Technische Universität Braunschweig

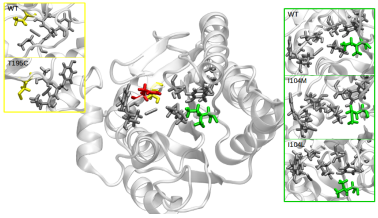
Institut für Physikalische und Theoretische Chemie

Sensitivity analysis for assessing and controlling errors in theoretical spectroscopy and computational biochemistry

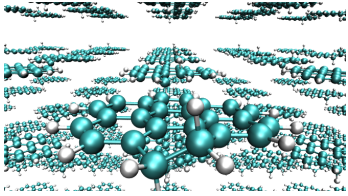
Christoph Jacob, 21. June 2022

Complex Chemical Systems

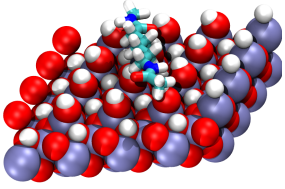
Enzymes and Biomolecules



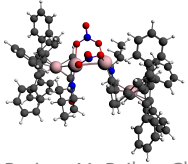
Molecular Materials



Surfaces and Interfaces



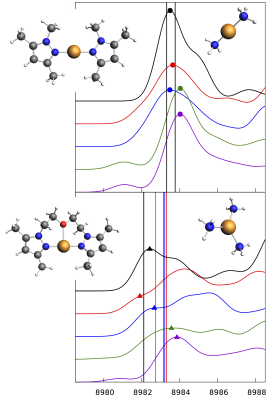
Transition Metal Complexes



Spin-DFT Review: M. Reiher, Ch. R. Jacob
Int. J. Quantum. Chem., **112** 3661 (2012).

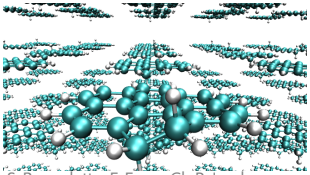
Theoretical Spectroscopy

X-ray Spectroscopy



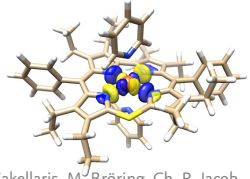
J. Rudolph, Ch. R. Jacob,
Inorg. Chem. **57**, 10591–10607 (2018).

Plasmons



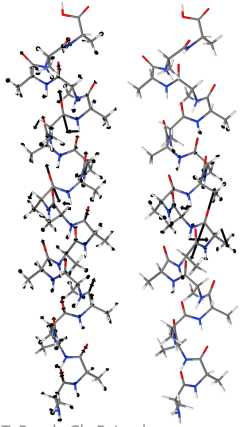
S. Bernadotte, F. Evers, Ch.R. Jacob,
J. Phys. Chem. C **117**, 1863 (2013).

EPR and Mössbauer



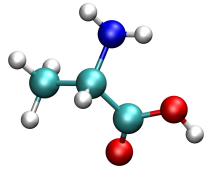
C. Sakellaris, M. Bröring, Ch. R. Jacob,
to be submitted.

Molecular Vibrations



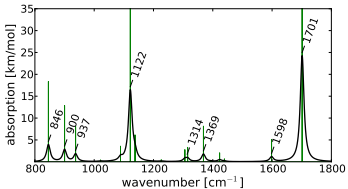
P. T. Panek, Ch. R. Jacob,
J. Chem. Phys. Lett. **16**, 3084 (2016).

Theoretical Spectroscopy



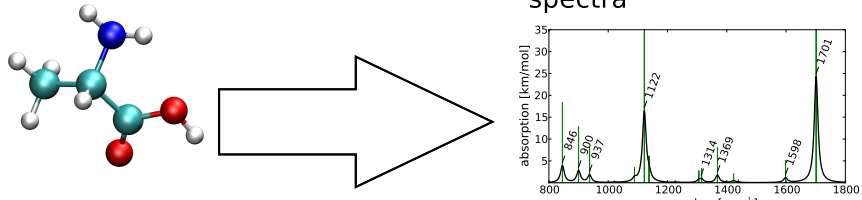
molecular structure

spectra



molecular properties

Theoretical Spectroscopy

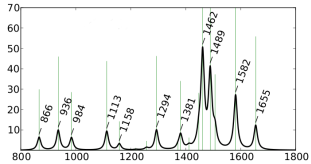


Why can quantum-chemical calculations be useful for spectroscopy?

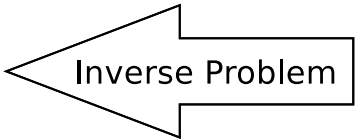
- additional information
  - assignment of peaks to vibrational modes, orbitals, …
- further insights
  - derivation of qualitative rules and chemical concepts

Inverse Theoretical Spectroscopy

Molecular Properties



Spectra

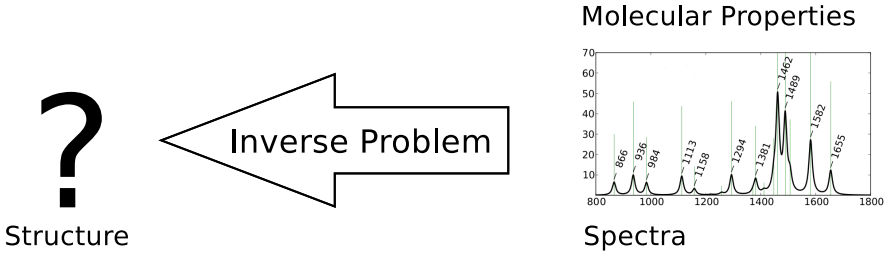


?

Structure

Structural information from spectroscopic data?

Inverse Theoretical Spectroscopy

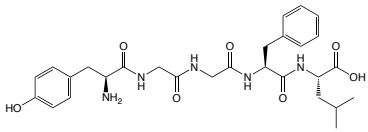


Structural information from spectroscopic data?

- most spectroscopies provide only *indirect* structural information
- quantum-chemical calculation can establish link between structure and spectra
- structural assignment from comparison of experimental spectrum to spectra calculated for (many) possible structures

Example: Structures from Gas-Phase IR Spectroscopy

Gas-phase structure of Leucine-Enkephalin anion (deprotonated)



F. Schinle, Ch. R. Jacob, A. B. Wolk, J.-F. Greisch, M. Vonderach, P. Weis, O. Hampe, M. A. Johnson, M. M. Kappes, *J. Phys. Chem. A* **118**, 8453–8463 (2014).

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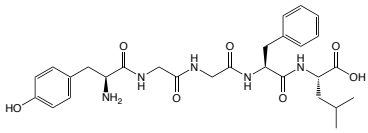
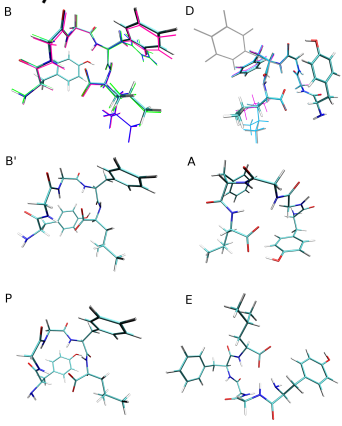


- generation of many possible conformer structures



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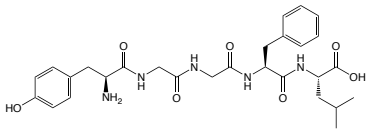
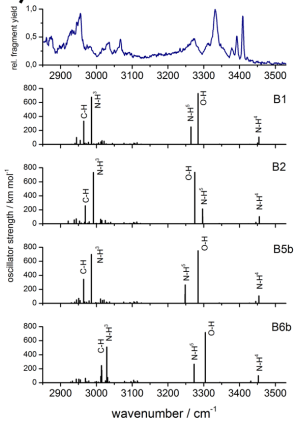


- generation of many possible conformer structures
- calculation of vibrational spectra for candidate structures



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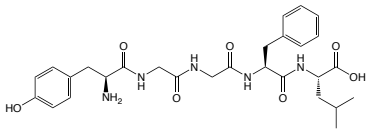

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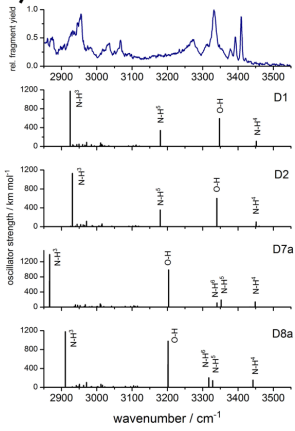

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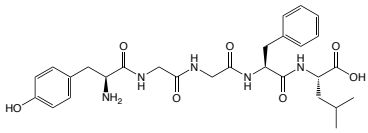
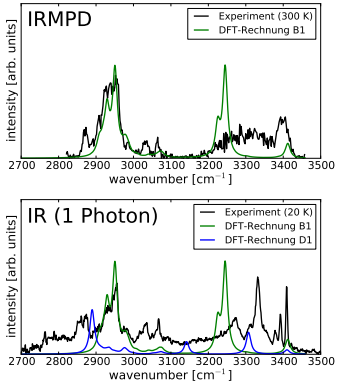


- generation of many possible conformer structures
- calculation of vibrational spectra for candidate structures
- structure assignment based on (subjective?) comparison between calculated and experimental spectra



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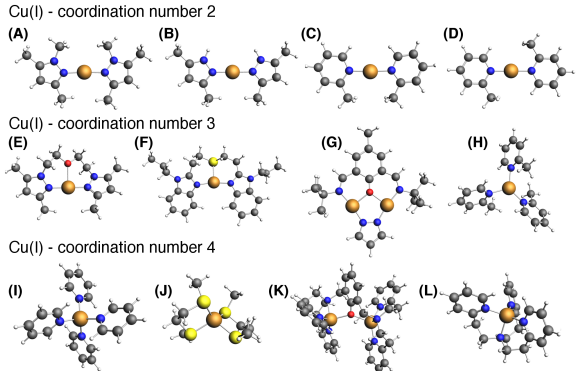
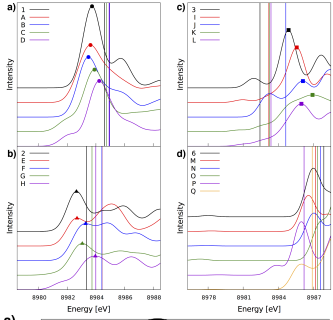
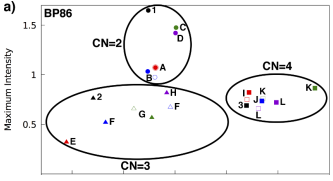
Example: Coordination Geometry from Cu K-edge XAS

- Goal: assignment of coord. number and geometry from XAS

→ calculations of spectra for model Cu(I) complexes





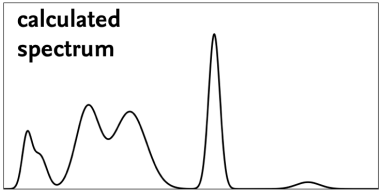


J. Rudolph, Ch. R. Jacob, *Inorg. Chem.* **57**, 10591 (2018).

Theoretical Spectroscopy with Error Bars

Calculated spectra are affected by uncertainties

- in molecular structure
  - structural distortions
  - simplified molecular model
- in chemical environment
  - solvent effects
  - environment model
- in computational methodology
  - quantum-chemical calculations (e.g., xc functional in DFT)
  - approximations of theoretical spectroscopy



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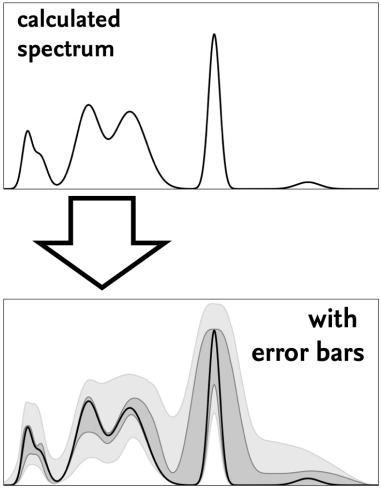

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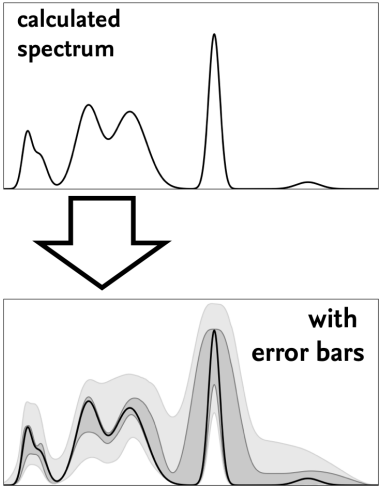

Goal: Systematically quantify uncertainties in calculated spectra

- *Uncertainty Quantification* is a subfield of applied mathematics that provides tools widely used in simulation science

  for a textbook, see, e.g.: R. Smith, "*Uncertainty Quantification*", SIAM Press, 2014.

- applications of such tools in quantum chemistry are just emerging

  see, e.g.: G. N. Simm, J. Proppe, M. Reiher, *CHIMIA* **71**, 202–208 (2017).

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First step: Structural sensitivity of calculated spectra

$$\boldsymbol{R} \xrightarrow{\text{QC model}} \{E_n, f_n\} \xrightarrow[\text{broadening}]{\text{empirical line}} \sigma(E; \boldsymbol{R})$$

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First step: Structural sensitivity of calculated spectra

$$\boldsymbol{R} \xrightarrow{\text{QC model}} \{E_n, f_n\} \xrightarrow[\text{broadening}]{\text{empirical line}} \sigma(E; \boldsymbol{R})$$

- given input structures within an interval $\boldsymbol{R}_0 + \Delta\boldsymbol{R}$ with $|\Delta\boldsymbol{R}| \leq d_{\max}$, what is the range of possible calculated spectra?
- given a probability distribution for the input structures $p(\boldsymbol{R})$, what is the probability distribution of the calculated spectra $p(\sigma)$?

Structural Sensitivity of Calculated Spectra

Local sensitivity analysis

- consider small distortions of reference structure $\boldsymbol{R}_i$
- (local) structural sensitivity

$$\delta\sigma_i(E) = \left.\frac{\partial\sigma(E;\boldsymbol{R})}{\partial R_i}\right|_{\boldsymbol{R}_0}$$

- calculated by numerical diff.

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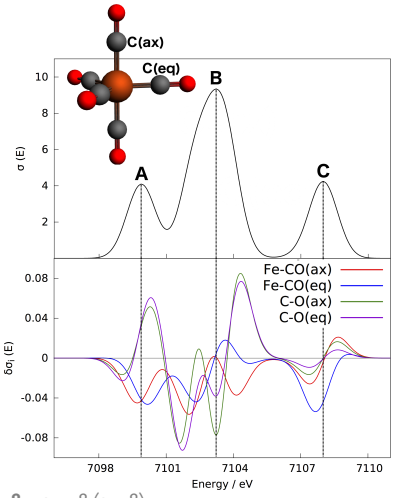
Example: XES spectrum of $Fe(CO)_5$

- considered distortions of selected bond lengths



S. W. Oung, J. Rudolph, Ch. R. Jacob, *Int. J. Quantum Chem.* **118**, e25458 (2018).

Structural Sensitivity of Calculated Spectra

- calculated spectra depend on $3N - 6$ structural parameters
- initially consider linearized model (i.e., first-order Taylor expansion)

$$\sigma(E; \boldsymbol{R}_0 + \Delta\boldsymbol{R}) \approx \sigma(E; \boldsymbol{R}_0) + \sum_{l\alpha} \delta\sigma_{l\alpha}(E)\Delta R_{l\alpha}$$

Structural Sensitivity of Calculated Spectra

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$$\sigma(E; \boldsymbol{R}_\mathrm{o} + \Delta\boldsymbol{R}) \approx \sigma(E; \boldsymbol{R}_\mathrm{o}) + \sum_{l\alpha} \delta\sigma_{l\alpha}(E)\Delta R_{l\alpha}$$

Principal component analysis (PCA) of structural sensitivities

- collect all local structural sensitivities $\delta\sigma_{l\alpha}(E_j)$ in a matrix $\boldsymbol{X}$
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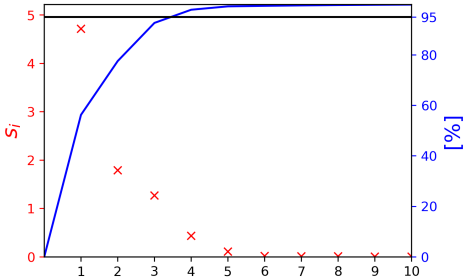
  - $3N$ rows of $\boldsymbol{X}$ each contain a (discretized) difference spectrum
- perform singular value decomposition $\boldsymbol{X} = \boldsymbol{U} \cdot \boldsymbol{S} \cdot \boldsymbol{V}^T$
  - columns of $\boldsymbol{U}$ define principal component distortions q_k
  - columns of $\boldsymbol{V}$ give structural sensitivities $\delta\sigma_k^{\mathrm{PC}}(E)$ w.r.t. q_k
  - diagonal matrix $\boldsymbol{S}$ contains rapidly decreasing singular values $s_k \geq 0$

T. Bergmann, M. O. Welzel, Ch. R. Jacob, *Chem. Sci.* **7**, 1862-1877 (2020)

PCA of Structural Sensitivity

- singular values s_k decrease rapidly



$\Rightarrow$ only few principal components required

$$\sigma(E; \boldsymbol{R}_\mathrm{o} + \Delta\boldsymbol{R}) \approx \sigma(E; \boldsymbol{R}_\mathrm{o}) + \sum_{k=1}^{k_\mathrm{max}} \delta\sigma_k^\mathrm{PC}(E)\Delta q_k$$

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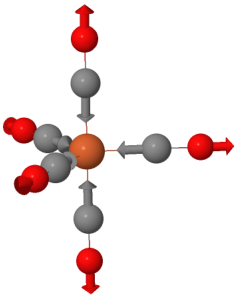
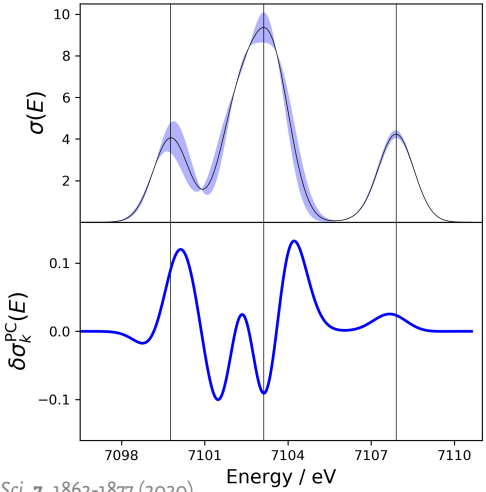
Principal Component Structural Sensitivities

1st principal component



$s_1 = 4.72$



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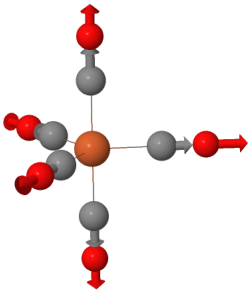
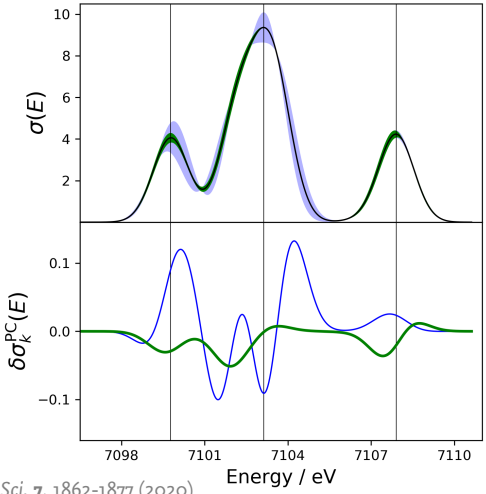
Principal Component Structural Sensitivities

2nd principal component



$s_2 = 1.79$



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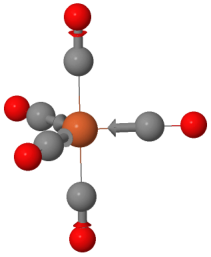
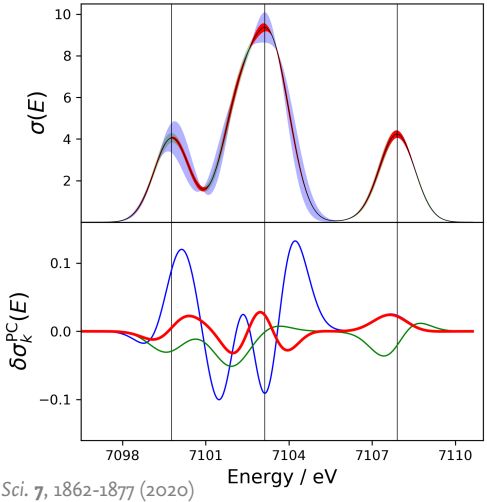
Principal Component Structural Sensitivities

3rd principal component



$s_3 = 1.27$



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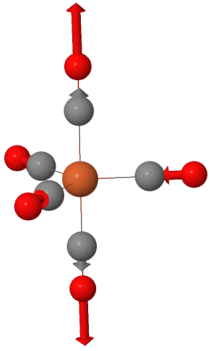
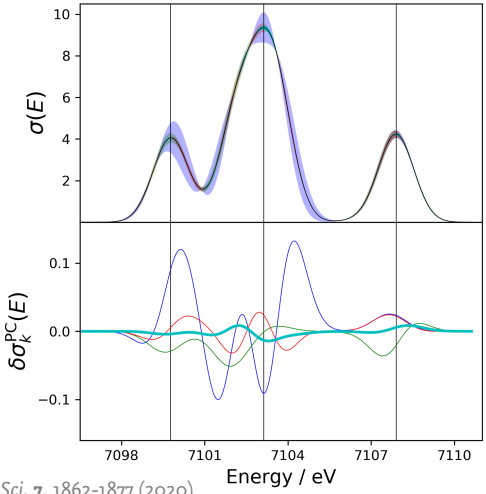
Principal Component Structural Sensitivities

4th principal component



$s_4 = 0.44$



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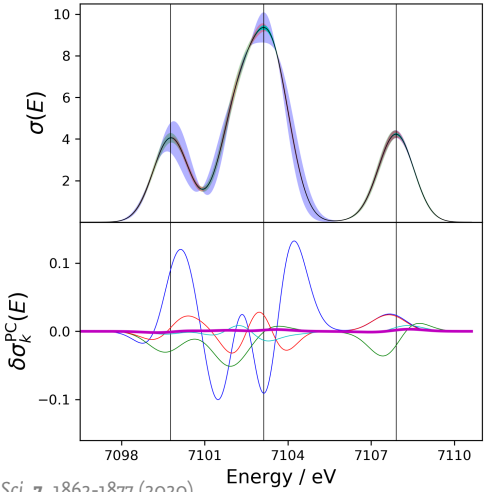
Principal Component Structural Sensitivities

all remaining principal components

$$\sum_{k>4} s_k = 0.18$$

→ here: only 4 principal component distortions (out of 33) required

$$\Delta\sigma(E;\Delta\boldsymbol{R}) \approx \Delta\sigma(E;\Delta q_1,\ldots,\Delta q_4)$$



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Surrogate Models of Structural Sensitivity

Linearized model

$$\sigma(E;\boldsymbol{R}) \approx \sigma(E;\boldsymbol{R}_0) + \sum_{k=1}^{k_{\max}} \delta\sigma_k^{\mathrm{PC}}(E)\Delta q_k$$

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More general surrogate models (*Sobol expansion*)

$$\sigma(E;\boldsymbol{R}) \approx \sigma(E;\boldsymbol{R}_0) + \sum_{k=1}^{k_{\max}} \delta\sigma_k^{(1)}(E;\Delta q_k) + \sum_{k<l}^{k_{\max}} \delta\sigma_{k,l}^{(2)}(E;\Delta q_k,\Delta q_l) + \cdots$$

- one-mode contributions $\delta\sigma_k^{(1)}(E;\Delta q_k)$
  - linearized model corresponds to first-order Taylor expansion
  - can be refined by using higher-order Taylor expansion
- two-mode contributions $\delta\sigma_{k,l}^{(2)}(E;\Delta q_k,\Delta q_l)$
  - could be approximated by second-order Taylor expansion

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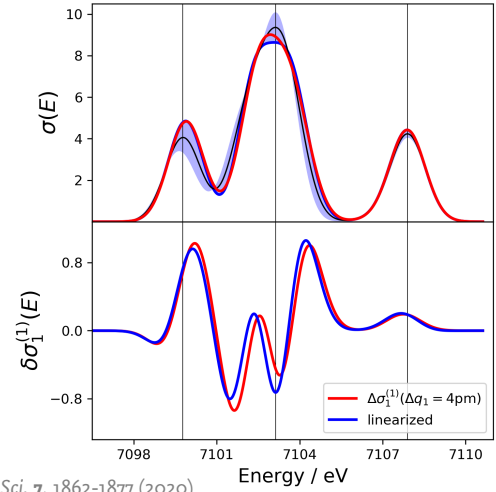
Surrogate Models of Structural Sensitivity

- assess linearized model for 1st principal comp.
- $\Delta q_1 = 4$ pm



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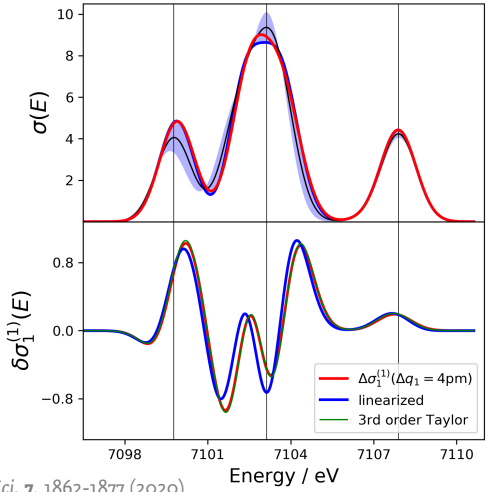

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Surrogate Models of Structural Sensitivity

- assess linearized model for 1st principal comp.
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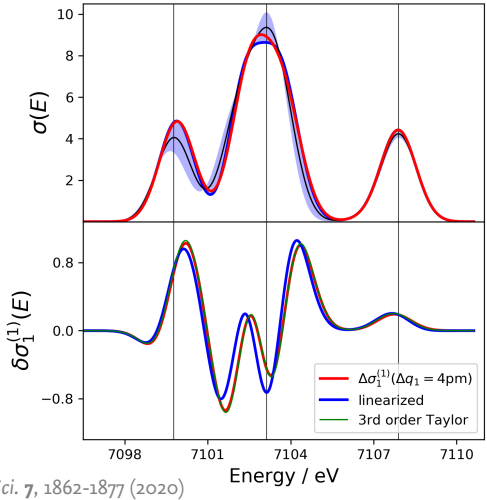
Surrogate Model for $Fe(CO)_5$

- 4 principal components
- 3rd order Taylor expansion for one-mode contributions
- neglect two-mode (and higher-order) contributions



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Theoretical Spectroscopy with Error Bars

- Given structural distortions with $|\Delta \boldsymbol{q}| \leq d_{\text{max}}$, what is the range of possible spectra?

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- for one-mode expansion:

$$\max_{|\Delta \boldsymbol{q}|<d_{\max}} \sigma(E;\boldsymbol{R}) \leq \sigma(E;\boldsymbol{R}_0) + \sum_{k=1}^{k_{\max}} \max_{|\Delta q_k|<d_{\max}} \delta\sigma_k^{(1)}(E;\Delta q_k)$$

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  - for linearized model: evaluate $\delta\sigma_k^{(1)}(E;\Delta q_k)$ for $q_k = \pm d_{\max}$
  - for higher-order Taylor expansion:
    sample interval $[-d_{\max},\ldots,+d_{\max}]$ to find min and max

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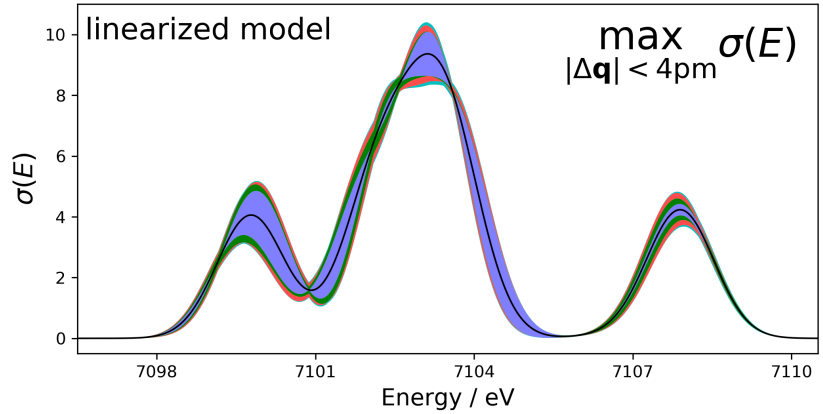
Theoretical Spectroscopy with Error Bars

Example: XES spectrum of $Fe(CO)_5$ with error bars



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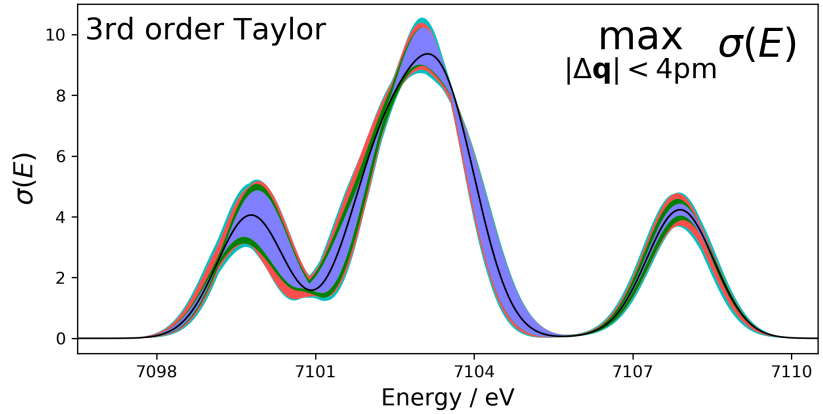

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Theoretical Spectroscopy with Error Bars

- Given a probability distribution for the structural distortions $p(\Delta \boldsymbol{q})$, what is the probability distribution of the calculated spectra $p(\sigma)$?
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- for one-mode expansion:
  - expectation value (mean):

$$\left\langle \sigma(E;\boldsymbol{R}) \right\rangle = \sigma(E;\boldsymbol{R}_0) + \sum_{k=1}^{k_{\max}} \left\langle \delta\sigma_k^{(1)}(E;\Delta q_k) \right\rangle$$

$$= \sigma(E;\boldsymbol{R}_0) + \sum_{k=1}^{k_{\max}} \int \delta\sigma_k^{(1)}(E;\Delta q_k)\, p_k(\Delta q_k)\, \mathrm{d}q_k$$

  - integrals can be calculated numerically

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$$\begin{aligned}\mathrm{Var}\Big(\sigma(E;\boldsymbol{R})\Big) &= \sum_{k=1}^{k_{\max}} \mathrm{Var}\Big(\delta\sigma_k^{(1)}(E;\Delta q_k)\Big) \\ &= \sum_{k=1}^{k_{\max}} \left(\int \left(\delta\sigma_k^{(1)}(\Delta q_k)\right)^2 p_k(\Delta q_k)\,\mathrm{d}q_k - \left\langle \delta\sigma_k^{(1)}(\Delta q_k) \right\rangle^2 \right)\end{aligned}$$

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Theoretical Spectroscopy with Error Bars

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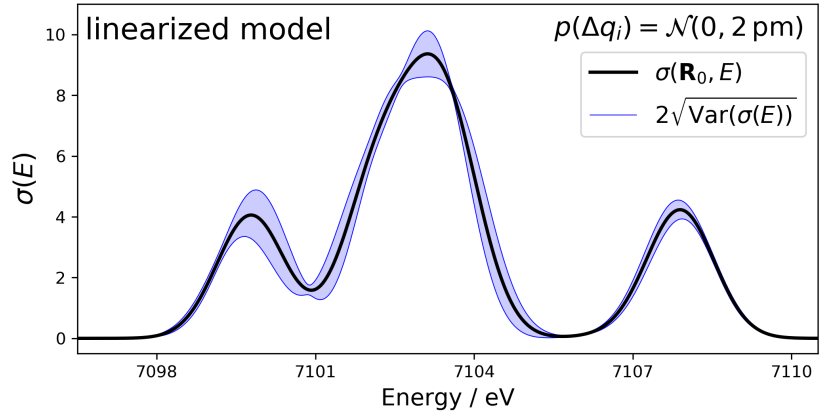

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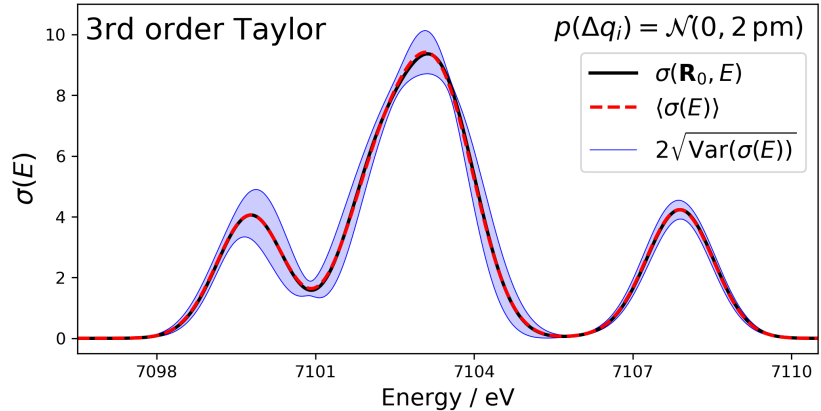

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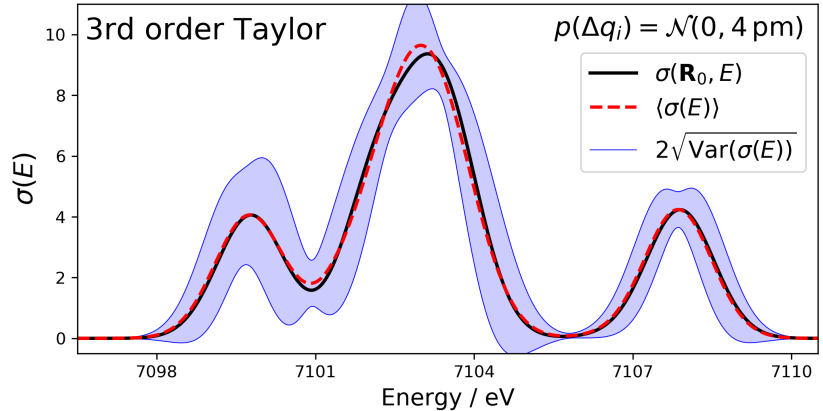

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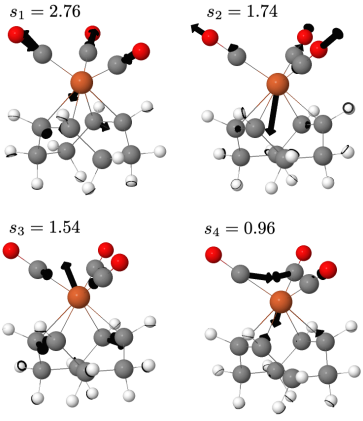
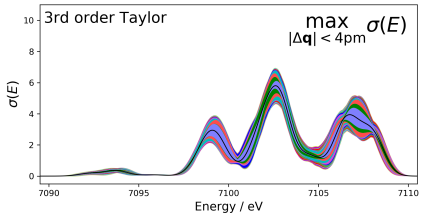
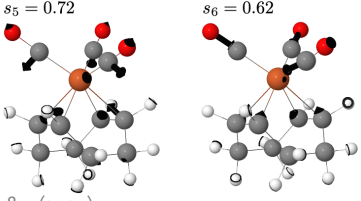
Theoretical Spectroscopy with Error Bars

Example: XES spectrum of $Fe(CO)_3(cod)$ with error bars







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Theoretical Spectroscopy with Error Bars

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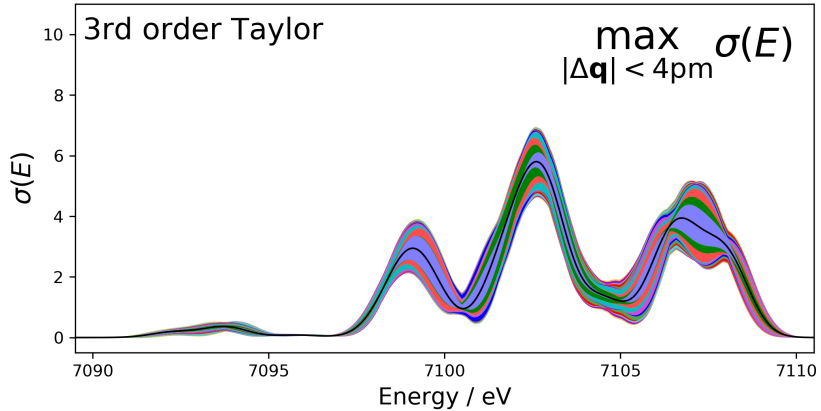

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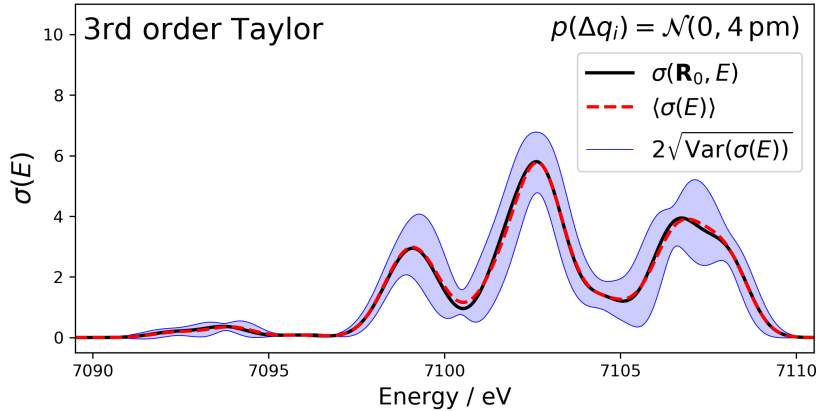

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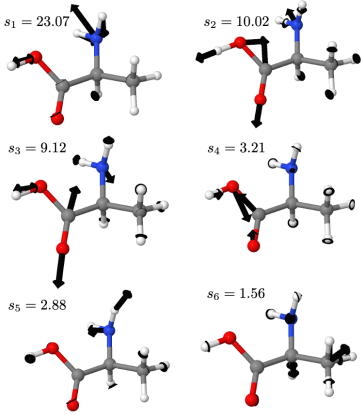
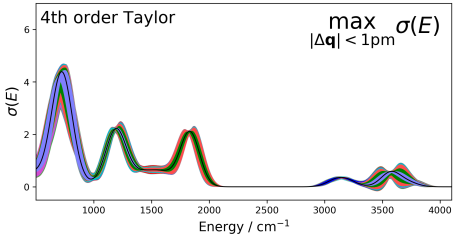
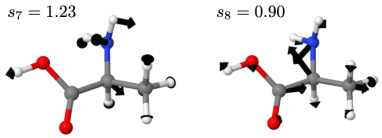
Theoretical Spectroscopy with Error Bars

Example: IR spectrum of Alanine with error bars







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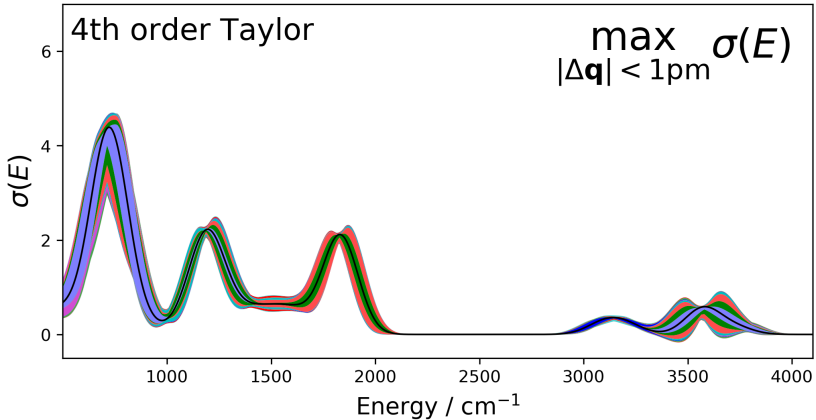
Theoretical Spectroscopy with Error Bars

Example: IR spectrum of Alanine with error bars



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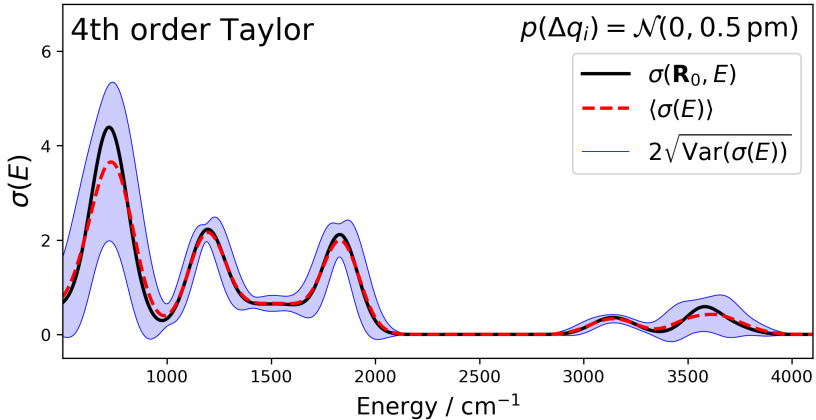

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Summary: Structural Sensitivity in Theoretical Spectroscopy

Quantifying uncertainties in spectra due to structural sensitivity

- identification of influential and non-influential structural distortions
  - consider linearized model of structural sensitivity
  - principal component analysis provides most influential distortions
- reduced-dimensional surrogate model of structural sensitivity
  - Sobol expansion provides framework for systematic refinement
  - here: low-order Taylor expansion for one-mode contributions
- statistical analysis of uncertainty propagation
  - uncertainties in input molecular structure need to be provided
  - uncertainties in calculated spectra can be calculated efficiently

$\Rightarrow$ **rigorous (structural) "error bars" for calculated spectra**

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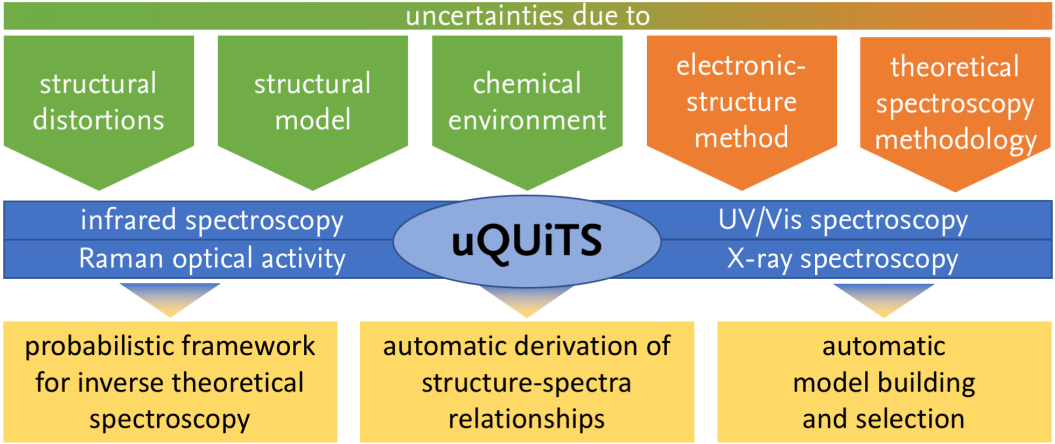
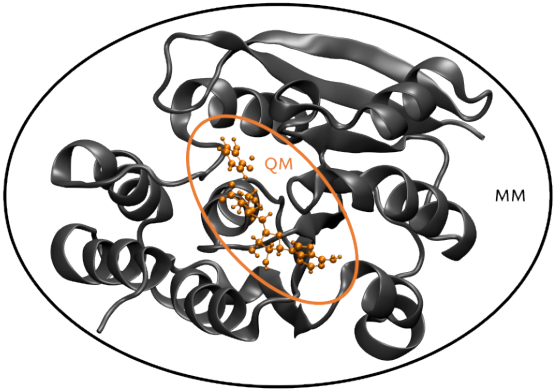
Outlook: Uncertainty Quantification in Theoretical Spectroscopy



QM/MM: Basics and Challenges



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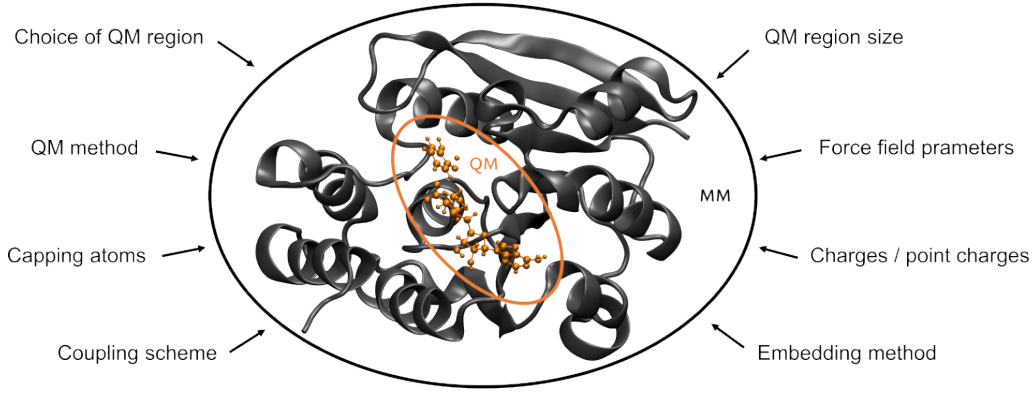

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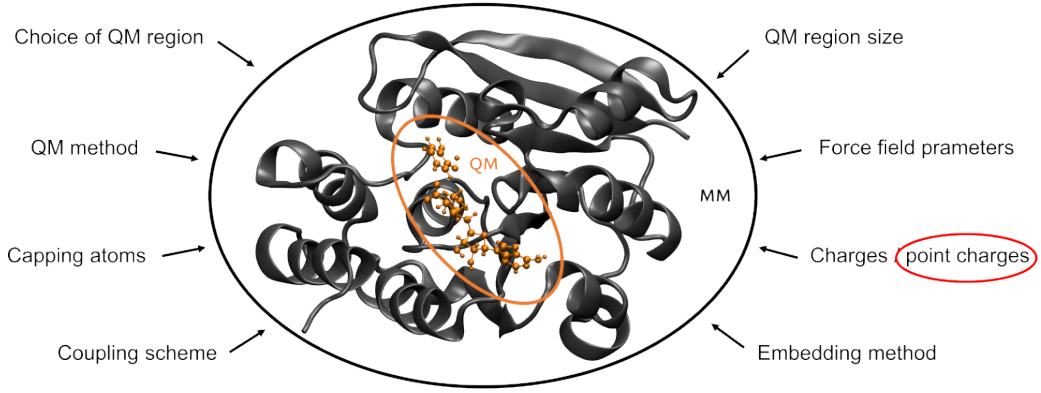

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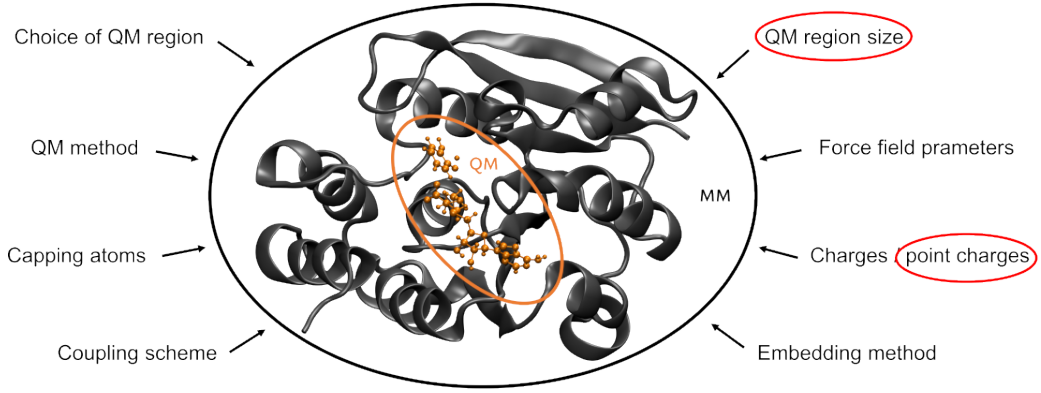
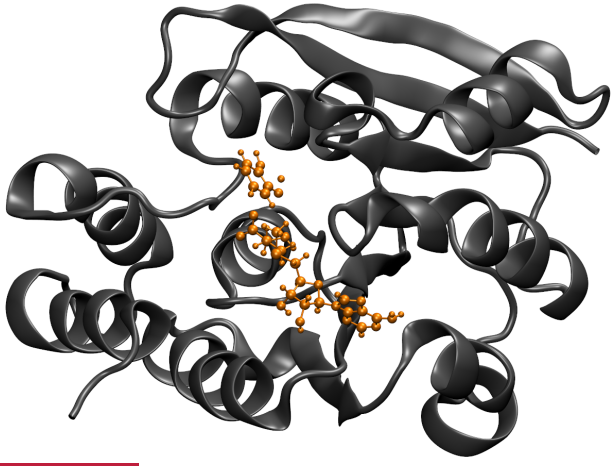


Which residues should be included in the QM region?



- Distance-based:
  very simple, often used
- More advanced schemes:
  CDA, CSA, FSA, etc.
- **Our Idea**:
  minimize sensitivity w.r.t.
  variation of the QM charges

Model system:
catechol *O*-methyltransferase

H. J. Kulik, J. Zhang, J. P. Klinman, T. Z. Martínez, *J. Phys. Chem. B* **120**, 11381–11394 (2016).
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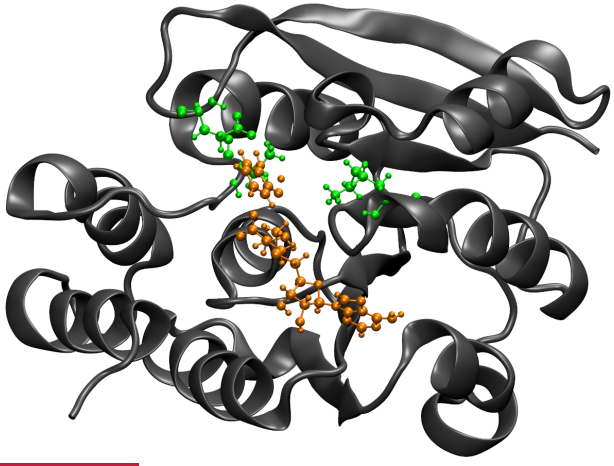

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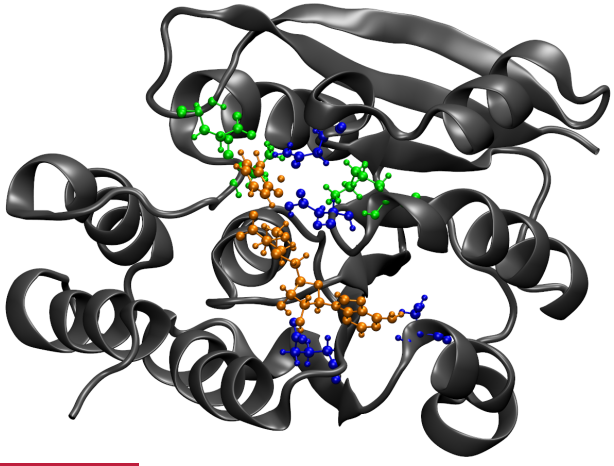

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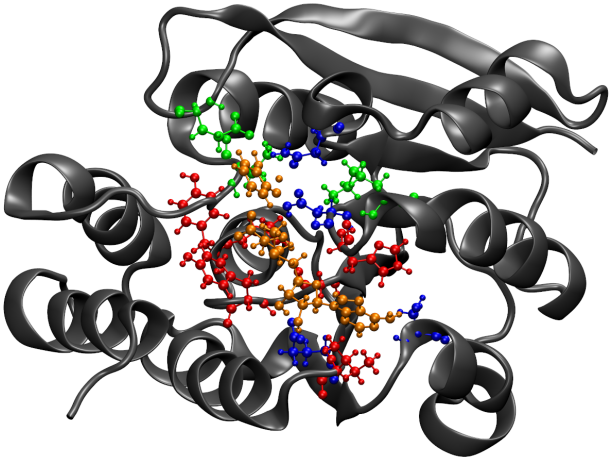

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  very simple, often used
- More advanced schemes:
  CDA, CSA, FSA, etc.
- **Our Idea**:
  minimize sensitivity w.r.t.
  variation of the QM charges

Model system:
catechol *O*-methyltransferase

H. J. Kulik, J. Zhang, J. P. Klinman, T. Z. Martínez, *J. Phys. Chem. B* **120**, 11381–11394 (2016).
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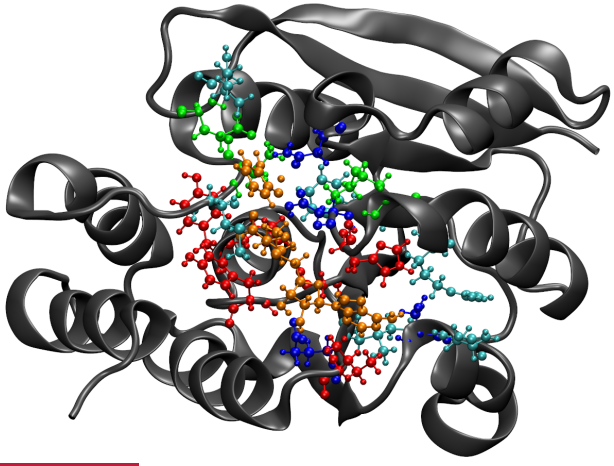

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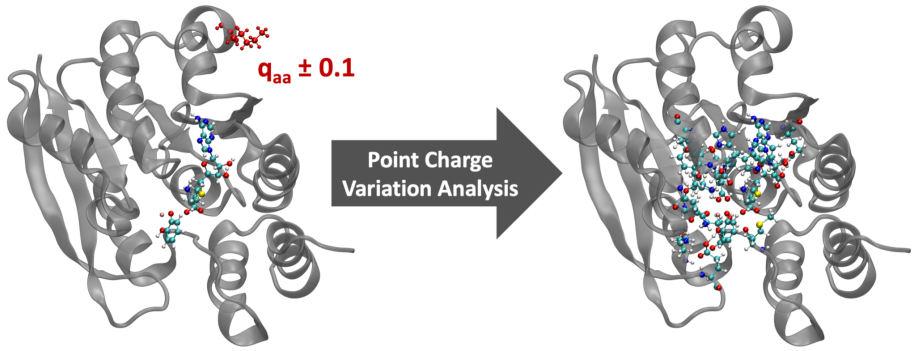
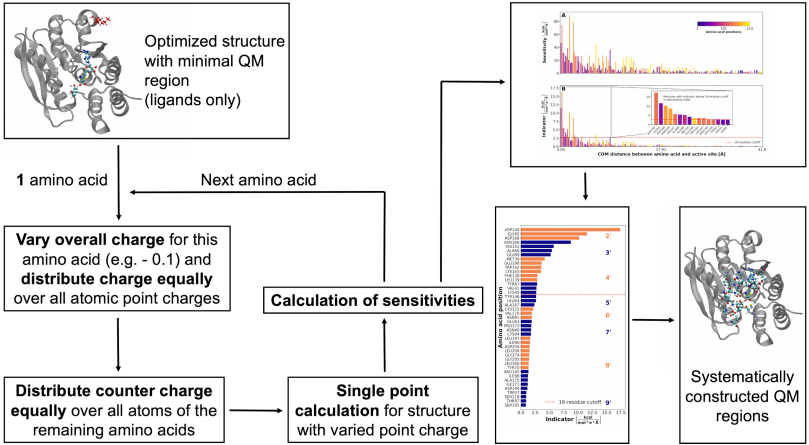
Point Charge Variation Analysis for QM/MM Calculations

⇒ **Idea: Vary point charges of MM atoms and analyze the impact on QM properties**



F. Brandt, Ch. R. Jacob, *J. Chem. Theory Comput.* **18**, 2584–2596 (2022).

QM-Region Selection with PCVA



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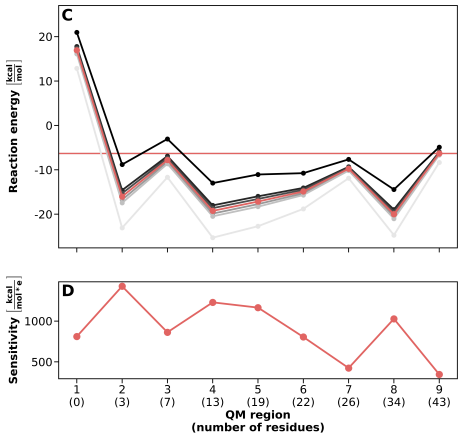
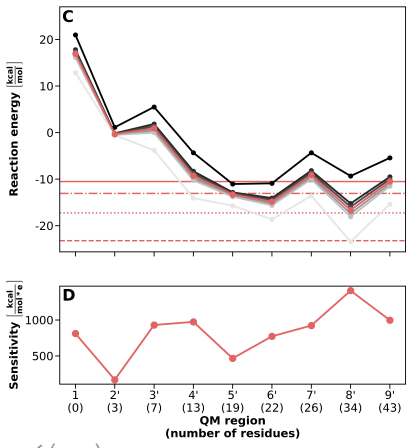
Distance-Based vs. PCVA-Based QM-Region Construction

Distance-Based



PCVA-Based



F. Brandt, Ch. R. Jacob, *J. Chem. Theory Comput.* **18**, 2584–2596 (2022).

Summary: Sensitivity Analysis for Assessing and Controlling Errors

- Many Sources of Uncertainty in Quantum Chemistry
  - sensitivity analysis can be used to assess and control errors
  - high-dimensional parameter spaces of many sources of uncertainty
- Structural Sensitivity in Theoretical Spectroscopy
  - construction of low-dimensional surrogate models
  - statistical analysis of error propagation to calculated spectra

  T. Bergmann, M. O. Welzel, Ch. R. Jacob, *Chem. Sci.* **7**, 1862-1877 (2020).
- Point-Charge Sensitivity in Computational Biochemistry
  - analysis of point-charge sensitivity to judge quality of QM/MM models
  - construction of QM region to minimize uncertainties to reaction energy

  F. Brandt, Ch. R. Jacob, *J. Chem. Theory Comput.* **18**, 2584–2596 (2022).

$\Rightarrow$ **Growing Toolbox for Uncertainty Quantification in Quantum Chemistry**

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