Metalloprotein Simulations:
a Neural Network based Approach

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Outline

Metalloproteins are important biomolecules that incorporate metal-ion cofactors. They are essential for various biological functions, among others, involved in infections and diseases.

Metal-sites are notoriously difficult to describe via classical MD simulations as they involve coordinate bonds. Transition metals with their open shell of d-electrons further require the quantum level of theory. However, quantum mechanics (QM) is not feasible for huge systems, while molecular mechanics (MM) is not very accurate.

We have developed a hybrid QM/MM[1] approach that employs **N**eural **N**etworks[2] (NN) for increased efficiency and additionally introduces a **Bu**ffer **R**egion to reduce artifacts and smooth the transition between QM and MM: **BuRNN**[3].

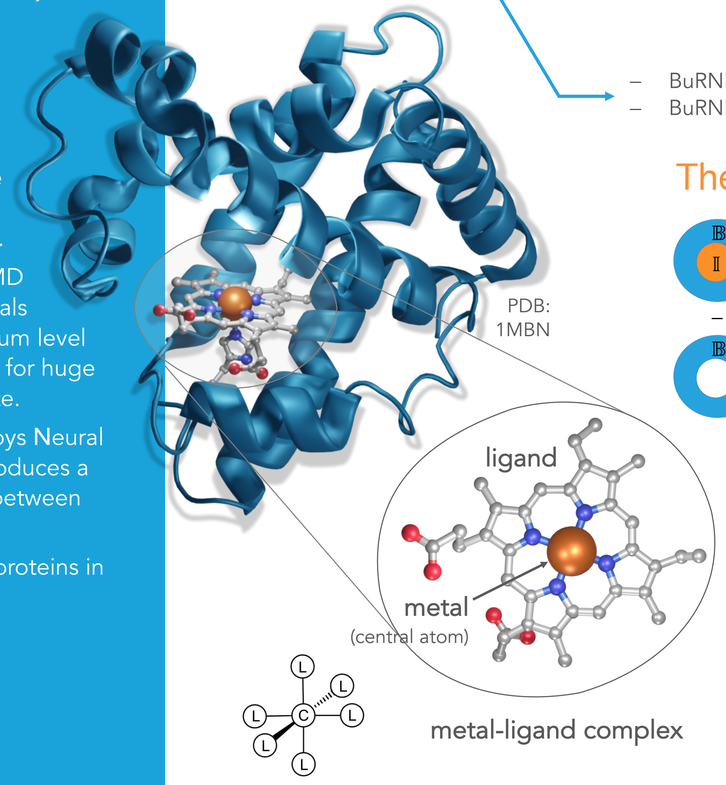
We aim to apply this NN/MM simulation method to metalloproteins in order to investigate their complex nature.

In short

- accurate metalloprotein simulations require QM
- **BuRNN** is a novel alternative to QM/MM simulations
- **BuRNN** is an efficient NN/MM simulation approach

Next steps

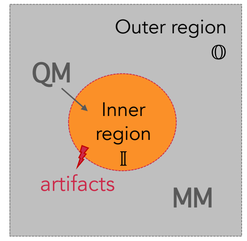
- release of the BuRNN code in the **GROMOS** Software
- training and simulation of porphyrin systems



QM/MM[1] simulations are **powerful**:
- **accurate** for small part - **QM** level of theory (inner region 𝕀)
- **efficient** for rest - classical **MM** force fields (outer region 𝕆)

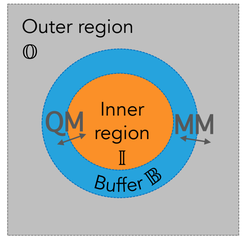
QM/MM simulations are **limited**:
- **high** computational **costs**
- **artifacts** at the interface

QM/MM
"conventional method"



- BuRNN **reduces costs** by machine learning
- BuRNN **reduces artifacts** by embedding scheme

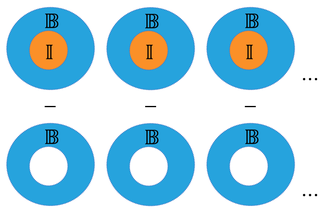
The BuRNN Approach



BuRNN[3] introduces **Buff**er **R**egion:
- buffer 𝔹 described at both levels
- $V^{MM}_{\mathbb{B}} - V^{QM}_{\mathbb{B}}$ **smooths transitions**
- 2 QM calculations required
- **artifacts** at the interface **cancel**
- **full electronic polarization** of 𝔹 by 𝕀

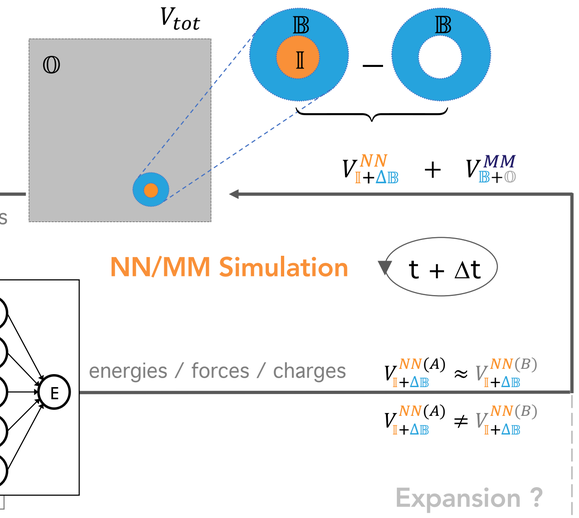
BuRNN employs **N**eural **N**etworks:
- difference of 2 QM calculations trained by **deep NN**[3]
- **interaction energies simplify** training
- second NN for charge training

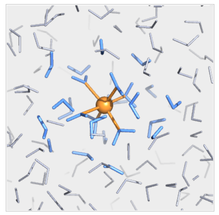
The BuRNN Workflow



$$V_{tot} = V^{QM}_{\mathbb{I}+\mathbb{B}} - V^{QM}_{\mathbb{B}} + V^{MM}_{\mathbb{B}} + V^{MM}_{\mathbb{O}(\mathbb{I}+\mathbb{B}+\mathbb{O})} \cong V^{NN}_{\mathbb{I}+\Delta\mathbb{B}} + V^{MM}_{\mathbb{B}+\mathbb{O}}$$

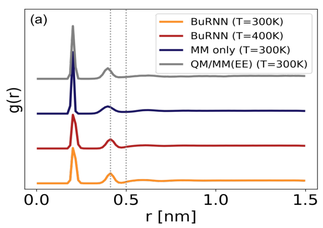
Training Set Generation

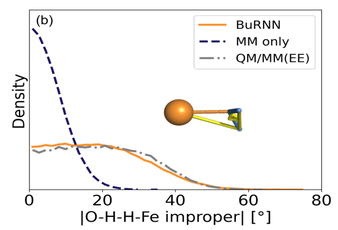


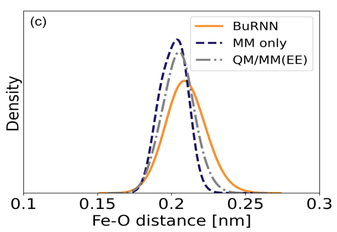


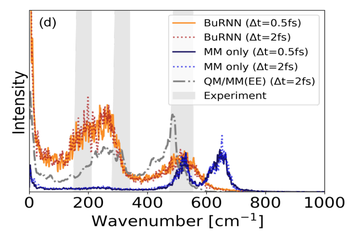
Proof of Concept

$[Fe(H_2O)_6]^{3+}$ complex in water:
- **small** system with **metal-ligand interactions**
- **stable** simulations, expected geometries
- **agreement** with **QM/MM** and **experiments**









Training Set Generation
- **sampling** of configurations (coordinates) by MD simulations
- **extending** configurations by QM energy minimization and adaptive sampling
- **2 QM calculations** for each configuration: 𝕀+𝔹 and 𝔹
- **training database** for energy (force) differences and charges

Neural Network Training
- training atomistic NN on **interaction energies** (forces) with SchNet[4]
- training atomistic NN on partial **charges without** final **pooling layer**

Hybrid NN/MM Simulations
- BuRNN implemented in GROMOS[5] with direct interface to SchNetPack[6]
- **buffer region** by **cut-off**
- MM terms $V^{MM}_{\mathbb{B}+\mathbb{O}}$ with force field
- QM interaction energies by a **call of the NN** $V^{NN}_{\mathbb{I}+\Delta\mathbb{B}}$
- partial charges to **polarize** 𝔹 by 𝕀 in the interaction with 𝕆
- **validation** by 2 individual NNs (**A** and B)
- comparing the NN $V^{NN(A)}_{\mathbb{I}+\Delta\mathbb{B}} \approx V^{NN(B)}_{\mathbb{I}+\Delta\mathbb{B}}$?
- **expanding training set** when predictions diverge $V^{NN(A)}_{\mathbb{I}+\Delta\mathbb{B}} \neq V^{NN(B)}_{\mathbb{I}+\Delta\mathbb{B}}$ and retrain

More details: read the BuRNN paper!

References

1. Warshel & Levitt. *J. Mol. Biol.* 103, 227–249 (1976).
2. Behler. *Phys. Chem. Chem. Phys.* 13, 17930–17955 (2011).
3. Lier, Poliak, Marquetand, Westermayr & Oostenbrink. *J. Phys. Chem. Lett.* 13, 3812–3818 (2022)
4. Schütt, Sauceda, Kindermans, Tkatchenko & Müller. J. Chem. Phys. 148, 241722 (2018)
5. Schmid, Christ, Christen, Eichenberger & van Gunsteren. Comput. Phys. Commun. 183, 890–903 (2012)
6. Schütt, Kessel, Gastegger, Nicoli, Tkatchenko & Müller. J. Chem. Theory Comput.15, 448–455 (2019)

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