# An enquiry into theoretical bioinorganic chemistry:
# **How heuristic is the character of present-day quantum chemical methods?**

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# **How heuristic is the character of present-day quantum chemical methods?**

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**Paper intended to be provocative in order to stimulate discussion on future developments of theoretical approaches**

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# Predictive power of quantum chemical calculations on active sites?

**DFT**: functionals parametrised on data of test molecule set;
statistical analysis of energy errors known for test set;
not (never?) systematically improvable

*Can one expect that energies of crucial steps in metalloenzyme catalysis are reliably reproduced?*
*Or properties (=energy derivatives)?*

**WFT**: if accurate —> expensive (often unfeasible);
hence, structures often taken from DFT;
in principle, systematically improvable total energies,

*but does this consistently improve the relative energies?*

*What to do if not much is know about a new system?*

# Are quantum chemical calculations on active sites most useful only *a posteriori* to rationalize experiment?

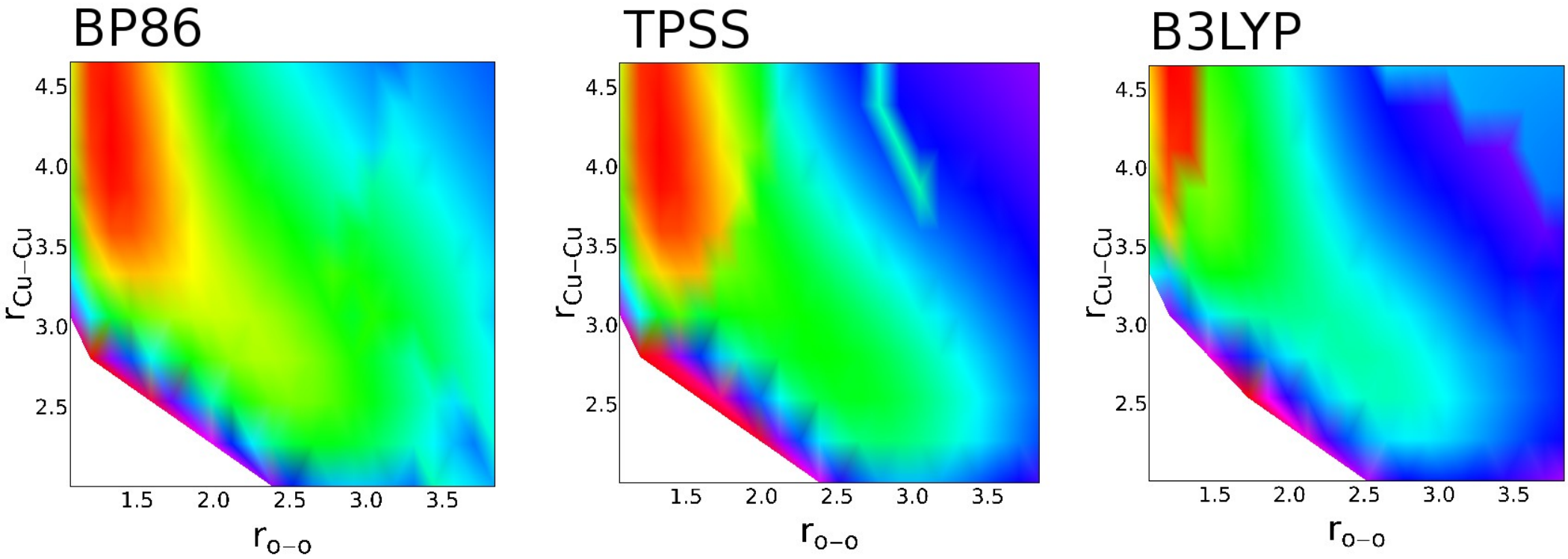
Danger to pick the most consistent result though this might be:

"**the right answer for the wrong reason**"

*Example*: DFT spin state splitting energies seem OK,
but spin density distributions not the same

# Thesis 1: Method-inherent approximations difficult to control

Correlation diagrams for a better “look and feel” of results;
**example:** $Cu_2O_2^{2+}$ bis-μ-oxo vs. side-on peroxo; triplet state

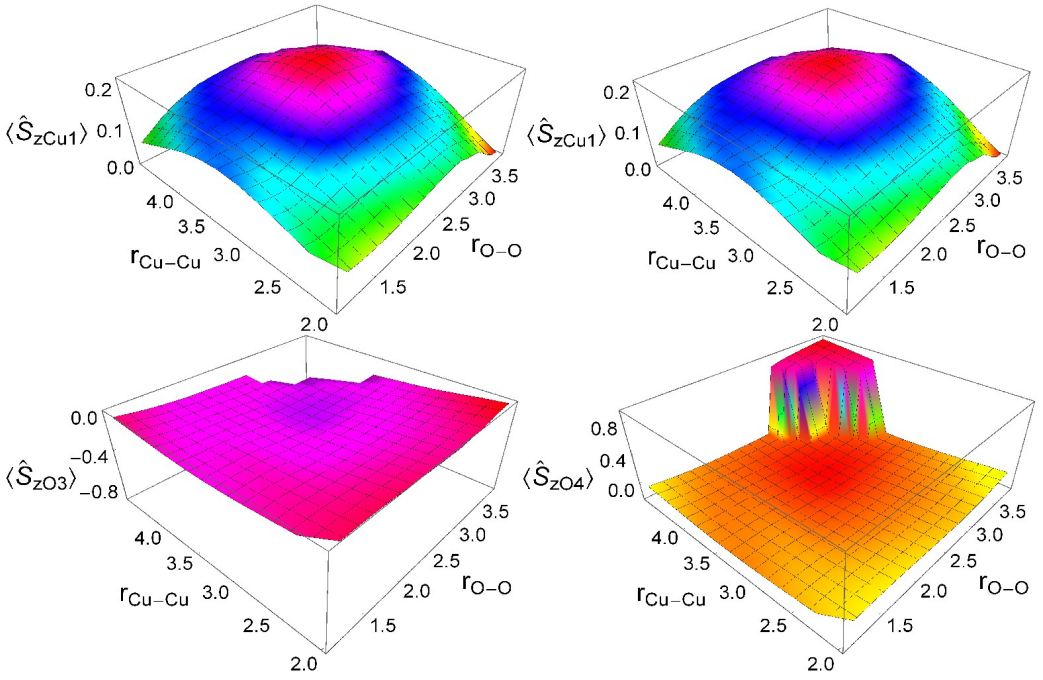


# Correlation diagrams provide insight

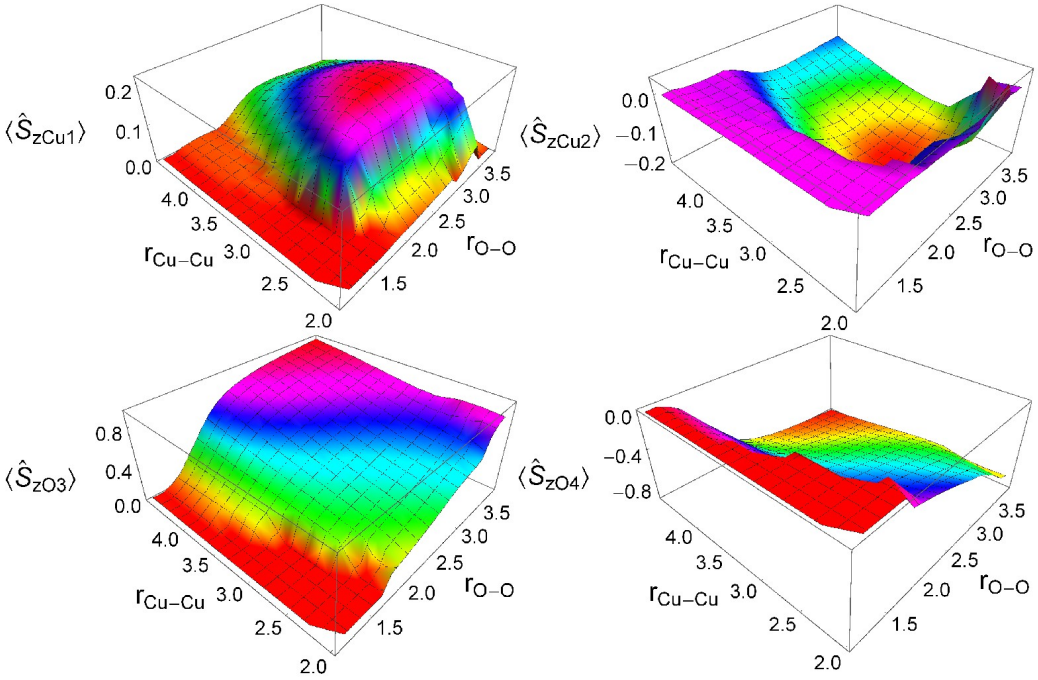
... into flexibility of a structure (potential energy well depth/width),
... into emergence of properties etc.

Example: two broken-symmetry solutions for $Cu_2O_2^{2+}$

BS1




BS2



# Thesis 2: Structural models of active sites can be difficult to construct

... because of: system size (active center+protein environment), solvation, dynamics

"convergence" depends on system under study

*many examples known from the literature*

# Example: De novo protein design

**Pre-requisite: In silico design and re-engineering of enzymes require reliable prediction of energy barrier heights !**

Kinetics depend exponentially on activation energy

—> *Small energy changes have dramatic effects on catalysis.*

Apart from method-inherent errors,

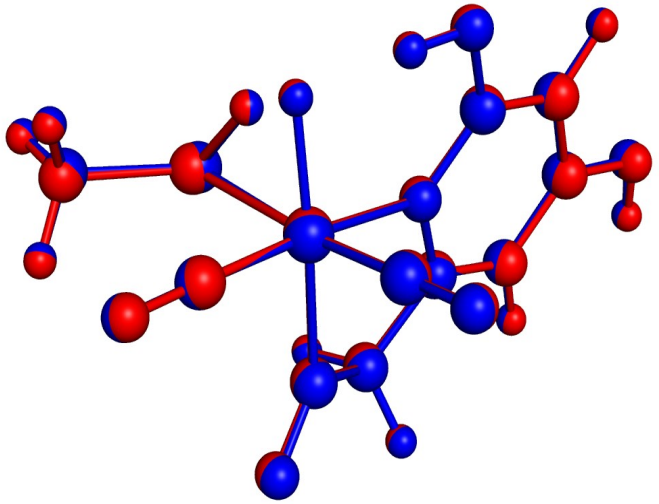
*structural models can produce these energy modulations*.

# Transition state flexibility in [Fe] hydrogenase

Distort transition-state model along normal coordinates (protein environment and water neglected)

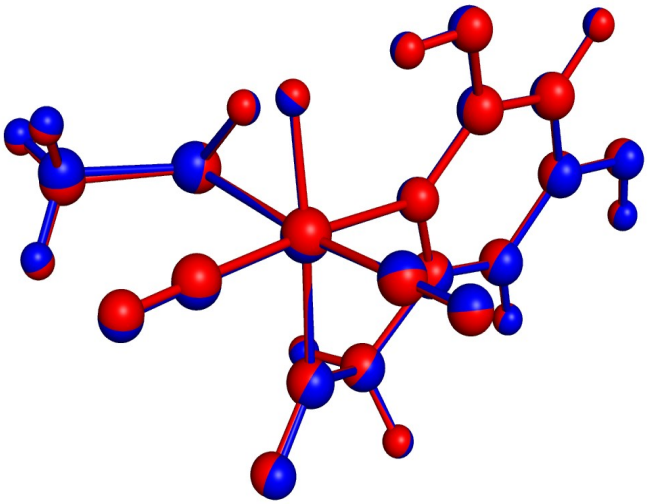
Allowed increase in energy: 10 kJ/mol

Mode 2



68 $cm^{-1}$

Mode 3



79 $cm^{-1}$

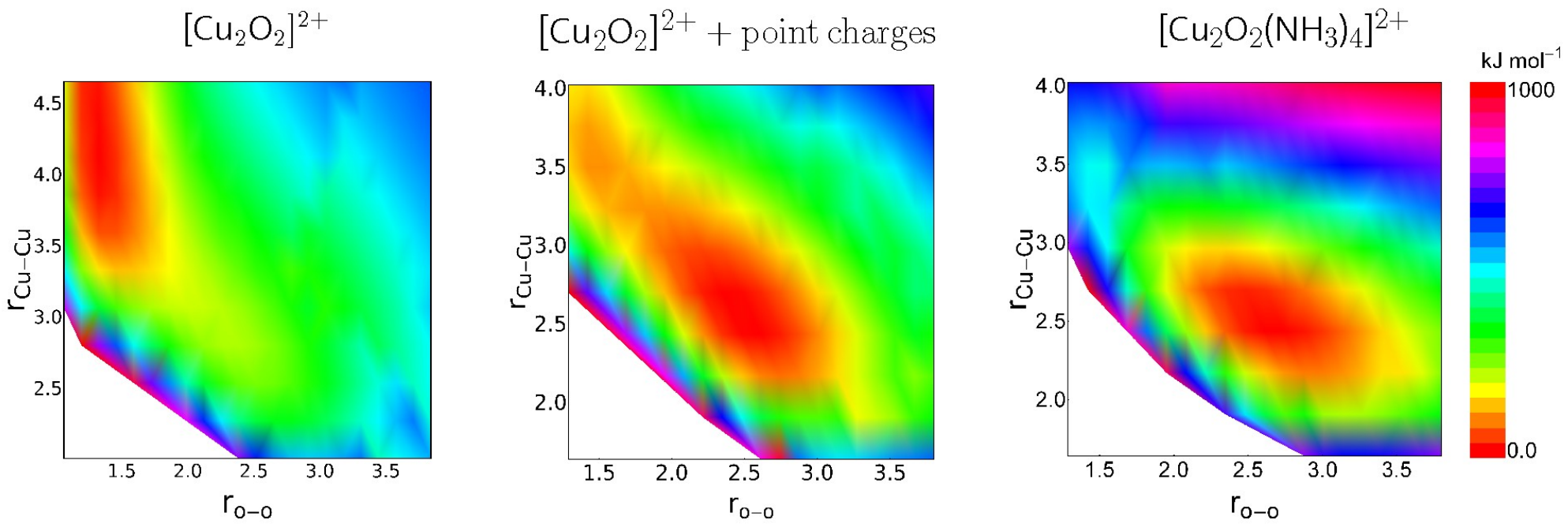
blue: transition state, red: distorted transition state

# Thesis 3: Transferable results ?

**How to compare many individual results** obtained for
(a) **different model structures**
(even result for a small model that does not fit to exp. may yield insight into chemistry of active site)
(b) **different/modulated active sites performing similar chemistry**

*Study correlation diagrams? — like in the "old days" but quantitative*

triplet



# Conclusions

Can we expect major breakthrough yielding a universal quantum chemical method with reliable error estimates?

If not: **How to cope with the method insufficiencies?**
**Standard protocols to uncover these insufficiencies?**

**How to relate the data obtained?**

**Use/invent concepts** that relate calculated data like

*correlation diagrams*
(cuts through potential energy hypersurface, property surfaces, ...)

*concept of transition state flexibility*
(for de novo design/re-engineering of active sites, design of biomimetic catalysts, ...)