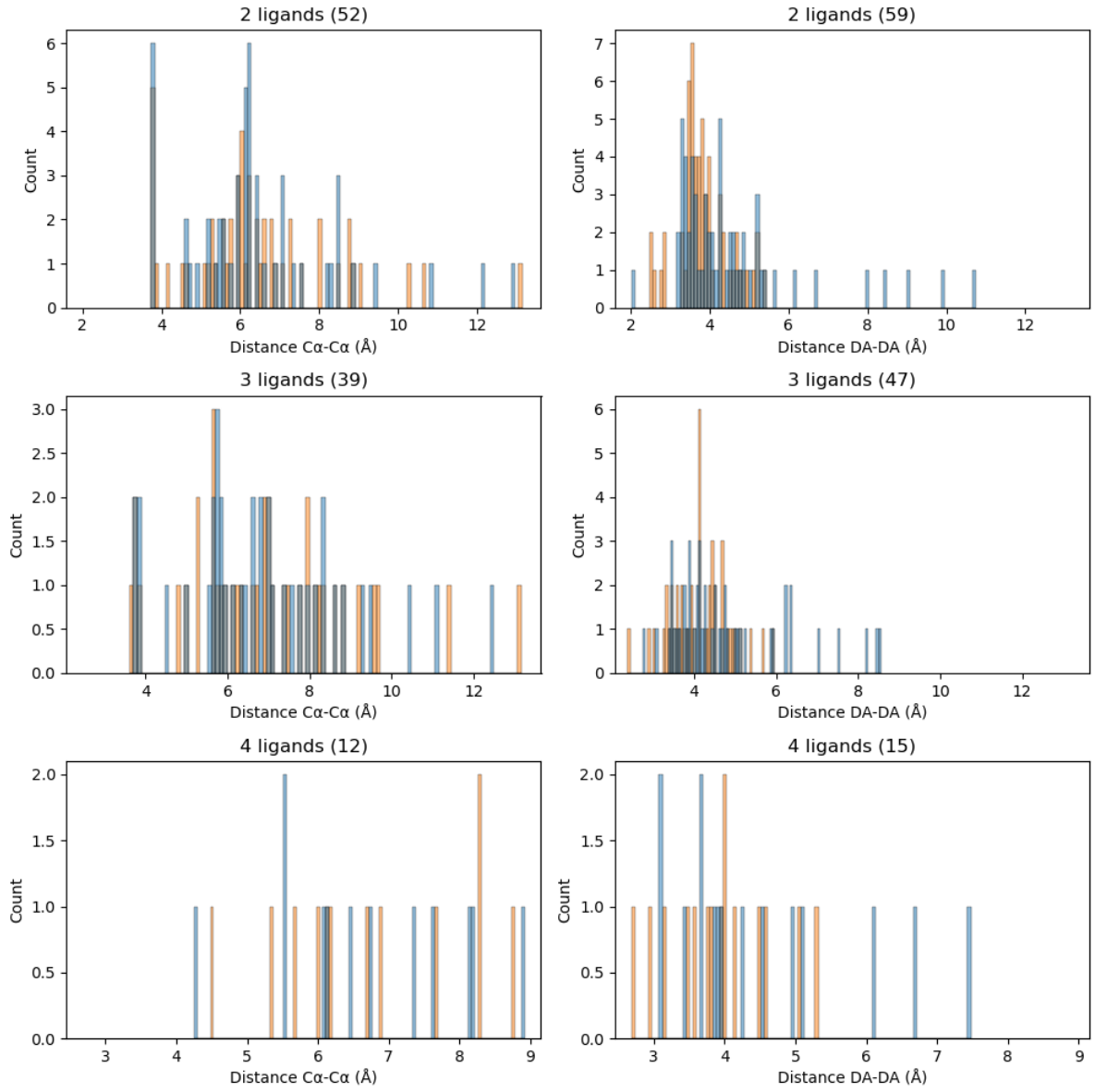

***Figure S6**. **Frequency counts of Cα-Cα (left) and donor atom (right) distances in mercury sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands.** The number of distances included in each panel is also shown.*

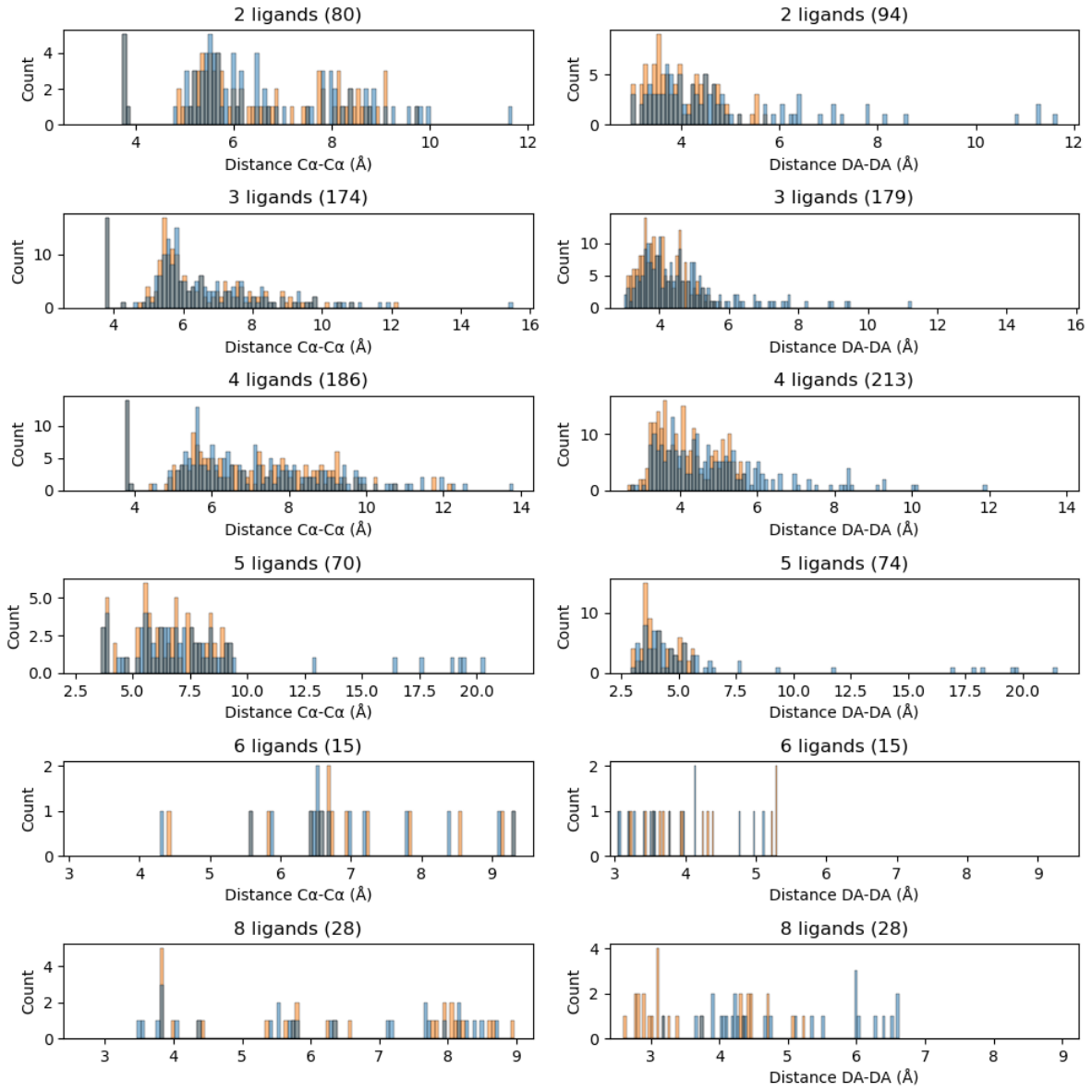

Figure S7. Frequency counts of Cα-Cα (left) and donor atom (right) distances in potassium sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

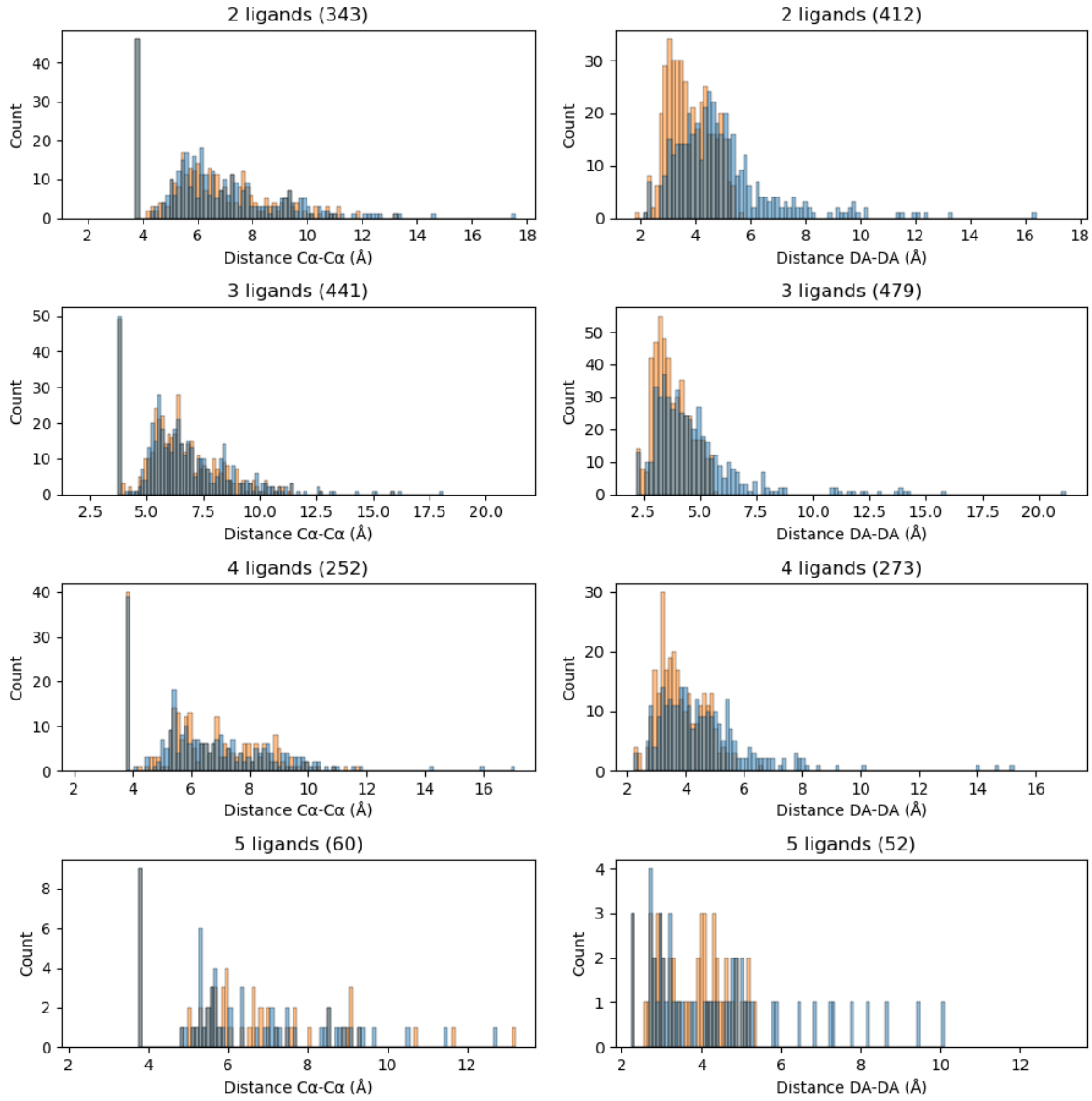

***Figure S8**. **Frequency counts of Cα-Cα (left) and donor atom (right) distances in magnesium sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands.** The number of distances included in each panel is also shown.*

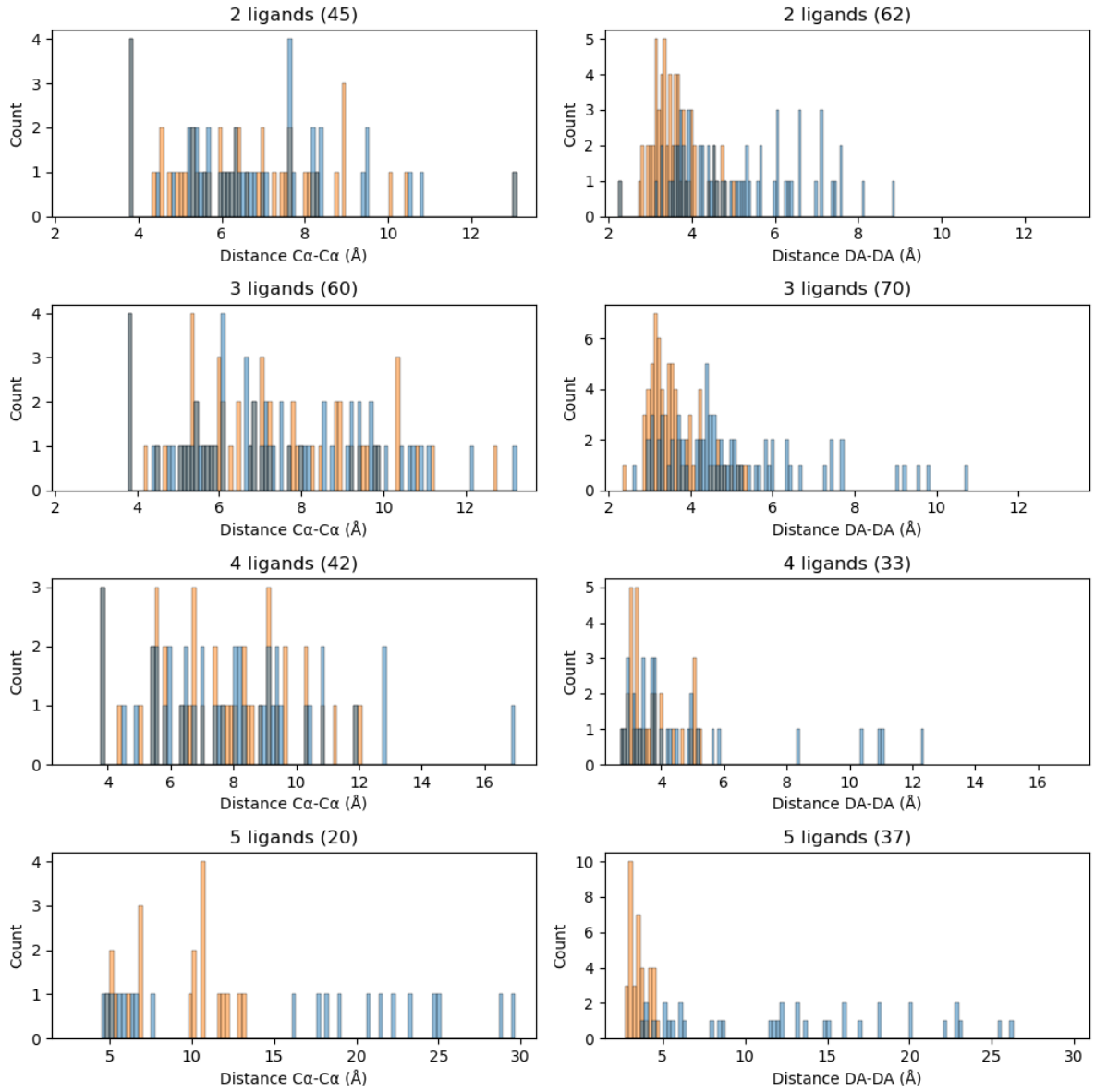

Figure S9. Frequency counts of Cα-Cα (left) and donor atom (right) distances in manganese sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

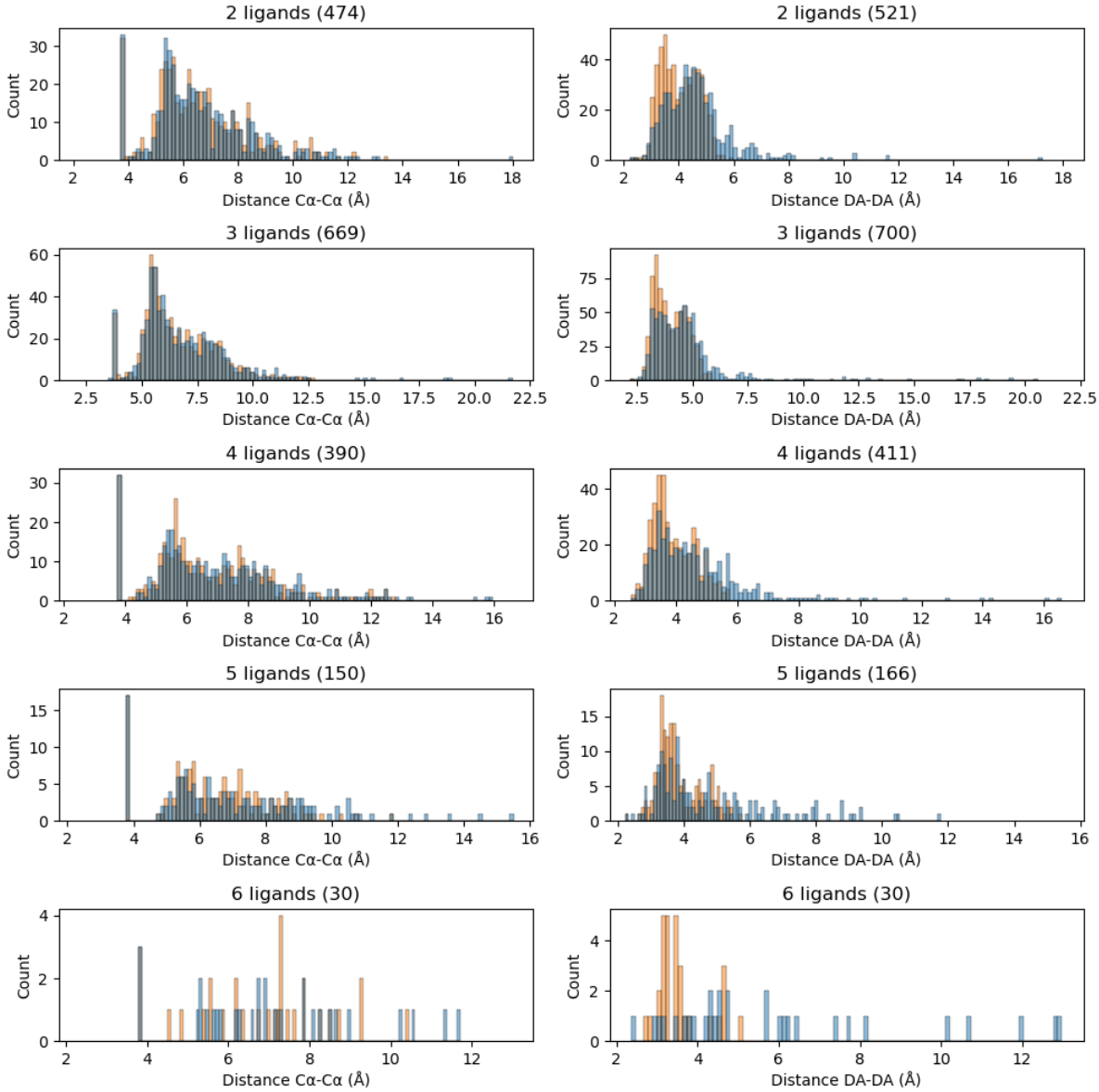

Figure S10. Frequency counts of Cα-Cα (left) and donor atom (right) distances in sodium sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

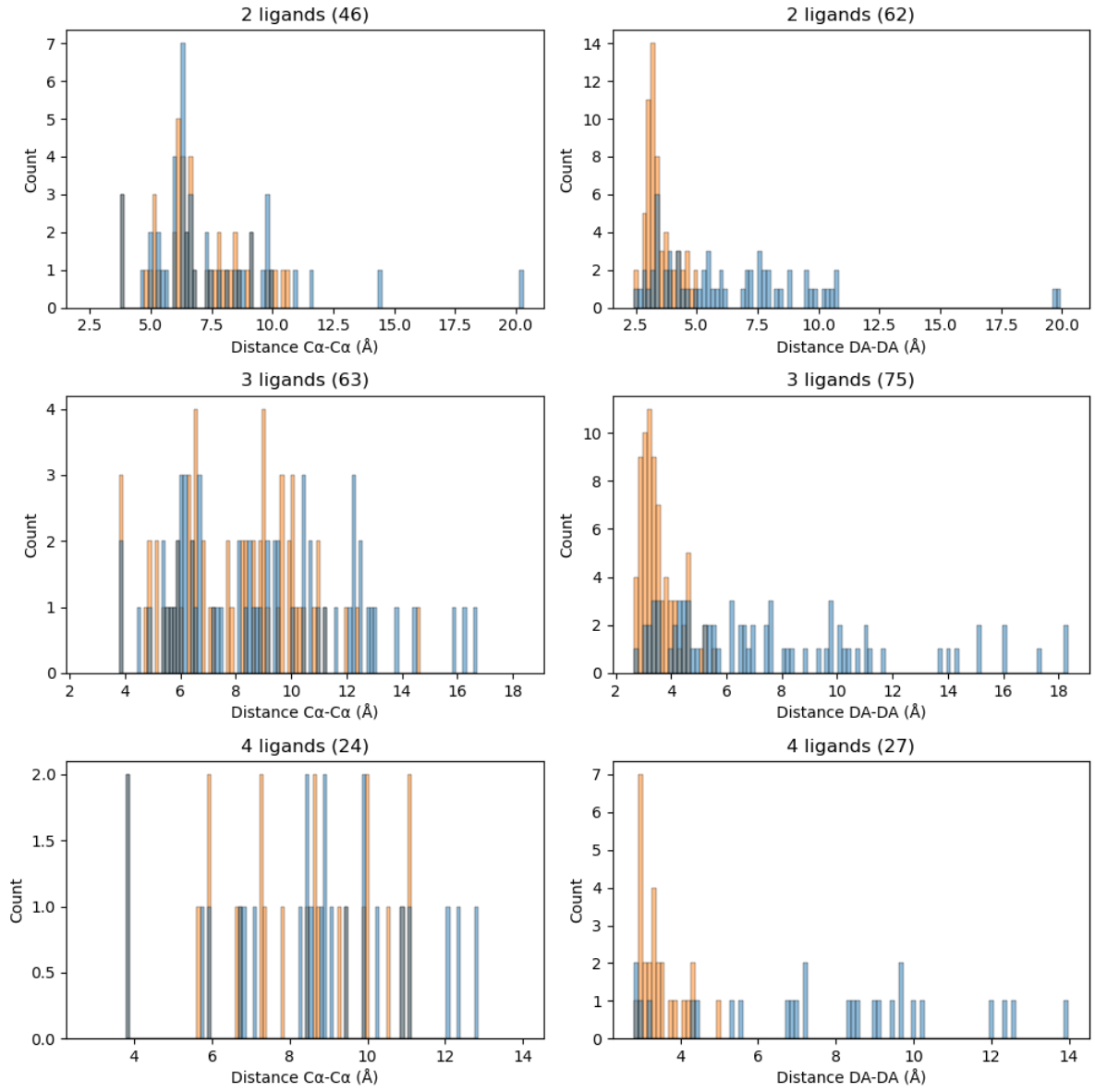

Figure S11. Frequency counts of Cα-Cα (left) and donor atom (right) distances in nickel sites (orange: holo; blue: apo) separated by the number of endogenous metal ligands. *The number of distances included in each panel is also shown.*

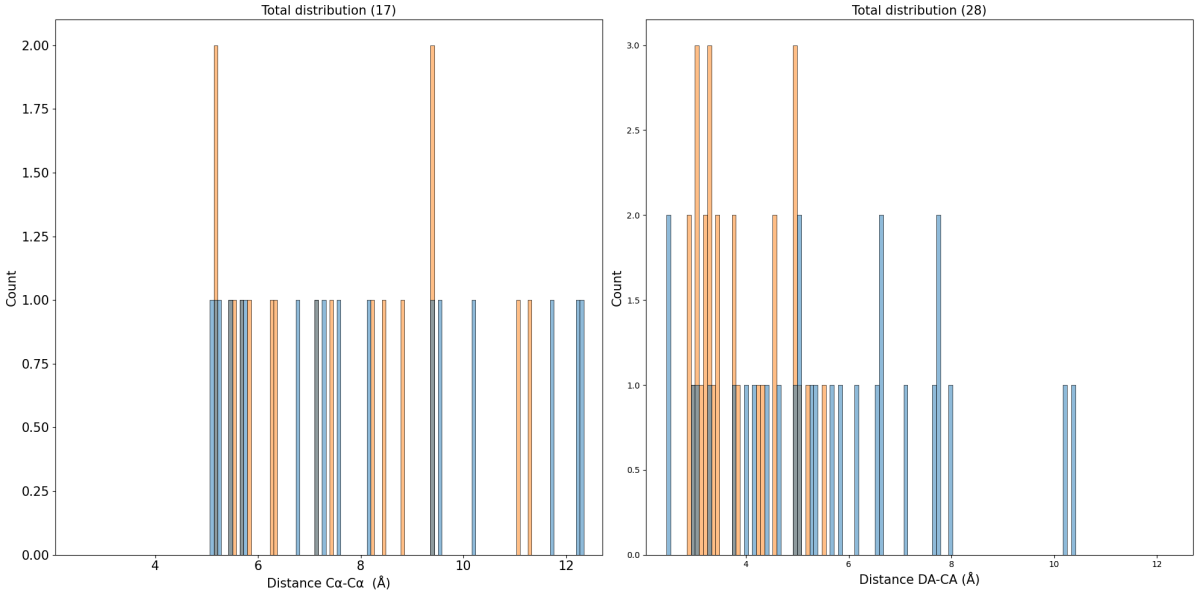

Figure S12. Frequency counts of Cα-Cα (left) and donor atom (right) distances in lead sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

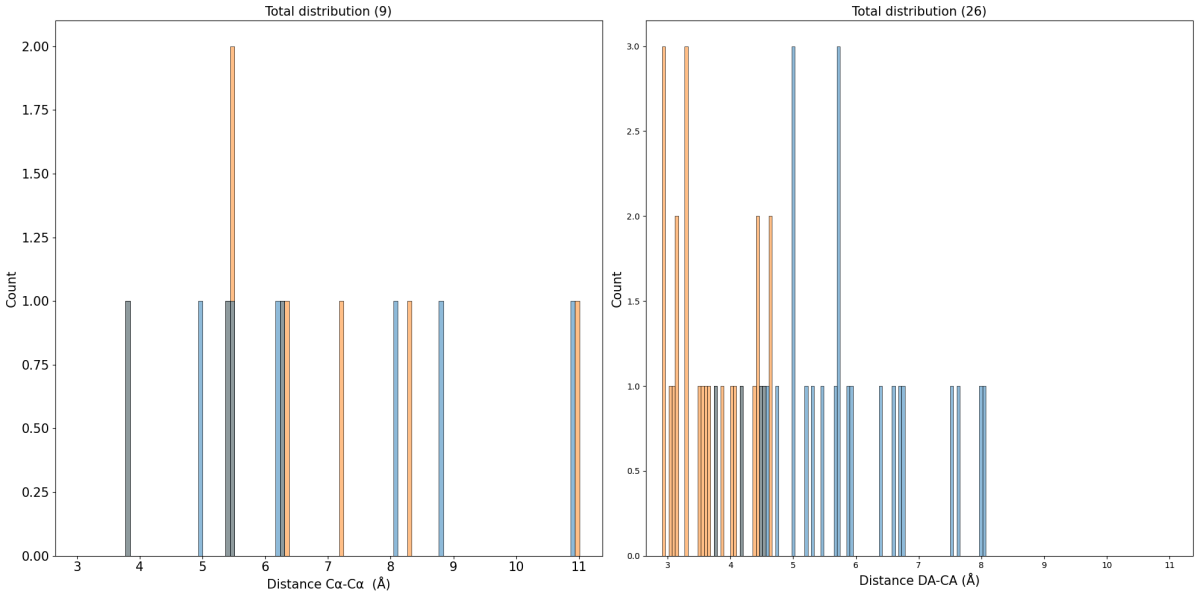

Figure S13. Frequency counts of Cα-Cα (left) and donor atom (right) distances in praseodymium
sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

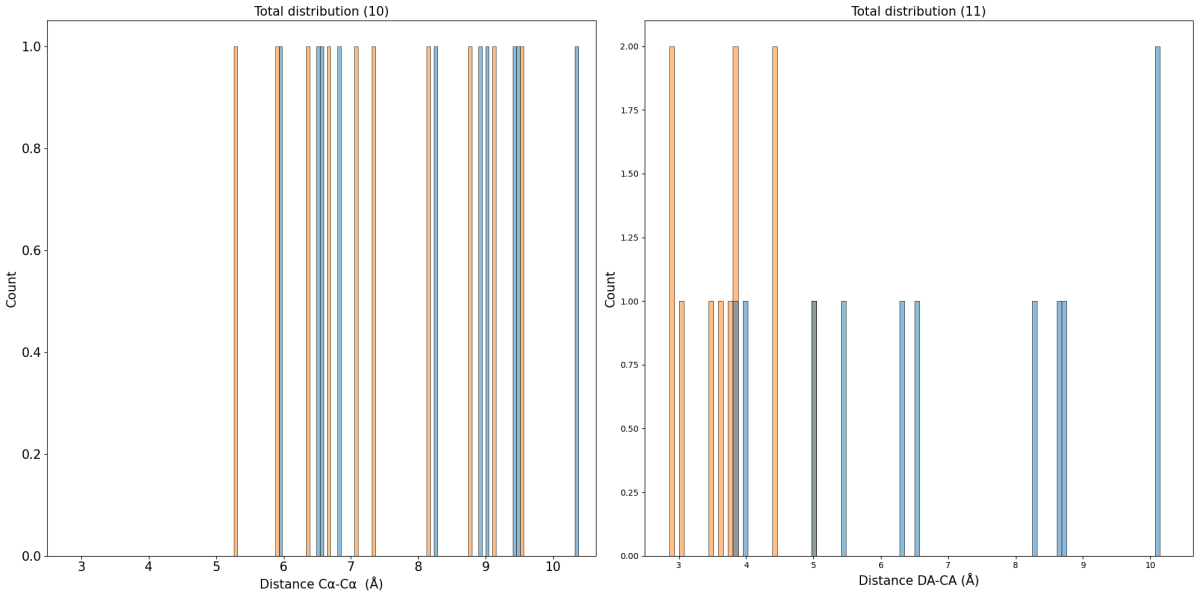

Figure S14. Frequency counts of Cα-Cα (left) and donor atom (right) distances in platinum sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

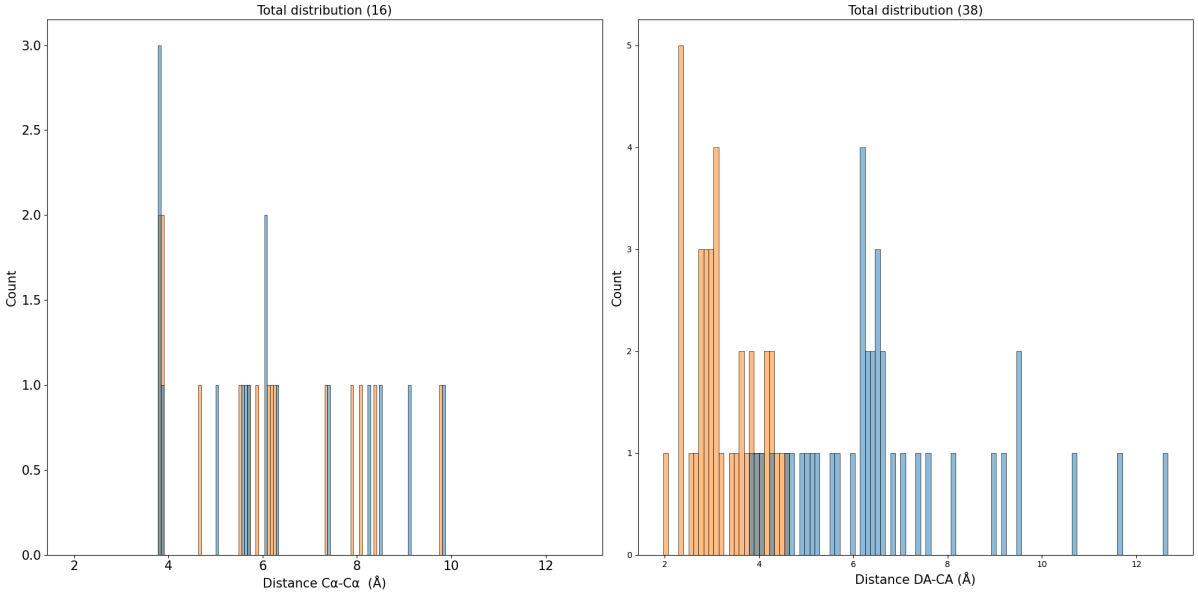

Figure S15. Frequency counts of Cα-Cα (left) and donor atom (right) distances in samarium sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

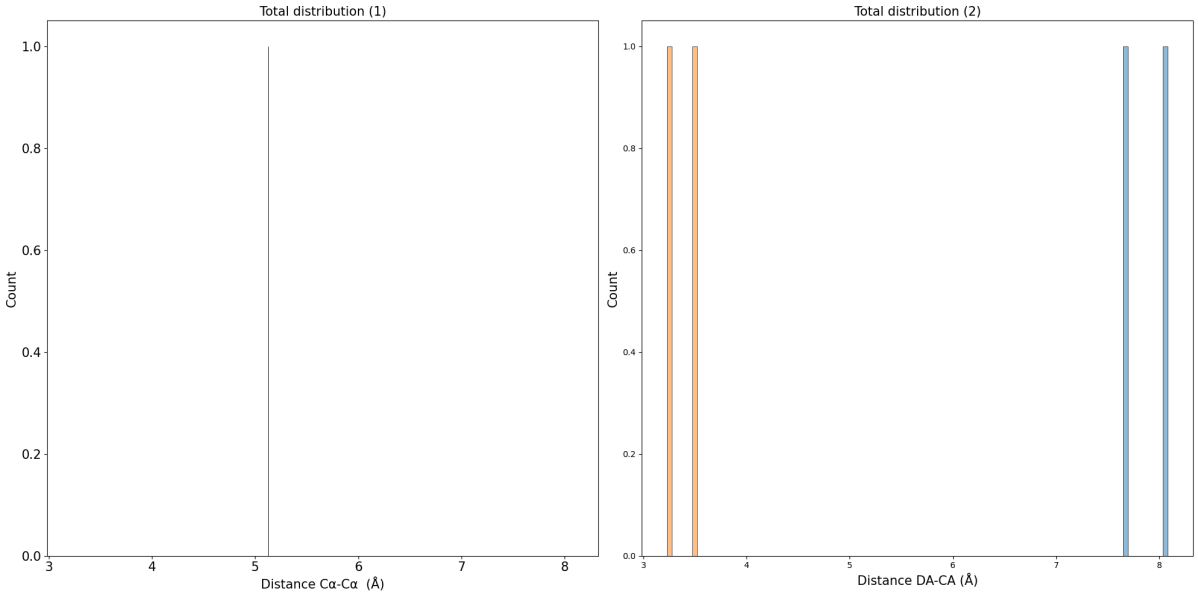

Figure S16. Frequency counts of Cα-Cα (left) and donor atom (right) distances in yttrium sites (orange: holo; blue: apo). *There were not enough data to meaningfully separate by the number of endogenous metal ligands. The number of distances included in each panel is also shown.*

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Article

A Comparison of Bonded and Nonbonded Zinc(II) Force Fields with NMR Data

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Abstract: Classical molecular dynamics (MD) simulations are widely used to inspect the behavior of zinc(II)-proteins at the atomic level, hence the need to properly model the zinc(II) ion and the interaction with its ligands. Different approaches have been developed to represent zinc(II) sites, with the bonded and nonbonded models being the most used. In the present work, we tested the well-known zinc AMBER force field (ZAFF) and a recently developed nonbonded force field (NBFF) to assess how accurately they reproduce the dynamic behavior of zinc(II)-proteins. For this, we selected as benchmark six zinc-fingers. This superfamily is extremely heterogenous in terms of architecture, binding mode, function, and reactivity. From repeated MD simulations, we computed the order parameter (S^2) of all backbone N-H bond vectors in each system. These data were superimposed to heteronuclear Overhauser effect measurements taken by NMR spectroscopy. This provides a quantitative estimate of the accuracy of the FFs in reproducing protein dynamics, leveraging the information about the protein backbone mobility contained in the NMR data. The correlation between the MD-computed S^2 and the experimental data indicated that both tested FFs reproduce well the dynamic behavior of zinc(II)-proteins, with comparable accuracy. Thus, along with ZAFF, NBFF represents a useful tool to simulate metalloproteins with the advantage of being extensible to diverse systems such as those bearing dinuclear metal sites.

Keywords: zinc; zinc-finger; NMR; order parameter; heteronuclear NOE; molecular dynamics; AMBER; ZAFF; metals; metalloprotein

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1. Introduction

Zinc is an essential element for all cells [1]. It is the second most abundant transition metal ion in living organisms after iron. Zinc(II)-binding proteins are key players in an extensive variety of biochemical processes such as protein synthesis and degradation, DNA metabolism and repair, and neurotransmission [2,3]. In order to obtain a detailed understanding at the atomic level of the mechanisms by which zinc(II)-binding proteins carry out their function, it is important to have information on their 3D structures and on their dynamics properties. The former is typically obtained through structural biology methods, such as X-ray diffraction, NMR spectroscopy or cryo-EM. The information on dynamics is more difficult to probe experimentally in a direct manner, NMR spectroscopy being the most apt technique to this end [4,5]. Alternatively, classical molecular dynamics (MD) simulations provide a powerful tool to understand how metal binding impacts the behavior of a protein in solution, at both the structural and dynamics level [6–8]. The reliability of simulations is related to the availability of an accurate force field (FF) [9].

Different models have been developed to parameterize metals in biological systems and their protein ligands (i.e., the protein residues containing the atoms that interact directly with the metal ion via the coordination bond) [10,11]. The two major approaches are the bonded and nonbonded models. The former incorporates explicitly the coordination bonds

between the metal and the donor atoms of the protein as well as of any other molecule (e.g., inhibitor) interacting directly with the metal. The coordination bond is represented via bond and angle terms, while the torsion term is usually neglected. The charges are often computed using the RESP method for the metal cation and for the ligands [12]. One main disadvantage of such a model is that it entails a burdensome parametrization for each specific system under study. In this work, we used the well-known and extensively used zinc AMBER force field (ZAFF) [13]. On the other hand, the nonbonded approach treats the metal ion as a sphere with appropriate electrostatics and van der Waals (vdW) terms to describe the interaction with the ligands. This strategy reflects the nature of the zinc(II) interactions in the binding sites, permitting transient modifications of the coordination geometry or exchanges with the solvent or nearby protein residues. Moreover, this model is convenient in terms of computational speed [14,15]. Thus, as an alternative to the aforementioned ZAFF model, we used a nonbonded parametrization of zinc(II) that was developed by some of us relatively recently. Two additional approaches are available in the literature, namely the cationic dummy model and the polarizable model. In the cationic dummy model, the metal is covalently bound to dummy particles with a defined geometry. Because there are no bonds between the dummy sites and the ligands, this rigid complex can move freely around its frame, change coordination geometry and exchange ligands. The charge of the metal is distributed over the entire complex, to reflect the partially covalent nature of the coordination bonds [10]. Finally, the polarizable model aims to reproduce the charge delocalization as a function of the coordination environment [16–18]. However, the polarizable approach is expensive from a computational point of view and hence it is seldom used in MD simulations [10,11].

The aim of this work was to assess the bonded and nonbonded models for the parametrization of zinc(II) sites with respect to their capability to provide accurate information on the dynamics of zinc(II)-binding proteins. Both models are not particularly demanding in terms of computational cost and differ mainly because the nonbonded approach is more easily portable to a variety of different systems and it is suitable to model ligand exchanges in the metal coordination sphere, while it may result in less stable MD trajectories due to e.g. the metal detaching from the protein. A strategy already adopted for the validation of FFs in proteins that do not harbor metal cofactors is to compare experimental NMR observables with predictions obtained from the simulations [19]. For the present investigation we focused on ^{1}H-^{15}N nuclear Overhauser effect (Het-NOE) data [20] measured for zinc-finger proteins. Het-NOE data are good reporters of protein backbone mobility on the sub-ns time scale, which can be sampled very well by classic MD simulations. Our results suggest that both models are well suited to reproduce the experimentally observed dynamics over the entire protein. In particular, there are no significant differences between the models even for the dynamics of the protein residues within the zinc(II) binding sites.

2. Results

2.1. Background

In this work, we focused on zinc-fingers (ZFs), which are among the most structurally diverse metalloprotein domains. They present various architectures, metal binding modes, functions, and reactivity [21,22]. Here, we selected NMR structures (PDB codes: 2NAX, 5JPX, 2JOX, and 2L7X) of ZFs that were characterized also through heteronuclear nuclear Overhauser effect (Het-NOE) measurements [23–26]. To further expand the structural diversity of our dataset, i.e., target different protein topologies, we included two additional ZF structures (PDB codes: 1CHC, 2K9H), for which unfortunately there are no relaxation data available [27,28]. Our benchmark structures contained one or two independent zinc(II) sites as well as, in one case, a binuclear site (Figure 1).

In this study, we aimed to evaluate two different FFs for zinc(II). The agreement with experimental data is a reliable measure of the accuracy of the FFs [9,19,29,30]. NMR spectroscopy is used to obtain information about protein motions on a broad range of

timescales, as nuclear spin relaxation rate reports on the internal motions on different timescales as well as on the overall rotational diffusion of the molecule. The three commonly measured NMR relaxation rates are the spin-lattice relaxation rate (R_1), the spin-spin relaxation rate (R_2), and Het-NOE data for all the ^{1}H-^{15}N moieties in the protein. Het-NOE data are extremely sensitive to fast protein dynamics [31–33]. Since all amino acids except Pro contain at least one N-H moiety within the peptide bond, these data provide a comprehensive coverage of the flexibility of the entire protein chain.

A core assumption of most strategies to interpret NMR relaxation data in proteins is the decoupling of the overall and the internal motions. Information about local motions is derived by fitting suitable parametric functions to the relaxation rates, e.g., as done in the so-called model-free approach [31,34,35]. The latter is termed model-free because the parameters are derived without the need to invoke a specific model for the internal motion. The model-free analysis of the data mentioned in the previous paragraph outputs a set of parameters for each N-H bond in the protein. In particular, the order parameter (S^2) describes the magnitude of the angular fluctuation of each bond vector, reflecting the flexibility of the polypeptide at those sites with respect to the overall frame [31,34]. However, we chose to compare the MD-derived S^2 with the Het-NOE data rather than the NMR-derived S^2 values, because Het-NOEs are experimental data that can be used without any interpretation or assumption and report on the relevant timescale of dynamics (sub-ns).

2.2. Analysis of the MD Simulations and Comparison of Simulated vs. Experimental Dynamics

The overall protein fold remained stable during the production phase for all systems, as shown by the RMSD values of the backbone (Supplementary Figures S1–S6). When using the NBFF, the electrostatic nature of the coordination allows transient distortions of the zinc(II) site and may lead, in principle, to the protein losing its metal cofactor [10,14]. For this reason, we inspected the donor atom–metal distances throughout the trajectories. The zinc(II) coordination was maintained during all MD runs, with fluctuations of 0.04 Å around the equilibrium distances. This behavior agrees with previous reports for other systems [14,36]. Instead, in the bonded simulations, the metal was kept fixed to the donor atoms through covalent bonds [13], so there was no need to monitor these distances. These data indicated that all MD runs, with both FFs, were suitable for our subsequent analyses. As mentioned in the preceding section, we used these trajectories to compute the S^2 parameters. In turn, this information allowed us to assess whether there were differences in the accuracy of the protein dynamics simulated with the two FFs based on the comparison with the experimental NMR observables.

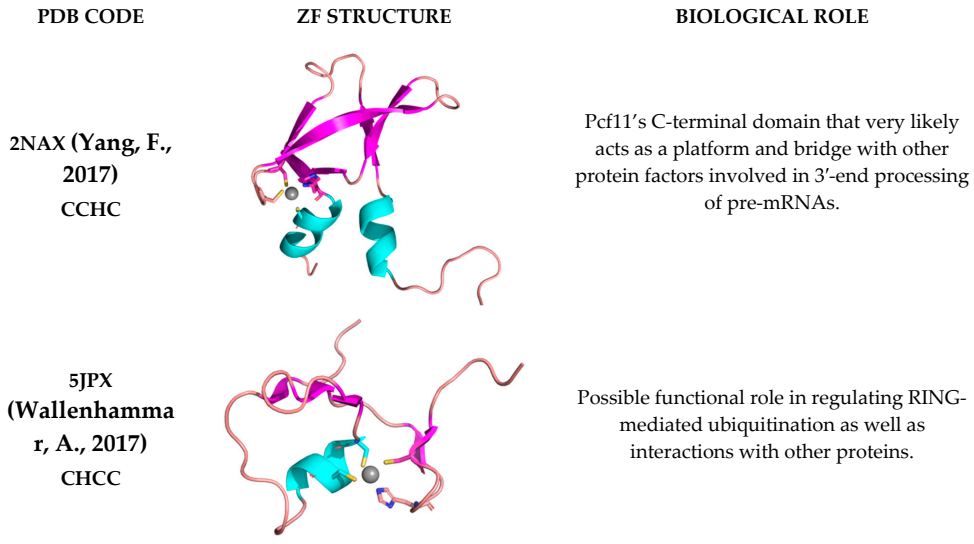

Figure 1. *Cont.*

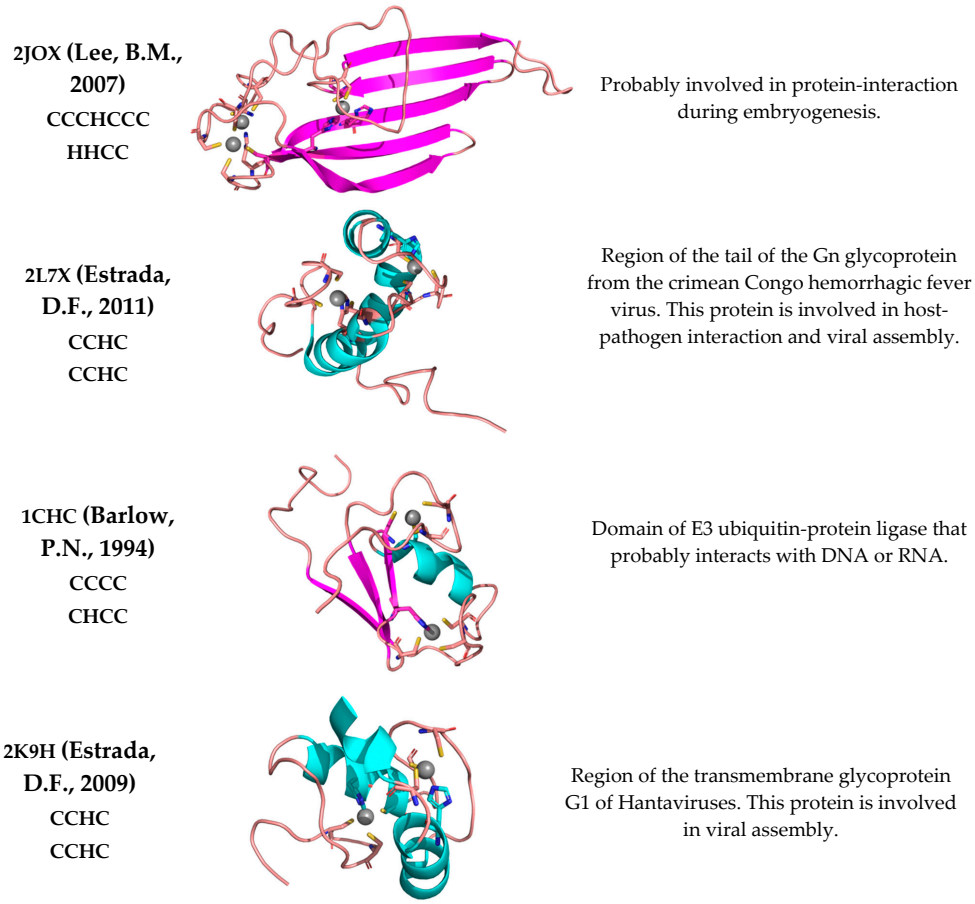

Figure 1. Zinc-fingers used to test the bonded and nonbonded FF. The first column reports the PDB code of the structure together with the amino acid pattern(s) binding the zinc(II) ion(s) [23–28,37,38]. The third column reports information about their biological role.

The first protein in our benchmark set is 2NAX. This structure contains seven β strands, a short N-terminal 3_{10}-helix and a longer C-terminal α helix (Figure 1). The residues interacting with the zinc(II) ion are Cys^{564} and Cys^{567}, located on the β2β3-hairpin, and His^{596} and Cys^{599} on the C-terminal α helix. Figure 2 shows the averaged MD-computed S^2 for both FFs superimposed to the Het-NOE data.

The mean S^2 values computed from the MD runs with the two FFs are almost the same, with a remarkably similar trend over the protein sequence. Moreover, both computed S^2 display, as expected, high values (>0.7) for regions of secondary structure and lower values for loop regions, identifying a rigid domain in both cases. The ligands participating in metal coordination are encompassed in regions with higher stability than the protein average, whereas the N- and C-termini and loop regions experience significant flexibility. Additionally, with respect to the experimental Het-NOE data, we observed a fully satisfactory agreement, which can be quantitatively expressed by computing the Pearson coefficient. For the 2NAX protein, we obtained a coefficient of 0.82 for the NBFF and of 0.89 for the ZAFF (Table 1). Besides the protein termini, the Het-NOE indicates the presence of a rigid domain, as described above, except around residue 558, which is well captured by our simulations. The simulations with the NBFF display higher than expected flexibility at residues 569–570, which is not observed with ZAFF. This is arguably the largest deviation between the two sets of simulations. The Het-NOE data indicates that the N-terminal helix is looser than the C-terminal; indeed, in the publication reporting the structure, helix α1 was described as tending to partially unfold [23]. We analyzed the trajectories considering and excluding this secondary structure to see whether its presence would influence the prediction of S^2 values for the whole protein. This was not the case, showing that the local

dynamics of helix α1 are effectively decoupled from the rest of the system. Although we inspected several structural factors, namely (i) the distances between the donor atoms, (ii) the distribution of water molecules around the metal site, and (iii) the hydrogen bond patterns, we did not highlight possible causes of the behavior of helix α1.

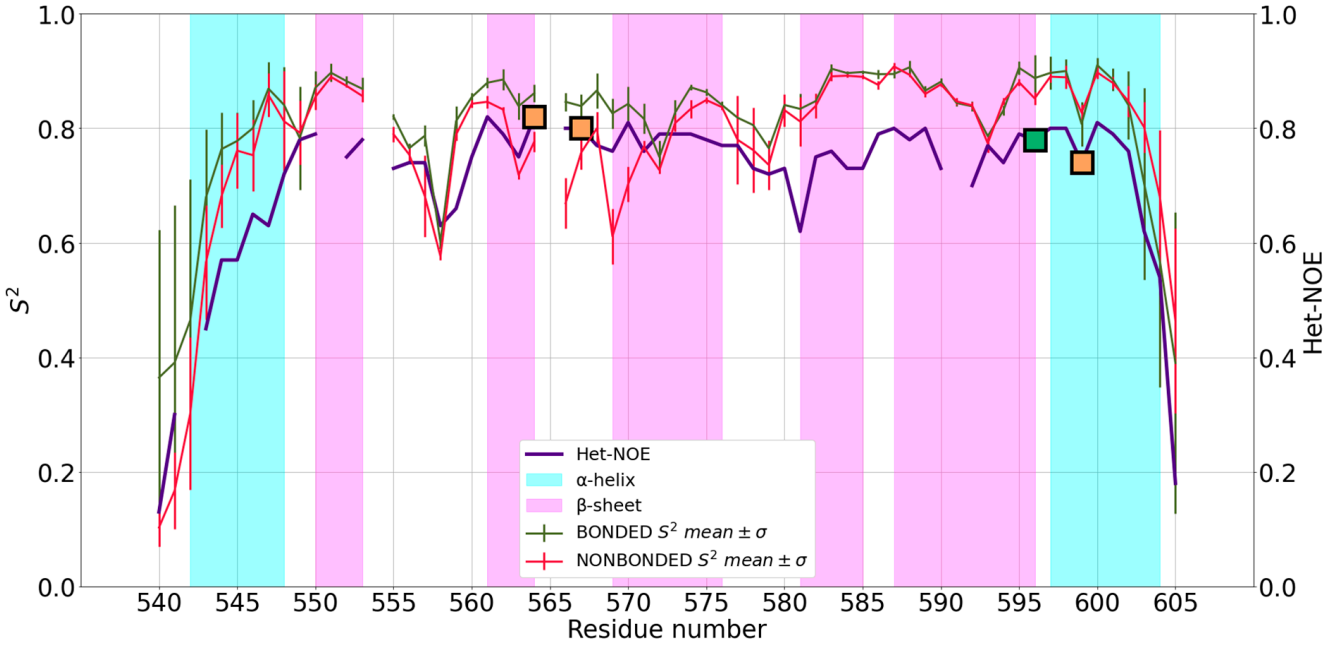

Figure 2. Mean S^2 of 2NAX and standard deviation (SD) for bonded (red) and nonbonded (green) simulations superimposed to Het-NOE data (purple). Orange squares represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green squares represent zinc(II)-binding His residues.

Table 1. Pearson coefficients computed for each zinc(II) FF with respect to the Het-NOE data. For 2JOX, it was not possible to apply the ZAFF. 1CHC and 2K9H are not reported since there are no experimental data available.

Zinc-Fingers	Pearson Coefficient for NBFF	Pearson Coefficient for ZAFF
2NAX	0.82	0.89
5JPX	0.68	0.69
2JOX	0.77	n.a.
2L7X	0.79	0.84

5JPX presents a ββαβ core domain, with two additional short strands and a disordered N-terminal tail (Figure 1) [24]. The MD-computed S^2 values for the two FFs are perfectly superimposable in the regions corresponding to secondary structures and show very small differences for loop regions. Both FFs reproduce the local protein dynamics as described by the Het-NOE data (Figure 3), with Pearson coefficients of 0.68 and 0.69 for the NBFF and ZAFF, respectively.

The core encompassing the ligands (Cys^{92}, His^{95}, Cys^{111} and Cys^{114}) is stable during all trajectories, with mean S^2 values around 0.8, corresponding to well folded secondary structures. The region Arg^{118}-Asp^{122} was not characterized experimentally due to signal broadening [24], so no Het-NOE data are available for these residues. The MD simulations provided information about this region indicating that the region 118–122 is highly flexible also on the sub-ns timescale.

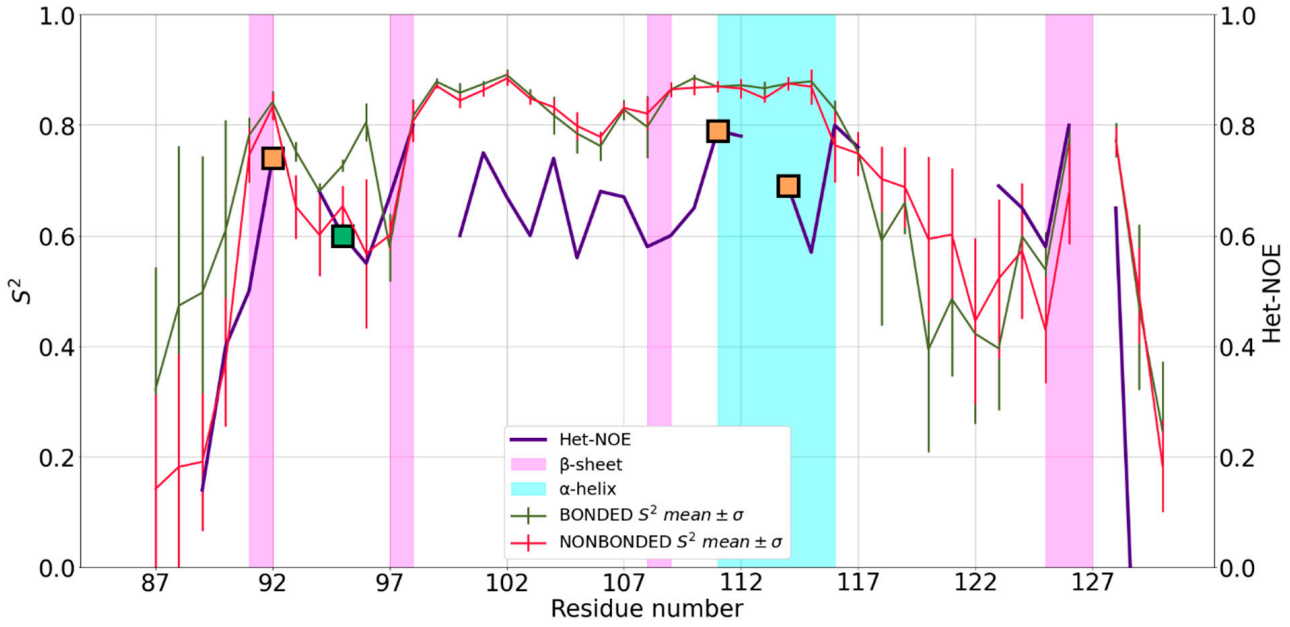

Figure 3. Mean S^2 of 5JPX and standard deviation (SD) for bonded (red) and non-bonded (green) simulations superimposed to Het-NOE data (purple). Values on y-axis were truncated at 0 because S^2 has no negative values. Orange squares represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green squares represent zinc(II)-binding His residues.

2JOX is composed by an antiparallel β-sheet with five strands, with both sides of the sheet being solvent exposed. The sheet is stabilized by a mononuclear zinc(II) site (His^{59}, His^{71}, Cys^{88} and Cys^{91}) through cross strand interactions. An additional binuclear site (Cys^{2}, Cys^{5}, Cys^{30}, His^{66} for one zinc(II) ion, and Cys^{30}, Cys^{33}, Cys^{61}, Cys^{64} for the other one) holds together the N-terminal region (Figure 1). In this binuclear cluster, Cys^{30} acts as a bridge between the two zinc(II) ions [25]. Due to the specific chemical structure of the binuclear cluster, it was not possible to investigate the system using ZAFF, as it is parametrized mainly for mononuclear sites. At the same time, 2JOX was particularly challenging for the NBFF. Trajectory visualizations and the analysis of donor-metal distances show that during the simulations, the bridging residue acts as a ligand only towards $zinc^{109}$. In other words, the binuclear site splits into two mononuclear sites, with $zinc^{108}$ being coordinated by three residues. The coordination geometry of the latter is kept during all trajectories. Although the computed mean S^2 (Figure 4) show some discrepancies when superimposed to the experimental Het-NOE data, the overall local protein dynamics is well represented, with a Pearson coefficient of 0.77 (Table 1).

In the N-terminal tail, the loop region 29–39 has a higher predicted flexibility than observed in the experimental data. Notably, for five out of the 11 residues in this region, experimental Het-NOE values are lacking [25]. The mobility enhancement is caused by the displacement of $zinc^{108}$ from $zinc^{109}$, which leads to the rearrangement of this region, resulting in higher solvent exposure and a wider conformational space available. In the β-sheet part of the protein, where the mononuclear site lies, the agreement with the experimental data is excellent. Our simulations are fully consistent with the experimentally observed flexibility in the β1-β2 portion of the sheet, also involving the terminal regions of the two strands. The β-turns between strands β1-β2 and β3-β4 have a higher mobility than the turns between β2-β3 and β4-β5, since they comprise some of the ligands of the zinc(II) ions (Figure 4). The role in metal coordination of these residues restricts their conformational freedom.

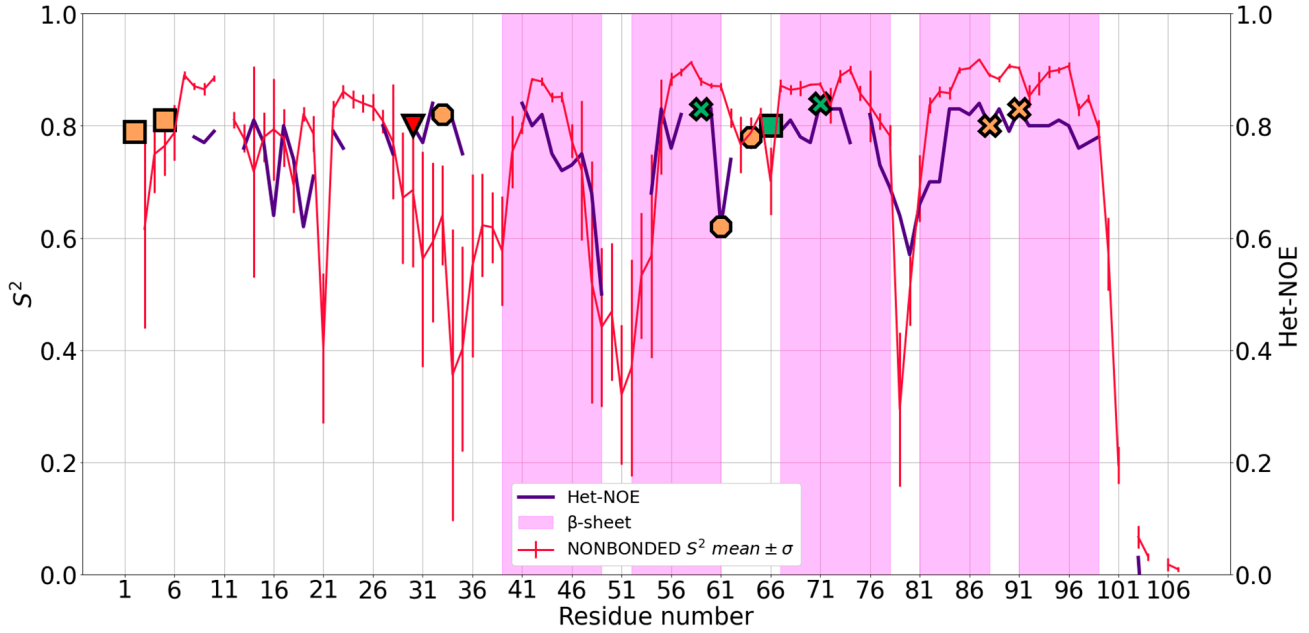

Figure 4. Mean S^2 of 2JOX and standard deviation (SD) for nonbonded (red) simulations superimposed to Het-NOE data (purple). It was not possible to apply ZAFF to the system. The y-axis was truncated at 0 because S^2 had no negative values, hence some Het-NOE data for the last protein residues were not visible. Orange markers represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green markers represent zinc(II)-binding His residues. Residues belonging to the same site are represented with the same marker shape (crosses for the mononuclear site; circles for the binuclear site except the bridging Cys^{30}, which is represented as a red triangle).

The 2L7X structure features two zinc fingers, with an additional α3 that packs against the dual zinc finger fold (Figure 1). The N- and C-terminal regions are unstructured and flank the central part of the domain. The first zinc finger (ZF1) bears a zinc(II) ion coordinated by Cys^{736}, Cys^{739}, His^{752} and Cys^{756}, while in ZF2, the coordination is carried out by Cys^{761}, Cys^{764}, His^{776} and Cys^{780} [26]. The S^2 values computed from the trajectories with the two FFs are almost superimposable and agree with a rigid and compact structure (Figure 5). ZF1, ZF2 and the linker in between them behave as one entity, whereas the two tails display enhanced flexibility. For both FFs, the predicted dynamics correlate well with the experimental information.

For the 1CHC and 2K9H systems, there are no experimental data for results validation. Thus, we investigated only the relationship between the S^2 values predicted for the trajectories with the two FFs (Supplementary Figures S7 and S8), as well as with the structural features of the proteins. 1CHC has a split-βαβ topology with an amphipathic α-helix spanning the triple-stranded antiparallel β-sheet [27]. The predicted S^2 values for both FFs are highly similar and agree with the ZF topology, revealing a stable core with values around 0.8 for the secondary structure elements and for the loop regions harboring the ligands (Supplementary Figure S7). The N- and C-termini flank the compact core and show high flexibility, as expected for unstructured regions. A relevant discrepancy between the behaviors observed with each FF is the enhanced mobility of Cys^{32}, which is caused by the lower stability in the NBFF simulations of the secondary structure it belongs to. 2K9H features a novel CCHC dual ZF fold; the ligands of the zinc(II) ions are Cys^{548}, Cys^{551}, Cys^{568} and His^{564} for the first ZF, and Cys^{573}, Cys^{576}, His^{590} and Cys^{594} for the second one [28]. This protein has a highly compact structure, which is reflected by the MD-computed mean S^2 value of each FF. The obtained results are closely superimposable with some discrepancies in the loop region immediately following Cys^{576} (Supplementary Figure S8).

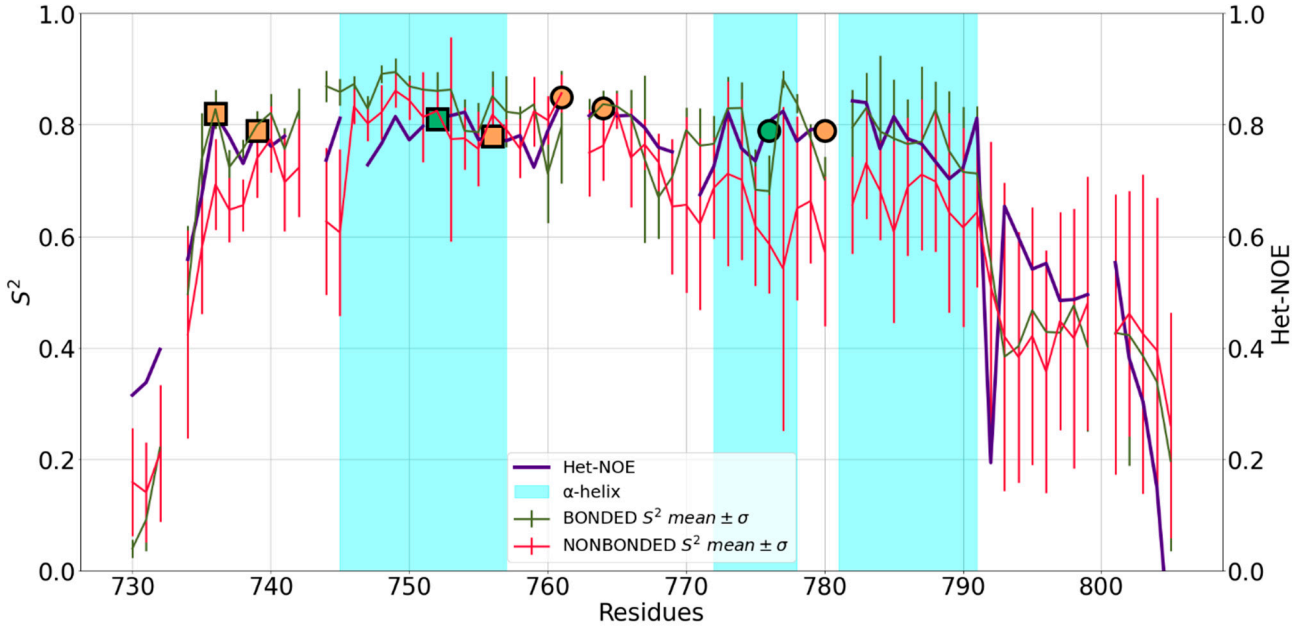

Figure 5. Mean S^2 of 2L7X and standard deviation (SD) for bonded (red) and nonbonded (green) simulations superimposed to het-NOE data (purple). Values on y-axis were truncated at 0 because S^2 had no negative values. Orange markers represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green markers represent zinc(II)-binding His residues. Residues belonging to the same site are represented with the same marker shape (squares: ZF1; circles: ZF2).

3. Discussion

All of the inspected ZFs bear Cys and His ligands coordinating zinc(II) ions in a tetrahedral geometry. The computed results for the two FFs are almost always overlapping and agree with the protein dynamics shown by the Het-NOE data. This is generally true for the regions with limited flexibility (characterized by $S^2 > 0.8$ and Het-NOE > 0.7) as well as for the regions with high flexibility outside or within secondary structure elements. To quantify the agreement, we computed the Pearson correlation coefficient between the mean S^2 of each FF and the corresponding Het-NOE data (Table 1). The Pearson coefficient is an indicator of how accurately each FF represents the experimental trend. The results obtained are satisfactory, with values ranging from 0.68 to 0.89. For the 2JOX protein, the Pearson coefficient is 0.77, suggesting that the NBFF can be useful for systems containing multinuclear sites, for which the traditional ZAFF parametrization is less suitable.

The Pearson coefficients for the ZAFF simulations are marginally better than those obtained with the NBFF, indicating that the two FFs have comparable accuracy. By inspecting this behavior in greater detail, we observed that in some cases, the initial regions of secondary structure elements were not perfectly maintained (information obtained from DSSP analysis, not shown) throughout the trajectories with the NBFF. We speculate that this small destabilization could be due to the electrostatic interaction between the residues forming the secondary structures and the zinc(II) site. In line with this, the mean S^2 values computed from NBFF trajectories have higher standard deviations than those computed for the ZAFF simulations. This means that the individual trajectories differ more from each other with the former FF than with the latter.

Based on our results, the NBFF and ZAFF are equally reliable for the investigation of zinc(II)-binding proteins, albeit the MD runs with the former have slightly higher standard deviations. In fact, for all the ZFs tested here, both FFs could reproduce properly the local protein dynamics shown by the Het-NOE data. One significant advantage of the NBFF is that it allows dealing with such a diverse protein superfamily as the ZF superfamily. In fact, it can be applied to systems bearing diverse coordination environments in a seamless manner without the need to use a metal center parameter builder, such as

MCPB.py [39]. A recent study investigated the ability of different models to reproduce the zinc(II) coordination and the ligand binding in metalloproteins [36]. Among them, the NBFF, used also here, stood up for its great performance in reproducing the geometry and maintaining the correct distances between the ligands and the metal. In contrast, the coordination by His residues was not consistently kept in simulations performed with other non-bonded models [36].

Initially, the NBFF has been tested on the challenging computation of dissociation free energies using alchemical free-energy perturbation for eight zinc(II) proteins with known dissociation constants, featuring very good agreement between computed and experimental dissociation energies [14]. In this contribution, we further validated the NBFF against experimental NMR data probing protein dynamics. An apparent difference among the trajectories obtained with ZAFF and NBFF was that the use of the former resulted in steadier RMSD profiles and more persistent secondary structure elements than for NBFF. This is likely due to the stabilization of the protein topology conferred by the four fixed bonds between the polypeptide chain and each zinc(II) ion. Nevertheless, the S^2 order parameters calculated from MD trajectories show a highly satisfactory correlation with experimental Het-NOE values for both ZAFF and NBFF, with no significant deviations between the two. Overall, we can conclude that NBFF is well capable of reproducing both energetics parameters and dynamics behavior in zinc(II)-proteins, and thus constitutes a widely adoptable FF for MD simulations of such systems [14,15].

4. Methods

4.1. Molecular Dynamics Simulations

We performed all MD simulations using the pmemd tool of version 20 of the AMBER software suite. The ff14SB force field (FF) was used to describe the protein chain, whereas the ZAFF [13] and nonbonded FF (NBFF) [14] were applied to the zinc(II) ion and its ligands. For four out of our six selected systems (1CHC, 2JOX, 2L7X and 2K9H), five separate simulations using either the ZAFF or the NBFF were carried out, each of 500 ns duration. Thus, in total, we accumulated 2.5 µs of dynamics with each zinc(II) FF for each system. For the remaining two systems (2NAX and 5JPX), the simulations were 400 ns long, for a total of 2.0 µs of dynamics with each FF for each system with an integration time step of 2 fs; we saved one frame every 5000 steps.

For NMR structures, which are available from the Protein Data Bank as bundles of conformers, we used the first one, since it is usually the one with either the lowest conformational energy or with the best agreement with the NMR restraints [40]. All simulations were performed as follows: the selected protein was embedded in a truncated octahedron box with walls 10 Å away from the solute in each direction. Periodic boundary conditions were applied, and the system was explicitly solvated with TIP3P water model.

The minimization process was performed at 0 K in two steps: (i) minimizing only water molecules and keeping the protein fixed; (ii) minimizing the whole system. For this process, a combination of Steepest Descendent and Conjugated Gradient algorithms was exploited. Subsequently, the system was heated to 300 K at constant volume using the weak-coupling algorithm. The system was then equilibrated at constant pressure and temperature in NPT ensemble using a Berendsen barostat. During the heating procedures, bond constraints were imposed on X-H bonds using the SHAKE algorithm, omitting the force evaluation of bonds containing hydrogen. The latter protocol was applied also for the MD production runs, with an increased number of integration steps. The input files used for the simulations are provided as Supplementary Materials, using the example of 2L7X.

The root mean square deviation (RMSD) is a measure of the similarity between two superimposed 3D structures, defined by the formula:

$$\mathrm{RMSD} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} d_i^2}$$

where the averaging is performed over n pairs of equivalent atoms, and d_i is the distance between two atoms each belonging to a conformation [41]. We computed RMSD values over the backbone atoms to keep track of how the protein behaved during the simulations. RMSD data were computed relative to the equilibrated structure using cpptraj [42]. The latter software was exploited to compute the distances between the atom participating in the coordination and the zinc(II) ion. The content of secondary structures was computed using DSSP. Its dictionary contains eight classes of possible structures: random coil, parallel beta-sheet, antiparallel beta-sheet, 3–10 helix, alpha-helix, Pi (3–14) helix, turn and bend [43].

4.2. Order Parameters

The order parameter (S^2) describes the magnitude of the angular fluctuation of a chemical bond vector such as the N-H bond in proteins, reflecting the flexibility of the polypeptide at those sites with respect to the overall protein frame [31,34]. For $S^2 = 0$, the internal motion spans all possible orientations, whereas $S^2 = 1$ corresponds to complete rigidity [34,35]. Using our simulations, we computed the S^2 values for the backbone N-H vectors of all the investigated systems with the isotropic reorientational eigenmode dynamics (iRED) method [29]. The final order parameters with their respective standard deviations (SDs) were obtained by averaging the results for the independent simulations run with each FF. For each protein, we compared the averaged S^2 obtained with the two zinc(II) FFs to assess their similarity. In addition, to evaluate how well the experimental data were reproduced by the tested FFs, we computed the Pearson correlation coefficient with respect to the Het-NOE data using the pandas library [44,45].

VMD was used for the inspection of trajectories, and Pymol for the visualization of extracted frames [46,47].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms24065440/s1.

Author Contributions: Conceptualization, A.R.; methodology, A.G.; validation, M.B.; formal analysis, M.B.; investigation, M.B.; resources, A.R.; data curation, M.B. and A.G.; writing—original draft preparation, M.B.; writing—review and editing, M.B., M.P. and A.R.; visualization, M.B.; supervision, A.R.; project administration, M.P. and A.R.; funding acquisition, A.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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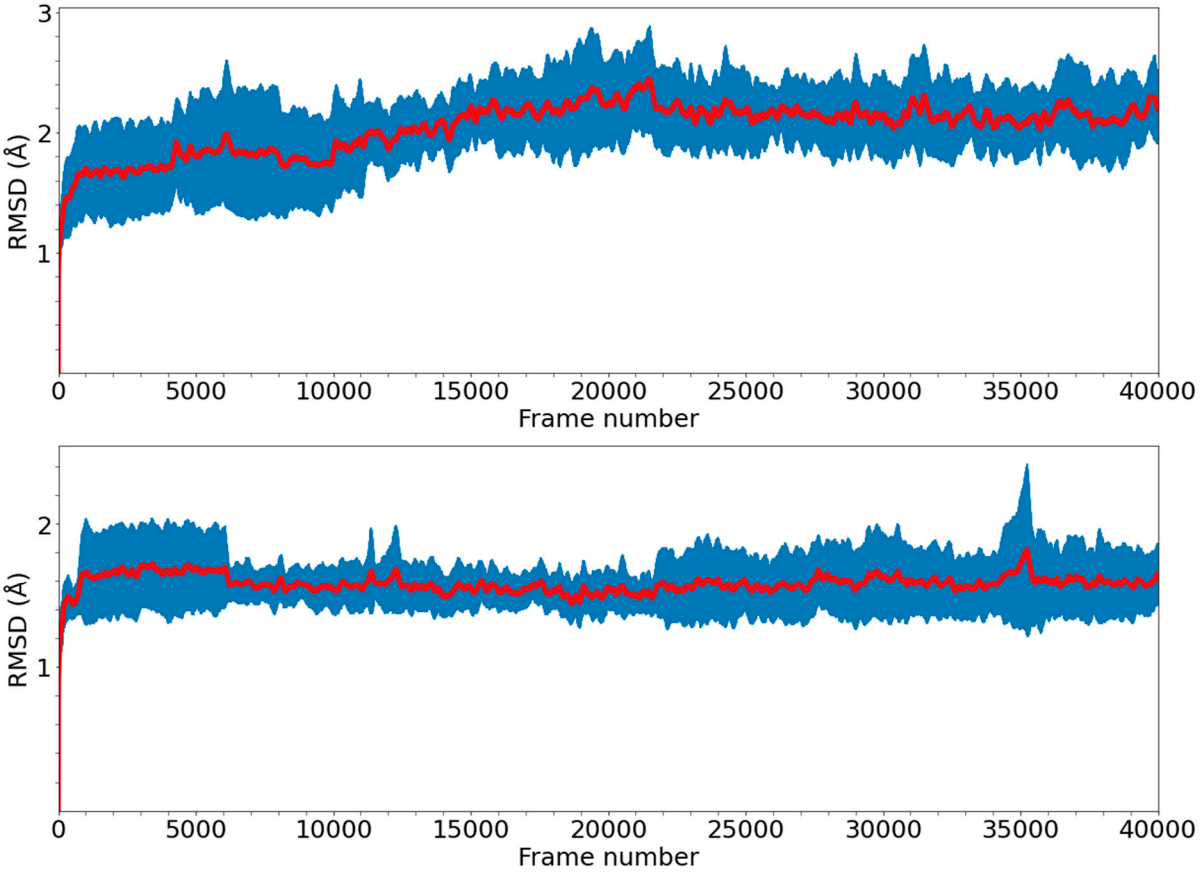

Figure S1. Smoothed mean RMSD for 2NAX computed for the NBFF (upper panel) and ZAFF (lower panel).

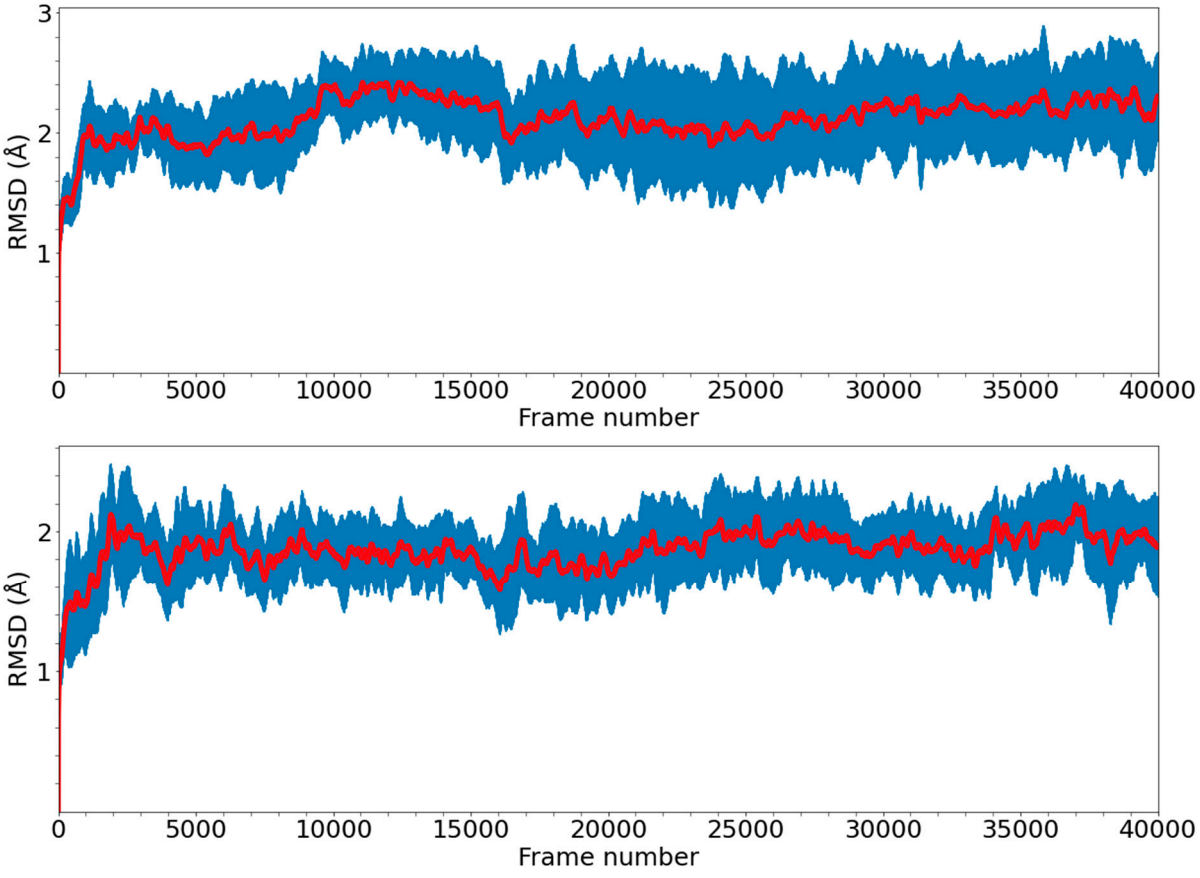

Figure S2. Smoothed mean RMSD for 5JPX computed for the NBFF (upper panel) and ZAFF (lower panel).

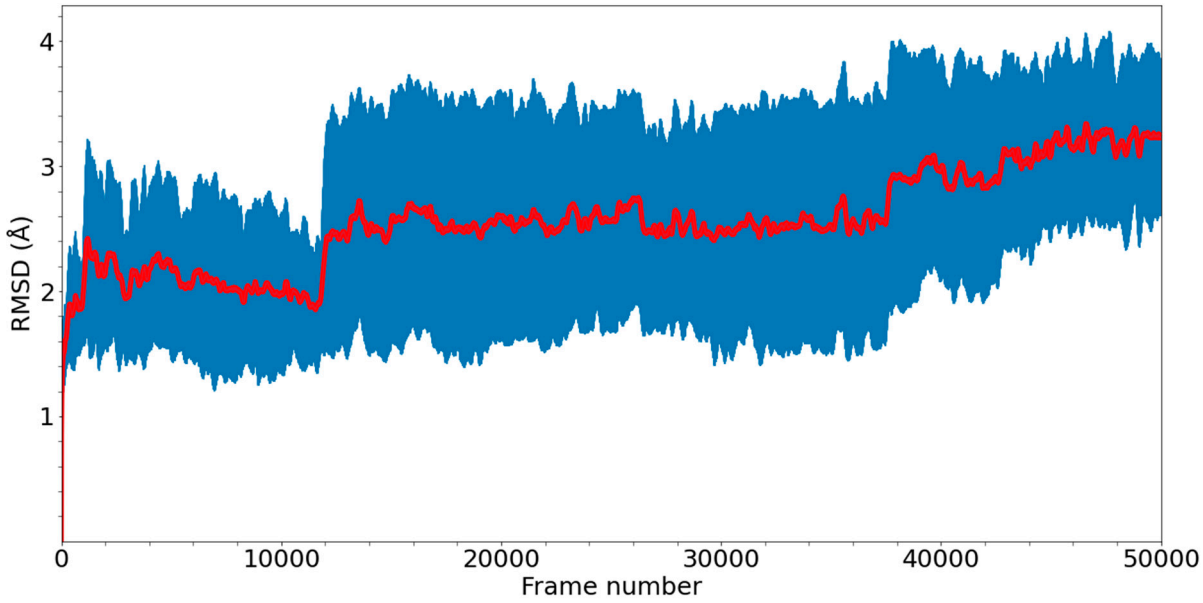

Figure S3. Smoothed mean RMSD for 2JOX computed for the NBFF. Simulations with ZAFF were not performed since it is not parametrized for binuclear sites.

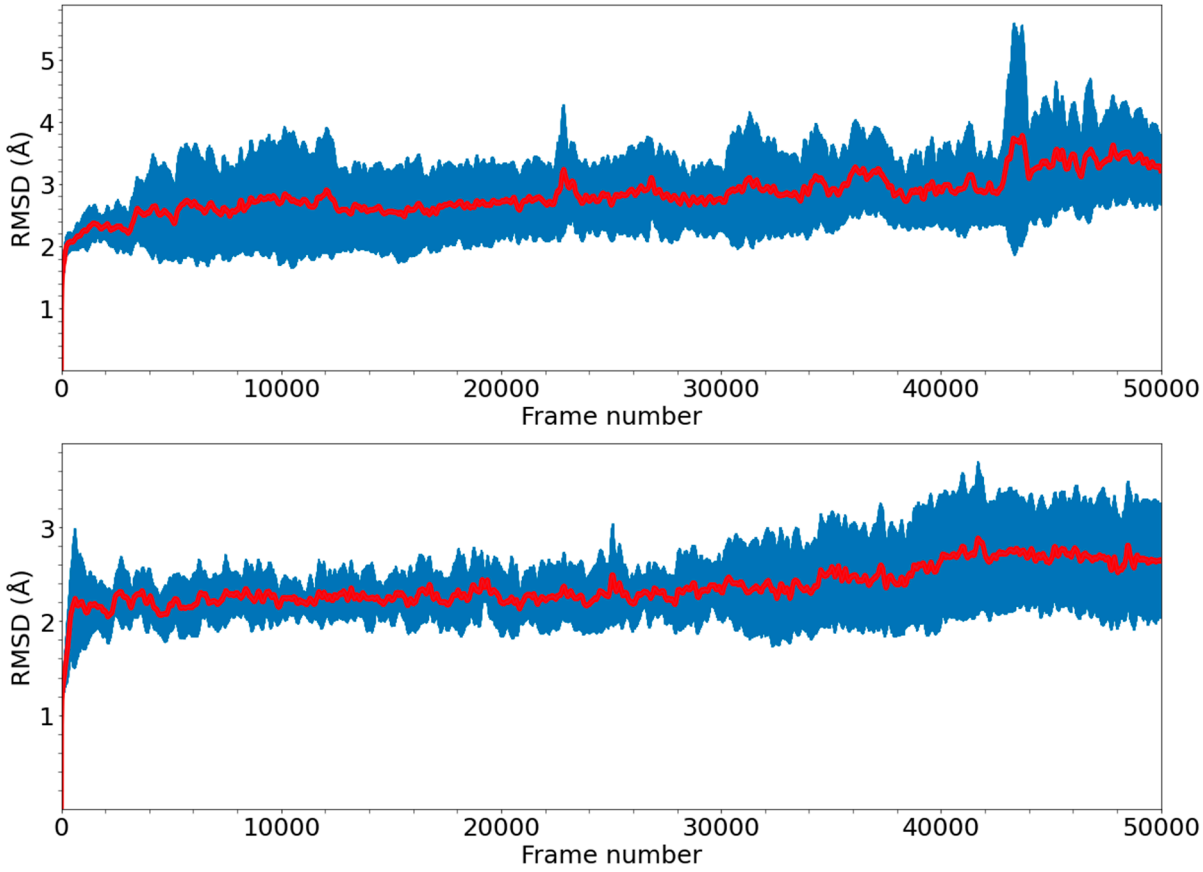

Figure S4. Smoothed mean RMSD for 2L7X computed for the NBFF (upper panel) and ZAFF (lower panel).

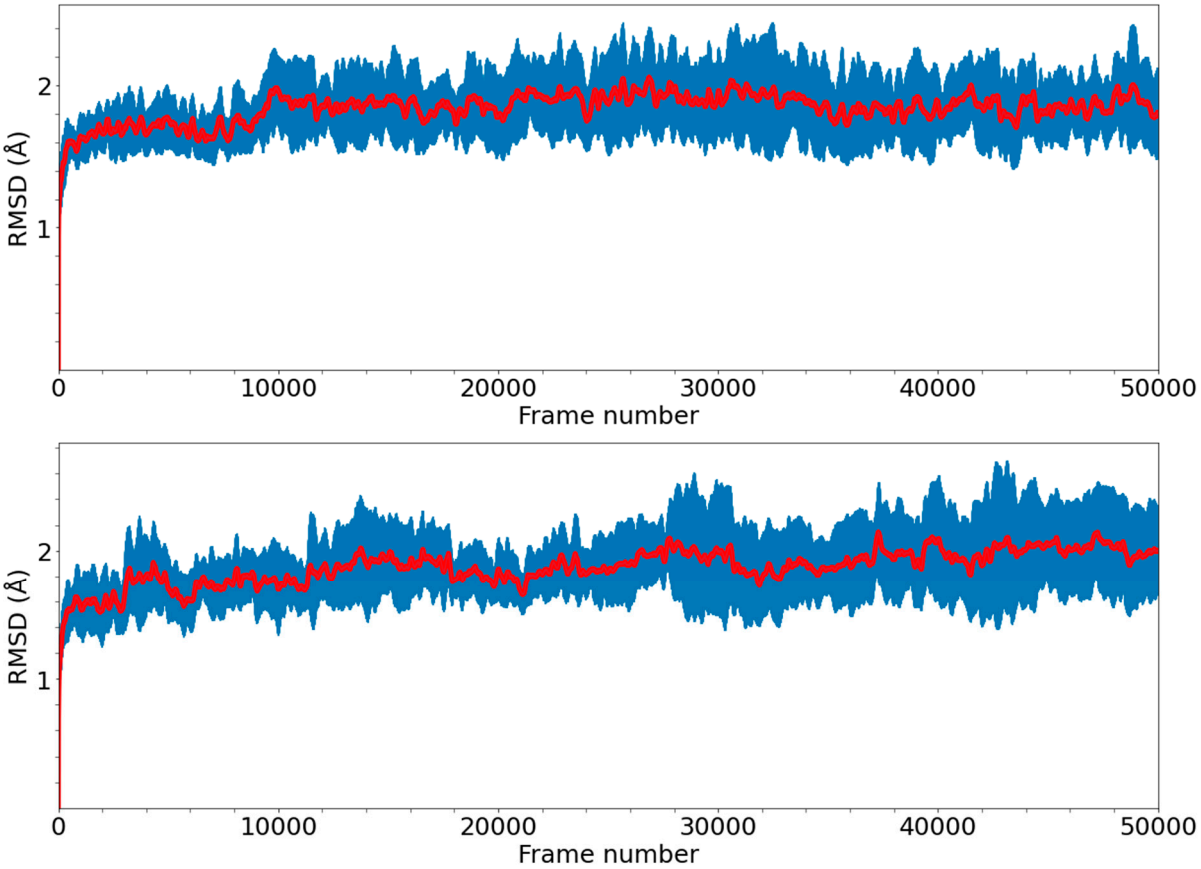

Figure S5. Smoothed mean RMSD for 1CHC computed for the NBFF (upper panel) and ZAFF (lower panel).

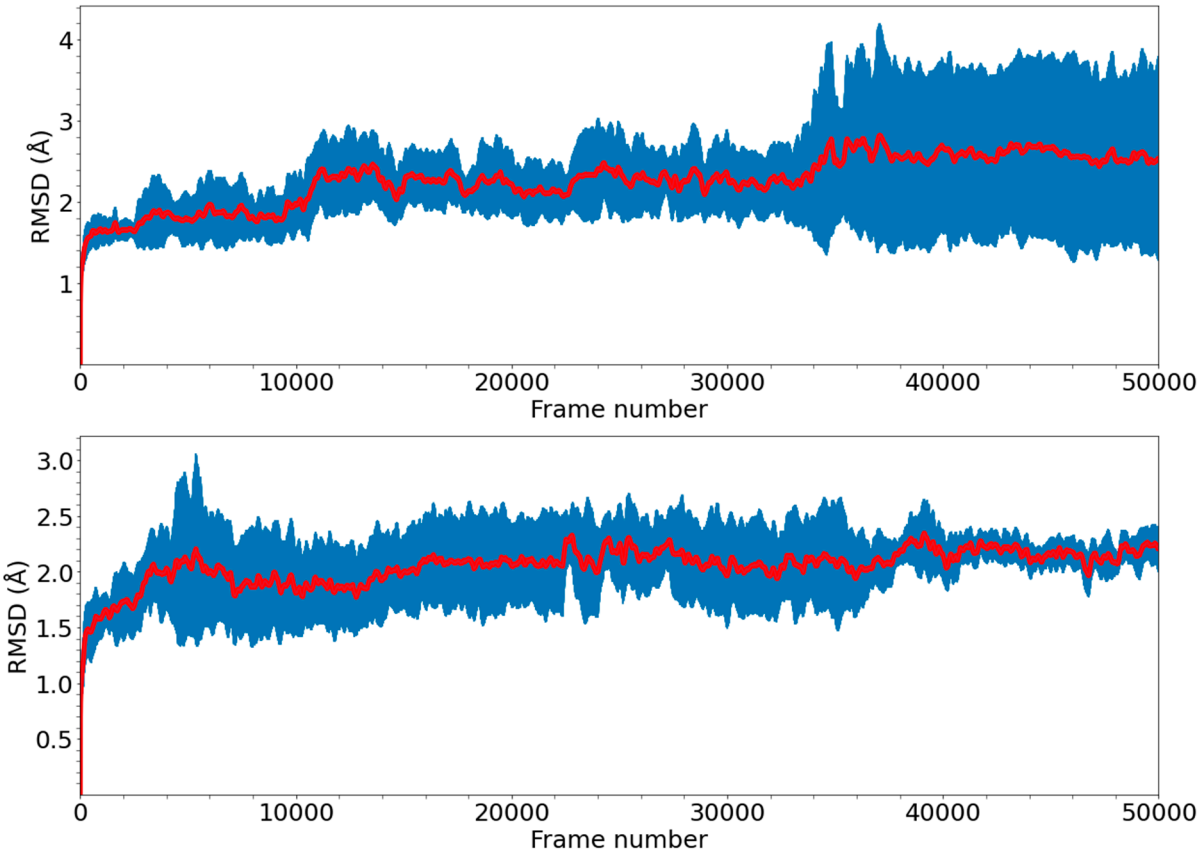

Figure S6. Smoothed mean RMSD for 2K9H computed for the NBFF (upper panel) and ZAFF (lower panel).

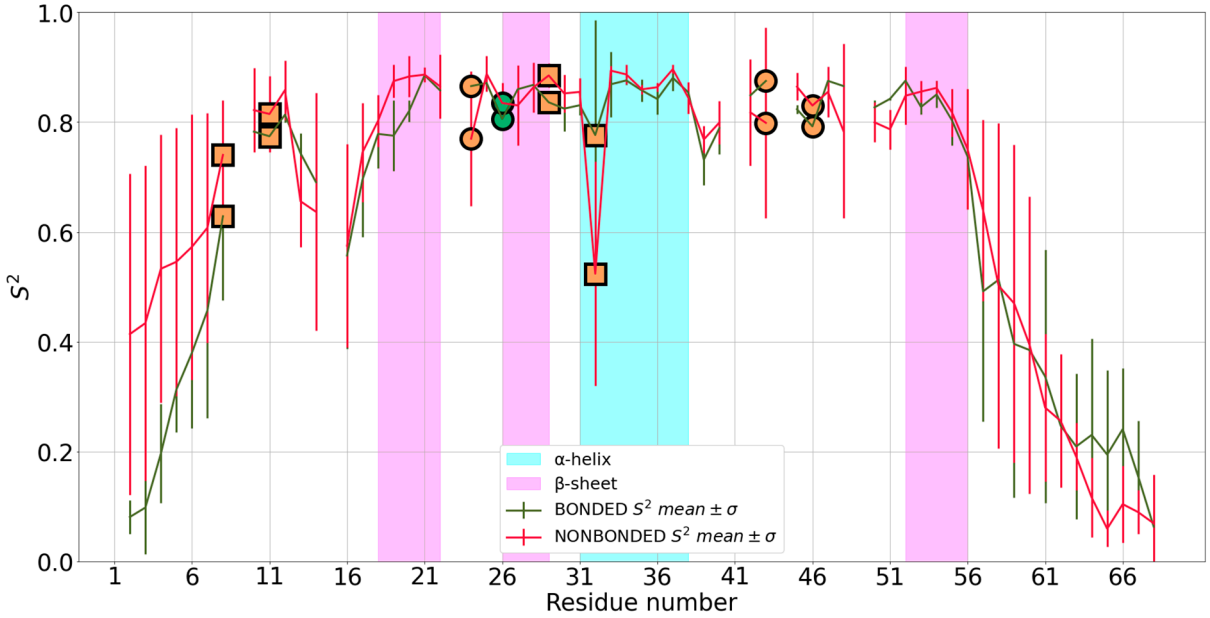

Figure S7. Mean S^2 of 1CHC and standard deviation (SD) for bonded (red) and nonbonded (green) superimposed. Orange markers represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green markers represent zinc(II)-binding His residues. Residues belonging to the same site are represented with the same marker shape.

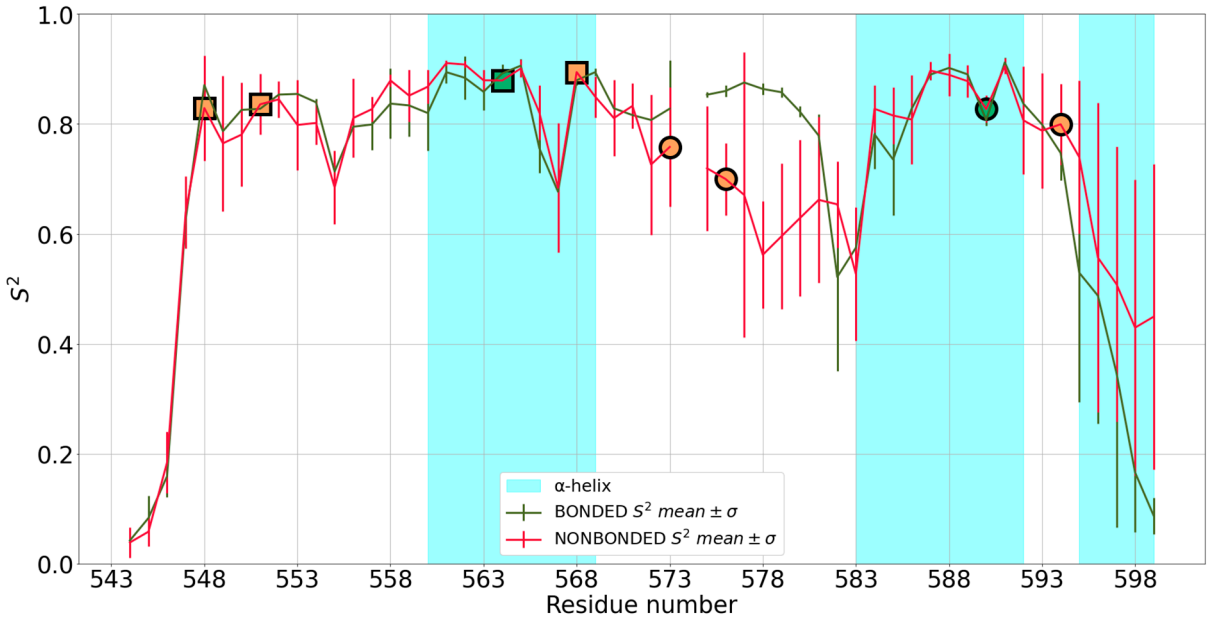

Figure S8. Mean S^2 of 2K9H and standard deviation (SD) for bonded (red) and nonbonded (green) superimposed. Orange markers represent the position in the sequence of zinc(II)-binding Cys residues, whereas the green markers represent zinc(II)-binding His residues. Residues belonging to the same site are represented with the same marker shape.

The following input files were used for 2L7X and are reported here as an example of the protocol used to run the MD simulations for all systems.

NONBONDED SIMULATIONS input files

min.in

```
Minimization with Cartesian restraints for the solute
 &cntrl
 imin=1, maxcyc=200,
 ntpr=5,
 ntr=1,restraint_wt=10,restraintmask='1-77'
/
```

min2.in

```
Minimization with Cartesian
 &cntrl
 imin=1, maxcyc=500,
 ntpr=5,
 ntr=0
/
```

heat1.in

```
Heating up the system equilibration stage 1
 &cntrl
  nstlim=50000, dt=0.002, ntx=1, irest=0, ntpr=500, ntwr=5000, ntwx=50,
  tempi =100.0, temp0=300.0, ntt=1, tautp=2.0, ig=-1,

  ntb=1, ntp=0,

  ntc=2, ntf=2,

  nrespa=2,
&end
```

heat2.in

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Constant pressure constant temperature equilibration stage 2
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  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,
```

```
  nrespa=1,
&end
```

dina.in

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Constant pressure constant temperature production run
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  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina2.in

```
Constant pressure constant temperature production run
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  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina3.in

```
Constant pressure constant temperature production run
 &cntrl
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  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,
```

```
  nrespa=1,
&end
```

dina4.in

```
Constant pressure constant temperature production run
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  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina5.in

```
Constant pressure constant temperature production run
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  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

BONDED SIMULATIONS input files

min.in

```
&cntrl
 imin=1, maxcyc=200,
 ntpr=5,
 ntr=1,restraint_wt=10,restraintmask=':1-77'
/
```

min2.in

```
Minimization with Cartesian
 &cntrl
 imin=1, maxcyc=500,
 ntpr=5,
 ntr=0
/
```

heat1.in

```
Heating up the system equilibration stage 1
 &cntrl
  nstlim=50000, dt=0.002, ntx=1, irest=0, ntpr=500, ntwr=5000, ntwx=50,
  tempi =100.0, temp0=300.0, ntt=1, tautp=2.0, ig=-1,

  ntb=1, ntp=0,

  ntc=2, ntf=2,

  nrespa=2,
&end
```

heat2.in

```
Constant pressure constant temperature equilibration stage 2
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  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina.in

```
Constant pressure constant temperature production run
 &cntrl
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  ntb=2, ntp=1,

  ntc=2, ntf=2,
```

```
  nrespa=1,
&end
```

dina2.in

```
Constant pressure constant temperature production run
 &cntrl
  nstlim=50000000, dt=0.002, ntx=5, irest=1, ntpr=500, ntwr=50000, ntwx=5000,
  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina3.in

```
Constant pressure constant temperature production run
 &cntrl
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  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina4.in

```
Constant pressure constant temperature production run
 &cntrl
  nstlim=50000000, dt=0.002, ntx=5, irest=1, ntpr=500, ntwr=50000, ntwx=5000,
  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

dina5.in

```
Constant pressure constant temperature production run
 &cntrl
  nstlim=50000000, dt=0.002, ntx=5, irest=1, ntpr=500, ntwr=50000, ntwx=5000,
  temp0=300.0, ntt=1, tautp=2.0,

  ntb=2, ntp=1,

  ntc=2, ntf=2,

  nrespa=1,
&end
```

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Hunting down zinc(II)-binding sites in proteins with distance matrices

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Hunting down zinc(II)-binding sites in proteins with distance matrices

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Motivation

In recent years, high-throughput sequencing technologies have made available the genome sequences of a huge variety of organisms. However, the functional annotation of the encoded proteins often still relies on low-throughput and pricey experimental studies. Bioinformatics approaches offer a promising alternative to accelerate this process. . In this work, we focus on the binding of zinc(II) ions, which is needed for 5% to 10% of any organism's proteins to achieve their physiologically relevant form

Results

To implement a predictor of zinc(II)-binding sites in the 3D structures of proteins we used a neural network, followed by a filter of the network output against the local structure of all known sites. The latter was implemented as a function comparing the distance matrices of the Cα and Cβ atoms of the sites. We called the resulting tool Master of Metals. The structural models for the entire proteome of an organism generated by AlphaFold can be used as input to our tool in order to achieve annotation at the whole organism level within a few hours. To demonstrate this, we applied Master of Metals to the yeast proteome, obtaining a precision of about 76%, based on data for homologous proteins.

Availability and implementation

Master of Metals has been implemented in Python and is available at https://github.com/cerm-cirmmp/Master-of-metals.

Keywords

Metalloproteins; Bioinorganic chemistry; metalloproteome; transition metals; structural biology

Introduction

Metalloproteins are a diverse class of proteins that contain metal ions as integral components of their structures. They are found in all forms of life, from bacteria to humans, and are involved in numerous physiological processes, including catalysis, electron transfer, oxygen transport, and gene regulation. Metal ions can have a variety of roles in metalloproteins. They can act as structural elements, providing stability to the protein, or they can participate in catalysis, activating substrates or stabilizing reaction intermediates. Metal ions can also act as electron carriers, transferring electrons between redox-active sites, or they can regulate protein activity and transduce cellular signals [1-3]. Metalloproteins are also important targets for drug development. Many drugs target metalloproteins by exploiting their metal-binding sites to block their activity [4]. During bacterial infections, the host candeploy a protective mechanism, called 'nutritional immunity', which inhibits the growth of pathogens by restricting the availability of metal ions [5].

The investigation of metalloproteins at the whole organism or whole cell level is called metalloproteomics [6,7]. Owing to the difficulties of experimental metalloproteomics, bioinformatics has rapidly emerged as an alternative approach to mine metalloproteomes [8-10]. In this context, the 3D structure-based prediction of the occurrence of metal-sites , which makes use of the knowledge about the relative location in space of the amino acids possibly serving as donor atoms for metal coordination, is an area of application that has attracted a lot of attention [11]. The success of AlphaFold [12] and AlphaFold2 [13,14] in the CASP programs has given these kinds of approaches a considerable boost, thanks to the extensive availability of viable 3D structural models for proteins not yet described experimentally [15].

There are several tools available to figure out a protein's metal content (e.g., ZincFinder[16], ZincExplorer[17], Zincbindpredict[18]), the residues that bind a metal (e.g., IonCom[19], MIB[20]), and the location of the metal (e.g., AlphaFill[21], BioMetAll[22]). These predictors use sequence and/or structural information as their input. Pattern recognition is used by sequence-based predictors to pinpoint the amino acids that could bind a metal. In structure-based approaches, the position of metals is inferred via distance characteristics (BioMetAll) or homology to known structures (MIB, AlphaFill). Some sequence-based approaches use machine learning techniques. Recently, a tool (Metal3D) exploiting 3D convolutional neural networks, a deep-learning methodology, became available to predict the location of zinc(II) ions in protein structures [23].

In this work, we describe an approach for the prediction of zinc(II) metalloproteins based on 3D structural models generated by AlphaFold that leverages a collection of metal site templates, i.e. a pre-arranged spatial distributions of prospective metal ligands. In our methodology, triads or quadruplets of amino acids with appropriate relative spatial arrangements are identified by a machine learning algorithm and then ranked based on their structural similarity to a library of templates extracted from the MetalPDB database [24,25]. Our tool, called Master of Metals (MoM), can process an entire proteome in a few tens on minutes, with satisfactory accuracy. MoM is available at https://github.com/cerm-cirmmp/Master-of-metals.

Results

The metal binding site (MBS) is a substructure around the metal ion(s) that represents the macromolecular environment that the metal is sensing and can be automatically extracted from the 3D structures stored in the Protein Data Bank (PDB) [26]. This substructure ought to match the bare minimum environment that determines the functionality of the metal, or the "minimal functional site" [27]. In this work, we used the definition of MBS implemented in MetalPDB [24,25]; alternative definitions tend to yield similar results[28]. We implemented a machine learning (ML) approach to predict MBSs in the 3D structures of proteins, which we called Master of Metals (MoM).

The PDB contains two different types of structures of metalloproteins (MPs), depending on whether the deposited structure contains the physiological metal ion(s). In holo structures the metal is present and thus the side chains of the metal-binding protein residues (the metal ligands) are organized such that their donor atoms have a spatial configuration matching the coordination geometry preferences of the metal [29,30]. In apo-structures instead, the conformation of the side chains of the metal ligands may differ with respect to their counterparts in holo structures due to the absence of the metal ion. In particular, the donor atoms may be located at incorrect distances from one another and with the wrong geometry for metal binding [31]. We used only the holo structures to train MoM, whereas both apo and holo structures were employed to evaluate the tool performance.

Experimental datasets

To generate the holo-structure dataset, we selected from MetalPDB [24,25] all the physiologically relevant zinc(II) MBSs [32] and retained only those having a single metal ion (mononuclear sites) with three or more donor residues. We first grouped the sites by their metal-binding patterns. The distribution of these patterns is very unbalanced, with the 12 most frequent patterns, covering 70% of all MBSs (Supplementary Table S1). We retained only the patterns observed in at least 10 sites.

For each pattern present in more than 30 MBSs, we subsampled all the sites to obtain a smaller dataset, more uniformly distributed in the MBS space. Subsequently, for each pattern, we clustered all the MP structures based on their sequence similarity. The sites belonging to the same cluster were all at once selected exclusively for inclusion in the training or test datasets, thus ensuring that the two datasets did not contain similar proteins. MetalPDB contains information also on apo-structures [25], allowing us to retrieve all apo-sites linked to mononuclear zinc(II) MBSs. We kept only one apo-site for each MBS. In addition, to establish a negative dataset for validation, we chose an ensemble of proteins for which no metal-containing structure was present in the PDB. In total, our datasets contained 3083 holo sites, 231 apo sites and 500 negative proteins.

Performance of Master of Metals

For the holo and apo datasets we consider a prediction to be correct if the known site is included among the sites output by MoM. Table 1 reports the recall obtained for different values of the d_min threshold (see Methods), showing recall rates between 83% and 95% for holo MBSs. For the apo data the recall ranges between 66% and 86%. This lower recall is determined by the structural rearrangements caused by metal binding in a protein site [31]. Indeed, our tool exploits the position of Cα and Cβ atoms precisely because their extent of rearrangement upon metalation is typically less extensive than that of side chains. This resulted in a still satisfactory recall of 66% for apo-structures at the most stringent d_min threshold, with a corresponding FPR of only about 7%.

	Recall/TPR (%)		**FPR (%)**
d_min threshold	**Holo data**	**Apo data**	**Negative data**
0.25	82.7 ± 2.4	66.0 ± 1.4	6.60 ± 0.37
0.30	88.9 ± 1.2	74.3 ± 1.2	10.5 ± 0.2
0.35	91.9 ± 1.3	79.1 ± 1.6	14.2 ± 0.6
0.40	94.0 ± 1.3	80.6 ± 1.9	18.8 ± 0.5
0.45	95.2 ± 1.4	85.8 ± 1.9	25.0 ± 0.8

Table 1. Performance of Master of Metals. We measured the performance as the fraction of correctly predicted sites over the total number of experimental sites, TP/(TP+FN). In addition, we used the structures of the negative dataset to estimate the false positive ratio (FPR), given by the fraction of false positive predictions over the total number of negative proteins in the dataset.

Structure-based prediction of zinc MBSs in the Saccharomyces cerevisiae proteome

To perform a proteome-wide prediction of zinc(II) MBSs in *Saccharomyces cerevisiae*, we retrieved all the 6309 structural models of yeast proteins available from the AlphaFold database [21]. AlphaFold models include a measure indicative of the local accuracy of the prediction (plDDT). We retained the structures having at least 90% of their residues with a plDDT >0.7, reducing the dataset to 1500 models, in order not to bias the prediction results due to the quality of the AlphaFold models. Within the latter ensemble, we identified 191 zinc(II)-binding proteins.

For all the yeast proteins with a predicted MBS, we searched if there was already an experimental structure, by mapping their UniProt IDs to the PDB. Out of 191 proteins, 77 had a deposited structure and we observed that in 62 cases the MBS was correctly identified. This corresponds to a precision (PPV) of 80.5% and a false discovery rate of 19.5% (Figure 1A).

Figure 1: Validation of Master of Metals against the *S. cerevisiae* proteome. A) correct (dark grey, "positive") and wrong (light grey, "negative") predictions (outer doughnut) based on yeast proteins with deposited structure (inner doughnut, yellow), or on the structures of homologous proteins as well as visual inspection (inner doughnut, light blue); B) breakdown of the validation based on the proteins in the light blue wedge of panel A, as a function of their characteristics (inner doughnut, compare to the columns of Table 2), showing correct and wrong predictions (outer doughnut; light and dark colors, respectively) for each group. The total number of positives in panel A is 145, whereas the total number of negatives is 46.

We then looked for structurally characterized homologs of the remaining 114 proteins. BLAST retrieved close homologs having a deposited 3D structure for 75 proteins (Figure 1B). 46 of these structures (61%) contain one or more zinc(II)-binding sites, 16 bear different metals than zinc(II) (21%), and 13 are apo structures (17%). For 8 proteins, only distant homologs were detected (i.e. BLAST retrieved some hits that did not fulfill our thresholds), whereas for 31 proteins no related structures were found. The latter group included 9 proteins for which an experimental structure is available but lacks the region containing the predicted site because of the presence of an additional domain or motif in the AlphaFold model. For each yeast protein having a structurally characterized homolog, we superimposed its AlphaFold model to the experimental structure of the homolog. We assumed that if the homolog harbored an experimental zinc(II) MBS, then the predicted AlphaFold structure should also have a zinc(II) MBS.

For the 13 experimental apo-structures we qualitatively evaluated whether the spatial disposition of the residues in the predicted site suggested that it could be populated by a zinc(II) ion under appropriate conditions. In fact, it can happen that even in the 3D structure of an actual MP the MBS is not populated by its cognate metal, because of shortcomings in the sample handling procedures [33]. However, given that any incorrect prediction made by our tool can only be attributed to an apo structure, we anticipated that the predictions whose homologs are apo proteins would have the highest FP rate. Assuming mild rearrangements of the protein backbone, we determined that the predicted sites for 10 proteins in this group (76%) were unreliable because the disposition and/or orientation of the putative ligands was not appropriate for metal binding. However, 3 proteins (or 23% of all proteins) had sites resembling physiological ones (see Table 2).

	Homologs with zinc	Homologs with different metals	Apo homologs	Distant homologs	No homologs or no corresponding region	**Total**
Unreliable	7 (15%)	7 (44%)	10 (77%)		7 (23%)	32 (28%)
Good / Partial match	7 (15%)	4 (25%)	3 (23%)	2 (25%)	13 (42%)	28 (24%)
Perfect match	32 (70%)	5 (31%)	n.a.	6 (75%)	11 (35%)	54 (47%)
Total	**46**	**16**	**13**	**8**	**31**	**114**

Table 2. Results of the inspection of the structural models of the 114 predicted zinc(II) proteins lacking an experimental structure. Distant homologs are the proteins identified by BLAST in the PDB with an e-value > 10^{-5} or a sequence identity to the yeast protein of interest < 30%. Partial matches occur when at least two predicted metal-binding residues overlapped properly in the structural comparison, as opposed to complete matches, which occurred when all predicted metal-binding residues overlapped correctly.

We then inspected the 16 predicted zinc(II) proteins whose experimentally characterized homologs bear different metals. We obtained satisfactory superimpositions with the experimental sites for 9 proteins (56%), as shown in Figure 2E-F. For example, (Figure 2E), for the protein with UniProt ID Q05584 (cytoplasmic hydroxyacylglutathione hydrolase) the two sites predicted by our tool overlapped almost perfectly with all the metal-binding residues observed in the experimental structures of various homologs. Notably, the protein is annotated as a zinc(II) enzyme in UniProt. The proteins having a zinc(II)-binding homolog were separated in two groups, depending on their sequence similarity. The superimposition verified the positions predicted by our method for 8 out of 8 proteins (100%) that had only distant homologs (Table 2 and Figure 2A-B). The predicted sites were exactly overlaid to the real ones in 32 out of the 46 (70%) near-homolog structures containing zinc(II), whereas in another 7 structures (15%), our prediction only partially matched the experimental MBS. Finally, our prediction did not overlap with the experimentally observed MBS in 7 cases (15%).

The 31 models with no structural information from homologs are of high interest since they may contain zinc(II)-binding sites never observed before. The reliability of the predicted sites was qualitatively evaluated by the superimposition to the site used for the prediction. For 11 structures (35%) the overlap was perfect (Figure 2D), whereas the outcomes for 13 proteins (42%) were deemed satisfactory, given that the residues are arranged in a way that appears compatible with the binding geometry observed in the reference site. On the other hand, for 7 proteins (23%), the prediction appeared unreliable, e.g., because the putative ligands were in secondary structure elements preventing the reorientation of their SCs to coordinate the metal (Figure 2C).

Overall, MoM demonstrated a satisfactory performance in a real life scenario, namely the analysis of the proteome of an entire organism. Cumulatively, with a d_min threshold of 0.35 Å MoM had an error rate (false discovery rate, FDR, given by the ratio of false positives

over the total number of positive predictions) for all its predicted MBSs of 24% and a precision of 76% (Figure 1).

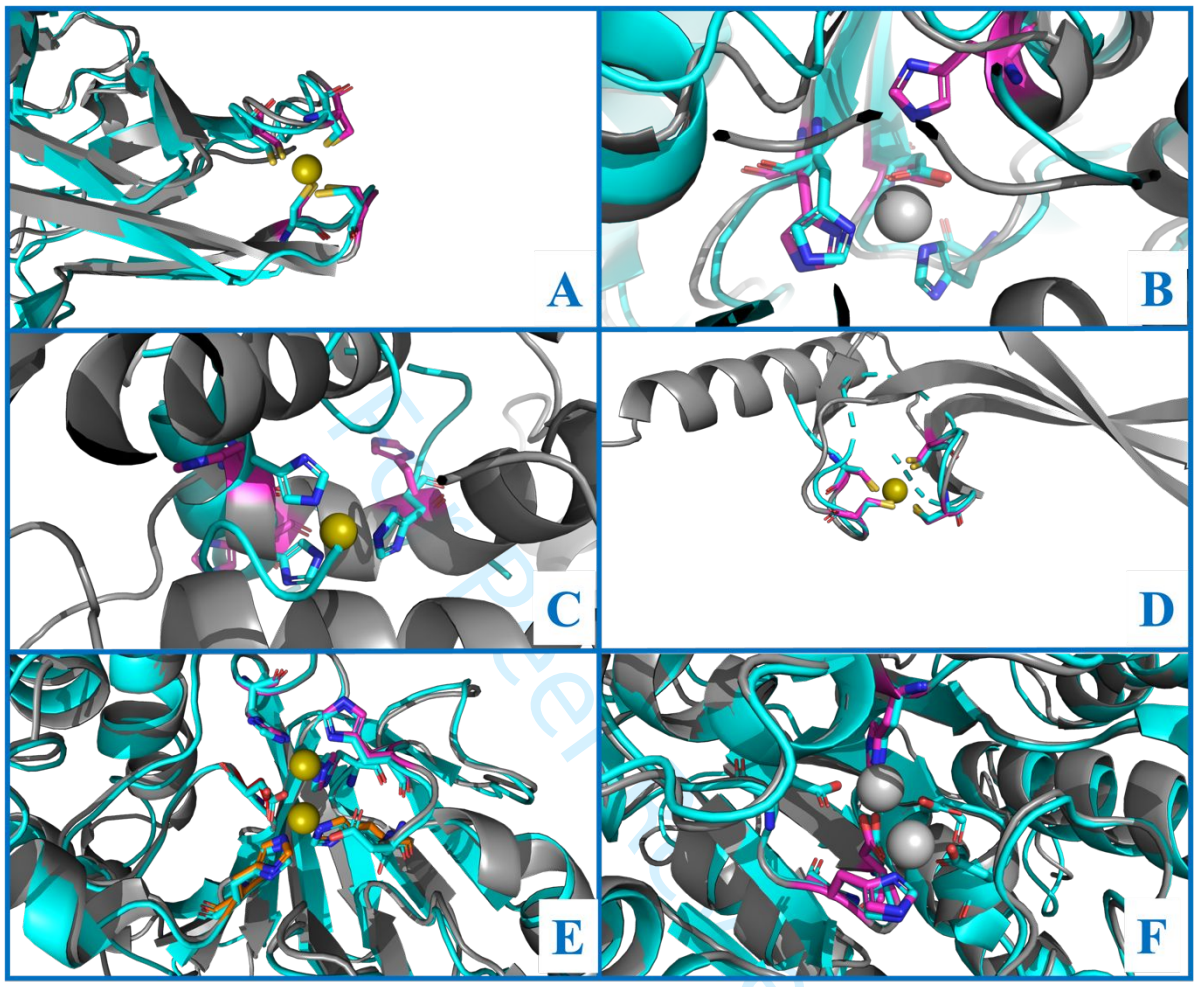

Figure 2. Examples of structure predictions by Master of Metals. A) a correct prediction, validated by superimposition to a distant homolog structure (PDB ID 5ZLQ [46]); B) a partial match, with two out of three residues correctly superimposed to the metal ligands of the manganese(II) ion of a distant homolog structure (PDB ID 5M45 [47]); C) an inaccurate prediction (superimposed to the 1BM6_2 [48] MetalPDB site), in which two of the three predicted His have a plausible spatial disposition, but the third His cannot be regarded a putative ligand since its positioning in the α-helix prevents any movement to form an MBS in the presence of the metal ion; D) a correct prediction for a protein lacking a homolog with known structure, validated by superposition of the AlphaFold structural model to the closest MetalPDB site (3BVO_1 [49]) identified by MoM; E) a correct prediction for two zinc(II) sites in spatial proximity, validated by superimposition to a homolog structure (PDB ID 2P18 [50]), which contains a dinuclear zinc(II) cluster; F) a partial match, where MoM predicted only one site containing a subset of the ligands to the two manganese(II) ions present in a homolog structure (1WVB). The color code is as follows: grey, AlphaFold structural models; fuchsia, predicted ligand residues; cyan, homolog structures or closest MetalPDB site. The zinc(II) ions are shown as olive green spheres, whereas all other metal ions are shown as grey spheres.

To obtain further insight into the performance of MoM, we performed a comparison with a previously published dataset consisting of 229 zinc(II)-proteins identified by sequence-based bioinformatics prediction of the MBS and detected by mass spectrometry in zinc-replete cells [34]. Out of these 229 proteins, we analyzed 157 structural models of sufficient quality. With a

d_min threshold of 0.35, MoM predicted the existence of a zinc(II) MBS for 151 of these models (96% of the dataset), yielding a false negative rate of 4%. At the level of individual residues, in 130 proteins (86% of the dataset) the current prediction included all or all but one of the previously proposed ligands.

Discussion

In this work we developed a tool for the prediction of zinc(II) MBSs in the 3D structure of proteins, by combining a neural network (NN) and a post-processing geometry filter. By design, the minimum number of metal ligands in the site is three, implying that the tool is most suited for the prediction of intra-chain sites [28]. The role of the NN is to extract from the input 3D structure all the groups of residues of the CHED type (Cys, His, Asp, Glu) [35] that constitute potential binding sites. We trained the NN on an extensive dataset of physiological zinc(II) MBSs. For the validation process, we clustered homologous proteins so that their sites would not be present in the training and validation sets at the same time; 20% of the experimental MBSs were kept as the independent validation dataset. Each of the candidate sites identified by the NN in the input 3D structure is filtered for geometrical similarity to all known MBSs with the same metal-binding pattern, by comparing their distance matrices for the Cα and Cβ atoms. By fixing a threshold for the deviation between the matrices (d_min), false positive sites are significantly reduced. The application of this similarity filter is justified by our previous work demonstrating that for zinc(II) [27] as well as iron-sulfur proteins [36], the same metal-binding motifs can occur in completely different folds. In fact, the MBSs of about 77% of all zinc(II)-protein superfamilies can be grouped in just 10 clusters [27]. In a similar fashion, related metal-binding structural motifs (which are similar to the MBS concept used here) can be identified within different, evolutionarily distant protein structures [37].

The recall of our predictor was nearly 92% with a d_min value of 0.35 Å. We applied the trained predictor to a dataset of apo-sites (i.e. sites extracted from the 3D structure of zinc(II)-proteins experimentally determined in the absence of their metal cofactor). For this group of structures there is no preorganization of the protein residues surrounding the metal ion, as it is instead the case for MBSs taken from holo structures after removing the ion from the coordinate file. Indeed, we observed a lower recall, of about 79%, which is still quite satisfactory. Notably, it is known that backbone rearrangements are typically modest upon metalation of apo-sites [31,38], which we exploited in the design of MoM as well as of other related tools [22,39]. To obtain an indication of the false positive rate (FPR) of the predictor, we examined 500 structures of proteins for which there is no reported interaction of physiological relevance with metal ions. MoM identified HPSs in 14% of them.

Our method may be used to predict all the zinc(II)-proteins of a given organism starting from its proteome sequence. To demonstrate this, we investigated the proteome of the yeast *Saccharomyces cerevisiae*. We decided to focus on this organism also because of the availability of a combined bioinformatics and proteomics analysis that provided a list of yeast zinc(II) proteins with experimental validation [34]. Our tool predicted the occurrence of a zinc(II) MBS in 191 proteins out of 1500 analyzed, of which 77 had a deposited experimental structure.

This allowed us to calculate an independent estimate of the precision (i.e., the percentage of predicted sites that are actually correct), namely 80.5%. Further validation of MoM resulted from the analysis of the remaining 114 predicted yeast zinc proteins against the experimental structures of homologous proteins from other organisms; the precision in this subgroup of proteins was 72%. By combining the two datasets, we obtain an overall estimate of the precision of the MBS predictions for the yeast proteome at about 76% and a false discovery rate of 24%. Finally, for a previously reported list of yeast zinc(II) proteins obtained by a combination of bioinformatics methods and mass spectrometry, we had a recall of 86%. These results are in between the recall measured for holo- and apo-sites at the 0.35 Å threshold that we used here.

Our tool can be compared with other software that perform the same task, developed or updated in the past few years. In particular, a deep-learning approach recently has been implemented in Metal3D [23]. With a value of the *p* parameter of Metal3D equal to 0.75, the latter tool achieves a recall close to 80% and a precision of about 82% for sites containing at least three ligands. The recall and precision of Metal3D have been estimated only on crystallographic structures of the holo form of zinc(II) proteins, hence only for sites already in the metal-bound conformation. We thus checked whether the structural rearrangements possibly occurring upon metalation reduced the software performance of Metal3D by using apo-structures as input, without finding any compelling evidence for such a trend. However, we noted that Metal3D seems more sensitive than our method to incomplete structures or to changes in the rotameric state of the metal ligands between the apo- and holo-structure, possibly because for such inputs the voxelized site computed by Metal3D is not a correct representation of the holo-MBS. An intriguing example is that of PDB entry 1T38 [40], whose zinc(II) site is unoccupied due to the additional tag present in the construct [40], leading to a significant rotation of the side chain of His29 as compared with the corresponding holo-structure (PDB code 1YFH [41]); in addition, the most N-terminal ligand, Cys5, is not observed in 1T38. Our tool but not Metal3D could identify the site in the 1T38 apo-structure. However, the AlphaFold model of the protein structure contained a properly preorganized apo-site, which Metal3D could detect with very high confidence. MoM featured a recall of about 90% on crystallographic structures of holo-zinc(II) proteins and of about 83% for the corresponding apo-structures, whereas the analysis of the predictions for the AlphaFold models of all yeast proteins indicated a recall in the range 75%-85%, depending on the chosen reference dataset, and precision of around 76%. We can thus conclude that our tool has a performance practically aligned with that of Metal3D despite its simpler architecture. Its simplicity allows the present method to achieve comparatively faster calculations, enabling the analysis of a full proteome, such as yeast, in a matter of hours.

Other related tools are BioMetAll [22] and MIB2 [42]. Besides their different methodologies, these tools are not appropriate for high-throughput applications to entire proteomes. MIB2 is available only as a web server designed for testing individual structures, whereas BioMetAll outputs for each input structure multiple possible sites, with no quantitative ranking of the predictions. AlphaFill instead fills the apo-sites in the AlphaFold models by docking the ions present in homologous proteins with a deposited PDB structure [21], thus relying strictly on the detection of a homology relationship.

In summary, we developed the MoM tool for the identification of potential zinc(II)-MBSs in 3D structural models. MoM can be conveniently run on entire proteomes, in order to obtain a prediction of any organism's entire zinc(II)-proteome. The tool is available at https://github.com/cerm-cirmmp/Master-of-metals. MoM has been applied to the yeast proteome, and the predictions validated against different datasets. Besides the precision, which we discussed in the previous paragraphs, our approach featured a false discovery rate of 24% with a threshold of 0.35 Å, which corresponds to three predicted MBSs in four being correct. When necessary, this aspect can be improved by applying a more stringent filter: using a threshold of 0.30 Å reduces the recall by less than one tenth while reducing false positives by about one third (Table 1). In any case, visual inspection of the results is strongly recommended.

Methods

Representation of the metal-binding sites

Selecting informative features is the first step in the design of a successful machine learning/statistical model. In our context, several different features describing the chemical-physical properties of metal-binding sites (MBSs) could be used[18,43,44]. In this work, we focused simply on the spatial configuration of the metal ligands. Thus, our input consisted of the Cartesian coordinates of the Cα and Cβ atoms, together with the aminoacidic type. We decided not to use the coordinates of further atoms in the side chains (SCs), because we previously observed that metalation of an apo-MBS is likely to induce a significant rearrangement of the SCs, whereas the backbone atoms are largely unaffected[31]. The backbone atoms should thus be at a position that is closer to the holo-structure than the SC atoms in experimental or predicted apo-structures. A 5-dimensional one-hot vector was used to specify the aminoacidic type; the first four positions indicate if each residue is one among Cys/His/Asp/Glu (CHED group [35]), whereas the fifth was used for all other aminoacids. In this way, a L-length structure (excluding Gly) is represented by a 2L x 3 matrix containing the *x*, *y*, *z* coordinates of the Cα and Cβ atoms of each residue and a L x 5 matrix indicating the type of aminoacid at each position.

Construction of the dataset of positives (holo sites and apo sites)

All zinc(II) sites annotated as "physiological", and therefore having a functional role in the protein, were selected from MetalPDB [24,25]. We retained only those having a single zinc(II) ion (mononuclear sites) with three or more protein residues acting as metal ligands. The MBSs were then grouped on the basis of their metal-binding pattern (i.e. the type and order of amino acids that bind directly to the metal ion). For example, all sites that bind the zinc(II) ion with a His followed in sequence by two Glu residues are grouped together as "His-Glu-Glu". To avoid analyzing similar MBSs several times, we subsampled sites with the same pattern if there were more than 30 of them. For this, we computed the difference between all possible pairs of MBSs having a given pattern. Such difference is mathematically defined as the mean absolute value of the difference between the adjacency matrices of the two MBSs, where the adjacency matrix of an MBS is the matrix containing the distances among all the Cα and Cβ atoms of the MBS. For all MBSs having a difference smaller than a threshold T (set at 0.1 Å) only one site was retained. Note that the specific identity of the retained MBS is not relevant as MoM works only

with the adjacency matrices. At the end of the sub-sampling, all remaining MBSs sharing the same pattern have a distance from each other greater then T. To remove protein redundancy due to homology we clustered all the proteins with at least 30% identity in any given pattern-based group by running the CD-HIT [45] program. Five sites were randomly selected for each cluster and included in the dataset of holo (i.e. metal loaded) MBSs. Sites belonging to the same cluster were never separated into different datasets for algorithm training, i.e. were all included in the training dataset or all included in the testing dataset.

MetalPDB contains information also on apo (i.e. devoid of their physiological metal cofactor) metalloprotein structures [25]. Thus, we retrieved all apo-sites linked to mononuclear zinc(II) MBSs. We retained only one apo-site for each protein.

Construction of the dataset of negatives

To construct the dataset of negatives, i.e. non-zinc-binding structures, we started from all sequences in the entire PDB and grouped them with CD-HIT [45] into clusters of sequences with at least 30% identity. All clusters containing one or more physiological metal-binding structures were then removed from the dataset. Finally, one structure from each remaining cluster was randomly selected.

MBS recognition pipeline/workflow

Our tool (Master of Metals, MoM) takes as input a pdb file. For each CHED residue, MoM creates a group of CHED structural neighbors, whose Cα distances among each other are within a given threshold. In this way, we extract a list of potential sites (PSs) from the protein structure. The threshold values were defined from a previous analysis [31] and taken equal to 13 Å. This procedure ensures that the residues in each PS are at reasonable distances, but we still do not know anything about their spatial configuration. We trained a graph neural network (GNN) to estimate the probability that a PS is an MBS (see next section). The PSs that have a probability value greater than 0.6 are named Highly Probable Potential Sites (HPPSs).

In practice, only some of the HPPSs are indeed real MBSs. To address this point, MoM compares each HPPS with all the MBSs of our training set that have the same metal-binding pattern (i.e. the type and order of amino acids that bind to the metal ion). For this comparison, all sites are represented as the adjacency matrices of their Cα and Cβ atoms. For each HPPS MoM identifies the MBS having the smallest difference to it (d_min). If d_min is lower than a given threshold (e.g., 0.35 Å), we propose that the HPPS is a real MBS. Fundamentally, this is grounded on the fact that there exists an experimentally validated MBS that has a shape, as defined by the positions of the Cα and Cβ atoms, very similar to the predicted HPPS.

Architecture, training and evaluation of performance of the GNN

MBSs can be represented suitably as graphs, where the Cα and Cβ atoms are the nodes, and the edges represent the interaction with neighboring atoms. Graph neural networks are machine learning models engineered to process data structured as graphs. The nodes of the graph are associated to vectors that represent their state, i.e. their feature values. The topology

of the graph, that is the set of relationships between all its nodes, is represented by the adjacency matrix A, whose (i, j)-th element is 1 if node i and node j are connected by an edge and 0 otherwise. In our case, values in A are scaled as exp(-d_ij/alpha) where d_ij is the euclidean distance between node j and node i and alpha is experimentally optimized.

In this work we used a graph convolutional network (GCN). GCNs take as input the adjacency matrix and the feature vectors of the nodes. A GCN is composed by multiple stacked layers. Each layer generates a new feature vector (called embedding) for each node, processing its feature vector and those of the nodes to which it is connected. Lastly, the embeddings of all the nodes are averaged and the resulting vector is fed to a fully connected layer with two outputs, acting as the classifier.

To train the GCN, the dataset of holo sites was randomly split into validation (20%) and training (80%) groups. All the sites belonging to the same CD-HIT cluster (see section "Construction of the dataset of positives") were assigned to the same group, thus ensuring that related MBSs are not found in different groups. The parameters of the model were optimized to maximize the performance of the training set (training process) using cross-validation and then tested on the validation set.

Evaluation of performance

In the holo and apo datasets each item is a single MBS (target site); this means that we have multiple items for proteins harboring multiple MBSs. The negative dataset is composed of whole protein structures. We used the holo training set to optimize our GCN, which was then tested on the holo validation set, as well as on the apo and negative datasets. In our workflow, for the holo and apo datasets a prediction is considered a success (true positive) if the site corresponds (at least two out of three metal ligands) to an MBS. Conversely, all experimental MBSs for which there was no prediction with a d_min value below the selected threshold are false negatives (FN). All predictions with a d_min value below the threshold for the structures in the negative dataset are false positives (FP). For our analyses, we used different performance measures, including:

Recall: TP/(TP+FN), also called sensitivity, true positive rate (TPR)

Precision: TP/(TP+FP), also called positive predictive value (PPV)

True negative rate (TNR): TN/(TN+FP)

False positive rate (FPR): FP / (TP+FP)

The same parameters were used to evaluate the results for the prediction of the zinc(II) proteome of yeast.

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Author contributions

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Antonio Rosato: Funding acquisition; Supervision; Visualization; Writing – review & editing

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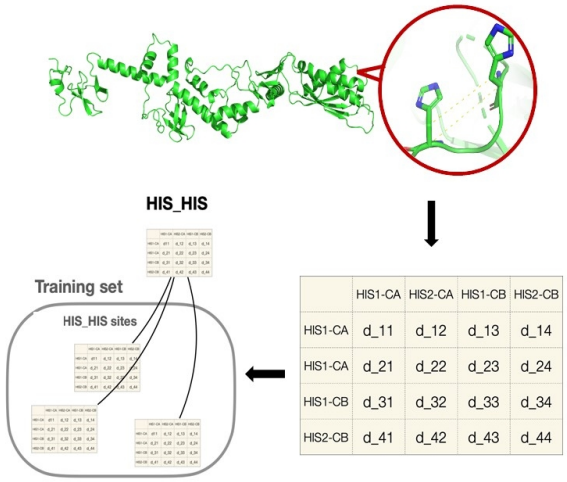

Zinc(II)-binding sites are predicted in structural models through comparison to the distance matrices of known sites

338x190mm (96 x 96 DPI)