Improving Macromolecular Structure Refinement with MetalCoord

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Challenges with metals

- **Complex dependencies:** Bond lengths and angles around metal atoms depend on their charge state, coordination geometry, and chemical environment.
- **Variable conformation:** The same metal atom can adopt different oxidation or coordination states, even within a single molecule or active site.
- **Incomplete local information:** At low resolution, not all atoms surrounding metal centres can be reliably located. Moreover, both the charge state and coordination geometry may vary during protein activity or even throughout data collection, making it challenging to construct a single and/or complete model.
- **Refinement challenges:** The combination of relatively poor electron density around metal sites and their context-dependent coordination geometries makes automated restraint generation difficult.

Aim of this work

- **Address persistent challenges** in modelling metal-ligand coordination chemistry, including: incorrect bond orders and nominal charge states in sandwich-type complexes; erroneous electronic state assignments in haem-like prosthetic groups.
- **Enhance structural refinement** through automated generation of context-aware restraints suitable for both crystallographic and cryo-EM applications.
- **Systematic and comprehensive updates** of all metal-containing ligand definitions in the PDB Chemical Component Dictionary (CCD).

Materials and Methods

Coordination Geometries classification

- Extract & filter high-quality metal environments from COD.
- Classify into ideal geometry classes using Procrustes analysis.
- Compile coordination dependent and independent statistics for stereo-chemical information.

Dataset:

- Starting: 429,579 metal fragments. After filtering: 228,063 single-metal fragments. Final: 189,671 reliable coordination geometries
- We expanded classification from initial 31 to 95 distinct coordination geometry classes
- The methodology comprehensively addresses all established coordination geometries, including: tetrahedral, octahedral, various sandwich-type complexes and many more

Application workflow

- **AceDRG** generates initial stereo-chemical information; **MetalCoord** generates context dependent information around metal atoms; **Servalcat** optimises the geometry.
- **Servalcat** and **coot** read and use generated restraints for refinement

Outcome:

- Updated monomer library with improved metal containing ligands
- Improved restrained refinement of metal-containing structures

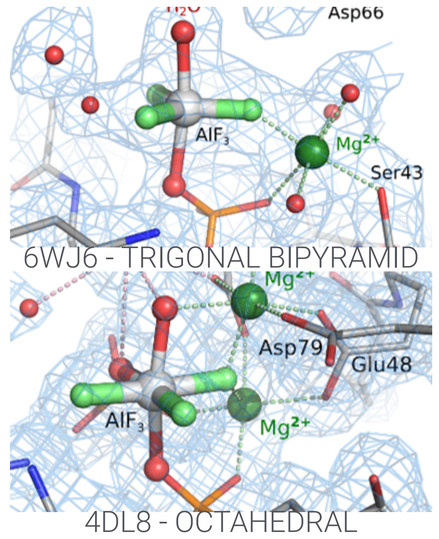
Results

- We manually reviewed all 884 CCD metal ligands; updated 809 with corrected chemistry
- **metalCoord** has been integrated with Servalcat, AceDRG, CCP4
- The CCP4i2 and CCP-EM Doppio GUIs now include MetalCoord (**see Martin Maly's poster, MS3_P5**)
- Coordination-dependent restraints for metal containing ligands improves refinement
- **metalCoord** and associated tables are available from CCP4 & GitHub

Examples

Refinement improvements:

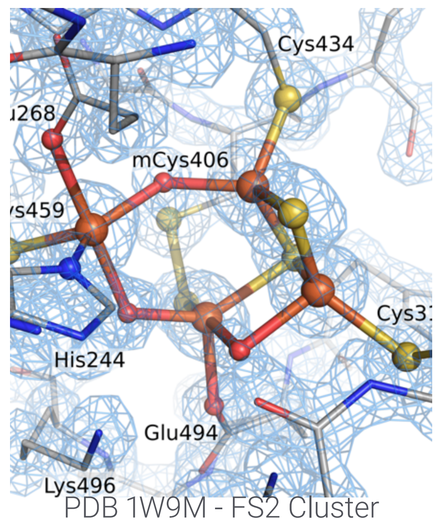
- Aluminium fluoride (monomer code AF3) exists in trigonal-bipyramidal (6WJ6) and octahedral coordination



6WJ6 - TRIGONAL BIPYRAMID

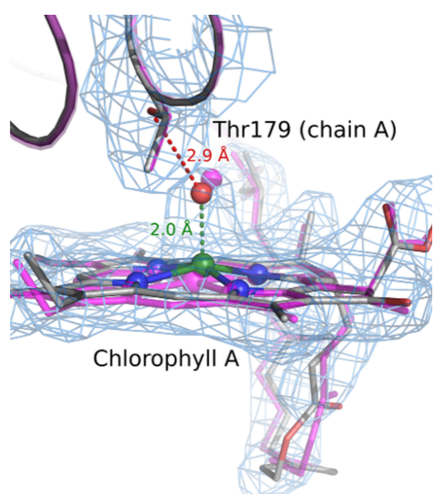
4DL8 - OCTAHEDRAL

- Iron–sulfur–oxygen cluster (monomer code FS2) are refined with improved geometry



PDB 1W9M - FS2 Cluster

- Chlorophyll A: Improved metal environment and fit to map



PDB 6WJ6 - chlorophyll A
Magenta - molecules from the PDB; all atoms colour - after refinement with metalCoord restraints

Resources

`https://github.com/Lekaveh/MetalCoordAnalysis` - Metal Coordination Analysis Tool (MetalCoord)
`https://github.com/MonomerLibrary/monomers` - CCP4 Monomer Library
`https://github.com/MonomerLibrary/monomers/blob/master/metals.json` - Typical interatomic distances between metals and other elements
`https://github.com/MonomerLibrary/monomers/wiki/Dealing-with-metals#typical-interatomic-distances` - Usage manual for distances

References

MetalCoord: "Improving macromolecular structure refinement with metal-coordination restraints". Babai KH, Long F, Malý M, Yamashita K & Murshudov GN (2024) *Acta Cryst. D80*(12):821–833.

Servalcat: "Cryo-EM single-particle structure refinement and map calculation using Servalcat". Yamashita K, Palmer CM, Burnley T & Murshudov GN (2021) *Acta Cryst. D77*(10):1282–1291.

AceDRG: "AceDRG: a stereochemical description generator for ligands". Long F, Nicholls RA, Emsley P, Gražulis S, Merkys A, Vaitkus A & Murshudov GN (2017) *Acta Cryst. D73*(2):112–122.

CCP-EM: "Recent developments in the CCP-EM software suite". Burnley T, Palmer CM & Winn M (2017) *Acta Cryst D73*(6), 469–477.

CCP4: "The CCP4 suite: integrative software for macromolecular crystallography". Agirre J et al. (2023) *Acta Cryst. D79*, 449–461.