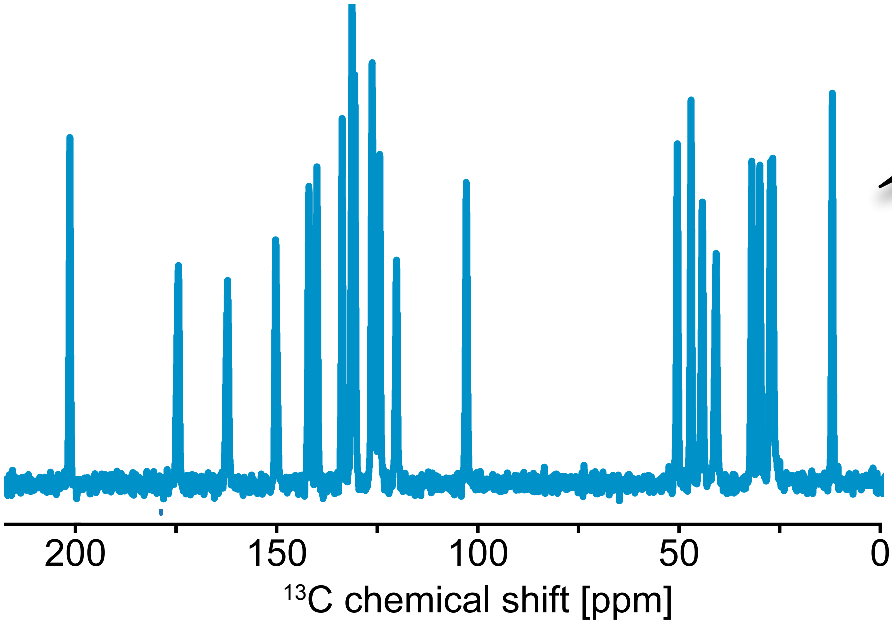
Advanced NMR & Imaging

Week 14: Structure Determination from Chemical Shifts

Objectives

- Understand how chemical shifts are related to structure.
- Understand how to calculate chemical shifts.
- Understand how chemical shifts can be used for strucutre determination.

A spectrum of chemical shifts



This is quite easy to measure.

If we could calculate chemical shifts,
we could deduce the coordinates of the atoms....

NMR Powder Crystallography

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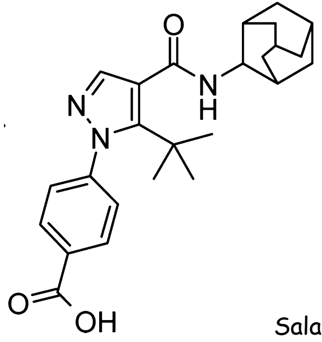
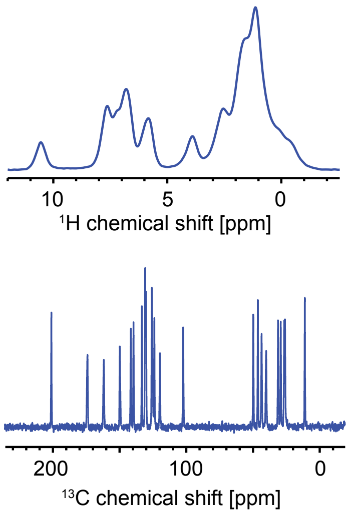
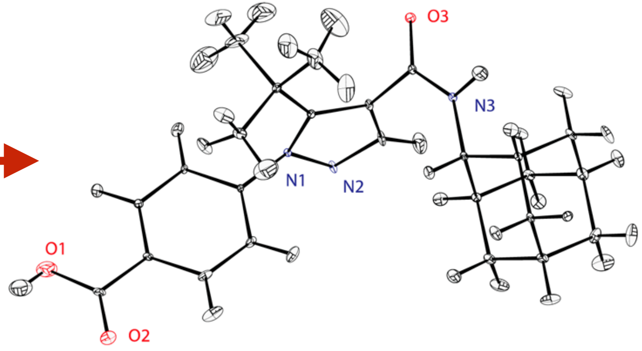


DNP Enhanced NMR



Chemical Shift Driven Structure Determination



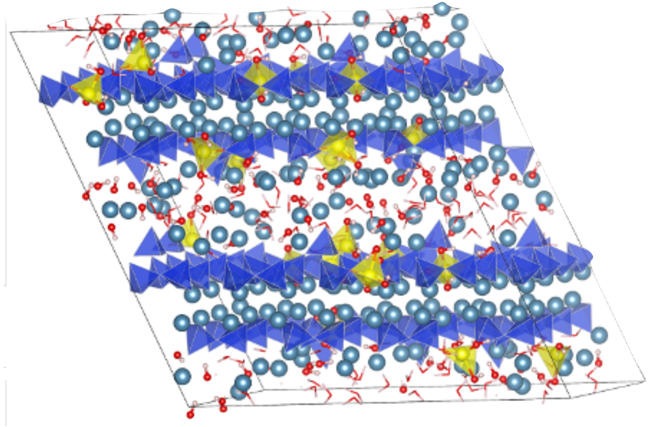
De novo full crystal structure of AZD8329 from a powder sample.
RMSD of 0.17 Å (ADP of 0.0095 Å^2); 100% confidence

Salager et al., J. Am. Chem. Soc. **132**, 2564 (2010),
Baias et al., Phys. Chem. Chem. Phys. **15**, 8069 (2013)
Baias et al., J. Am. Chem. Soc. **135**, 17501 (2013)
Hofstetter et al, J. Am. Chem. Soc. **139**, 2573 (2017)

Engel et al., Phys. Chem. Chem. Phys. **21**, 23385 (2019)
Hofstetter, et al., J. Am. Chem. Soc. **141**, 16624 (2019)
Cordova, et al., Nature Communications **12**, 2964 (2021)

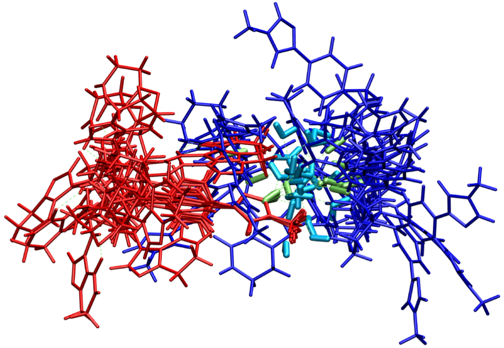
NMR UnCrystallography

Cementitious calcium silicate hydrates



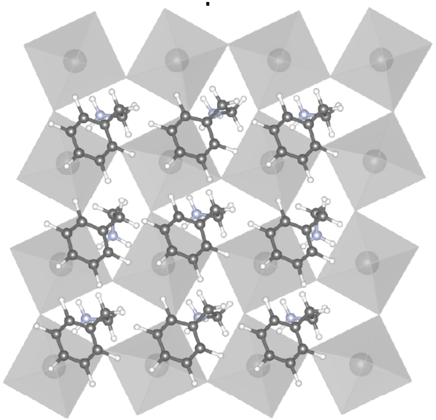
J. Phys. Chem. C **121**, 32, 17188 (2017)
J. Am. Chem. Soc. **142**, 25, 11060 (2020)
J. Am. Chem. Soc. **144**, 50, 22915 (2022)

Amorphous drugs



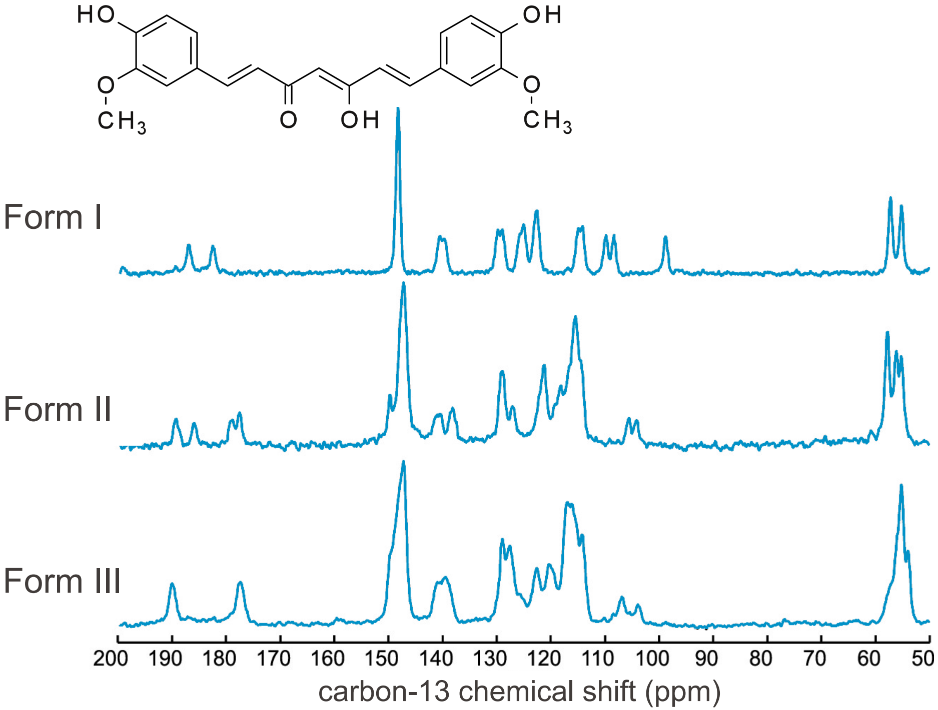
Nature Commun. **12**, 2964 (2021).
Nature Commun. **14**, 5138 (2023).

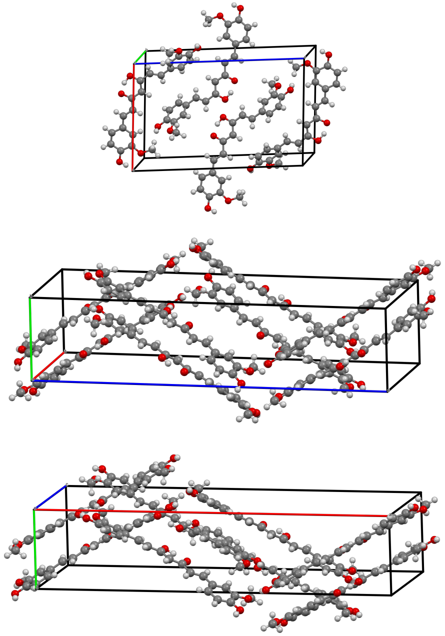
2D layered perovskites



J. Am. Chem. Soc. 143, 3, 1529 (2021)
Nature, 592, 381 (2021)
Science **370**, 74 (2020).

We Need to Talk About Chemical Shifts





chemical shifts contain all the information we need to determine complete 3D crystal structures

- spectra of curcumin from Dai, Terskikh, Brinkmann, Wu, Crisi. Growth Des. **20**, 7484 (2020)

We Need to Talk About Chemical Shifts

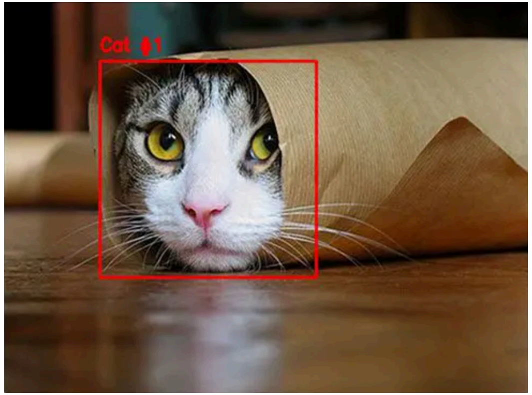
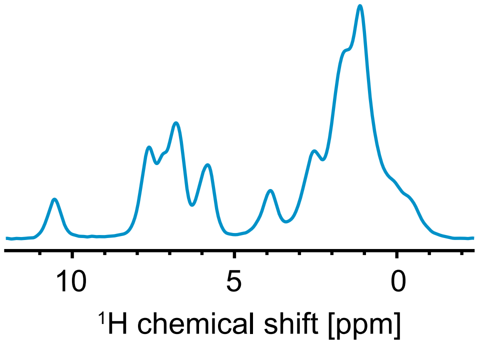


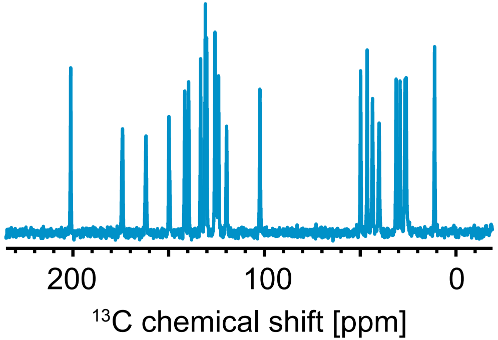
image recognition

google, apple

“A Cat”

We Need to Talk About Chemical Shifts





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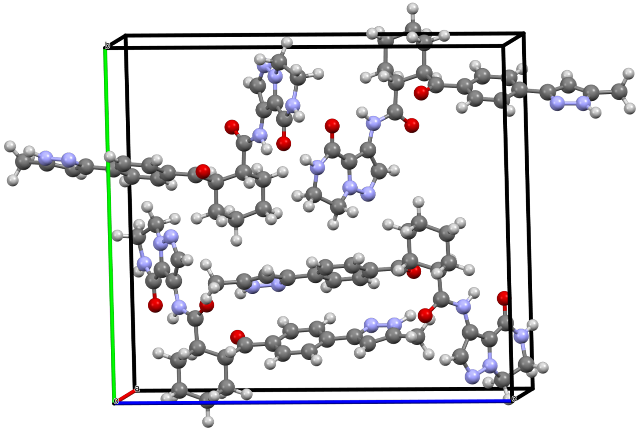
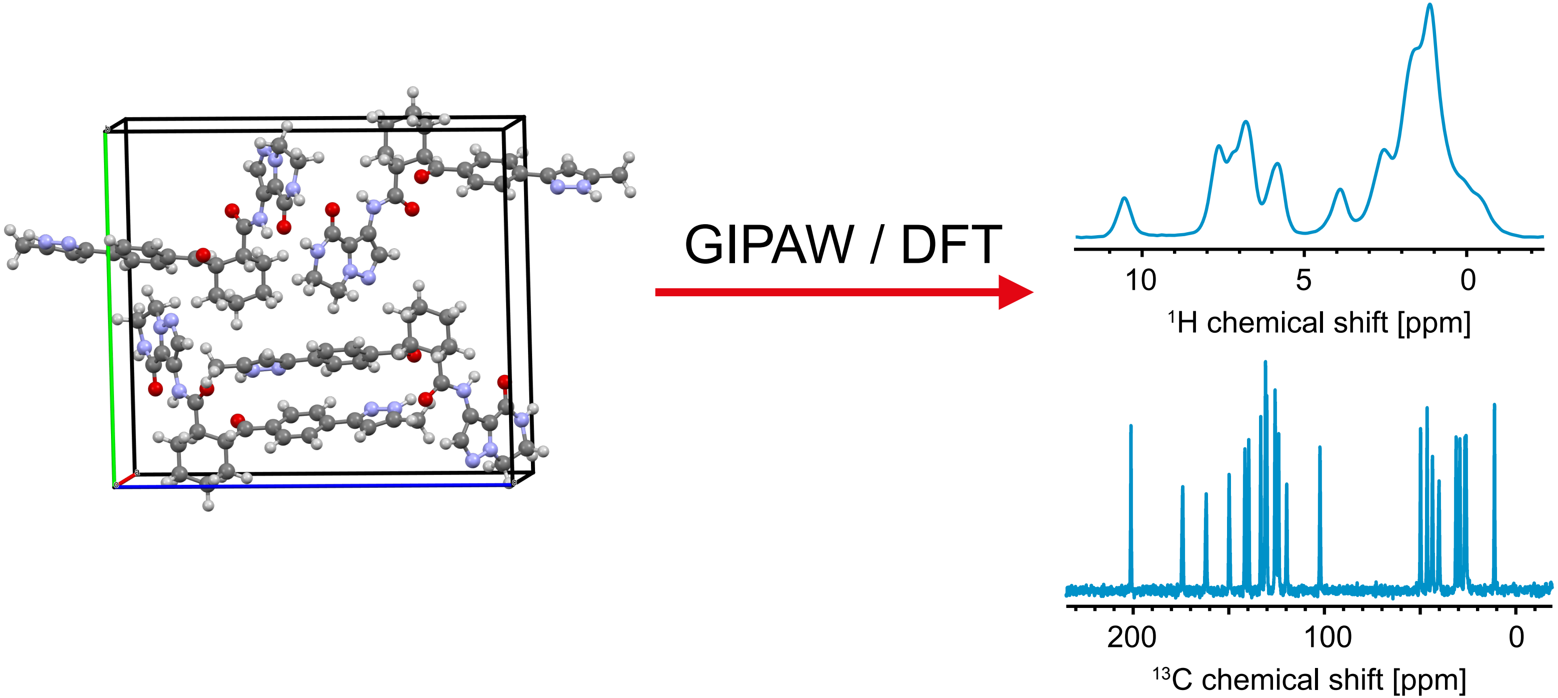


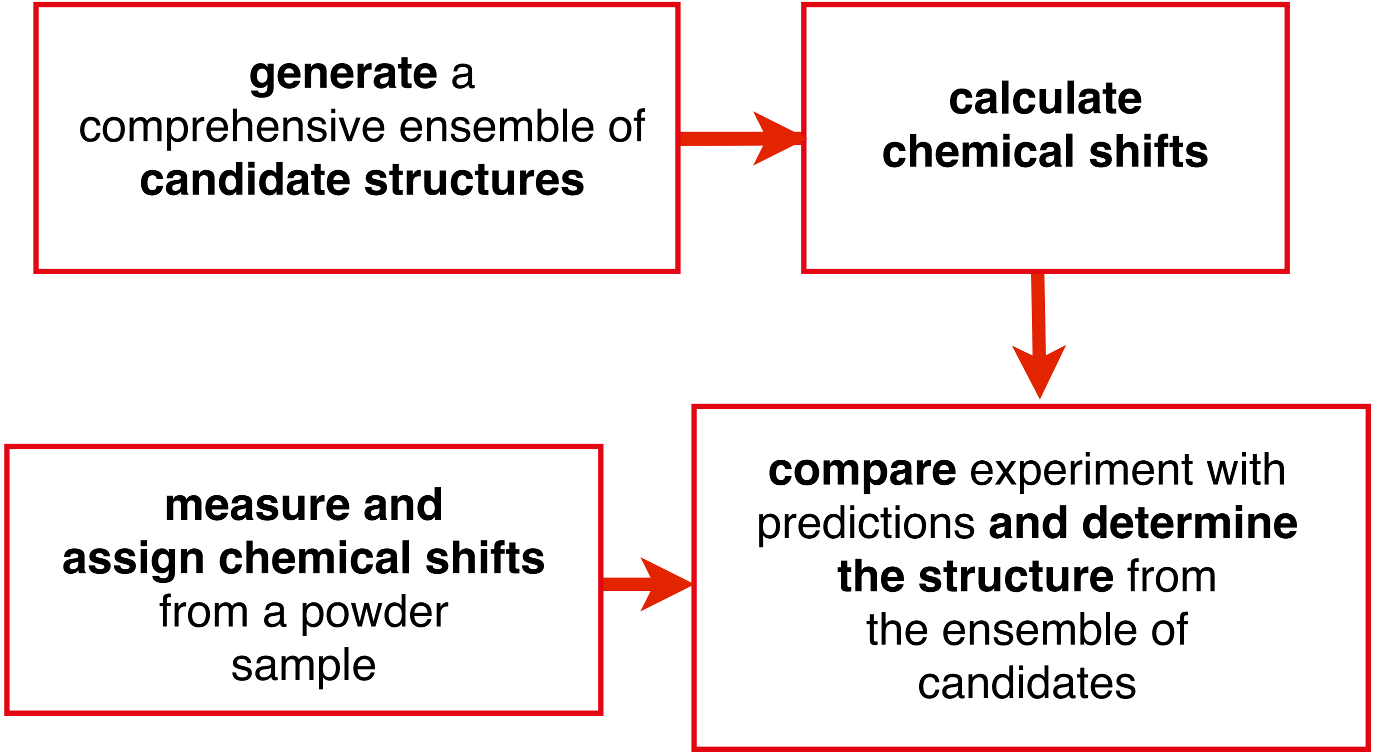
Why can’t we determine structures directly from chemical shifts?

Predicting Shifts from Structures


GIPAW / DFT

We can predict shifts directly from structures…

de novo Powder NMR Crystallography from Chemical Shifts



generate a comprehensive ensemble of **candidate structures**

calculate chemical shifts

measure and assign chemical shifts from a powder sample

compare experiment with predictions **and determine the structure** from the ensemble of candidates

Salager, Day, Stein, Pickard, Elena, Emsley, J. Am. Chem. Soc. 132, 2564 (2010),
Baias, Widdifield, Dumez, Thompson, Cooper, Salager, Bassil, Stein, Lesage, Day, Emsley, Phys. Chem. Chem. Phys. 15, 8069 (2013)
see also early study by Harper & Grant, Crys. Growth & Des. **6**, 2315 (2006)

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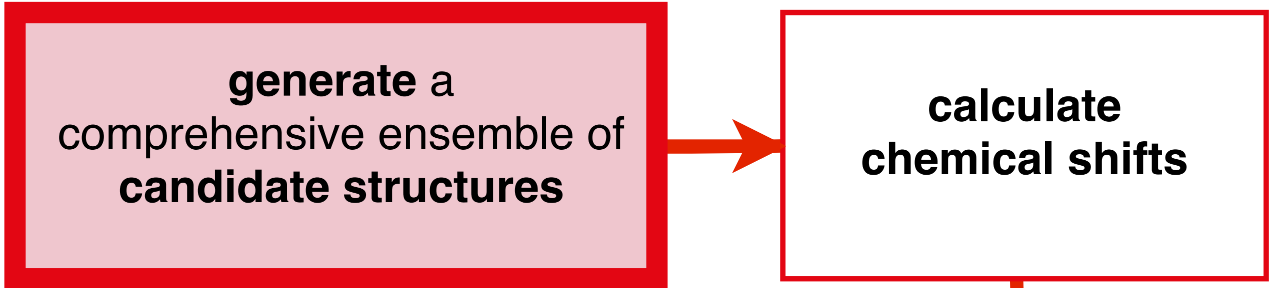

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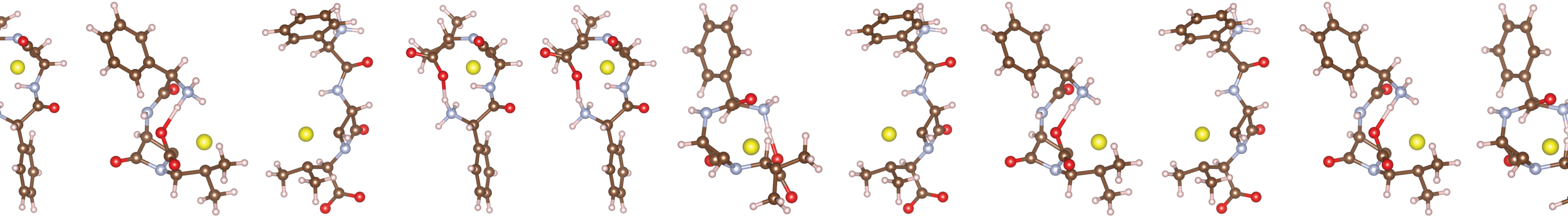

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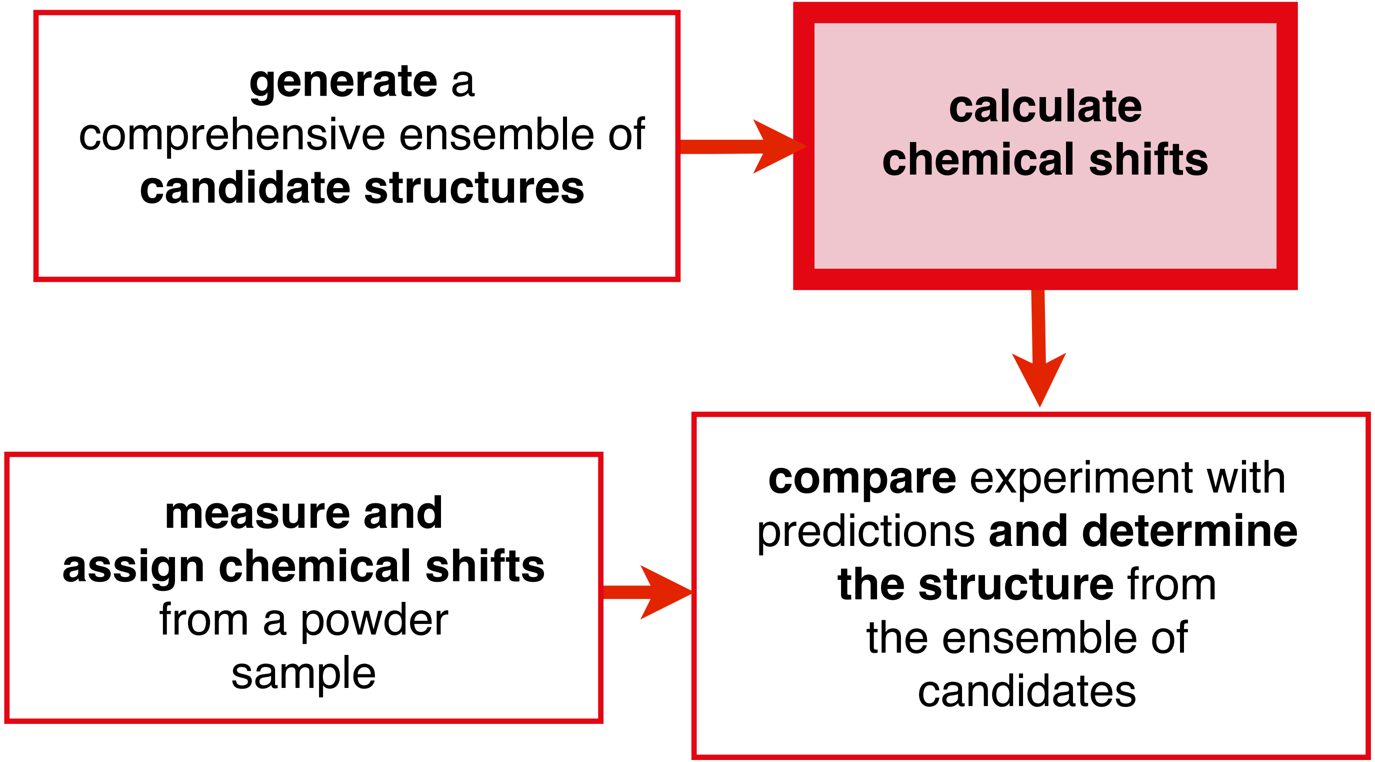
de novo Powder NMR Crystallography from Chemical Shifts



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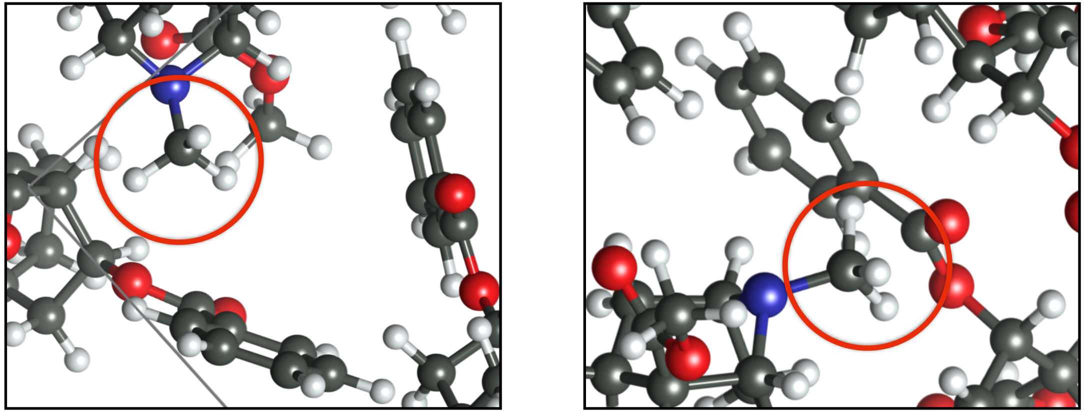
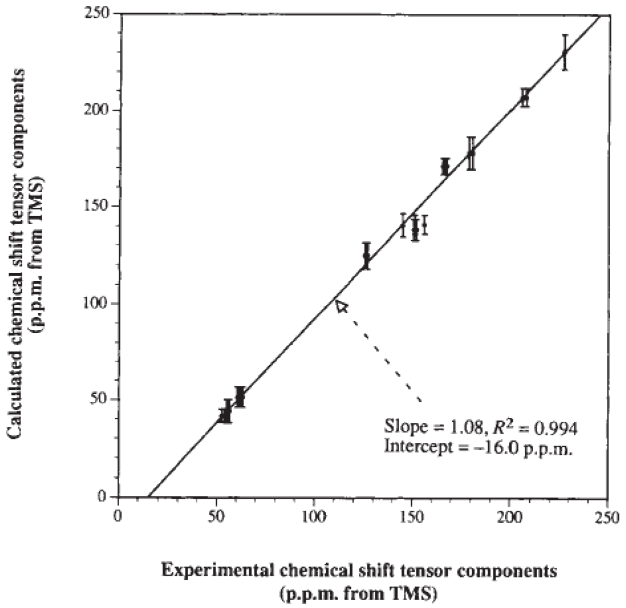
see also early study by Harper & Grant, Crys. Growth & Des. **6**, 2315 (2006)

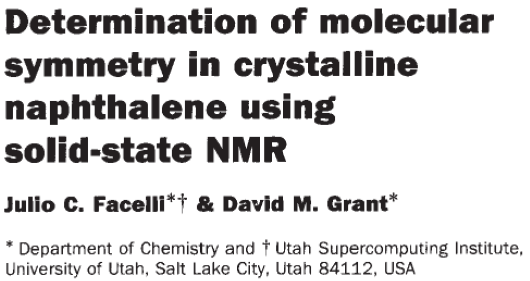
Predicting Shifts from Experience?



$\Delta\delta_{iso}$??

Ab Initio Calculation of Chemical Shifts

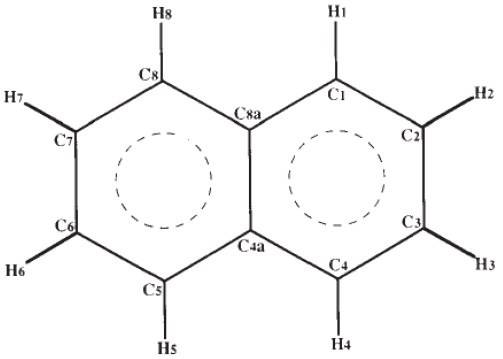




Determination of molecular symmetry in crystalline naphthalene using solid-state NMR

Julio C. Facelli*† & David M. Grant*

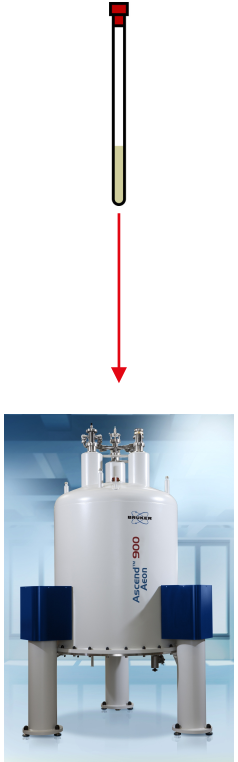
* Department of Chemistry and † Utah Supercomputing Institute, University of Utah, Salt Lake City, Utah 84112, USA

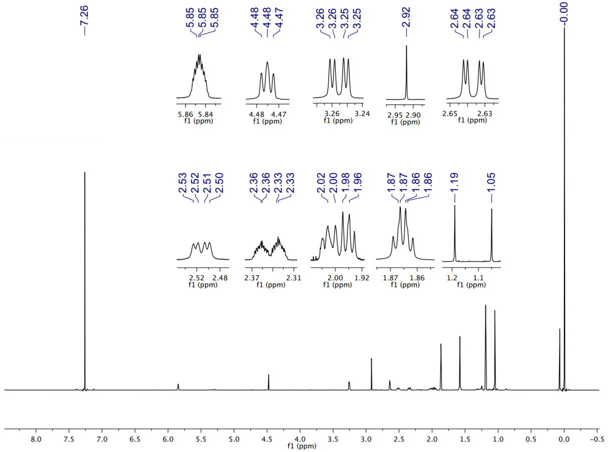


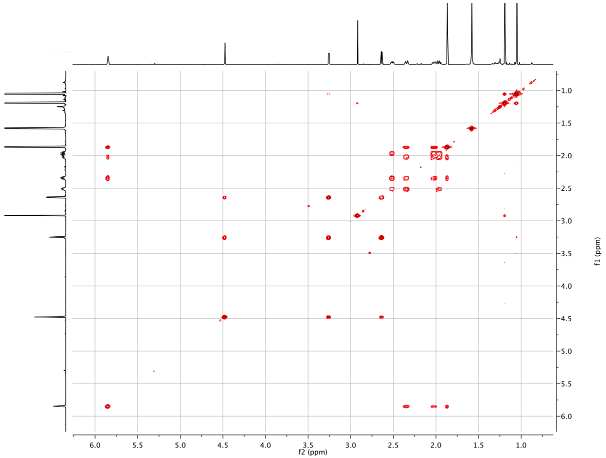
Ramsey, 1950s.
Facelli & Grant, Nature **365**, 325 (1993)
De Dios, Pearson & Oldfield, Science **260**, 1491 (1993)
Pickard & Mauri, Phys. Rev. B, 6324, (2001).
Sebastiani, Mod. Phys. Lett. B **17** 1301 (2003).

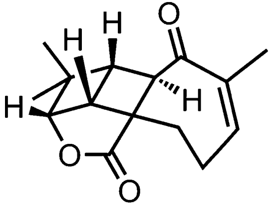
Hartman & Beran,
J. Chem. Theory Comput. **10**, 4862 (2014).
Hartman, Kudla, Day, Mueller, Beran,
Phys. Chem. Chem. Phys. **18**, 21686 (2016).

Why do we need computed shifts?









"The structure of aquatolide originally proposed on the basis of 1D and 2D NMR analysis [...] contains an **exceedingly rare [2]ladderane substructure**. Intrigued by this structural unit, we initiated **quantum-chemical calculations to verify the reported connectivity** in preparation for studies of the biogenesis of aquatolide in nature. As described below, however, these seemingly innocuous calculations set us on a **journey toward an extensive structural revision of this complex natural product**."

San Feliciano, A.; Medarde, M.; Miguel del Corral, J. M.; Aramburu, A.; Gordaliza, M.; Barrero, A. F., Aquatolide. A new type of humulane-related sesquiterpene lactone. *Tetrahedron Lett* **1989**, *30* (21),2851-2854,

Lodewyk, M. W.; Soldi, C.; Jones, P. B.; Olmstead, M. M.; Rita, J.; Shaw, J. T.; Tantillo, D. J., The Correct Structure of Aquatolide-Experimental Validation of a Theoretically-Predicted Structural Revision. *J Am Chem Soc* **2012**, *134* (45), 18550-18553.

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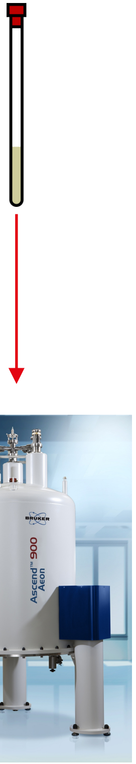

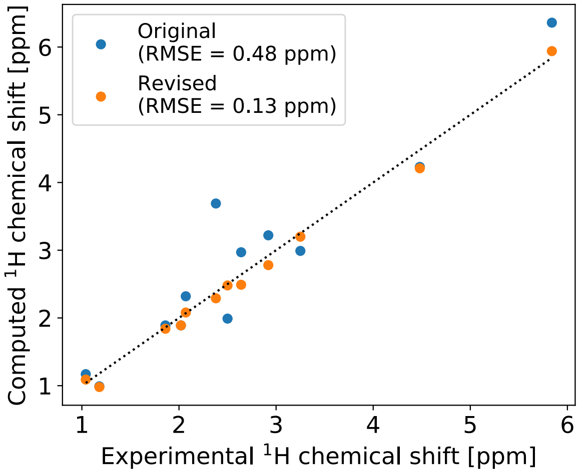

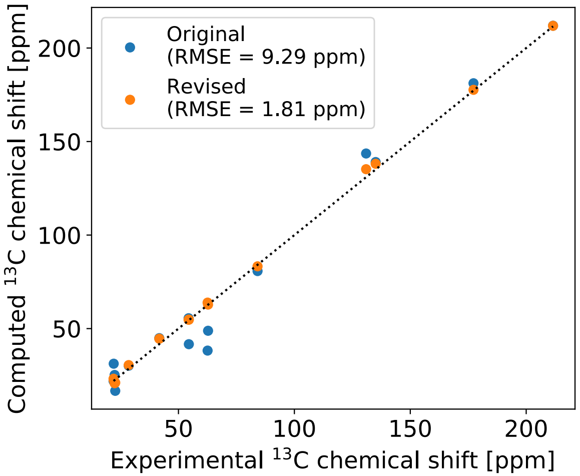

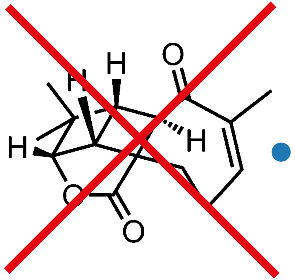

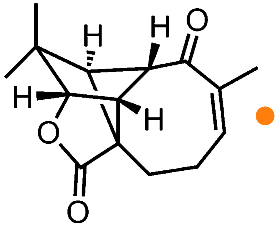

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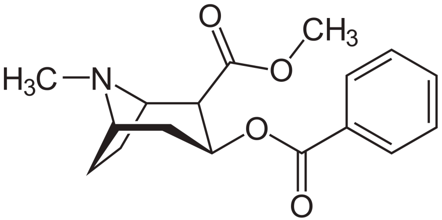
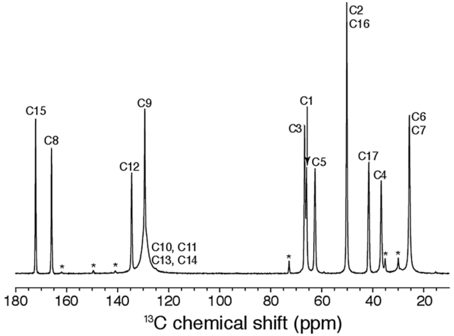
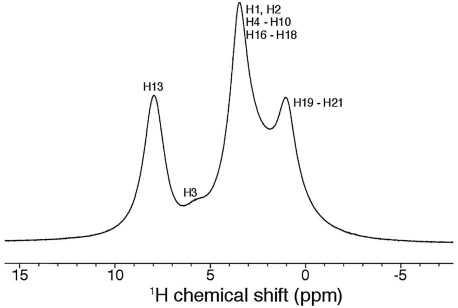
Why do we need computed shifts?

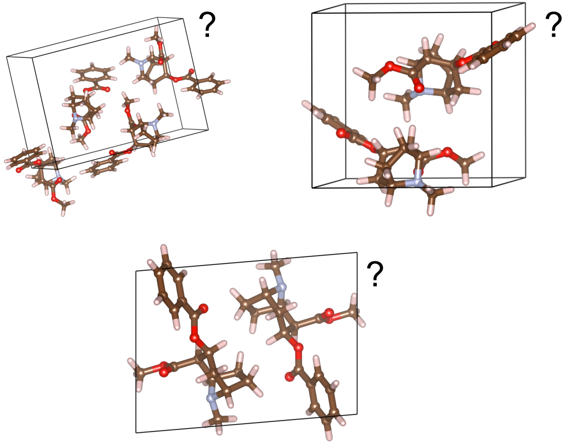
Microcrystalline powder







3D coordinates in the solid state?



Baias, M.; Widdifield, C. M.; Dumez, J. N.; Thompson, H. P. G.; Cooper, T. G.; Salager, E.; Bassil, S.; Stein, R. S.; Lesage, A.; Day, G. M.; Emsley, L., Powder crystallography of pharmaceutical materials by combined crystal structure prediction and solid-state H-1 NMR spectroscopy. *Phys Chem Chem Phys* **2013,** *15* (21), 8069-8080.

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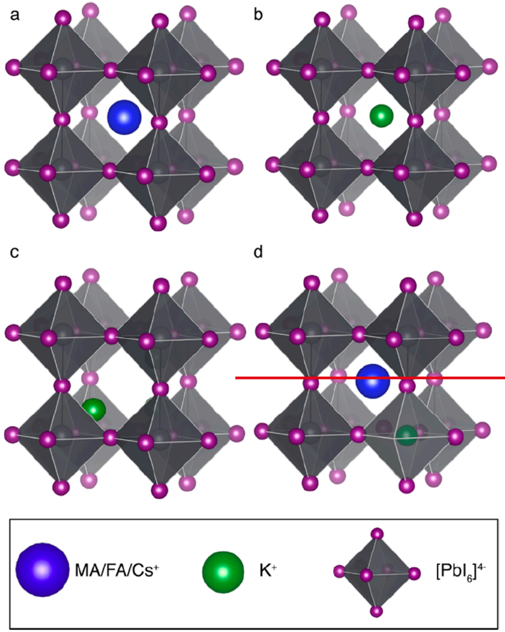
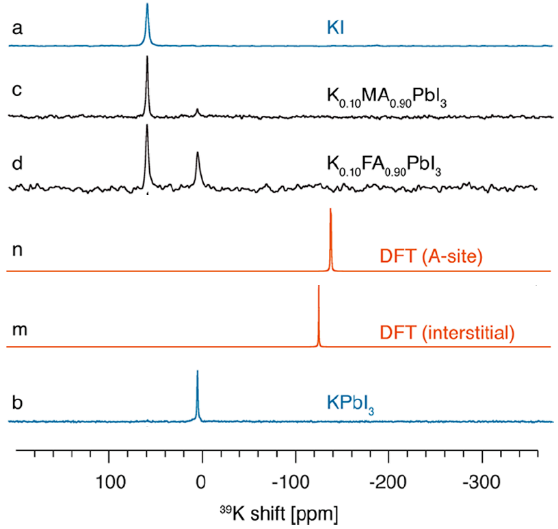


Figure 1. Schematic representation of hypothetical scenarios for potassium incorporation into the perovskite lattice: (a) parent $APbI_3$ lattice (A = MA, FA, Cs^+), (b) A-site replacement, (c) interstitial K + A-site vacancy, (d) B-site replacement + X-site vacancy.



Kubicki, D. J.; Prochowicz, D.; Hofstetter, A.; Zakeeruddin, S. M.; Gratzel, M.; Emsley, L., Phase Segregation in Potassium-Doped Lead Halide Perovskites from K-39 Solid-State NMR at 21.1 T. *J Am Chem Soc* **2018,** *140* (23), 7232-7238.

The NMR Hamiltonian

$$\begin{aligned}\mathcal{H}_S(NMR) = & -\hbar \sum_i \gamma_i B_{\text{ext}} \left(\bar{\bar{\mathbf{1}}} - \bar{\bar{\sigma}}\right) \mathbf{I}_i \\ & + \frac{1}{2}\hbar^2 \sum_i \sum_{i \neq i} \gamma_i \gamma_j \mathbf{I}_i \left(\bar{\bar{\mathbf{D}}}_{ij} + \bar{\bar{\mathbf{J}}}_{ij}\right) \mathbf{I}_j \\ & + \sum_{i,|\mathbf{I}_i| \geq 1} \mathbf{I}_i \bar{\bar{\mathbf{Q}}}_i \mathbf{I}_i\end{aligned}$$

$\mathbf{I}_i$: Nuclear spin i, $\mu_i = \gamma_i \hbar \mathbf{I}_i$

$\bar{\bar{\mathbf{D}}}_{ij}$: Dipolar coupling tensor

$\bar{\bar{\mathbf{J}}}_{ij}$: Scalar coupling tensor

$\bar{\bar{\mathbf{Q}}}_i$: Nuclear quadrupolar coupling tensor

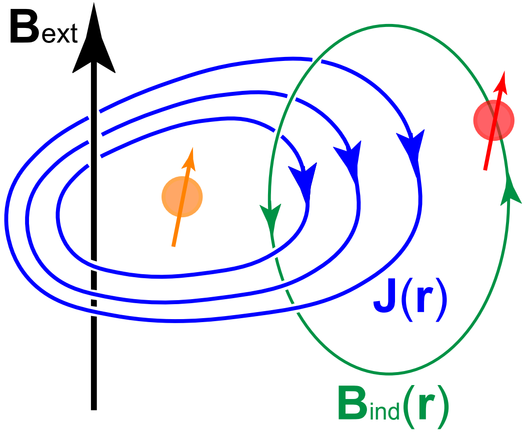
$\bar{\bar{\sigma}}$: Nuclear chemical shielding tensor

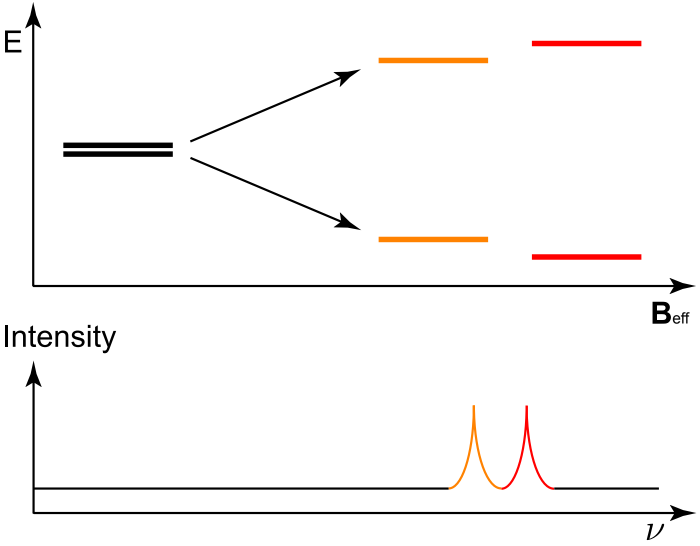
From Chemical Shielding to Chemical Shift

The applied (external) magnetic field induces current within the electron cloud, which in turns generates an induced magnetic field (Maxwell's equations)

$$\nabla \times \mathbf{B} = \mu_0 \mathbf{J} \qquad -\hbar\gamma_i B_{\text{ext}} \left(\bar{\bar{\mathbf{1}}} - \bar{\bar{\sigma}}\right) \mathbf{I}_i$$

$$B_{\text{ind}} = -\bar{\bar{\sigma}} B_{\text{ext}} \qquad B_{\text{eff}} = B_{\text{ext}} + B_{\text{ind}}$$





Isotropic chemical shielding: $\sigma = \dfrac{\bar{\bar{\sigma}}_{11} + \bar{\bar{\sigma}}_{22} + \bar{\bar{\sigma}}_{33}}{3}$

The chemical shift is then defined as: $\delta = \sigma_{\text{ref}} - \sigma$

From Chemical Shielding to Chemical Shift

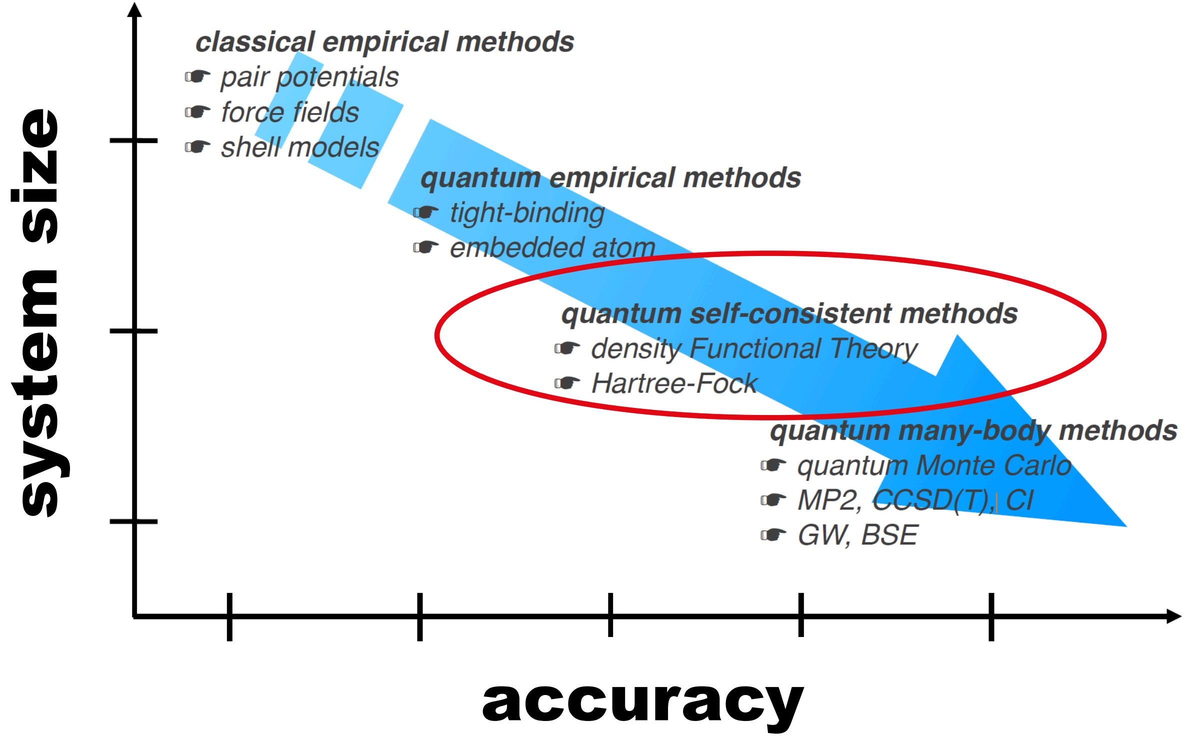
External magnetic field introduced via perturbation theory

$$|\Psi^{(0)}\rangle \longrightarrow |\Psi^{(1)}\rangle \longrightarrow \mathbf{J}^{(1)}(\mathbf{r}) \longrightarrow \mathbf{B}^{(1)}_{\mathrm{ind}}(\mathbf{r}) \longrightarrow \bar{\bar{\sigma}}(\mathbf{r})$$

$\lvert\Psi^{(0)}\rangle$	$\lvert\Psi^{(1)}\rangle$	$\mathbf{J}^{(1)}(\mathbf{r})$	$\mathbf{B}^{(1)}_{\mathrm{ind}}(\mathbf{r})$	$\bar{\bar{\sigma}}(\mathbf{r})$
Ground-state wavefunction	Perturbed wavefunction	Induced current	Induced magnetic field	Chemical shielding tensor

To compute the chemical shielding, we need "expensive" quantum mechanical computations.

From Chemical Shielding to Chemical Shift



Density Functional Theory

Goal: solve the Schrödinger equation

$$\mathcal{H}\Psi = E\Psi$$

This is too complicated, we need approximations!

1) Only treat **electrons** quantum mechanically:
Born-Oppenheimer approximation

$$\mathcal{H}_{\mathrm{el}}\Psi_{\mathrm{el}} = E_{\mathrm{el}}\Psi_{\mathrm{el}}$$

Born, M.; Oppenheimer, R., Zur Quantentheorie der Molekeln. *Annalen der Physik* **1927,** *389* (20), 457-484.

2) Replace the wavefunction by the electronic density:
Hohenberg-Kohn theorem

Every observable of a stationary quantum mechanical system can be calculated from the electronic density

$$\Psi \longrightarrow \rho(\mathbf{r}) = |\Psi|^2$$

$$E = E[\rho(\mathbf{r})]$$

Hohenberg, P.; Kohn, W., Inhomogeneous Electron Gas. *Physical Review* **1964,** *136* (3B), B864-B871.

Density Functional Theory

Kohn-Sham equation: replace the system of interacting particles (electrons) by a system of non-interacting particles which yield the same electronic density

$$\mathcal{H}\Psi = E\Psi \longrightarrow \left(-\frac{1}{2}\nabla^2 + V_{\text{eff}}(\mathbf{r})\right)\phi_i(\mathbf{r}) = \epsilon_i\phi_i(\mathbf{r})$$

$$\rho(\mathbf{r}) = \sum_i |\phi_i(\mathbf{r})|^2$$

$$E[\rho] = T_e[\rho] + V_{eN}[\rho] + V_{ee}[\rho]$$

Density Functional Theory

$$E[\rho] = T_e[\rho] + V_{eN}[\rho] + V_{ee}[\rho]$$

$$V_{eN}[\rho] = -\sum_I \int \frac{Z_I \cdot \rho(\mathbf{r})}{|\mathbf{R}_I - \mathbf{r}|} d\mathbf{r}$$

Interaction of the electrons with a classical potential generated by static nuclei

$$V_{ee}[\rho] = \iint \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \boxed{+ E_x[\rho]}$$

$$T_e[\rho] = -\frac{1}{2}\sum_i \int \phi_i^*(\mathbf{r})\nabla^2\phi_i(\mathbf{r})d\mathbf{r} \boxed{+ E_c[\rho]}$$

Interaction of the electron density at **r** with the electron density at **r**'. **But QM exchange should be taken into account!**

The kinetic energy is expressed for non-interacting electrons. **In reality, the multi-electron system is correlated!**

Self-interaction should also be dealt with

DFT: exchange-correlation

$$E_{xc}[\rho]$$

Computational cost

Accuracy

Hybrid functionals
B3LYP, PBE0, ...

$$E_{xc}^{\mathrm{hybrid}}[\rho(\mathbf{r}), \nabla\rho(\mathbf{r}), \Psi^{HF}(\mathbf{r})]$$

meta-GGA
M06-L, TPSS, ...

$$E_{xc}^{\mathrm{m-GGA}}[\rho(\mathbf{r}), \nabla\rho(\mathbf{r}), \nabla^2\rho(\mathbf{r})]$$

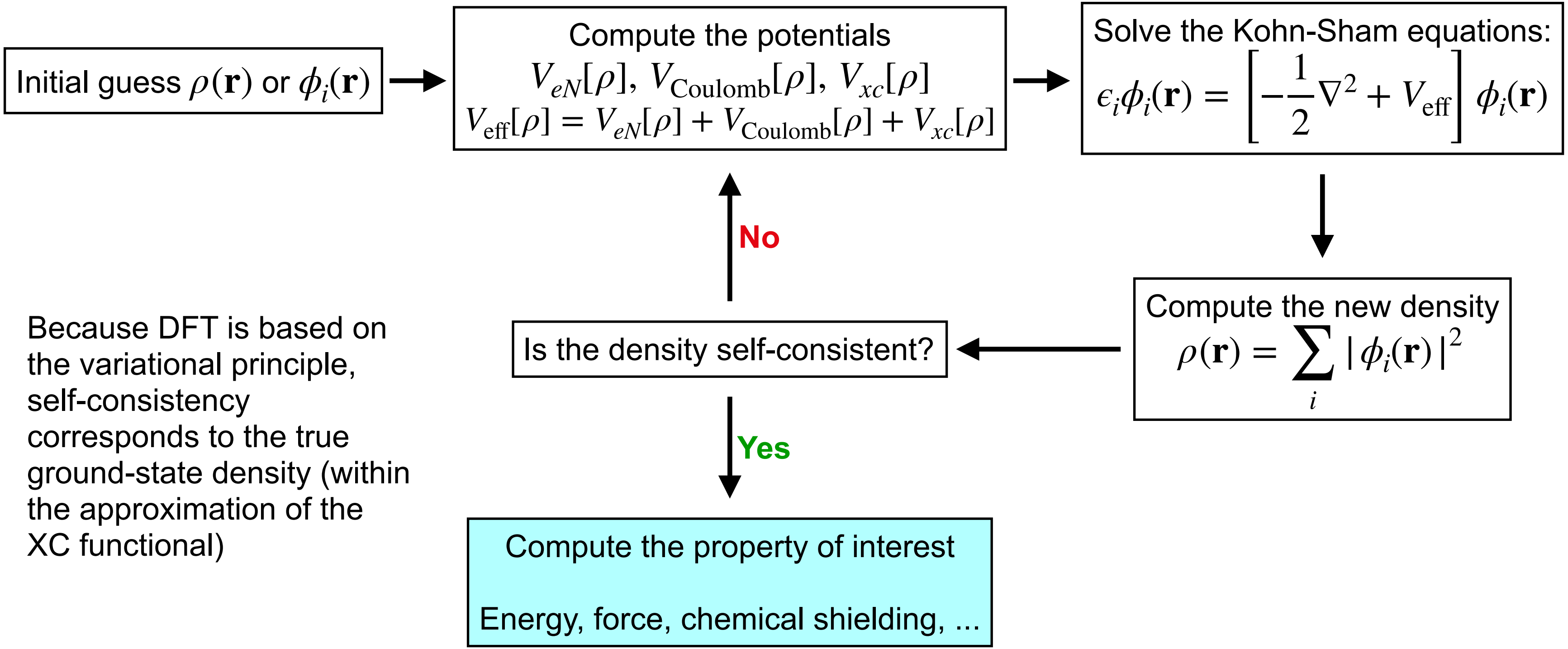
Generalised gradient approximation (GGA)
PBE, BP86, BLYP, ...

$$E_{xc}^{\mathrm{GGA}}[\rho(\mathbf{r}), \nabla\rho(\mathbf{r})]$$

Local density approximation (LDA)
VWN, PW92, ...

$$E_{xc}^{\mathrm{LDA}}[\rho(\mathbf{r})]$$

DFT: self-consistent field (SCF) loop and variational principle



Initial guess $\rho(\mathbf{r})$ or $\phi_i(\mathbf{r})$

Compute the potentials

$$V_{eN}[\rho],\ V_{\mathrm{Coulomb}}[\rho],\ V_{xc}[\rho]$$

$$V_{\mathrm{eff}}[\rho] = V_{eN}[\rho] + V_{\mathrm{Coulomb}}[\rho] + V_{xc}[\rho]$$

Solve the Kohn-Sham equations:

$$\epsilon_i \phi_i(\mathbf{r}) = \left[-\frac{1}{2}\nabla^2 + V_{\mathrm{eff}}\right]\phi_i(\mathbf{r})$$

Compute the new density

$$\rho(\mathbf{r}) = \sum_i |\phi_i(\mathbf{r})|^2$$

Is the density self-consistent?

No

Yes

Compute the property of interest

Energy, force, chemical shielding, ...

Because DFT is based on the variational principle, self-consistency corresponds to the true ground-state density (within the approximation of the XC functional)

DFT: remarks

DFT is exact in principle

Failures of DFT refer to failure of the XC functional

No functional (so far) is accurate for all properties of interest

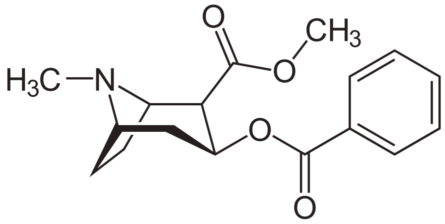
No matter what functional we use, there is always a case where it fails

Any functional can be applied to any electronic structure problem

The theory is *ab initio* but experience and intuition will determine which functional is best for a particular use

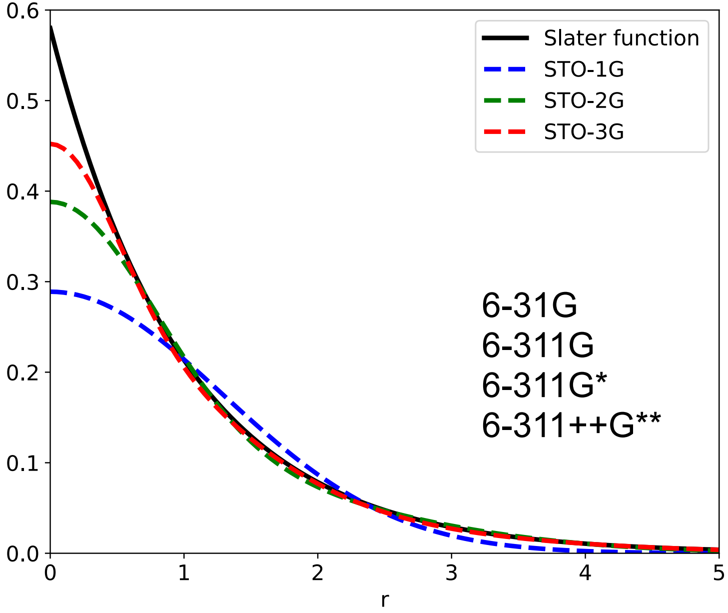
DFT: Software

Single molecules



Atomic orbital-like basis set

Gaussian (GTO)
ORCA (GTO)
ADF (STO)

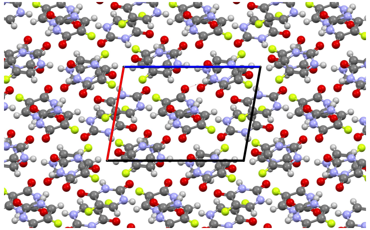


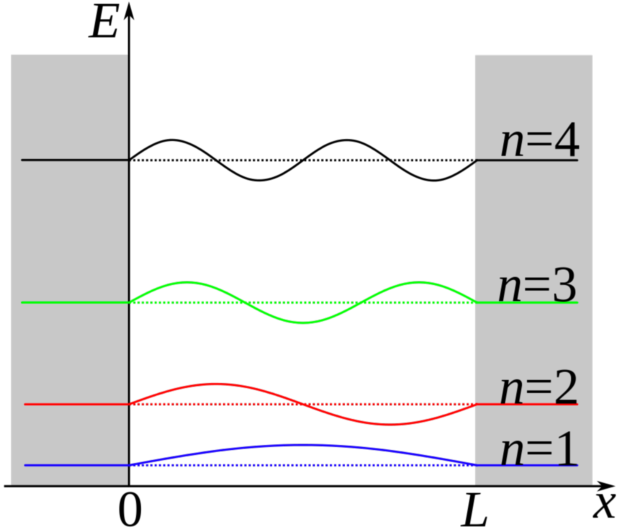
Gauge-Including Atomic Orbitals (GIAO) formalism for chemical shift computation

Periodicity is not taken into account

DFT: Software

Periodic systems





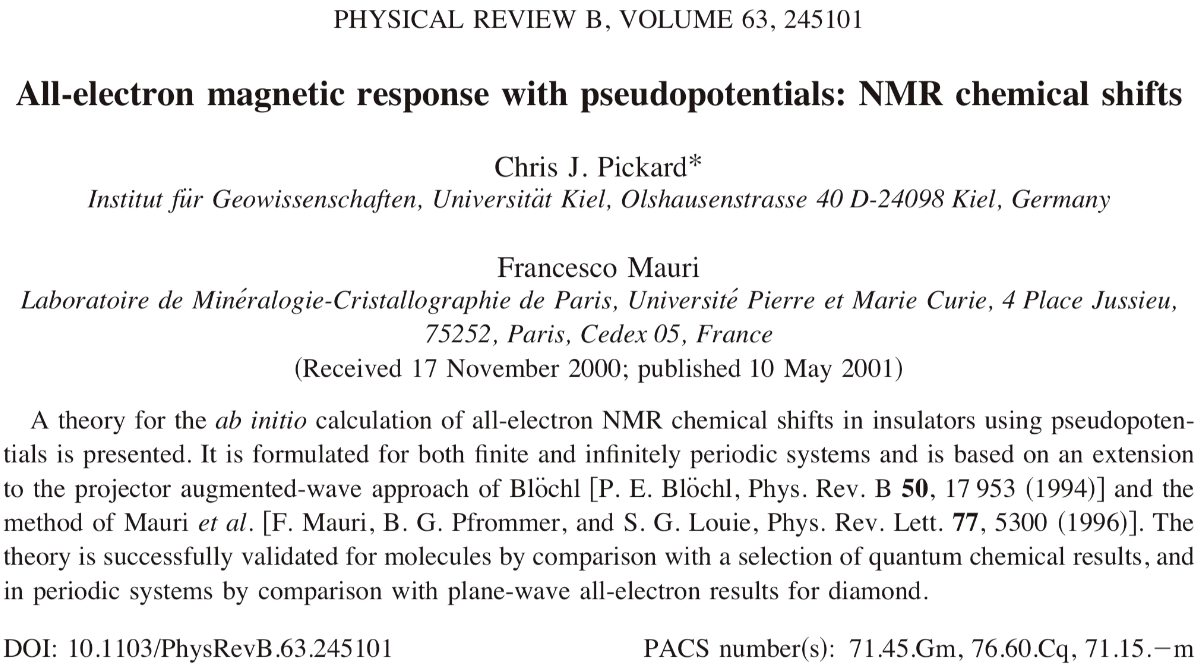
Plane wave basis set

CASTEP
Quantum ESPRESSO
VASP

Gauge-Including Projector Augmented Waves (GIPAW) formalism for chemical shift computation

More expensive than atomic orbital-like basis sets

Computing NMR shieldings in solids



PHYSICAL REVIEW B, VOLUME 63, 245101

All-electron magnetic response with pseudopotentials: NMR chemical shifts

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75252, Paris, Cedex 05, France

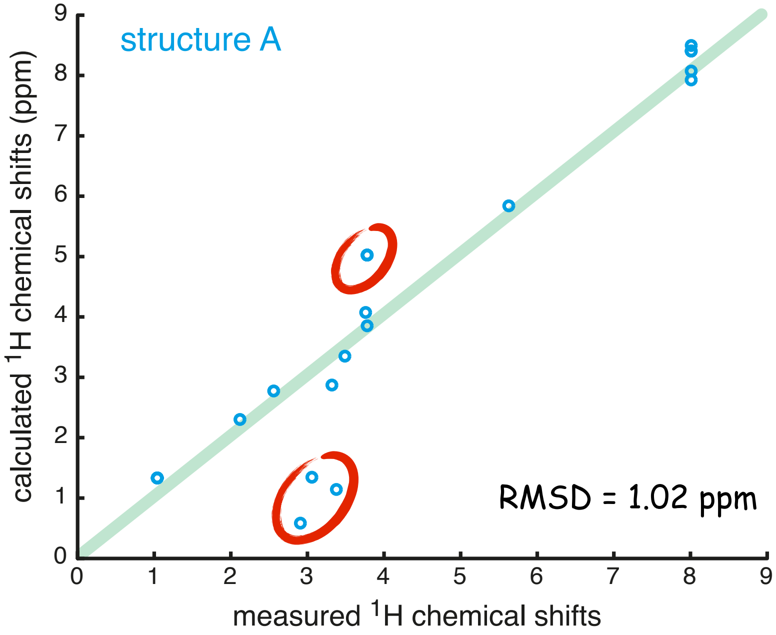
(Received 17 November 2000; published 10 May 2001)

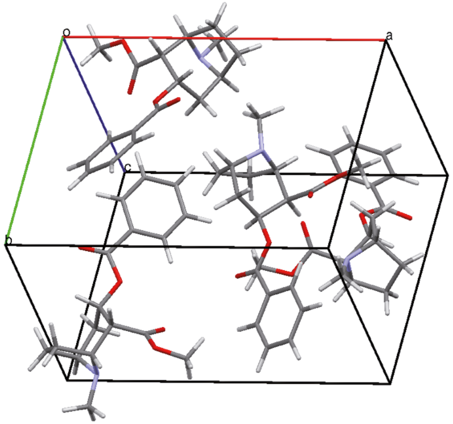
A theory for the *ab initio* calculation of all-electron NMR chemical shifts in insulators using pseudopotentials is presented. It is formulated for both finite and infinitely periodic systems and is based on an extension to the projector augmented-wave approach of Blöchl [P. E. Blöchl, Phys. Rev. B **50**, 17 953 (1994)] and the method of Mauri *et al*. [F. Mauri, B. G. Pfrommer, and S. G. Louie, Phys. Rev. Lett. **77**, 5300 (1996)]. The theory is successfully validated for molecules by comparison with a selection of quantum chemical results, and in periodic systems by comparison with plane-wave all-electron results for diamond.

DOI: 10.1103/PhysRevB.63.245101 PACS number(s): 71.45.Gm, 76.60.Cq, 71.15.−m

Examples: Molecular crystals

(Cocaine Free Base)





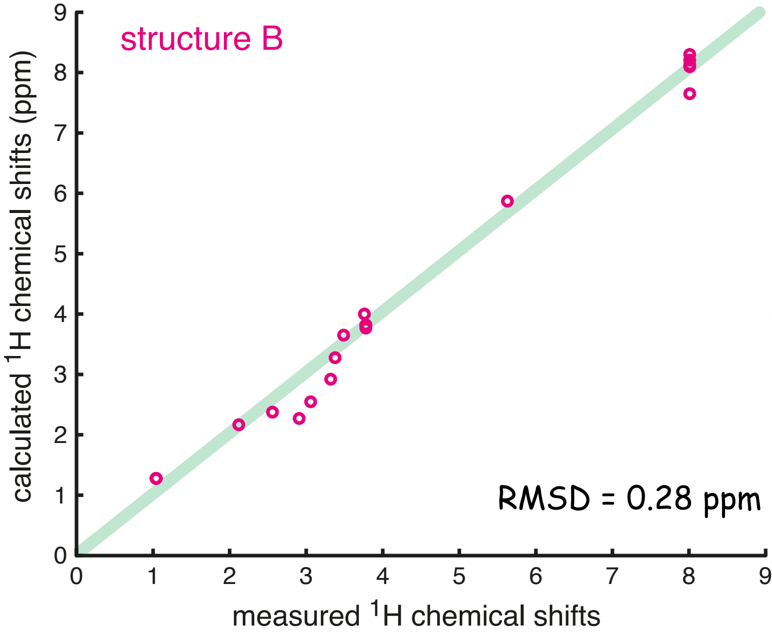
GIPAW planewave pseudo -potential
DFT-based calculations

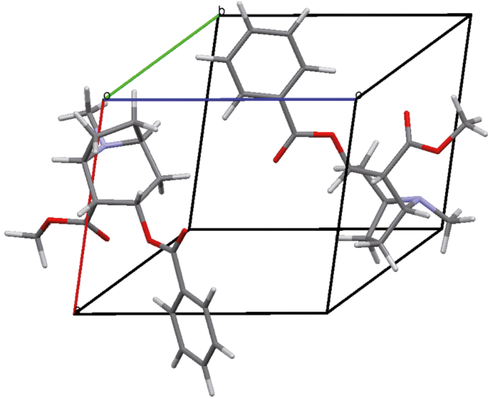
*Pickard and Mauri., Phys. Rev. B, **63**, 245101(2001).*
*Segall et al., J. Phys. -Condens. Matter **14**, 2717, (2002).*

J. Am. Chem. Soc. **132**, 2564 (2010),
Phys. Chem. Chem. Phys. **15**, 8069 (2013)

Examples: Molecular crystals

(Cocaine Free Base)





GIPAW planewave pseudo -potential
DFT-based calculations

*Pickard and Mauri., Phys. Rev. B, **63**, 245101(2001).*
*Segall et al., J. Phys. -Condens. Matter **14**, 2717, (2002).*

J. Am. Chem. Soc. **132**, 2564 (2010),
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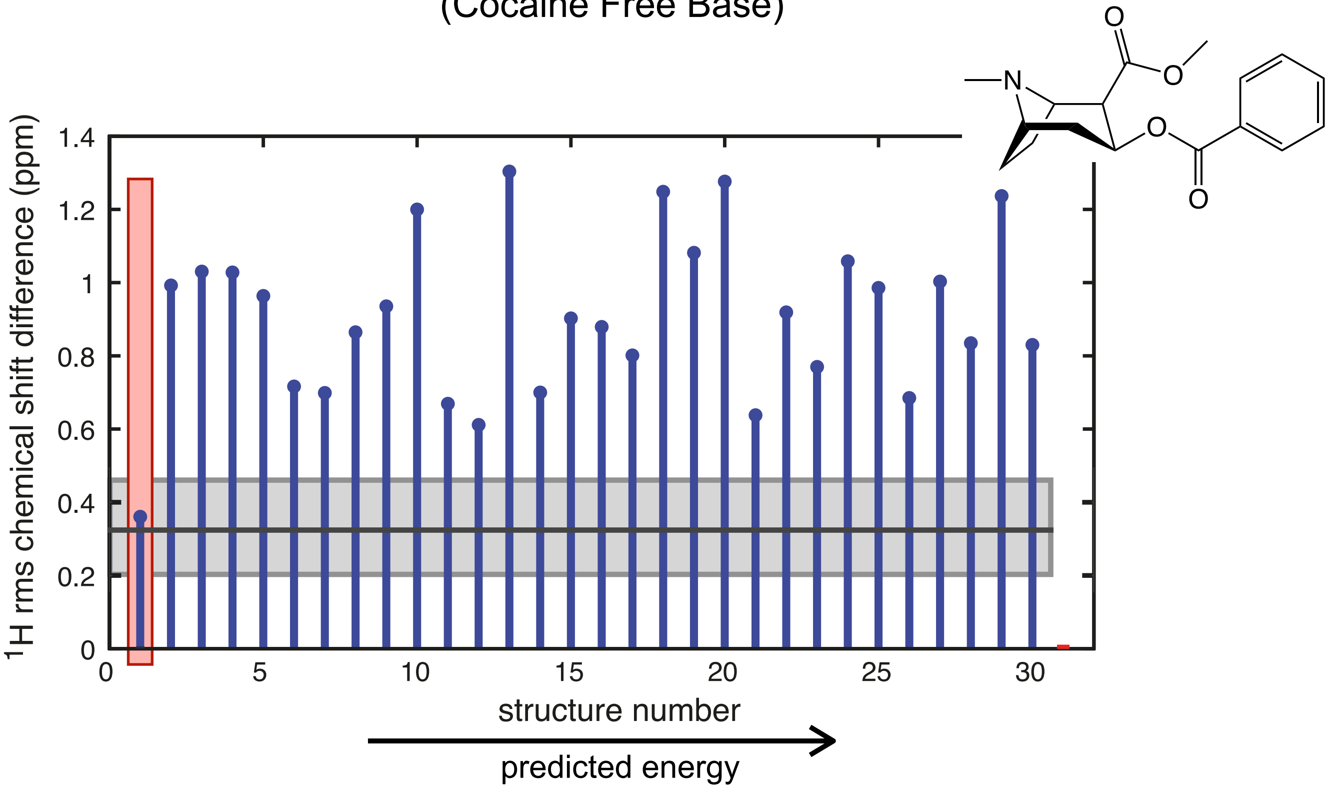
Examples: Molecular crystals

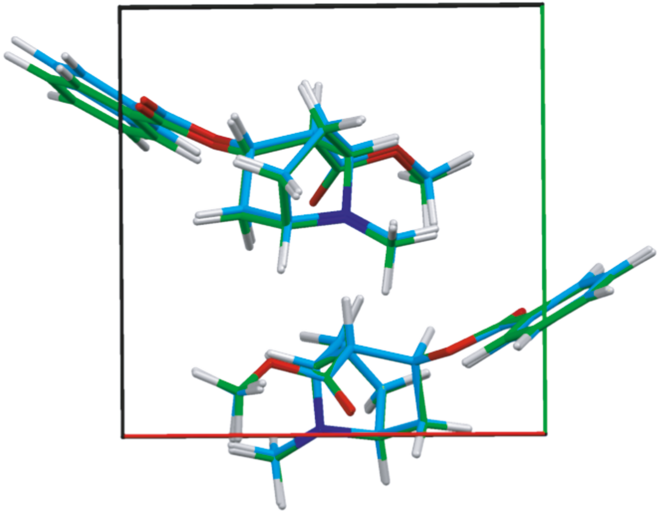
(Cocaine Free Base)



J. Am. Chem. Soc. **132**, 2564 (2010),
Phys. Chem. Chem. Phys. **15**, 8069 (2013)

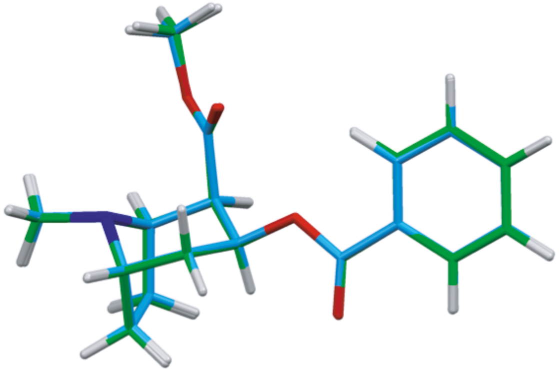
Powder NMR Crystallography from Proton Chemical Shifts

(Cocaine Free Base)



Unit Cell

ΔV to Single Crystal X-Ray: 0.8%



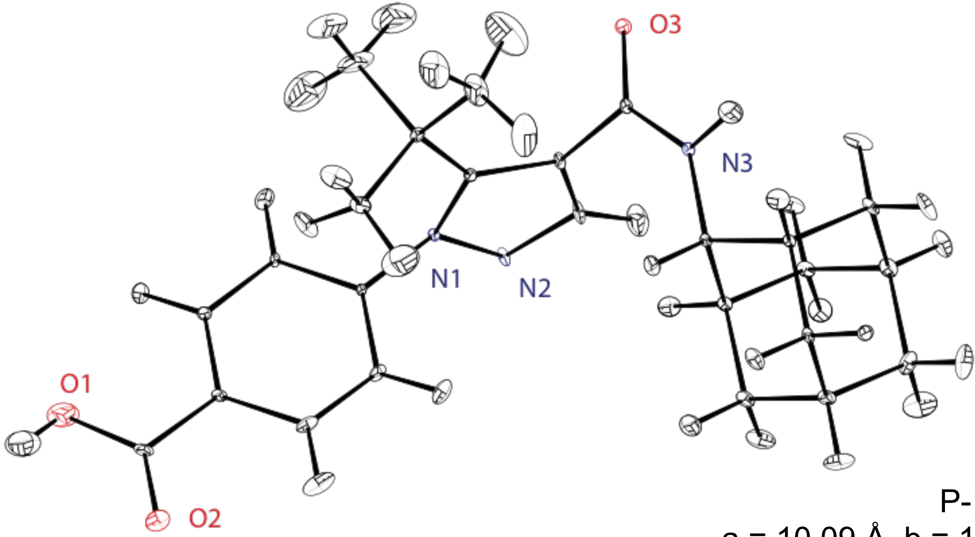
Single Molecule

RMSD to Single Crystal X-Ray: 0.07 Å

J. Am. Chem. Soc. **132**, 2564 (2010),
Phys. Chem. Chem. Phys. **15**, 8069 (2013)

De Novo Determination of a Previously Unknown Structure

(Form 4 of AZD8329, a large drug molecule)

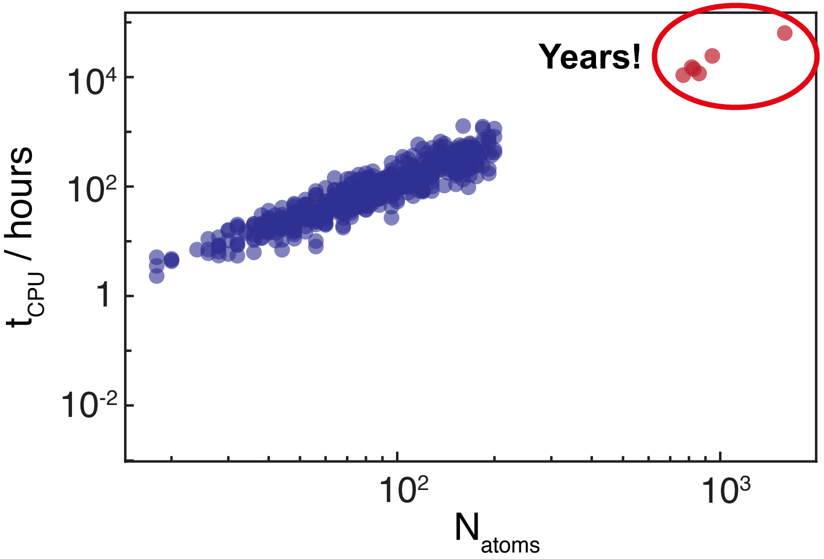


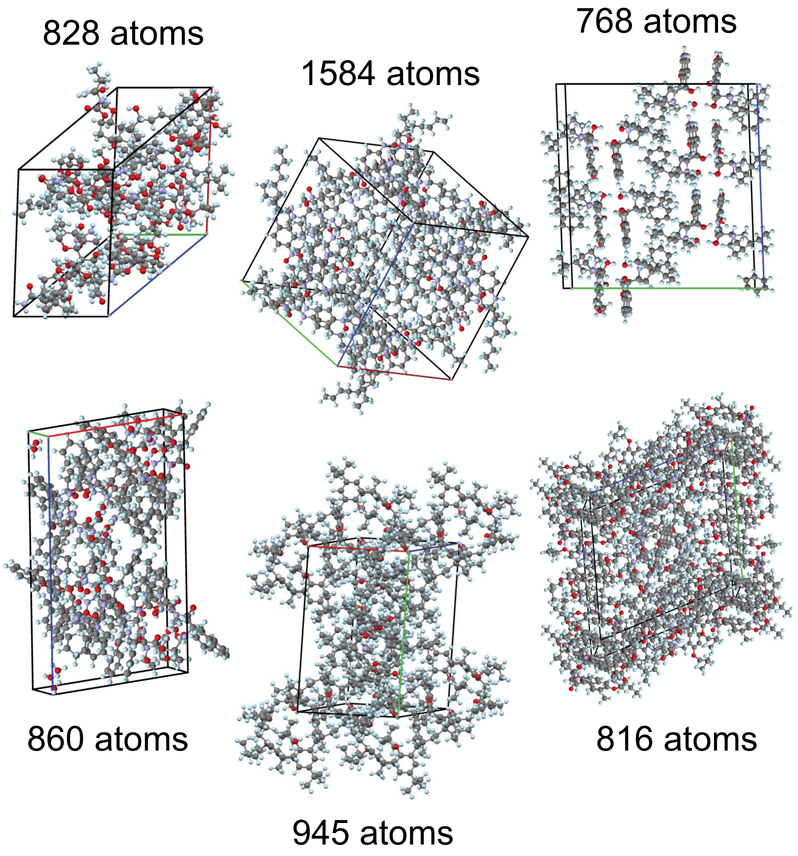
cis-conformation
P-1 triclinic space group
a = 10.09 Å, b = 11.39 Å, c = 13.17 Å
α = 99.1°, β = 59.5°, γ = 73.3°

First *de novo* determination of an unknown structure of an organic solid from a powder sample.
RMSD of 0.17 Å (ADP of 0.0095 Å2); 100% confidence.

J. Am. Chem. Soc. **135**, 17501 (2013)

Computational Time





DFT is widely used, but large system require a prohibitively large computational time. We need a way to accelerate the computation of chemical shifts

Paruzzo, F. M.; Hofstetter, A.; Musil, F.; De, S.; Ceriotti, M.; Emsley, L., Chemical shifts in molecular solids by machine learning. *Nat Commun* **2018,** *9.*

Machine Learning Chemical Shifts

Proteins

SHIFTX2
Han, B.; Liu, Y. F.; Ginzinger, S. W.; Wishart, D. S., SHIFTX2: significantly improved protein chemical shift prediction. *J Biomol Nmr* **2011,** *50* (1), 43-57.

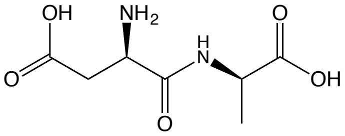
SPARTA+
Shen, Y.; Bax, A., SPARTA plus : a modest improvement in empirical NMR chemical shift prediction by means of an artificial neural network. *J Biomol Nmr* **2010,** *48* (1), 13-22.

PROSHIFT
Meiler, J., PROSHIFT: Protein chemical shift prediction using artificial neural networks. *J Biomol Nmr* **2003,** *26* (1), 25-37.

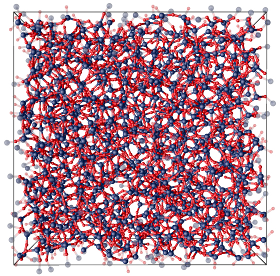
Gas-phase / solvated molecules

ACD NMR Predictor Software
https://www.acdlabs.com/products/adh/nmr/nmr_pred

MNova NMR Predictor
https://mestrelab.com/software/mnova/nmr-predict



Amorphous silicates

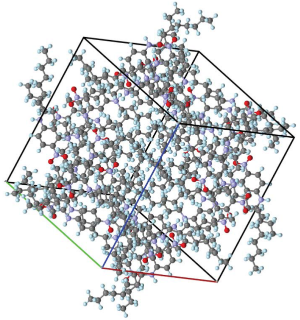


Cuny, J.; Xie, Y.; Pickard, C. J.; Hassanali, A. A., Ab Initio Quality NMR Parameters in Solid-State Materials Using a High-Dimensional Neural-Network Representation. *J Chem Theory Comput* **2016,** *12* (2), 765-773.

Molecular solids

ShiftML
https://shiftml.epfl.ch

Paruzzo, F. M.; Hofstetter, A.; Musil, F.; De, S.; Ceriotti, M.; Emsley, L., Chemical shifts in molecular solids by machine learning. *Nat Commun* **2018,** *9*.



Machine Learning

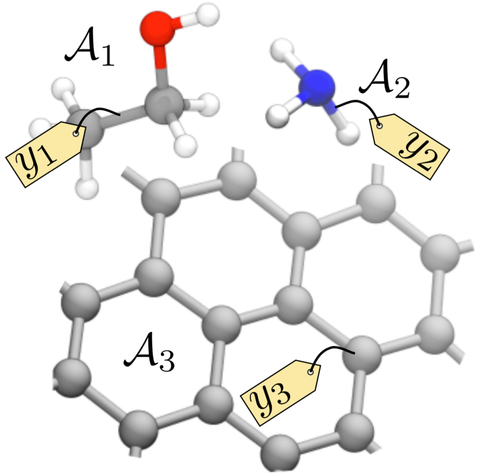
ML algorithms learn patterns from data only (statistical learning), without any rules given to them

The model is constructed using labelled training data,

Predictions can then be made very quickly for new data.

Machine Learning: ShiftML

Training Dataset
Experimental / computed



ML algorithms require a lot of consistent training data

Experimental data scattered across the literature, may lack consistency

Computed properties are generally better suited for statistical learning

ShiftML: 2,000 structures, 185,000 environments

Machine Learning: ShiftML

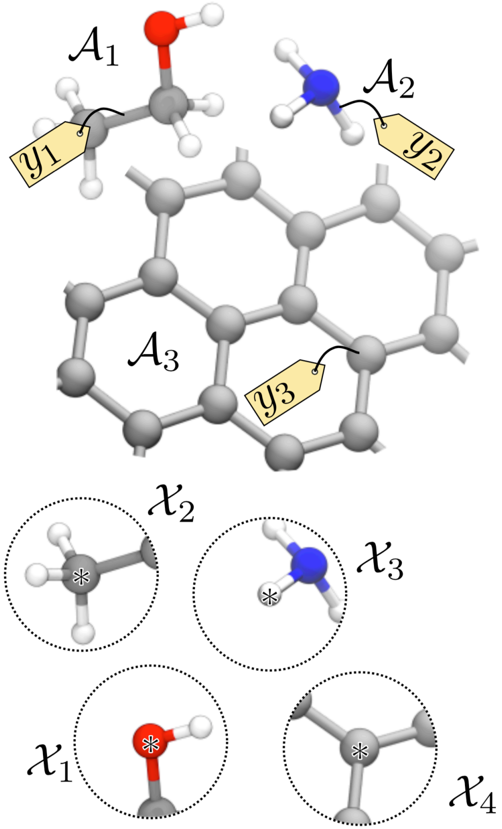
Dataset
Experimental / computed
→
Representation /
features

Vectors of numbers should be given as inputs to the ML model

These **feature vectors** should capture the property of interest

Chemical shift is determined by the **local atomic environment**

SOAP vectors: determines atomic positions around the nucleus of interest



Machine Learning: ShiftML

Dataset
Experimental / computed

→

Representation / features

→

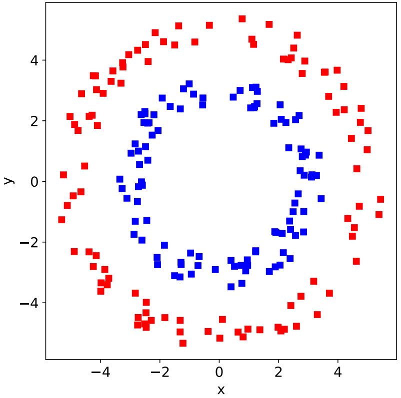
ML model
Neural network / KRR / ...

Kernel Ridge Regression (KRR): generalisation of linear regression

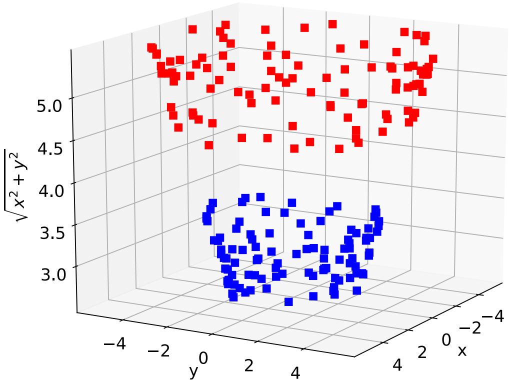
Gaussian kernel $k(x, x') = \exp\left(-\frac{1}{2\sigma^2}\|x - x'\|^2\right)$

Laplacian kernel $k(x, x') = \exp\left(-\frac{1}{\sigma}|x - x'|\right)$

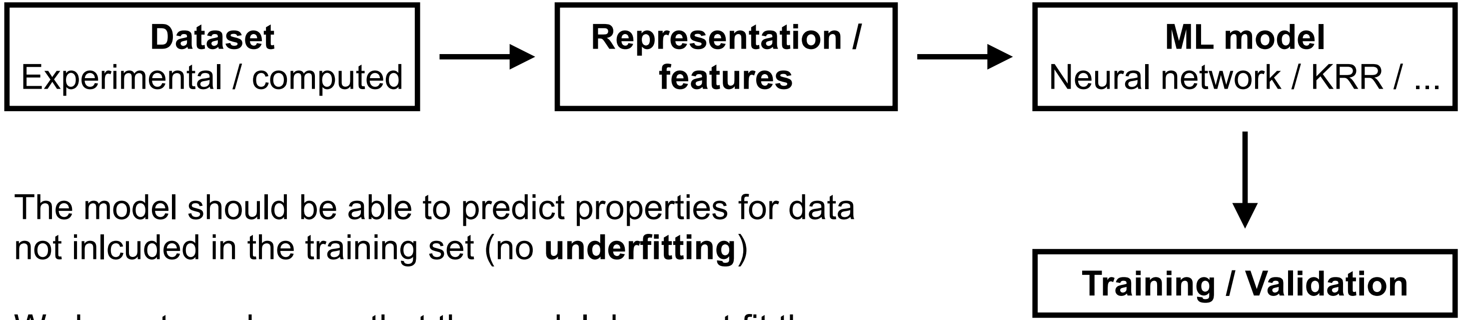
Apply a non-linear transformation (kernel function) to the input data to make the regression easier



$$(x, y) \longrightarrow \left(x, y, \sqrt{x^2 + y^2}\right)$$



Machine Learning: ShiftML



Dataset
Experimental / computed

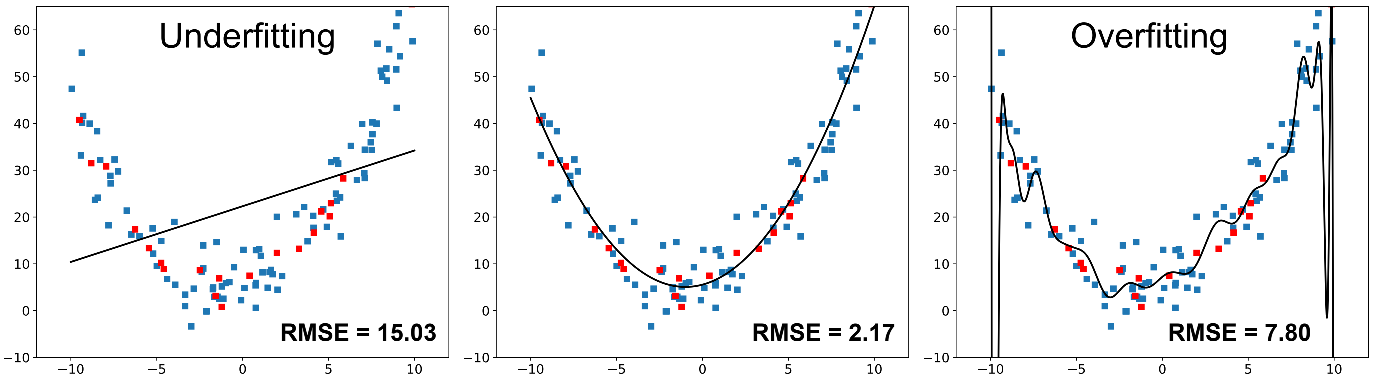
Representation / features

ML model
Neural network / KRR / ...

Training / Validation

The model should be able to predict properties for data not inlcuded in the training set (no **underfitting**)

We have to make sure that the model does not fit the noise from the training set (**overfitting**)



Machine Learning: ShiftML

Dataset
Experimental / computed

→

Representation / features

→

ML model
Neural network / KRR / ...

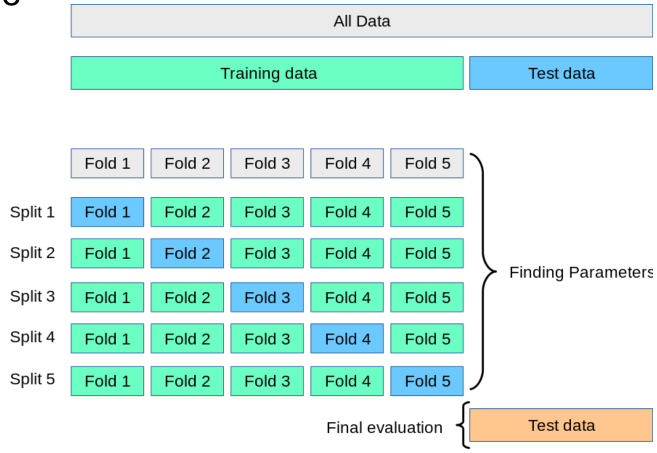
↓

Training / Validation

The model should be able to predict properties for data not included in the training set (no **underfitting**)

We have to make sure that the model does not fit the noise from the training set (**overfitting**)

Cross-validation can help us tune the parameters of the model



Machine Learning: ShiftML

Dataset
Experimental / computed

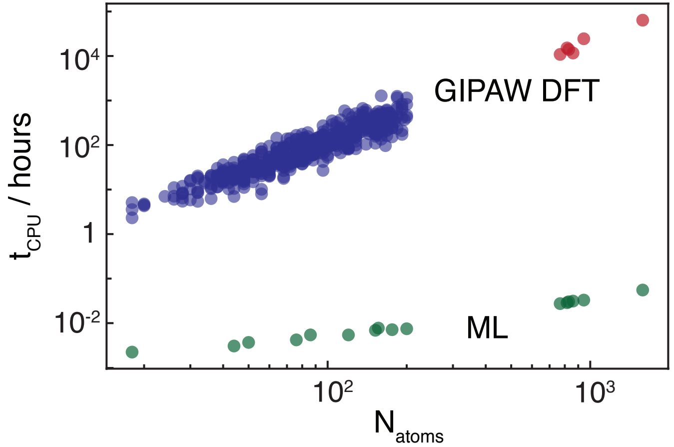
Representation / features

ML model
Neural network / KRR / ...

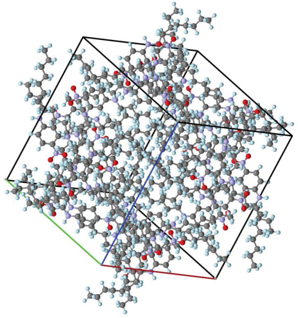
Training / Validation

Predictions

After training the model, predictions can be made very quickly

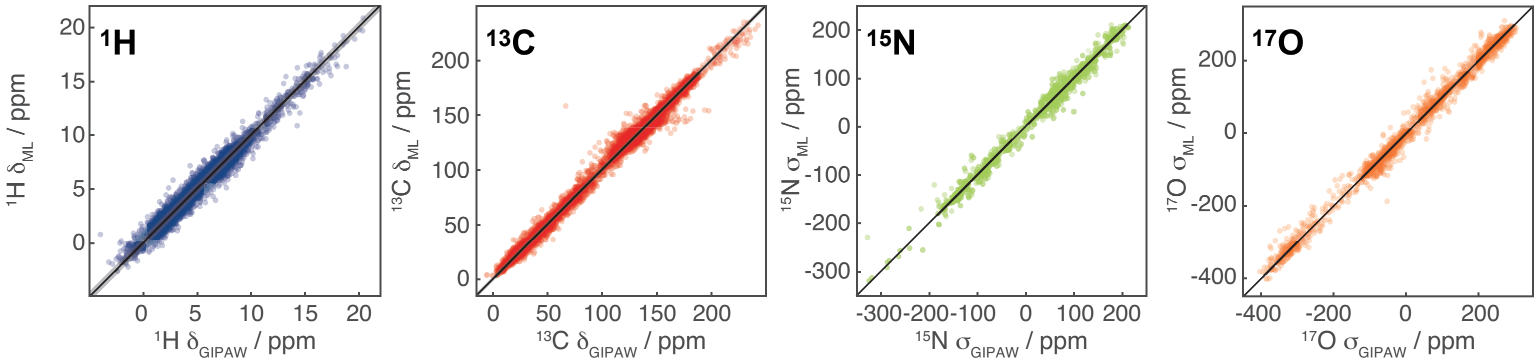


1584 atoms



Paruzzo, F. M.; Hofstetter, A.; Musil, F.; De, S.; Ceriotti, M.; Emsley, L., Chemical shifts in molecular solids by machine learning. *Nat Commun* **2018,** *9.*

ShiftML: Comparison with DFT



$R^2 = 0.97$

RMSE = 0.49 ppm

$R^2 = 0.99$

RMSE = 4.5 ppm

$R^2 = 0.99$

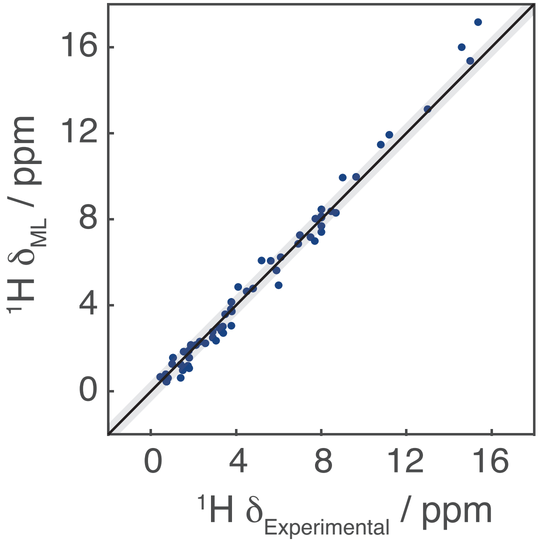
RMSE = 13.3 ppm

$R^2 = 0.99$

RMSE = 17.7 ppm

Paruzzo, F. M.; Hofstetter, A.; Musil, F.; De, S.; Ceriotti, M.; Emsley, L., Chemical shifts in molecular solids by machine learning. *Nat Commun* **2018,** *9.*

ShiftML: Comparison to Experiment

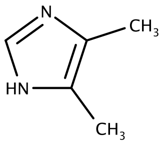


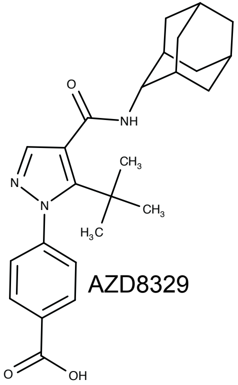
$R^2 = 0.99$

$\mathrm{RMSE}_{ML} = 0.50$ ppm

$\mathrm{RMSE}_{DFT} = 0.43$ ppm

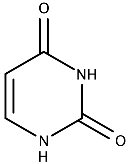
4,5-dimethylimidazole

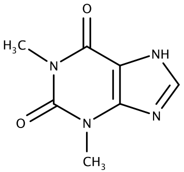




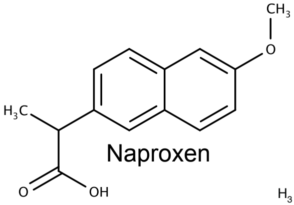
AZD8329

Uracil

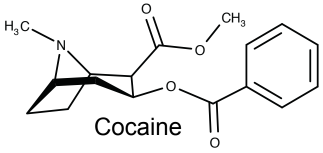




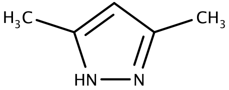
Theophylline



Naproxen



Cocaine



3,5-dimethylimidazole

Paruzzo, F. M.; Hofstetter, A.; Musil, F.; De, S.; Ceriotti, M.; Emsley, L., Chemical shifts in molecular solids by machine learning. *Nat Commun* **2018,** *9*.

Machine Learning: Remarks

High accuracy at low cost
- Ideal for large-scale screening

NOT *ab initio*
- ML methods can only reliably be applied to systems that are similar to the training set
- Prediction confidence is generally difficult to obtain

Conclusions

- **Chemical shifts can today be quite accurately predicted using computational methods, and they are widely used for assignment, elucidation, and strucutre determination**.
- DFT is the most widely used purely computational method to predict shifts
- Different methods/programs/basis sets are used for DFT predictions for single molecules or for periodic solids.
- Predictions based on experimental databases of chemical shifts are the most accurate tools for predicting chemical shifts in solution NMR today.
- Machine learning models are becoming increasingly important for both solids and liquids.

[none of today’s lecture content will be included in the exam]

Questions?