# Geometry Optimization Calculations of Dinuclear Fe Active Sites in Bacterial Metalloproteins

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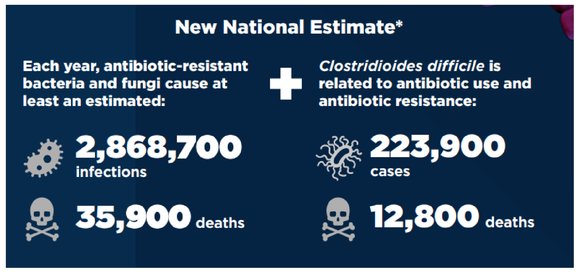
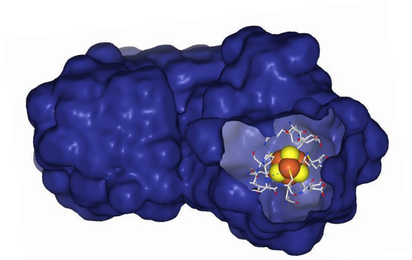
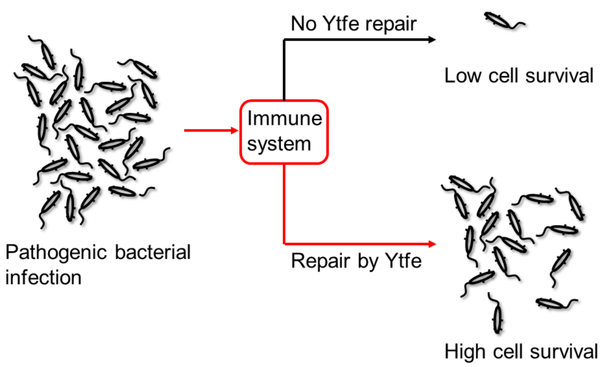
## Introduction & motivation




Pathogenic bacterial infections are a significant cause of human disease and death.[1]



Bacteria rely on FeS cluster metalloproteins to survive. The image above reveals an FeS cluster found within a bacterial DNA repair enzyme (PDB 2ABK).




Ytfe is a bacterial metalloprotein that helps pathogenic bacteria survive the immune system by repairing FeS clusters.[2]

**We want to study Ytfe to understand the mechanism of repairing FeS clusters.**

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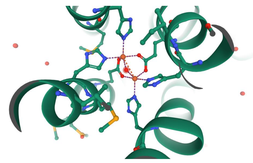
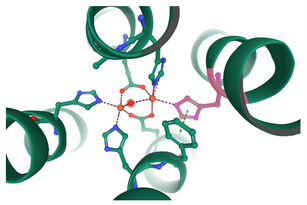
## Bacterial Metalloproteins

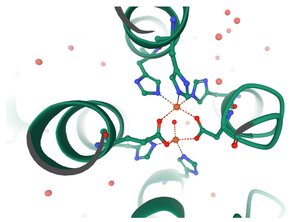
**Ytfe** boosts virulence of pathogenic bacteria by repairing FeS clusters. *Ytfe PDB ID 5FNN*



**MkA** boosts virulence of pathogenic bacteria through a currently unknown pathway.[3] *MkA PDB ID 6Q09*



**Hemerythrin** (Hr) is an oxygen-transport protein found in marine invertebrate phyla. *Hr PDB ID 1HMD*



**What about the structures of Ytfe and MkA enables such different function compared to Hr?**

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## Computational Methods

- Density functional theory (DFT) is a quantum mechanical modelling method.
- In DFT, the energy and associated properties of a system are calculable from the electron density of the system.

  *Functionals used: B3LYP and BPW91*
  *Basis sets: 6-31G(d) and 6-311G(d)*
- We performed DFT calculations to optimize the geometry of metalloprotein active sites by minimizing the energy of the system on a potential energy surface.
- Calculations were performed on the TCNJ ELSA high performance cluster.

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## Optimization Results

| Protein | $Fe_1$-O Bond Length (Å) Experimental | $Fe_2$-O Bond Length (Å) Experimental | $Fe_1$-O Bond Length (Å) Calculated | $Fe_2$-O Bond Length (Å) Calculated |
|---|---|---|---|---|
| MkA HLP | 1.71 | 2.48 | 1.74 (1.88) | 1.73 (1.86) |
| Hemerythrin | 2.16 | 1.78 | 1.73 (1.90) | 1.70 (1.78) |
| Ytfe | 1.89 | 1.98 | 1.71 (1.80) | 1.68 (1.79) |

Representative results (B3LYP, 6-31G(d)) comparing bond lengths within dinuclear Fe active sites. Experimental values are for Fe(III)-Fe(II) states. Calculated values are for Fe(III)-Fe(III) states and values in parentheses are for Fe(II)-Fe(II) states.

**Geometry calculations reproduced some general features of bacterial metalloprotein active sites. There are some discrepancies between calculated and experimental values.**

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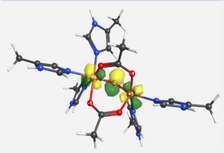
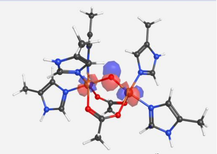
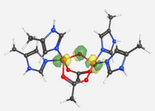
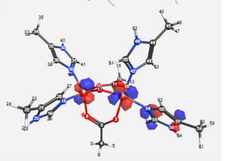
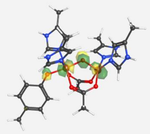
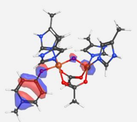
## Molecular Orbitals

| Protein | LUMO | HOMO |
|---|---|---|
| HR |  |  |
| Ytfe |  |  |
| MkA |  |  |

Representative lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) for Hr, Ytfe, and MkA (B3LYP, 6-31G(d)).

**LUMOs are similar across the series.**

**Ytfe HOMO has less electron density on its bridging oxide relative to Hr.**

**MkA HOMO is unique with significant electron density delocalized onto its Fe-bound tyrosine residue.**

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## Summary

- **Computational chemistry methods produced models of bacterial metalloprotein active sites.**
- **Differences between experimental and calculated bond lengths indicate the models need further optimization.**
- **Molecular orbitals suggest unique electron densities in Ytfe and MkA relative to Hr.**
- **Collectively these results form a proof-of-concept for modelling and investigating structural differences between Ytfe, MkA, and Hr.**

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## Future Directions

- **Calculations presented here ignored antiferromagnetic coupling (AFC) between iron centers.**
- **To improve the quality of our calculations, we will use a broken symmetry approach to account for AFC in bacterial metalloprotein active sites.**

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## Acknowledgments

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- **You for your time!**

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## References

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