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# Enhancing accuracy in molecular dynamics simulations: a web service for metal ions force field generation

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## INTRODUCTION

Molecular Dynamics (MD) simulations provide unique insight into the structural and dynamics of biological macromolecules, contingent upon their accuracy. Two primary determinants of accuracy include the precision of the MD model, particularly the molecular mechanics force field, and the depth of the sampling performed for the simulated system. The purpose of the conventional force fields is to approximate the energetics of interatomic interactions in MD with relatively simple mathematical formulas. Such force fields are predominantly tailored for biomolecules due to their composition from recurring building blocks, namely amino acids and nucleotides. However, their accuracy diminishes notably for molecules that incorporate metal ions. In particular, metal ions typically form coordination bonds at catalytic sites and are crucial for recapitulating accurately the biological behaviour of proteins.

## METHODS

The web service is a full-stack application built with Spring Boot for the backend, ReactJS for the frontend, and Docker for containerization.

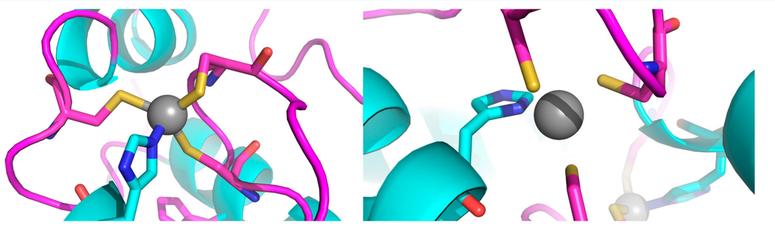
- **Backend** (Spring Boot): Manages RESTful APIs, business logic, offering modularity and scalability.
- **Frontend** (ReactJS): Provides a dynamic user interface with reusable components, efficiently fetching data from the backend.
- **Containerization (**Docker): Packages the application in separate containers for the frontend, backend, and database, ensuring consistency and smooth deployment across environments.

The **Amber** and **Gromacs** packages for MD were executed on the backend using Docker containers.

## RESULTS

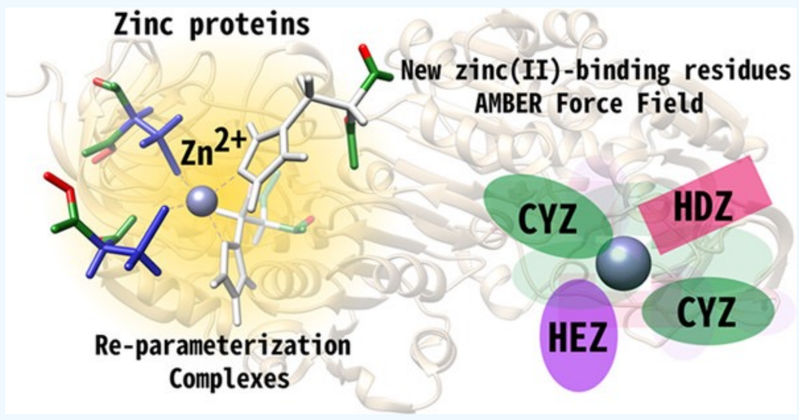
### Metal Binding model

Different models exist to parametrize the interaction of metal ions with a protein for subsequent MD simulations. The bonded model and the nonbonded model are the two main approaches.



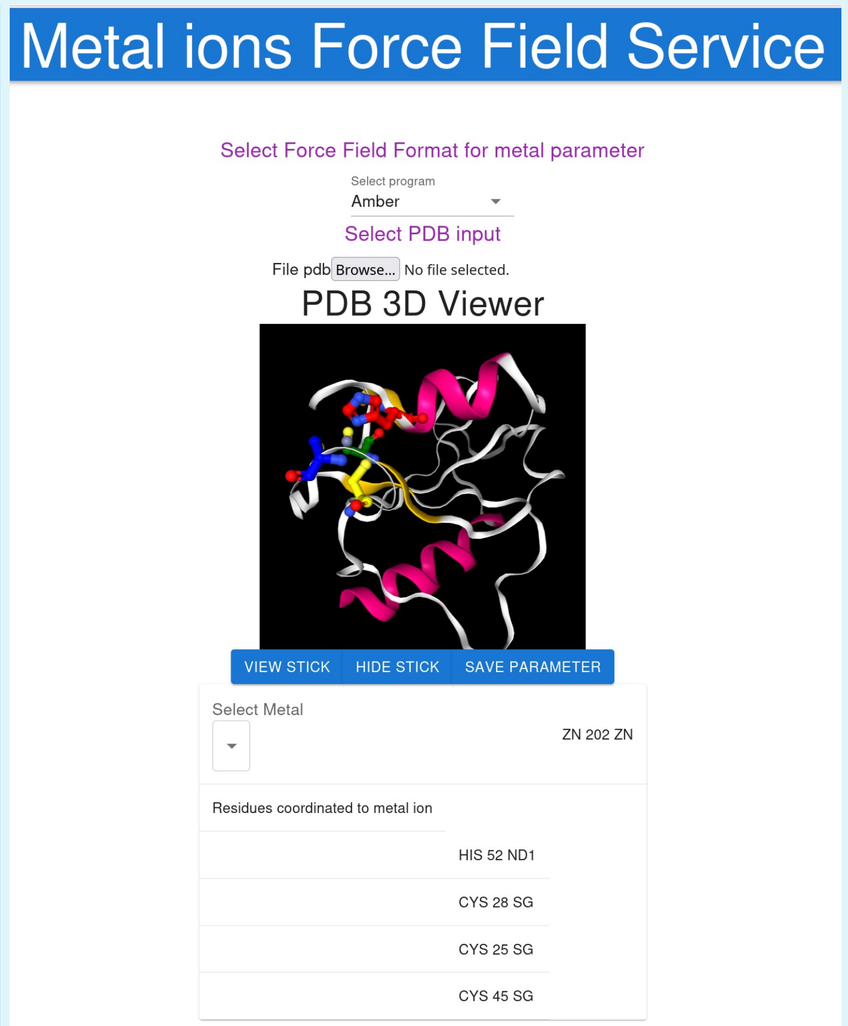
Zinc(II)-sites modeled with the bonded approach (left) and nonbonded one (right)

Recently [1], we proposed database-derived parametrization strategies for the nonbonded model. This involves creating novel force field parameters for both the metal and its binding residues (the metal-binding-site)




### Web service

The web service has been implemented to facilitate the setup of molecular dynamics for a protein that contains metals (currently, zinc ions). The service takes a structure in PDB format as input and automatically detects the position of the ions. Through the interface displaying the three-dimensional structure, the user can select the metal binding site. By pressing 'Save Parameter,' the service will create the files with the new parameters, which are then checked in the Docker container. If the check is successful, the parameter files become available for download in zip format.




## CONCLUSION

In this contribution, we propose a service that provides a web user interface for the development of force fields for proteins containing metals. Within this service, we have implemented the automatic generation of generalized force field for proteins that contain zinc ions [2]. The service facilitates the setup of Molecular Dynamics simulations using the Amber or Gromacs suite. At present, we are actively working to implement additional metals, such as copper and iron

1. Upgrading and Validation of the AMBER Force Field for Histidine and Cysteine Zinc(II)-Binding Residues in Sites with Four Protein Ligands. Macchiagodena M, Pagliai M, Andreini C, Rosato A, Procacci P. J Chem Inf Model. 2019. doi: 10.1021/acs.jcim.9b00407.
2. A Comparison of Bonded and Nonbonded Zinc(II) Force Fields with NMR Data. Bazayeva M, Giachetti A, Pagliai M, Rosato A. Int J Mol Sci. 2023. doi: 10.3390/ijms24065440.