Nuclear magnetic resonance spectroscopy with language transformers

R. Andreev

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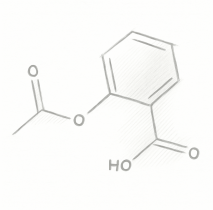
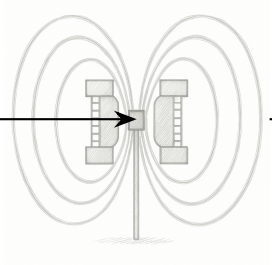
In part: MSc thesis, ETHZ (2025) – thanks to

- E. Konukoglu Computational Vision and Learning (D-ITET, ETHZ)
- Nicolas Schmid Applied Mathematics and Physics (ZHAW)
- M.-O. Ebert & S. Papalo Organic Chemistry (D-CHAB, ETHZ)
- A. Hove Lambda GPU Cloud, who provided some of the compute

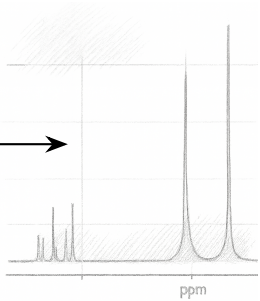
Nuclear magnetic resonance



analyte

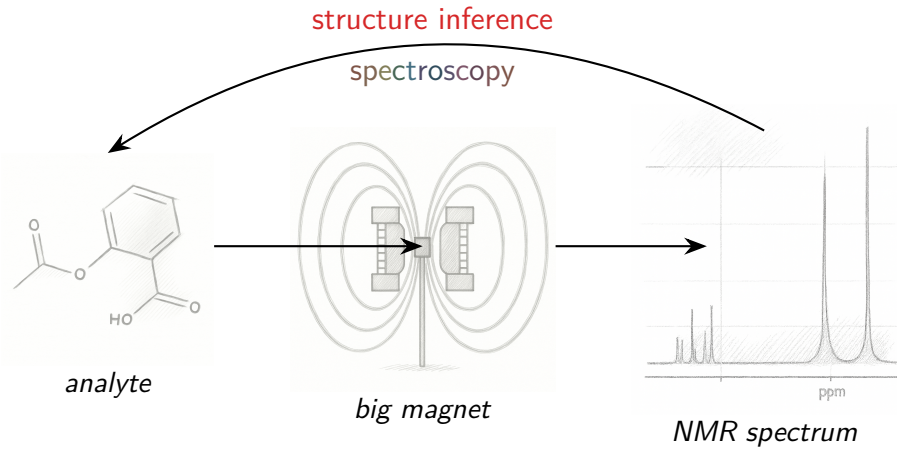


big magnet

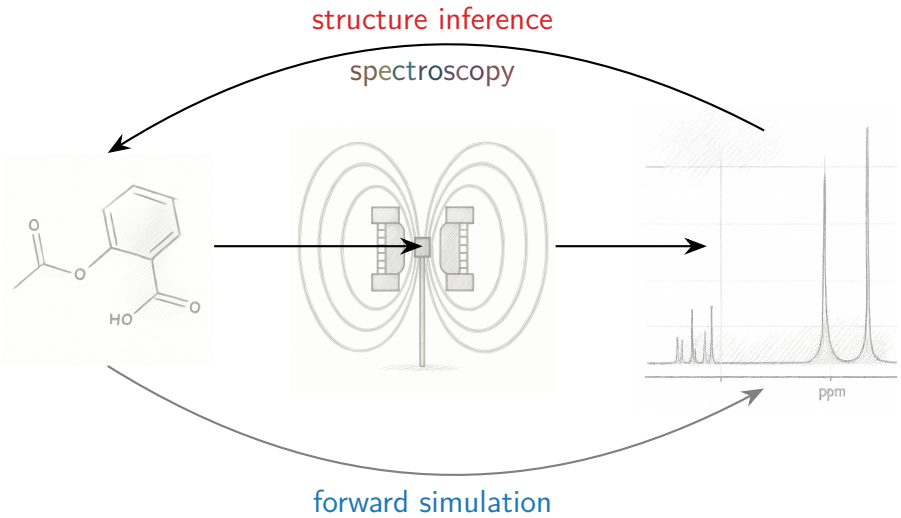


NMR spectrum

Nuclear magnetic resonance



Nuclear magnetic resonance

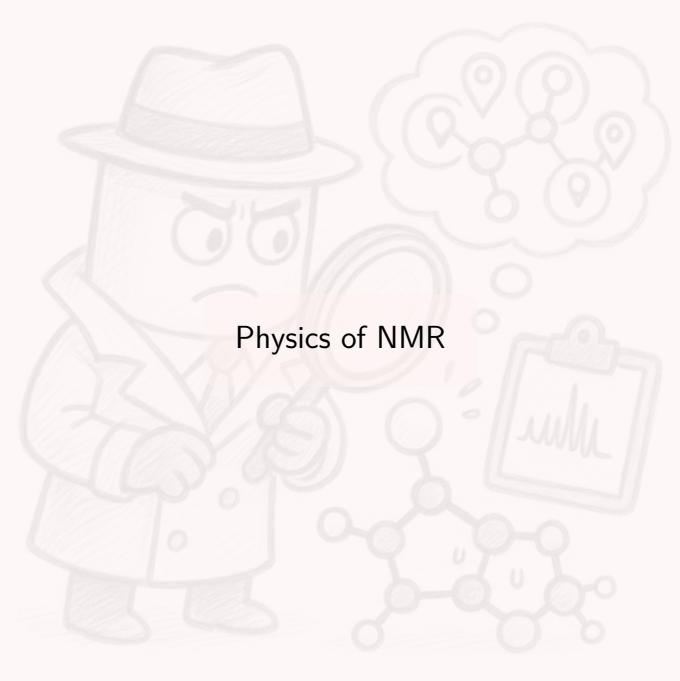


structure inference

spectroscopy

- Physics of NMR & examples
- Dataset & model by Alberts et al.
- Teaching molecules with GRIMACE
- Training & results
- Recap & outlook

forward simulation



Physics of NMR

In essence, NMR is a “bag of atoms”.

- The spin of a $\frac{1}{2}$-spin particle ($^1\mathrm{H}$, $^{13}\mathrm{C}$) is a normed vector $\psi \in \mathbb{C}^2$. Its observables are combinations of $\mathbb{I}$ and the Pauli matrices

$$\sigma_x = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix} \qquad \sigma_y = \begin{pmatrix} 0 & -i \\ i & 0 \end{pmatrix} \qquad \sigma_z = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}$$

- The operator $I_z = \frac{1}{2}\sigma_z$ has eigenvalues $\pm\frac{1}{2}$ and eigenvectors
- The Hamiltonian of a $\frac{1}{2}$-spin s in a z-magnetic field $\vec{B}_0$ is
- In NMR, we measure ω, and infer/interpret shielding and J-coupling
- Schrödinger eqn. $\partial_t \psi = -\frac{i}{\hbar}\widehat{H}\psi$ gives the spin evolution operator
- At thermal equilibrium, $\vec{B}_0$ causes a small excess of *up* spins ψ^{up}
- A radiofrequency pulse knocks those spins onto the x-axis
- Ignoring the relaxation, the spin state is $\psi(t) = \widehat{E}_t \widehat{P} \psi^{\mathsf{up}}$
- The macroscopic xy-magnetization $\widehat{M} = \sigma_x + i\sigma_y$ of s is observed as

$$\langle M(t) \rangle = \langle \psi(t) | \widehat{M} | \psi(t) \rangle = \langle \psi^{\mathsf{up}} | (\widehat{P}^\dagger \widehat{E}_t^\dagger \widehat{M} \widehat{E}_t \widehat{P}) | \psi^{\mathsf{up}} \rangle = e^{-i\omega t}$$

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$$\psi^{\mathsf{up}} = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \quad \text{and} \quad \psi_{\mathsf{down}} = \begin{pmatrix} 0 \\ 1 \end{pmatrix}.$$

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- Package the superposition of *all spins* in the *free induction decay*
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$$\hat{H} = \hbar\,\omega\, I_z \quad + \quad \ldots$$

with Larmor frequency

$$\omega \approx \quad -\gamma_{\text{isotope}}\, B_0\,(1 - \text{shielding}) \quad + \quad 2\pi \sum\nolimits_{s'} J_{ss'} \times (\pm\tfrac{1}{2})_{s'}$$

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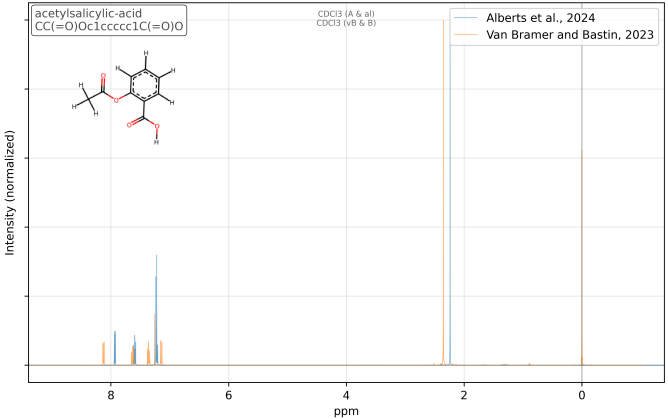

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$$\hat{E}_t = \begin{pmatrix} e^{+\frac{1}{2}i\omega t} & 0 \\ 0 & e^{-\frac{1}{2}i\omega t} \end{pmatrix}$$

assuming $\hat{H} = \hbar\omega I_z$ (notably, ignoring relaxation)

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$$\psi^{\mathsf{up}} \to \hat{P}\psi^{\mathsf{up}} \quad \text{where} \quad \hat{P} = \exp(-i\tfrac{\pi}{4}\sigma_y)$$

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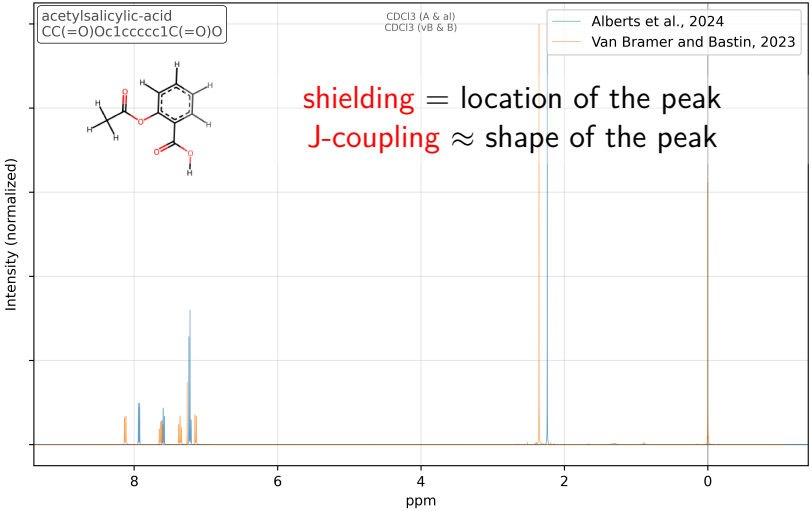
In essence, NMR is a “bag of atoms”.

^{1}H–NMR spectrum of acetylsalicylic acid (*aspirin*)

←



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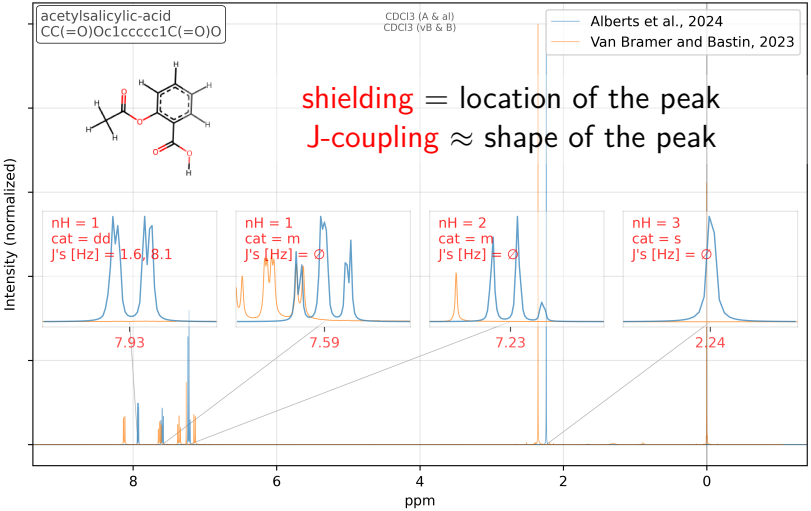
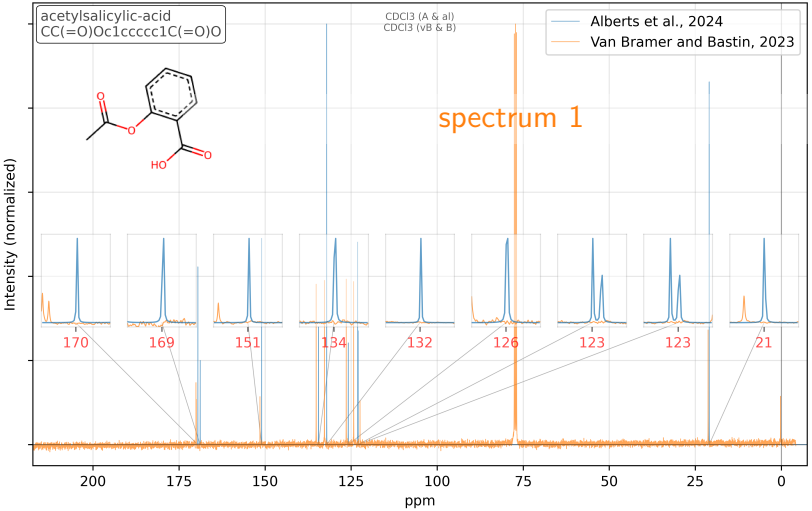


^{13}C–NMR spectrum of acetylsalicylic acid (*aspirin*)



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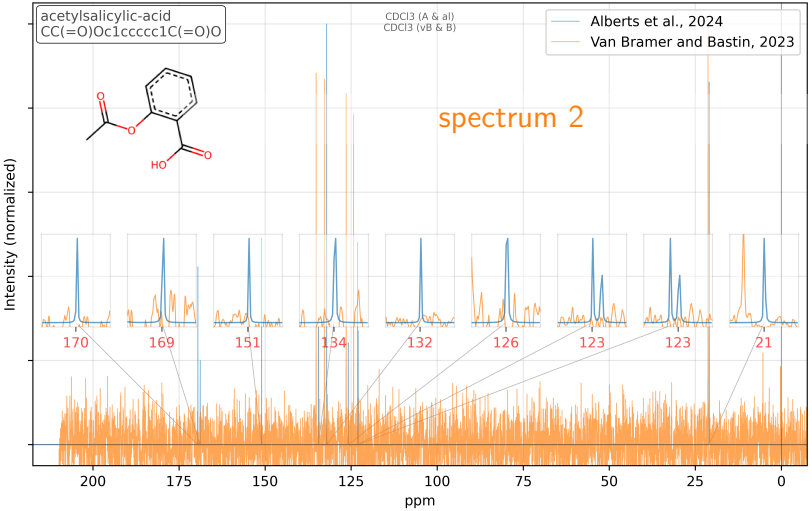

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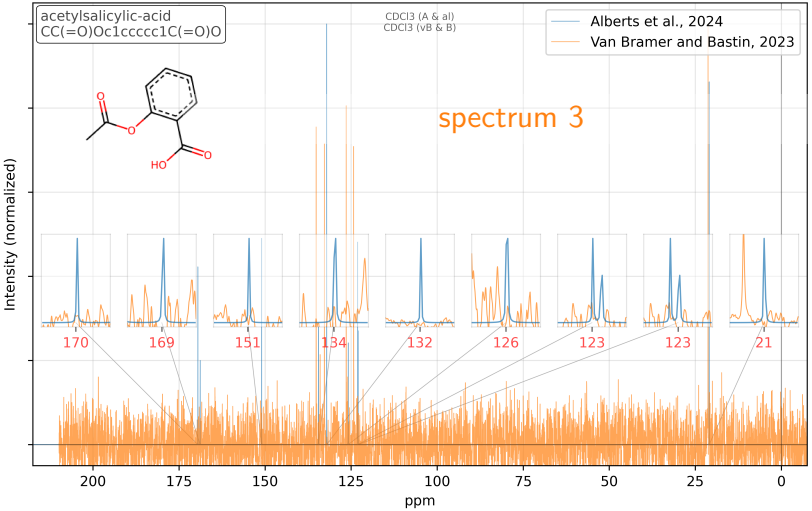

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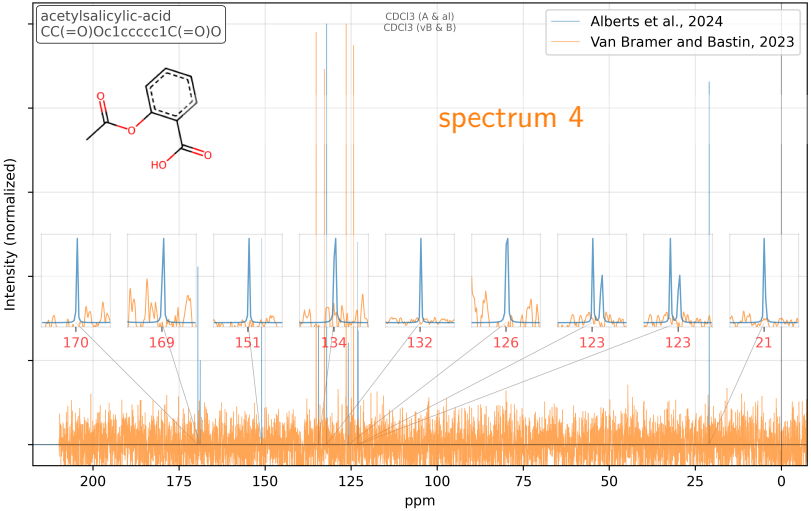

Annotations by MestReNova (via [1]):

^{1}H peaks:

```
...
{
  "category": "ddt",
  "centroid": 6.992,
  "delta": 6.993,
  "j_values": "0.88_2.02_8.79_",
  "nH": 1,
  "rangeMax": 7.021,
  "rangeMin": 6.965
},
...
```

^{13}C peaks:

```
...
{
  "delta (ppm)": 130.27,
  "integral": 0.00096,
  "intensity": 0.0512,
  "width (ppm)": 0.0119
},
...
```

HSQC peaks:

```
...
{
  "13C_centroid": 56.18,
  "13C_max": 56.91,
  "13C_min": 55.45,
  "1H_centroid": 3.813,
  "1H_max": 3.866,
  "1H_min": 3.759,
  "nH": 3.0  # !!!
},
...
```

Repackage as NMR text data for language transformers:

```
F|C16H23BrO4
Q|6.0:1.11-1.25@23|3.0:3.76-3.87@56.2|3.0:1.01-1.12@14.2|···|1.0:3.03-3.14@37.6
C|3.1@172|3.1@157|5.4@130|3.2@130|3.1@129|5.3@128|5.3@112|···|9.7@14.2
H|1:7.09-7.13:dp:0.86,1.8|1:6.96-7.02:ddt:0.88,2,8.8|···|3:1.04-1.09:t:6.4
```

– we use this as the de facto NMR spectrum

Problem statement:

$$\mathrm{F} + \mathrm{Q} + \mathrm{C} + \mathrm{H} \rightarrow \mathrm{MOLECULE}$$

Strychnine

- Strychnine is chiral, with fused rings and quite rigid
- Hong et al., "Biosynthesis of strychnine", Nature (2022) [2]
- Let's see the $^{1}\mathrm{H}$-NMR spectrum, both measured and simulated...

Many thanks to S. Papalo and M.-O. Ebert of LOC, ETH Zurich!

MestReNova v15.1.0-38027 with NMRPredict v1.11

OpenMM8.4.0 + ORCA6.1.0 / GNN predictor

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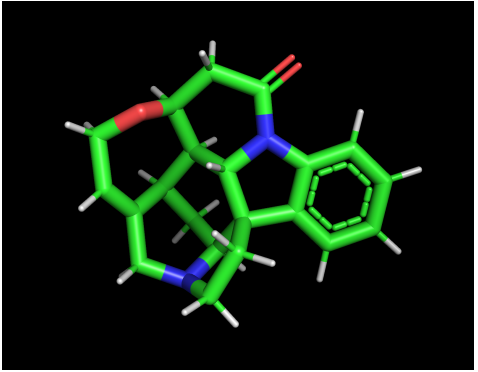

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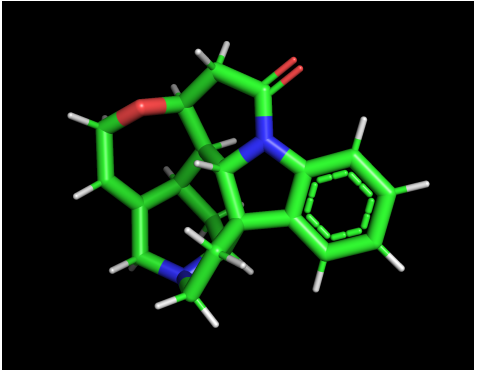

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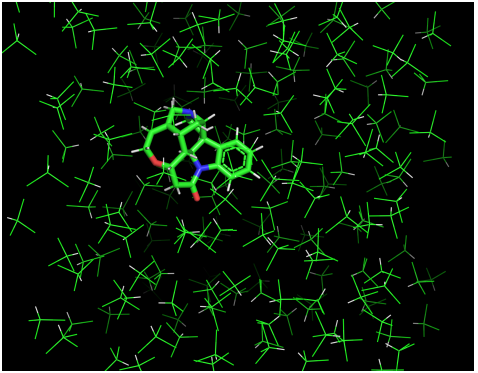
Strychnine

- Strychnine in chloroform-d, computed with OpenMM



- Hong et al., "Biosynthesis of strychnine", Nature (2022) [2]
- Let's see the ^{1}H-NMR spectrum, both measured and simulated...

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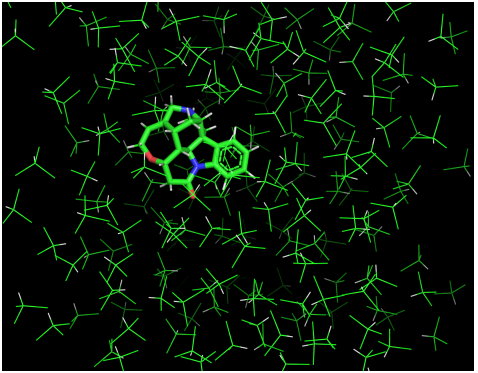

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- Hong et al., "Biosynthesis of strychnine", Nature (2022) [2]:

  Strychnine is a natural product that, through isolation, structural elucidation and synthetic efforts, shaped the field of organic chemistry.

  Currently, strychnine is used as a pesticide to control rodents because of its potent neurotoxicity.

  The polycyclic architecture of strychnine has inspired chemists [..].

  Here we report the biosynthetic pathway of strychnine, along with the related molecules brucine and diaboline.

- Let's see the ^{1}H-NMR spectrum, both measured and simulated...

  Many thanks to S. Papalo and M.-O. Ebert of LOC, ETH Zurich!

  MestReNova v15.1.0-38027 with NMRPredict v1.11

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OpenMM8.4.0 + ORCA6.1.0 / GNN predictor

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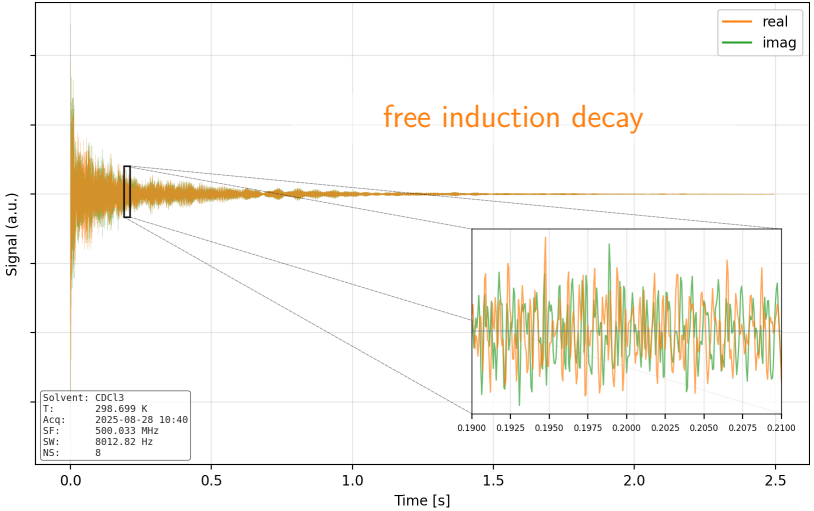

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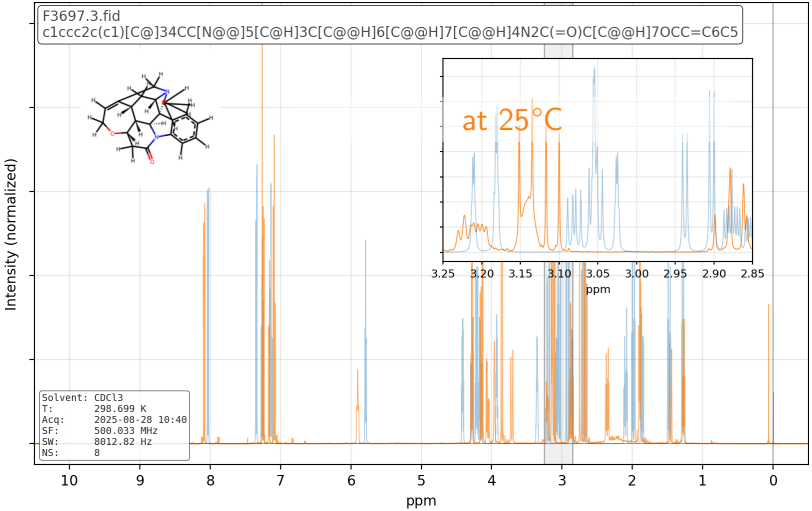

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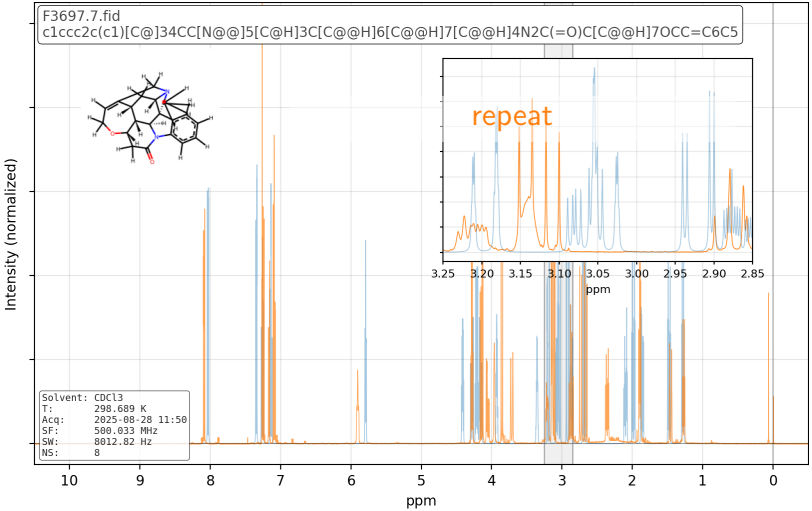

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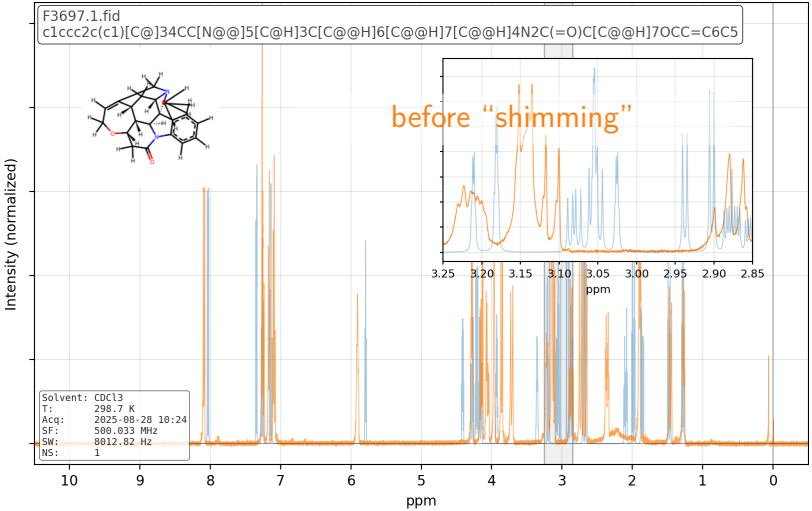

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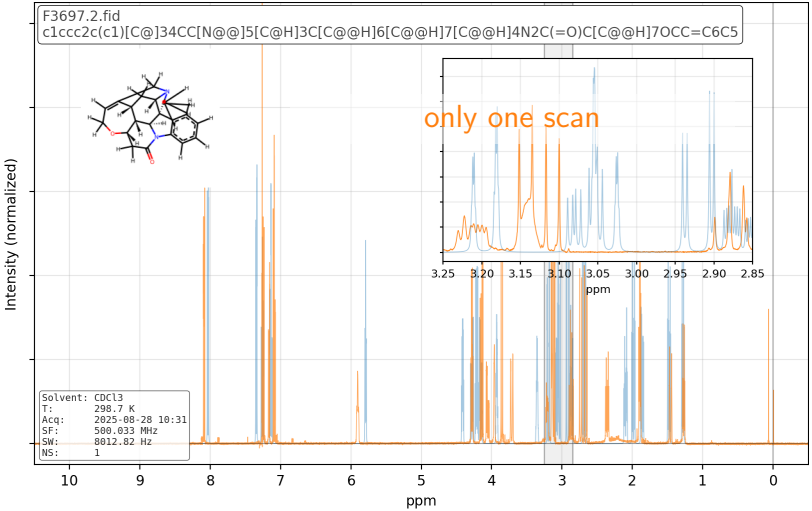

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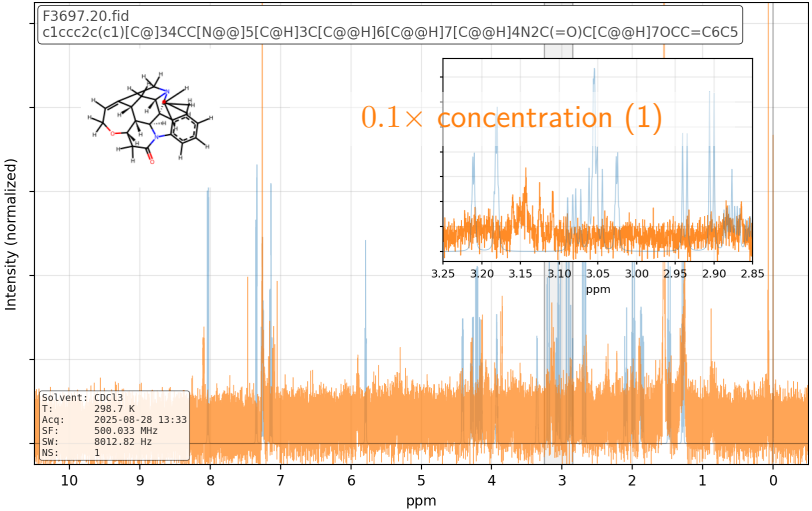

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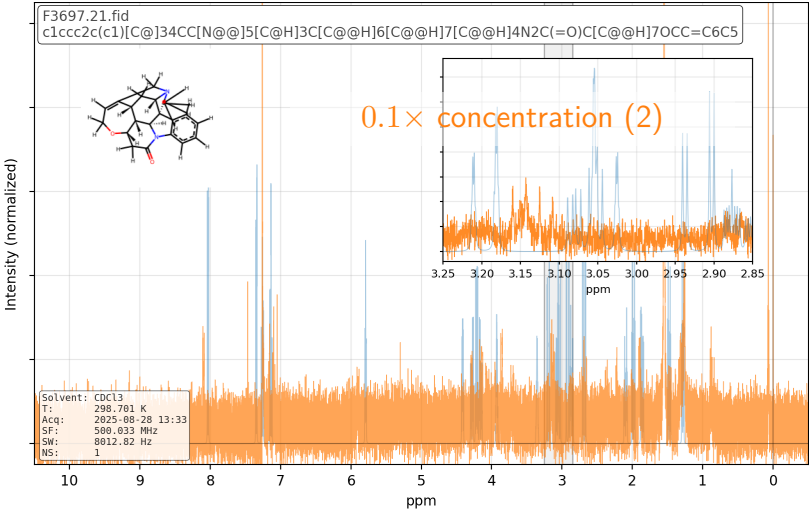

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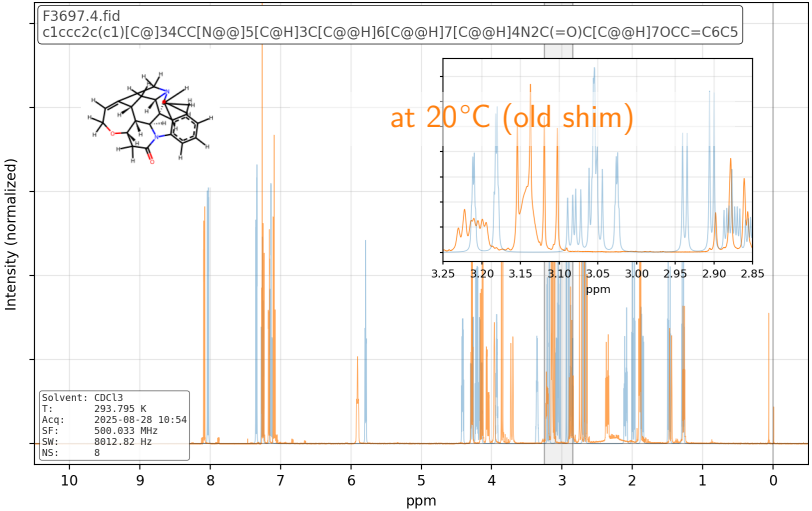

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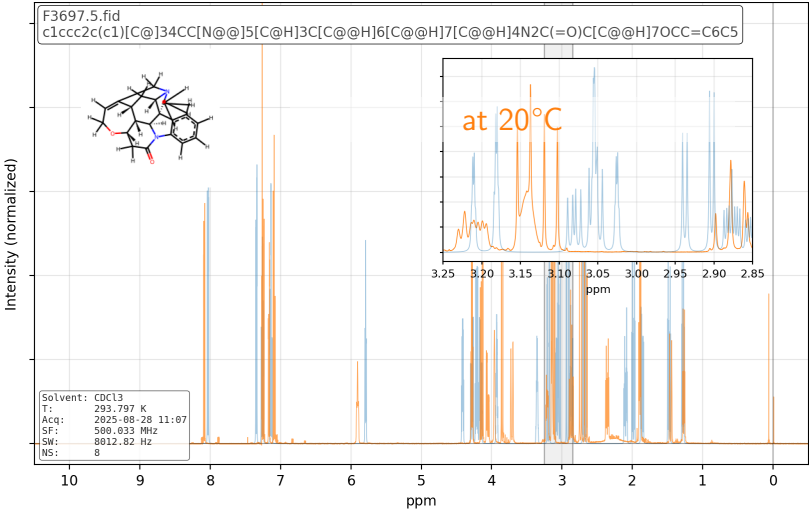

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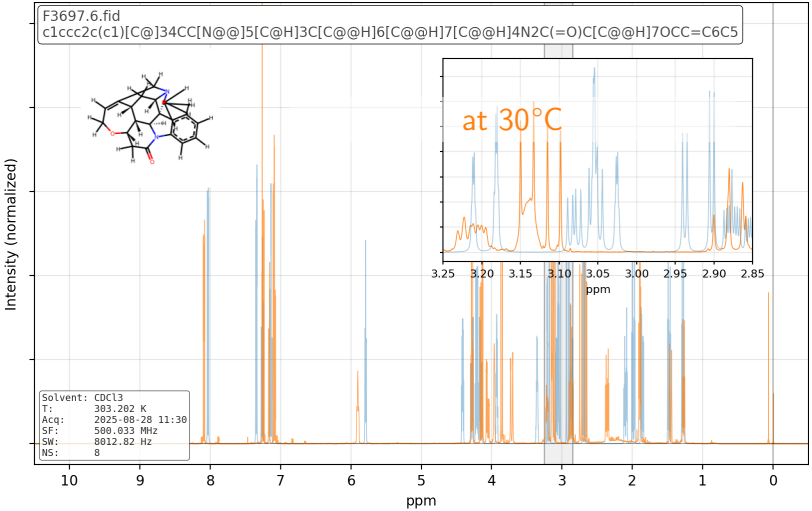

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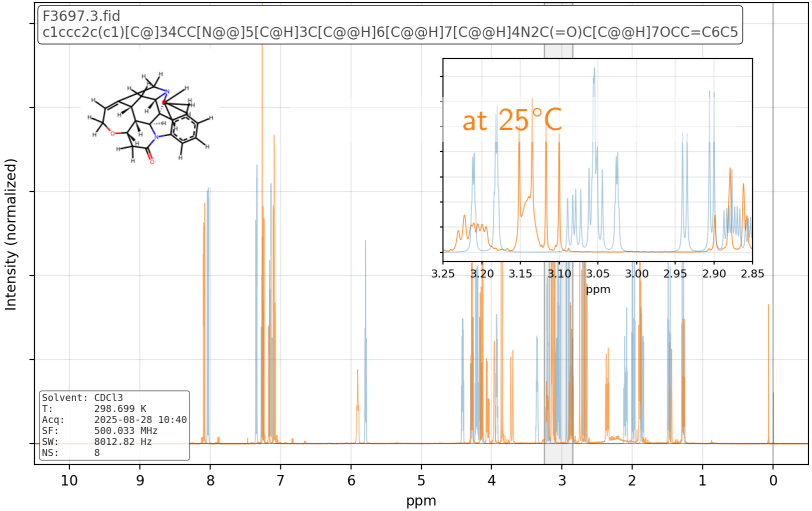

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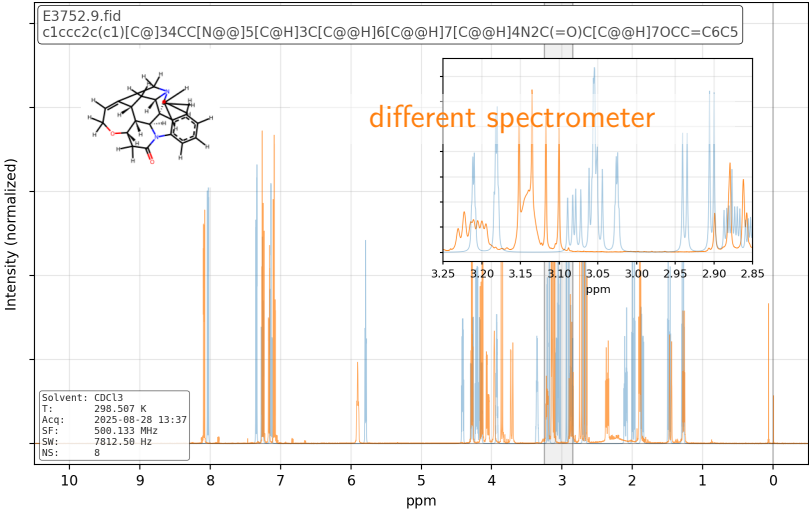

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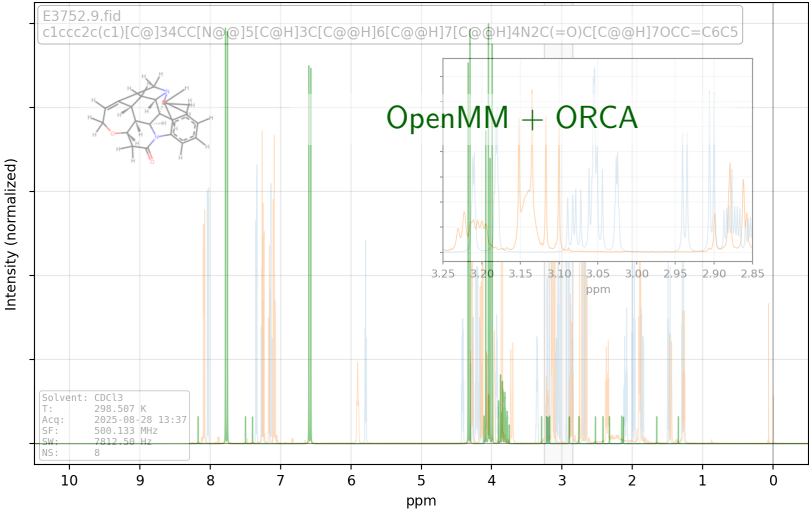

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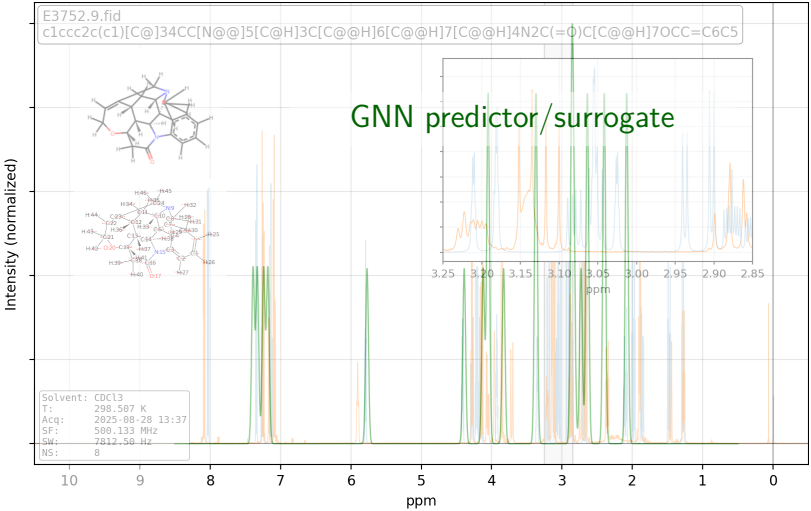

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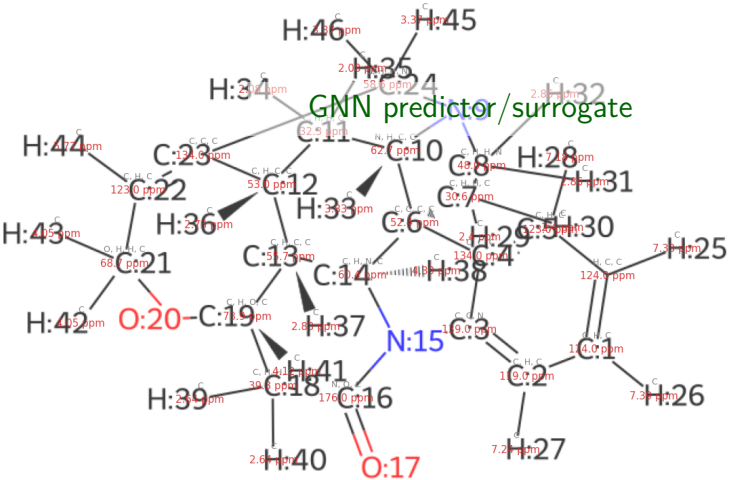

☞ ppm explorer on
the “multimodal spectroscopic dataset”
by Alberts et al., 2024 [1]

Dataset & model by Alberts et al.

- No large-scale open high-quality experimental dataset
- Alberts et al. [1] simulated spectra for ~795k molecules from USPTO [3]
- Alberts et al. [4, 5] trained transformers on simulated spectra

[4] M Alberts et al. "Learning the language of NMR: Structure elucidation from NMR spectra using transformer models". *ChemRxiv* (2023)

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[3] D Lowe. *Chemical reactions from US patents (1976–Sep2016)*. figshare, 2017

using MestReNova, similarly to

[6] F Hu et al. "Accurate and efficient structure elucidation from routine one-dimensional NMR spectra using multitask machine learning". *ACS Central Science* 10.11 (2024), pp. 2162–2170

Is it "representative"?

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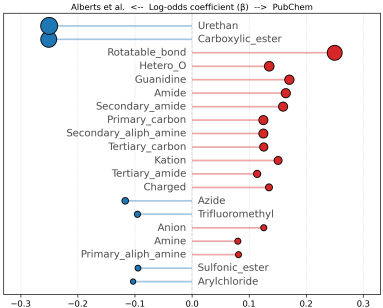

Molecule provenance,

Alberts et al. [1] vs PubChem [7]

is detected by logistic regression based on functional groups with AUC-ROC ~75%

Circle area = permutation importance $\lesssim 2\%$

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This is the dataset we use.

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- Alberts et al. [4] trained a ~30M° transformer to read a string like

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C 9 H 8 O 4 1HNMR | 7.97 7.90 dd 1H J 1.60 8.10 | 7.64
7.55 m 1H | 7.26 7.18 m 2H | 2.26 2.22 s 3H
```

- ...and infer the molecule as a *canonical* SMILES like

```
CC(=O)Oc1ccccc1C(=O)O
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- A SMILES is a (non-unique) serialization of the molecular graph
- At inference: beam search heuristic to generate the most likely SMILES
- Accuracy: Is the correct molecule among the top–N predictions?
- They reported accuracy of

~76% top–10 on $\mathrm{F} + \mathrm{H} \rightarrow \mathrm{SMILES}$
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  This is similar to, e.g., Hu et al. [6]
  But different from, e.g., Xiong et al. [8]

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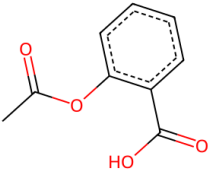
`CC(=O)Oc1c(cccc1)C(O)=O`
`CC(=O)Oc1c(C(O)=O)cccc1`
`c1cc(C(=O)O)c(OC(=O)C)cc1`
...



The hydrogens H are implied by chemical valency!

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Similarly:

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- We trained a ~83M° autoregressive transformer DistilGPT2
- ...to predict the *canonical* SMILES with accuracy

$$\sim 84\% \text{ top–10} \quad \text{on} \quad \mathrm{F} + \mathrm{Q} + \mathrm{C} + \mathrm{H} \longrightarrow \mathrm{SMILES}$$

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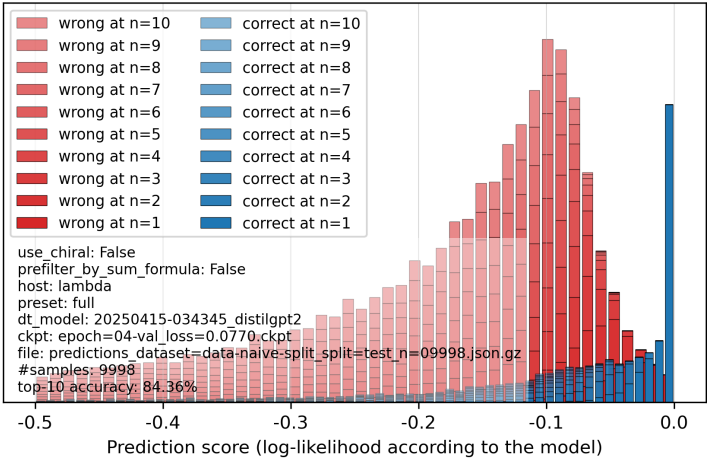
Let's have a look at the structure of the predictions:

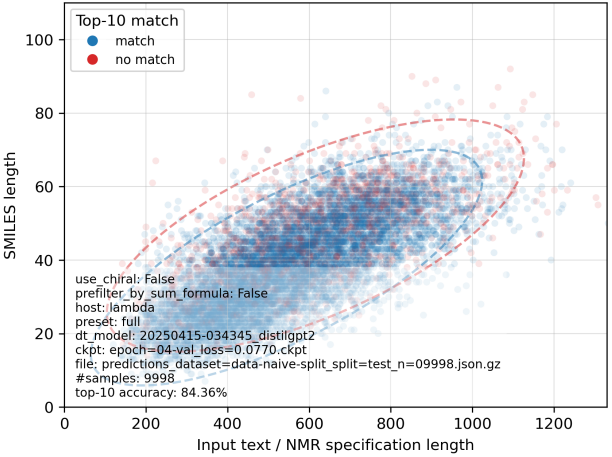
- Prediction confidence (log-likelihood of the sequence)
- Accuracy depending on SMILES length
- Diversity of predicted SMILES that serialize the correct structure
- Confidence mid-SMILES during inference
- Saliency maps: "attention" to SMILES syntax *vs.* molecular structure
- Dataset bias: in-patent SMILES similarity

Prediction confidence (log-likelihood of the sequence)



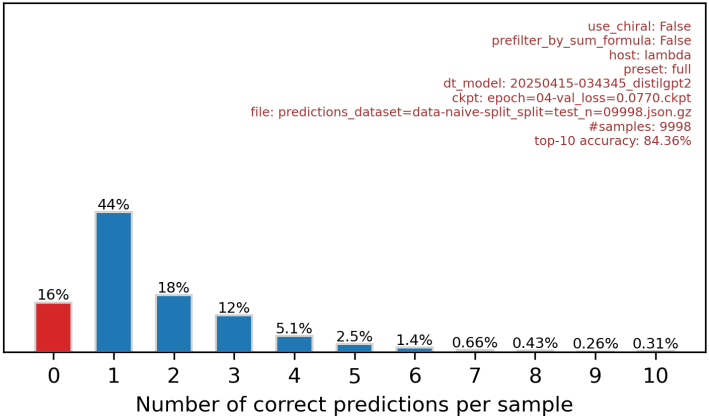
The model is more confident on correct predictions

Accuracy depending on SMILES length



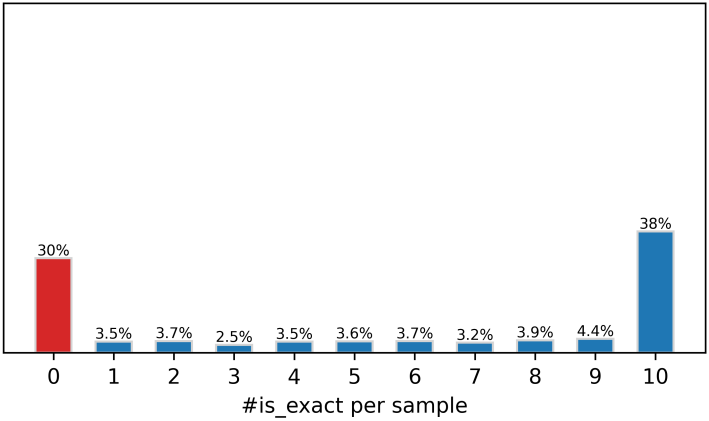
SMILES without a top–10 match are on average ~10 characters longer

Diversity of correctly predicted SMILES



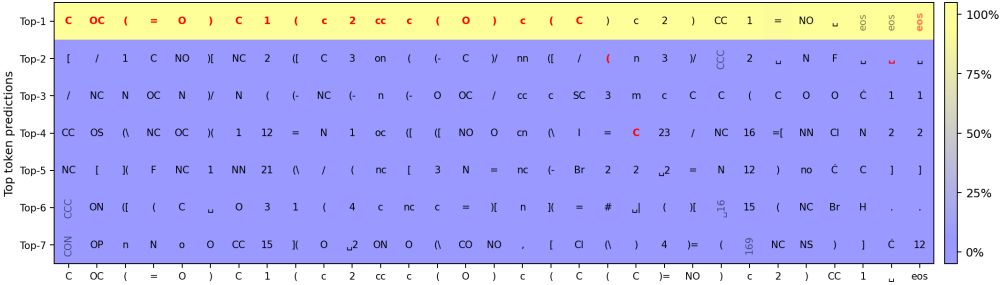
The model is unable to serialize molecules in alternate ways

Diversity of correctly predicted SMILES



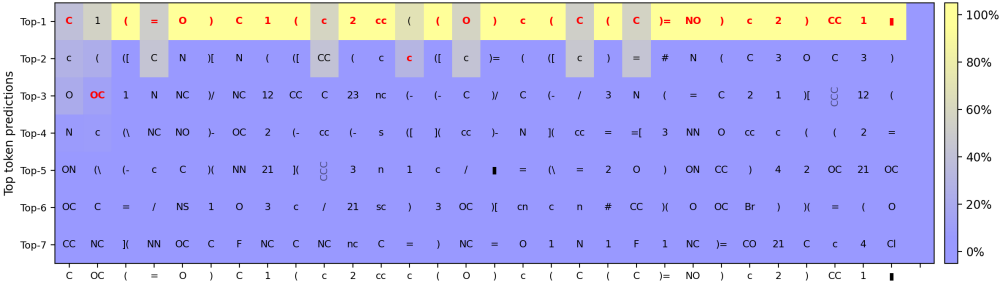
upcoming model...

Confidence mid-SMILES during inference



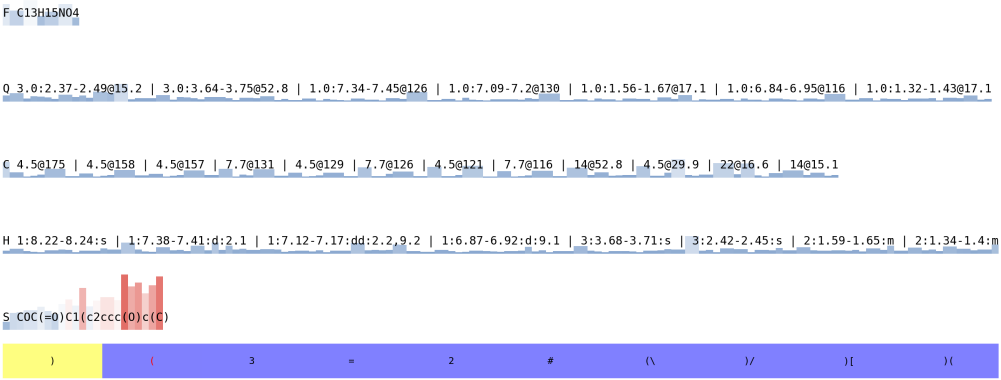
The model is confidently wrong — not a good prior for search

Confidence mid-SMILES during inference



upcoming model...

Saliency: SMILES syntax *vs.* molecular structure



The model may be focused on syntax rather than molecular structure

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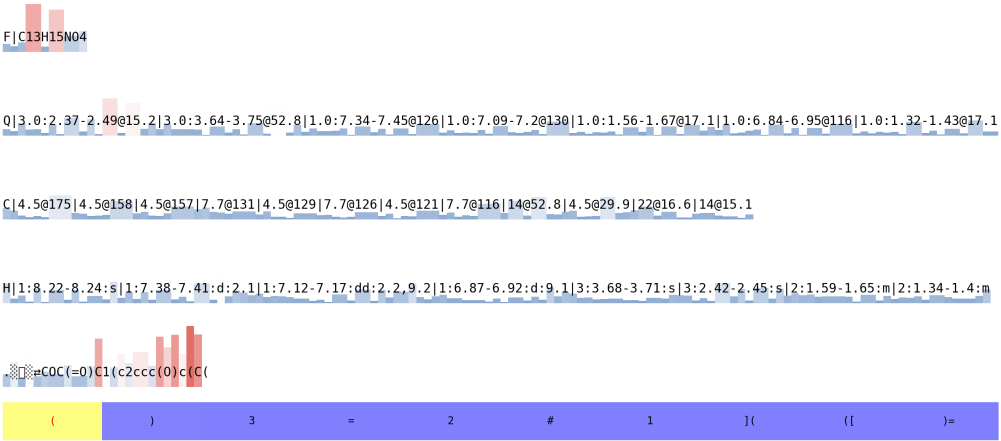

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In-patent SMILES similarity

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- US3956269 from 1976 has 26 compounds (~80% quantile), including
- The dataset is difficult to disentangle into a train/validation/test split, because of *similarity within* and *overlap between* patents
- In particular:
  - short SMILES are intrinsically easier to infer, while
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  - `Cc1ccc(OC(=O)CCC(=O)OOC(C)(C)C)cc1`
- The dataset is difficult to disentangle into a train/validation/test split, because of *similarity within* and *overlap between* patents
- In particular:
  - short SMILES are intrinsically easier to infer, while
  - long SMILES are made easier by in-patent association

In-patent SMILES similarity

- Alberts et al. [1] simulated spectra for ~795k molecules from USPTO [3]
- US3956269 from 1976 has 26 compounds (~80% quantile), including
  - `Cc1ccc(OC(=O)CCCC(=O)OOC(=O)CCCC(=O)Oc2ccc(C)cc2)cc1`
  - `Cc1ccc(OC(=O)CCCC(=O)OOC(·····C···)·····(C)··C)cc1`
  - `Cc1ccc(OC(=O)·CCC(=O)OOC(=O)·CCC(=O)Oc2ccc(C)cc2)cc1`
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  - They didn't, as far as we can tell
  - We embedded SMILES and used k-means to split (→ appendix)
- In particular:
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- In particular:
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⚠ The ~85% top–10 accuracy is very scenario-specific

⚠ The model learns chunks of SMILES – not molecular structure

Graph representation integrating multiple alternate chemical equivalents

GRIMACE

c1ccc(C(=O)O)c(c1)OC(C)=O

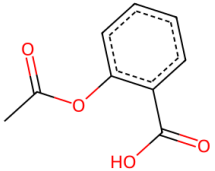
CC(=O)Oc1c(cccc1)C(O)=O

CC(=O)Oc1c(C(O)=O)cccc1

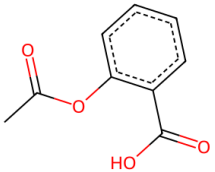
c1cc(C(=O)O)c(OC(=O)C)cc1

...

how many in total?



```
c1ccc(C(=O)O)c(c1)OC(C)=O
CC(=O)Oc1c(cccc1)C(O)=O
CC(=O)Oc1c(C(O)=O)cccc1
c1cc(C(=O)O)c(OC(=O)C)cc1
...
```



`c1ccc(C(=O)O)c(c1)OC(C)=O`

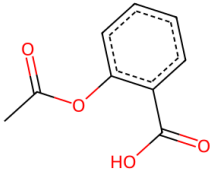
`CC(=O)Oc1c(cccc1)C(O)=O`

`CC(=O)Oc1c(C(O)=O)cccc1`

`c1cc(C(=O)O)c(OC(=O)C)cc1`

...

304 distinct serializations



"restricted" by `rdkit` to sensible variants

- It makes sense to train

  random serialization $\rightarrow$ molecular properties

  as data augmentation and regularization [9]
- Does it make sense to train

  NMR data $\rightarrow$ random serialization – ?
- Consider two serializations, shown to the model at random:

  `c1(ccccc1OC(=O)C)C(O)=O` and `c1(ccccc1OC(C)=O)C(O)=O`
- The model will eventually learn the next-token probabilities

  $\mathbb{P}(\boxed{=} \mid \underline{\text{prefix}}) \approx 50\%$ and $\mathbb{P}(\boxed{\texttt{C}} \mid \underline{\text{prefix}}) \approx 50\%$
- This training signal is weak, inconsistent and incomplete
- Key idea:

- It makes sense to train

$$\text{random serialization} \rightarrow \text{molecular properties}$$

- Does it make sense to train

$$\text{NMR data} \rightarrow \text{random serialization}$$

where the serialization changes from epoch to epoch?

- Consider two serializations, shown to the model at random:

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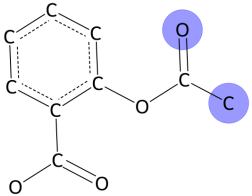

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- Does it make sense to train

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but:

- This training signal is weak, inconsistent and incomplete
- Key idea:

- It makes sense to train

$$\text{random serialization} \rightarrow \text{molecular properties}$$

- Does it make sense to train

$$\text{NMR data} \rightarrow \text{random serialization} \quad - \ ?$$

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- This training signal is weak, inconsistent and incomplete:
  - pulls one token at a time,
  - we can't cycle through many variants.
- Key idea:

- It makes sense to train

$$\text{random serialization} \rightarrow \text{molecular properties}$$

- Does it make sense to train

$$\text{NMR data} \rightarrow \text{random serialization} \quad - \ ?$$

- Consider two serializations, shown to the model at random:

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- This training signal is weak, inconsistent and incomplete
- Key idea: Let's supervise on the next-token distribution directly

Next-token supervision with GRIMACE

- Key idea: Let's supervise on the next-token distribution directly
- Sample serializations of the same molecule and tokenize them
- ...until a stopping criterion is met ($\rightarrow$ appendix)
- Construct the word tree (merge common prefixes and suffixes)
- Count samples passing each out-edge and normalize to probabilities
- To train, pick one path per epoch, supervise on those probabilities

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CC	(	=	O	)	O	c	1	c	(	C	(	O	)=	O	)	cc	cc	1

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CC	(	=	O	)	O	c	1	c	(	cc	cc	1	)	C	(	O	)=	O
c	1	(	cc	cc	c	1	OC	(	=	O	)	C	)	C	(	O	)=	O

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c	1	(	cc	cc	c	1	OC	(	=	O	)	C	)	C	(	O	)=	O
c	1	(	cc	cc	c	1	OC	(	C	)=	O	)	C	(	O	)=	O	

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c	1	(	cc	cc	c	1	OC	(	=	O	)	C	)	C	(	O	)=	O
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c	1	(	cc	cc	c	1	OC	(	=	O	)	C	)	C	(	O	)=	O
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	CC	(	=	O	)	O	c	1	c	(	cc	cc	1	)	C	(	O	)=	O
→	c	1	(	cc	cc	c	1	OC	(	=	O	)	C	)	C	(	O	)=	O
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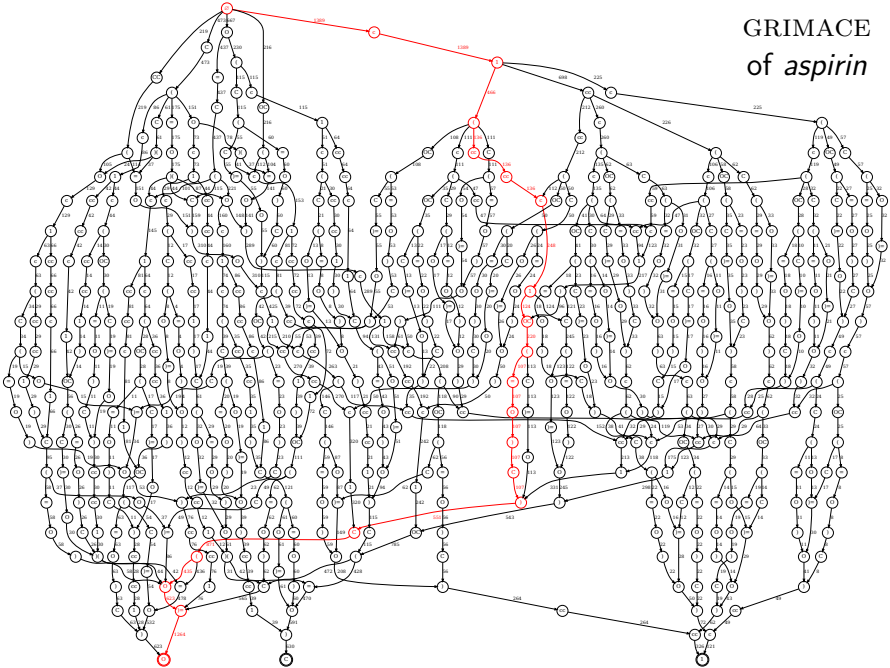
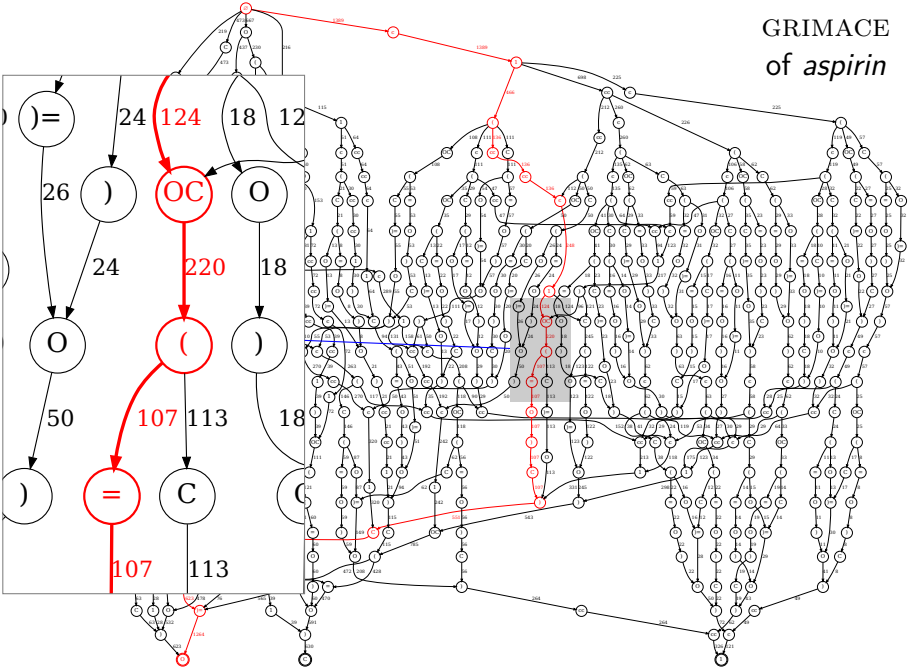
GRIMACE

of *aspirin*



GRIMACE

of *aspirin*



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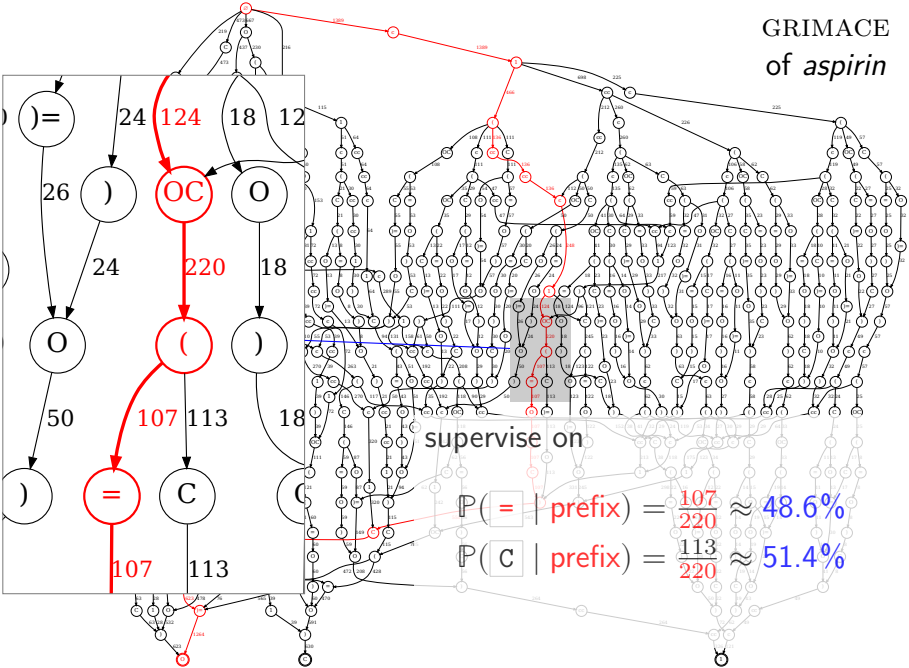
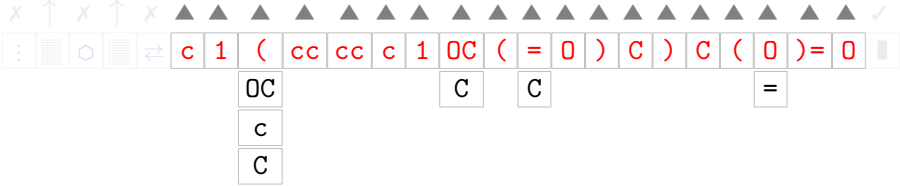


supervise on

$$\mathbb{P}(\boxed{=} \mid \text{prefix}) = \frac{107}{220} \approx 48.6\%$$

$$\mathbb{P}(\boxed{\texttt{C}} \mid \text{prefix}) = \frac{113}{220} \approx 51.4\%$$

We supervise the output with “teacher forcing” on sequences like



where

trigger tokens:

- ⋮ – vector embedding [10]
- ⬡ – functional group counts
- ⇄ – GRIMACE
- ▒ – not-a-token

supervision:

- ▲ – KL divergence $\times(1+q)^n$
- ✓ – cross-entropy
- ✗ – none
- ↑ – auxiliary head

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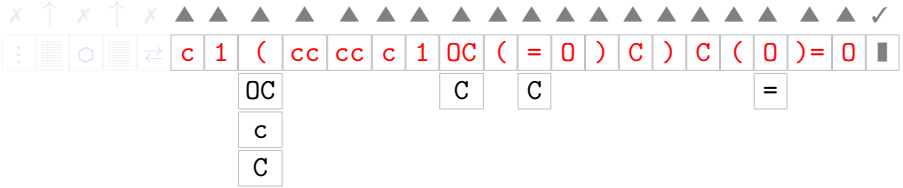

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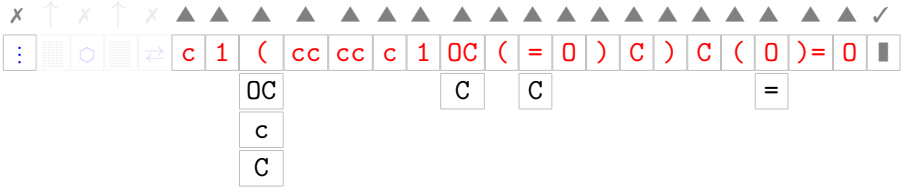

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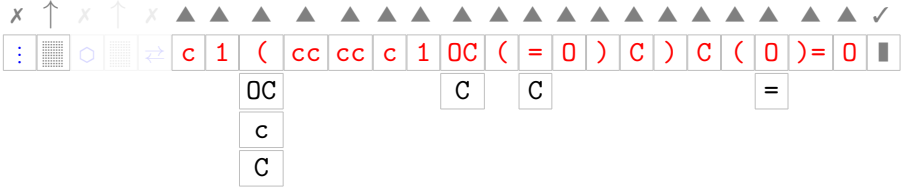

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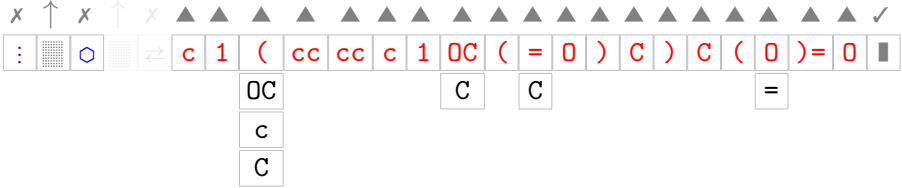

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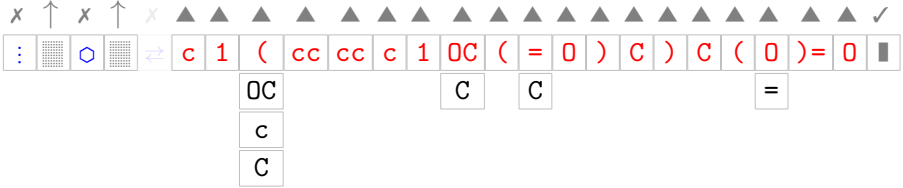

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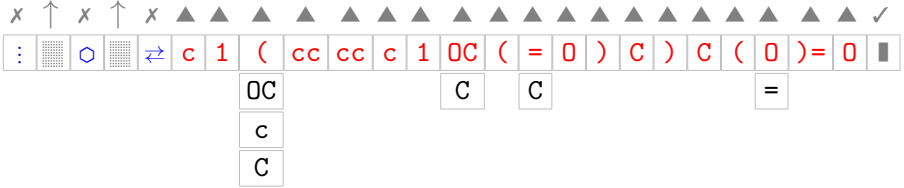

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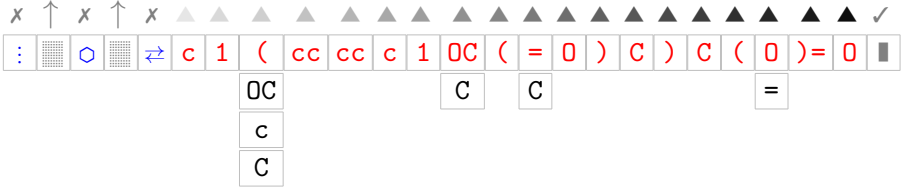

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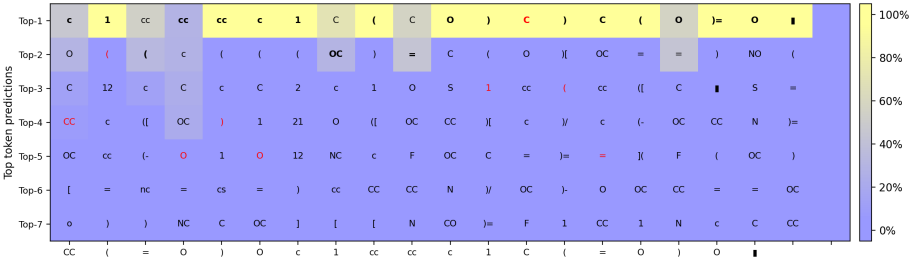
Inference with a trained model (*aspirin*)



bold: teacher-forced; red: canonical

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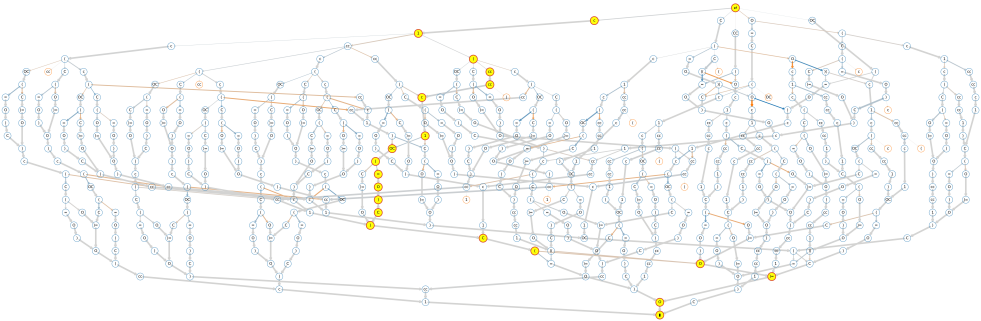


Training & results

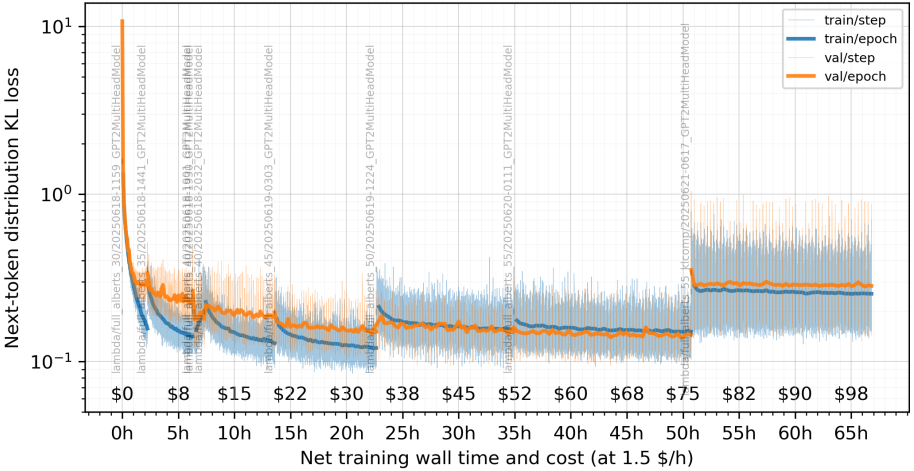
We trained

- the ~83M° DistilGPT2 decoder-only transformer
- on the Alberts et al. [1] dataset – up to ~560k training samples
- on an NVIDIA GH200 – ARM64 + H100: 96 GB VRAM, 64 vCPUs, 432 GiB RAM
- to infer

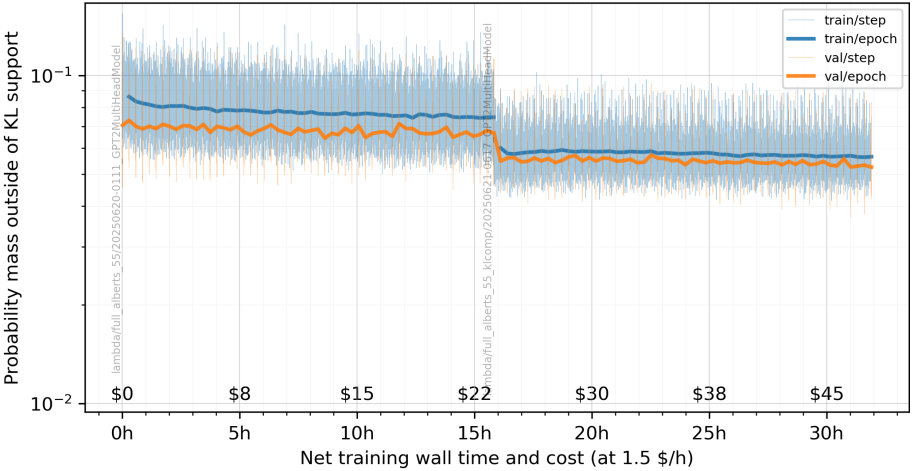
$$\mathrm{F} + \mathrm{Q} + \mathrm{C} + \mathrm{H} \rightarrow \boxed{\vdots}\,\boxed{\cdots}\,\boxed{\bigcirc}\,\boxed{\cdots}\,\boxed{\rightleftarrows}\ \mathrm{GRIMACE}\ \boxed{\blacksquare}$$

- through a curriculum of increasing SMILES length:
  1. 30 epochs on $|\mathrm{SMILES}| \leq 30$ from the pre-trained state
  2. 35 epochs on $|\mathrm{SMILES}| \leq 35$
  3. 40 epochs on $|\mathrm{SMILES}| \leq 40$
  4. 45 epochs on $|\mathrm{SMILES}| \leq 45$
  5. 50 epochs on $|\mathrm{SMILES}| \leq 50$
  6. 55 epochs on $|\mathrm{SMILES}| \leq 55$
  7. 55 epochs on $|\mathrm{SMILES}| \leq 55$ with KL geometric weight 5%

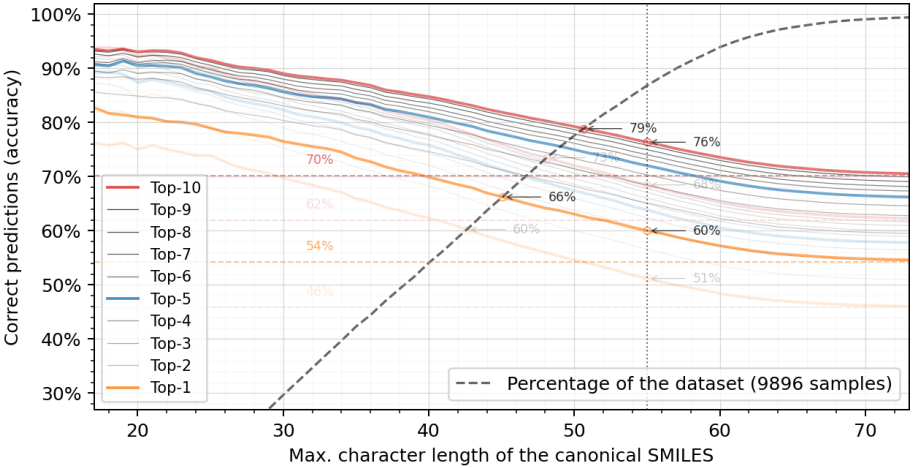
KL loss during training runs 1 to 6 (no KL weight) and 7 (with KL weight)



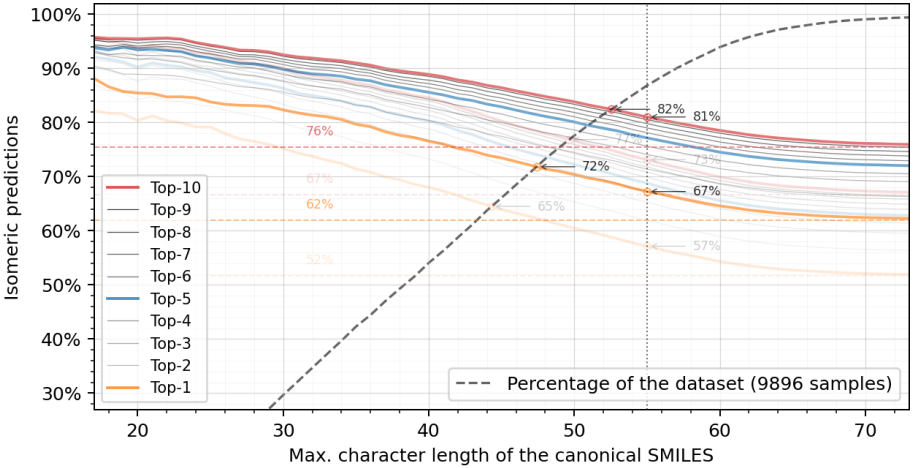
Off-support loss during training (last two runs: effect of KL weight)



Accuracy on the test set (exact match)

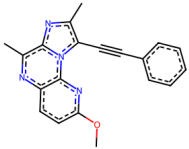


Accuracy on the test set (stereo-isomer match – ignoring stereochemistry)

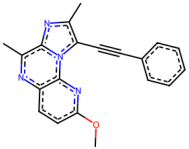


Example: the top–10 predictions for a test sample

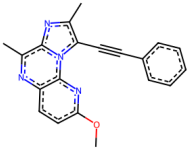
c1(C)c2n(c(C#Cc3ccccc3)c(C)n2)c2c(ccc(n2)OC)n1



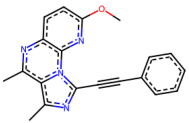
c1(C)c2n(c(C#Cc3ccccc3)c(C)n2)c2c(ccc(OC)n2)n1



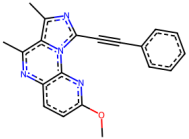
c1(C)c2n(c(C#Cc3ccccc3)c(n2)C)c2c(ccc(n2)OC)n1



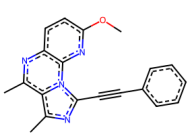
C(#Cc1ccccc1)c1n2c(c(C)nc3c2nc(cc3)OC)c(C)n1



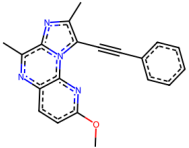
C(#Cc1ccccc1)c1n2c3c(ccc(n3)OC)nc(c2c(C)n1)C



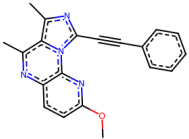
c1cccccc1C#Cc1n2c(c(C)nc3c2nc(cc3)OC)c(C)n1



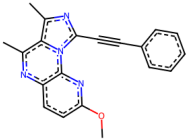
c1(C)c2n(c(C#Cc3ccccc3)c(n2)C)c2c(ccc(OC)n2)n1



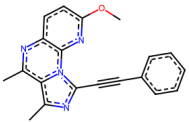
C(#Cc1ccccc1)c1n2c(c(C)nc3ccc(nc32)OC)c(C)n1



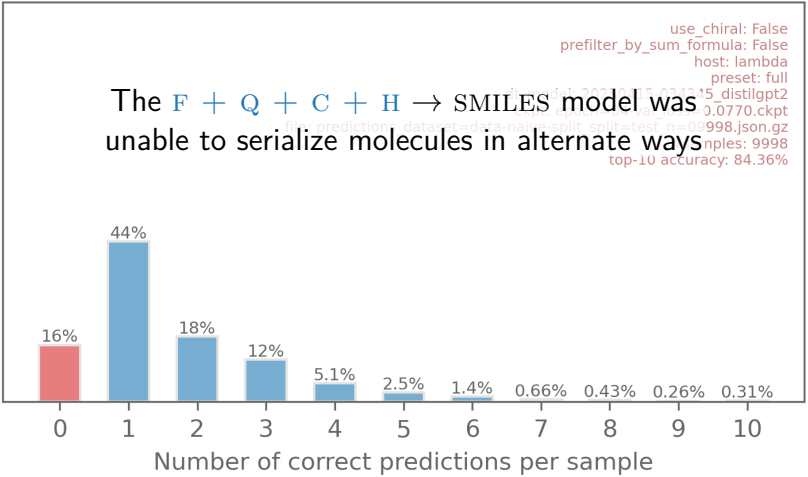
C(#Cc1ccccc1)c1n2c(c(C)nc3ccc(nc23)OC)c(C)n1



c1cc(cccc)C#Cc1n2c(c(C)nc3c2nc(cc3)OC)c(C)n1

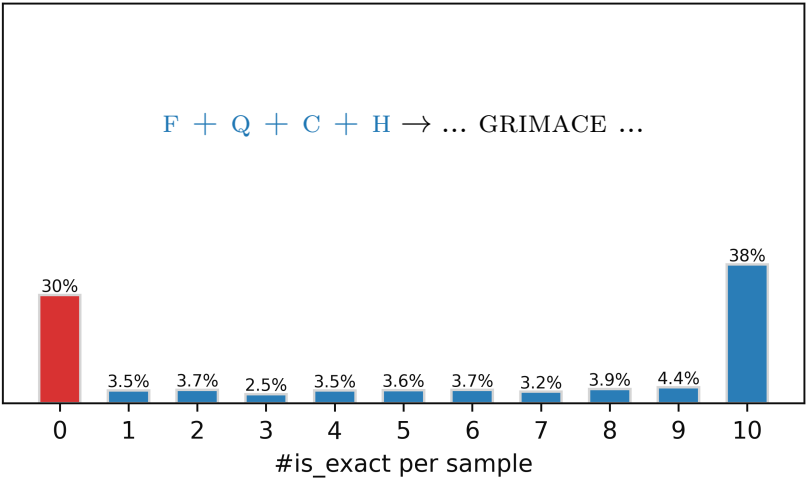


Diversity of predictions



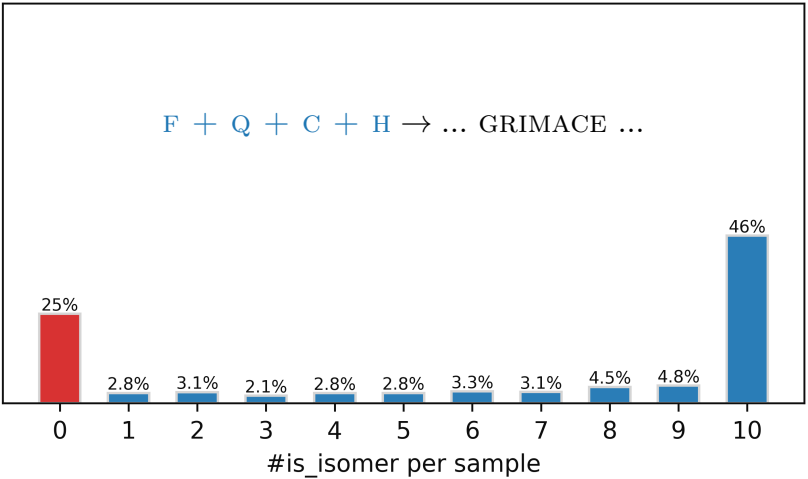
The $\mathrm{F} + \mathrm{Q} + \mathrm{C} + \mathrm{H} \rightarrow \mathrm{SMILES}$ model was unable to serialize molecules in alternate ways

Diversity of predictions



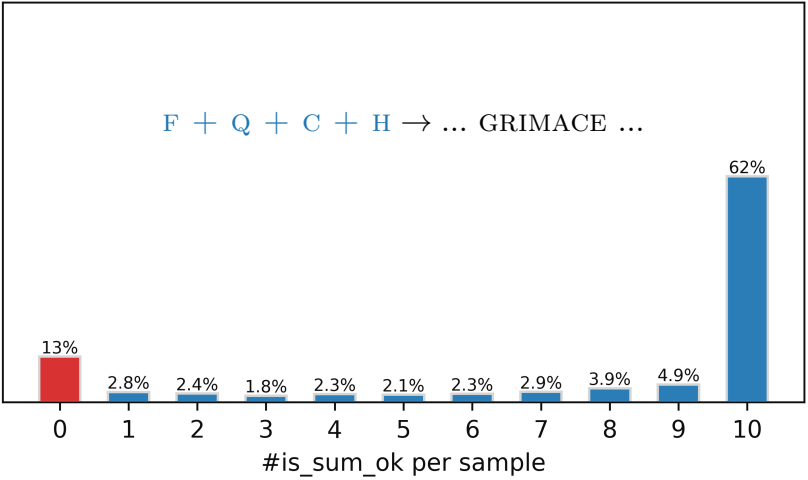
In 38% of test samples, all 10 predictions are exact

Diversity of predictions



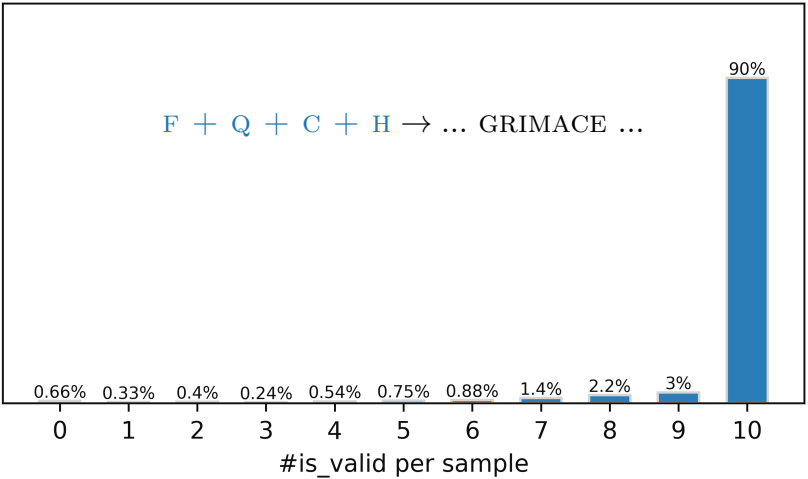
Stereo-isomer = equal connectivity (modulo 3d flags)

Diversity of predictions



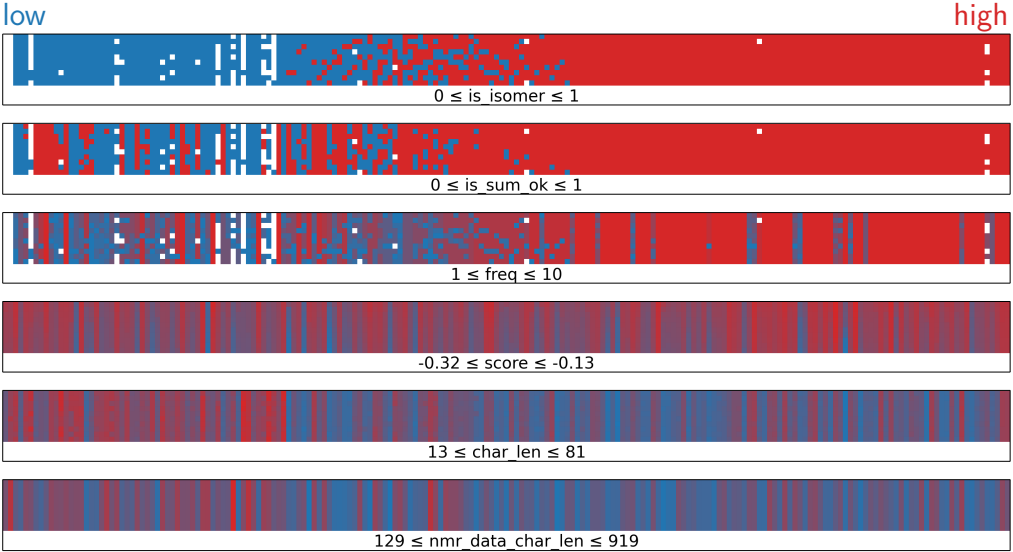
How often is the chemical sum formula correct?

Diversity of predictions

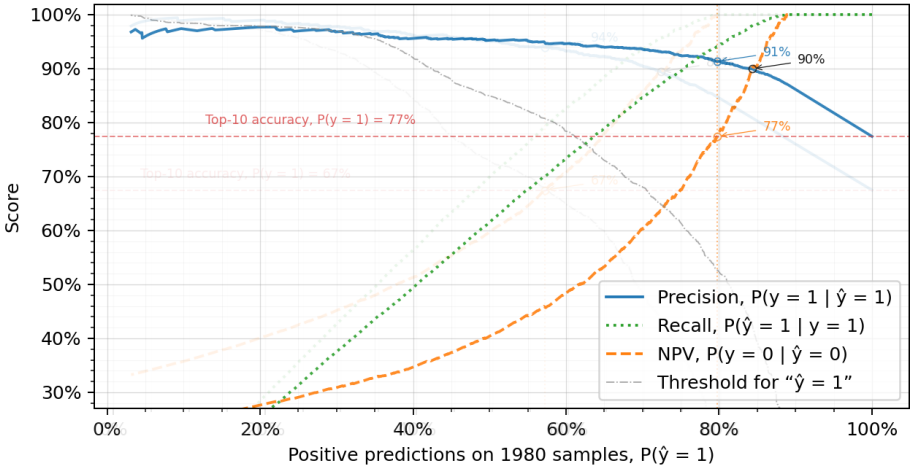


How often is the generated SMILES valid?

“Flag plot” of 10 hypotheses × 200 test samples



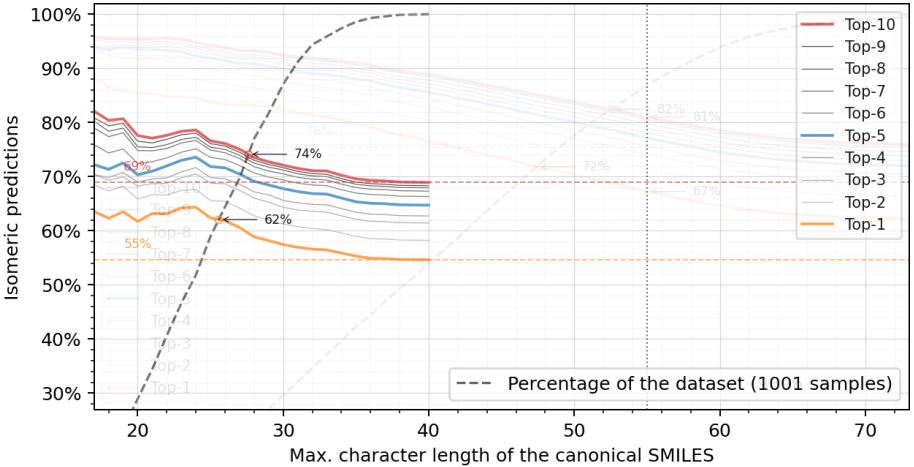
Data-informed confidence estimator – DICE



Meta-classifier for $y =$ "Is there a top–10 stereo-isomer match?" has $\mathbb{P}(\hat{y} = y) \approx 90\%$

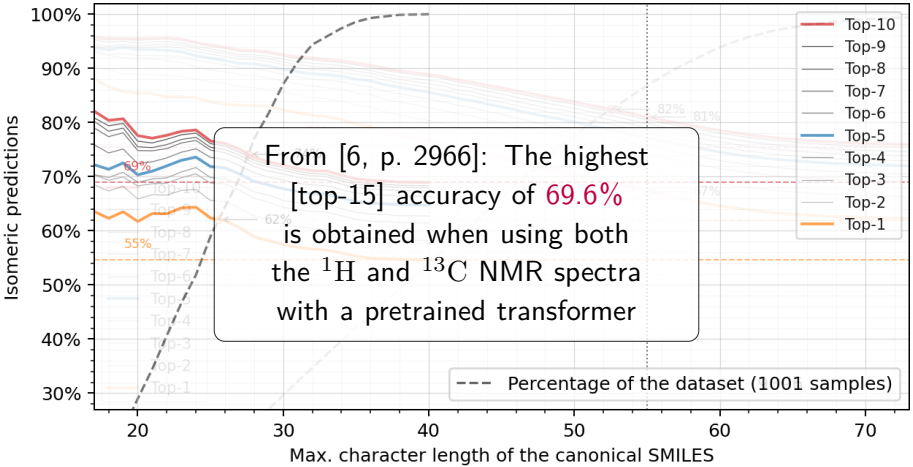
— for context —

Evaluation on SpectraBase – simulated w/ Mnova; as in Hu et al., 2024 [6][1]



[1] Stanford / NYU

Evaluation on SpectraBase – simulated w/ Mnova; as in Hu et al., 2024 [6][1]



From [6, p. 2966]: The highest [top-15] accuracy of 69.6% is obtained when using both the $^{1}\mathrm{H}$ and $^{13}\mathrm{C}$ NMR spectra with a pretrained transformer

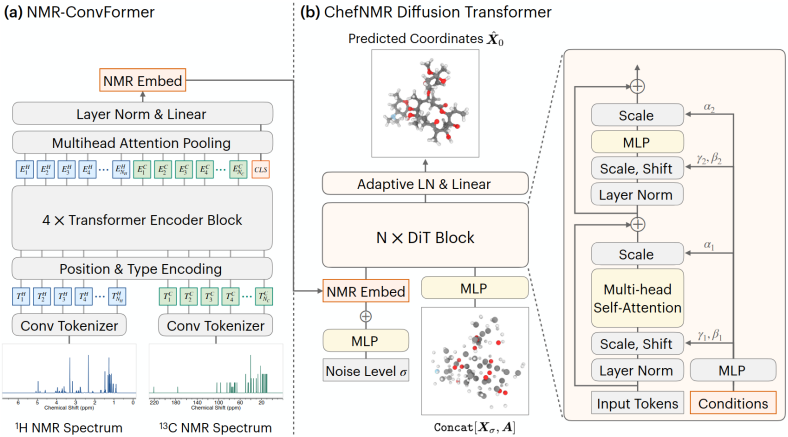
[1] Stanford / NYU

Table 3 from Alberts et al., 2024 [1][2]

	Top–1, %	Top–5, %	Top–10, %
IR	9.97 ± 0.46	21.23 ± 0.33	24.01 ± 0.42
MS/MS (CFM-ID, neg)	20.98 ± 0.23	39.32 ± 0.19	44.93 ± 0.29
MS/MS (CFM-ID, pos)	23.53 ± 0.21	42.59 ± 0.14	47.53 ± 0.31
MS/MS (SCARF, pos)	1.92 ± 0.11	5.26 ± 0.37	6.81 ± 0.48
MS/MS (ICEBERG, pos)	15.52 ± 2.10	31.46 ± 3.28	36.22 ± 3.45
$^{13}\mathrm{C}$	51.95 ± 0.29	70.01 ± 0.21	74.12 ± 0.30
$^{1}\mathrm{H}$	64.99 ± 0.31	81.94 ± 0.31	84.07 ± 0.32
$^{1}\mathrm{H} + {}^{13}\mathrm{C}$	73.38 ± 0.08	87.94 ± 0.14	89.98 ± 0.16

[2] IBM / UZH / EPFL / NCCR

From Figure 2/4 / Table 2 of "ChefNMR" by Xiong et al., 2025 [8][3]



[3] Princeton

From Figure 2/4 / Table 2 of "ChefNMR" by Xiong et al., 2025 [8][3]

Dataset	Model	Top–1		Top–10	
		Acc ↑	Sim ↑	Acc ↑	Sim ↑
SpectraBase	Hu et al.	45.24%	0.686	67.38%	0.847
	NMR-DiGress	43.56%	0.625	68.39%	0.817
	CHEFNMR-S	69.15%	0.807	85.30%	0.922
	CHEFNMR-L	72.04%	0.833	88.20%	0.940
USPTO	Hu et al.	38.02%	0.674	61.76%	0.845
	Alberts et al.*	73.38%	N/A	89.98%	N/A
	NMR-DiGress	22.51%	0.504	48.87%	0.761
	CHEFNMR-S	81.16%	0.902	92.90%	0.973
	CHEFNMR-L	81.57%	0.912	93.01%	0.973
SpectraNP	Hu et al.	19.26%	0.585	39.87%	0.774
	NMR-DiGress	2.12%	0.260	9.17%	0.485
	CHEFNMR-S	40.37%	0.583	64.37%	0.834
	CHEFNMR-L	40.15%	0.631	65.74%	0.860

[3] Princeton

From Figure 2/4 / Table 2 of "ChefNMR" by Xiong et al., 2025 [8][3]

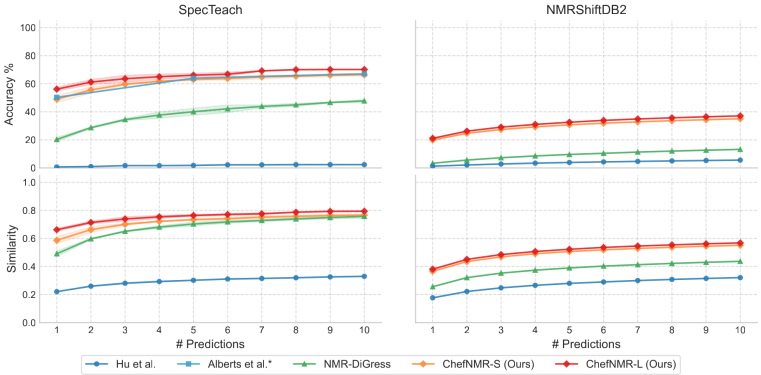


Figure 4: Zero-shot performance on experimental NMR spectra, shown as the mean ± standard deviation over three independent sampling runs. Models are trained on `USPTO`. Evaluation is on ^{1}H and ^{13}C spectra for `SpecTeach`, and on ^{13}C spectra for `NMRShiftDB2`.*: reported results.

[3] Princeton

The "oracle" of Jonas, 2019 [11][4]

[11] E Jonas. "Deep imitation learning for molecular inverse problems". *Advances in Neural Information Processing Systems*. Vol. 32. 2019

- Assumes the molecular formula is known
- Trains a neural net to complete a partial molecular graph
- The teacher/oracle presents *all valid typed one-bond completions*
- ...and the net is trained against this multi-hot target
- Candidate molecules are ranked by a forward NMR predictor
- ~56% top-1 accuracy on experimental $^{13}\mathrm{C}$-NMR (NMRShiftDB)

[4] U Chicago

Graph neural net encoder → latent → GRIMACE decoder [wip]

A simple graph "convolutional" neural net is a "bag of atoms" like NMR:

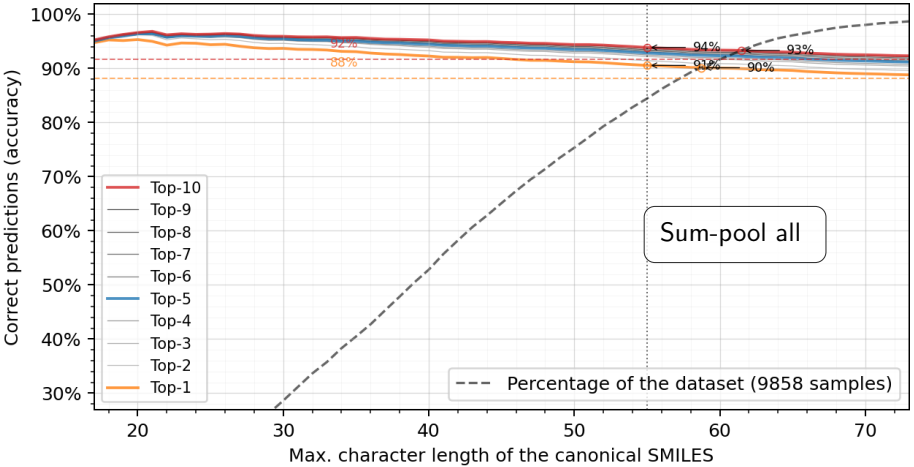
- Given atom features $h^{(0)}$, for each layer $\ell = 1, \ldots, L$:

$$h_v^{(\ell)} = \mathrm{Dropout} \circ \mathrm{SiLU} \circ \mathrm{MLP}^{(\ell)} \left(h_v^{(\ell-1)} + \sum_{u-v} h_u^{(\ell-1)} \right)$$

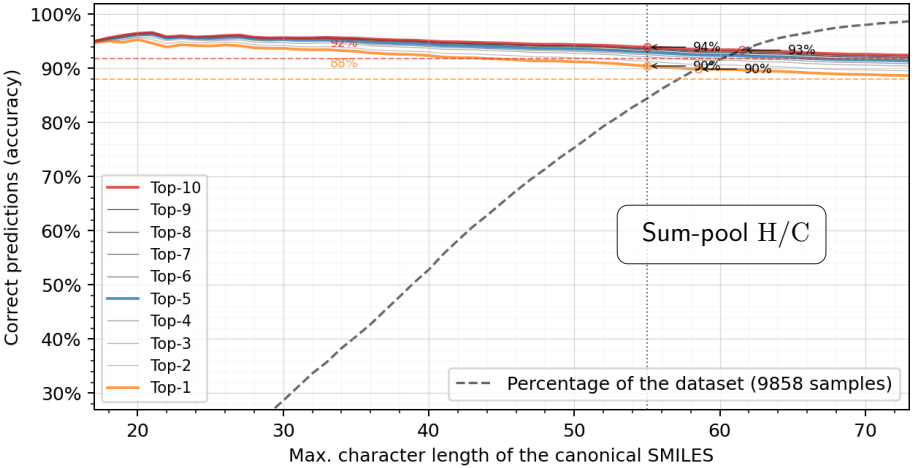
- Sum-pool $h_{\mathrm{mol}} = \sum_v h_v^{(L)}$, and transform further into latent $z \in \mathbb{R}^{256}$
- NMR twist: sum-pool only H and C atoms

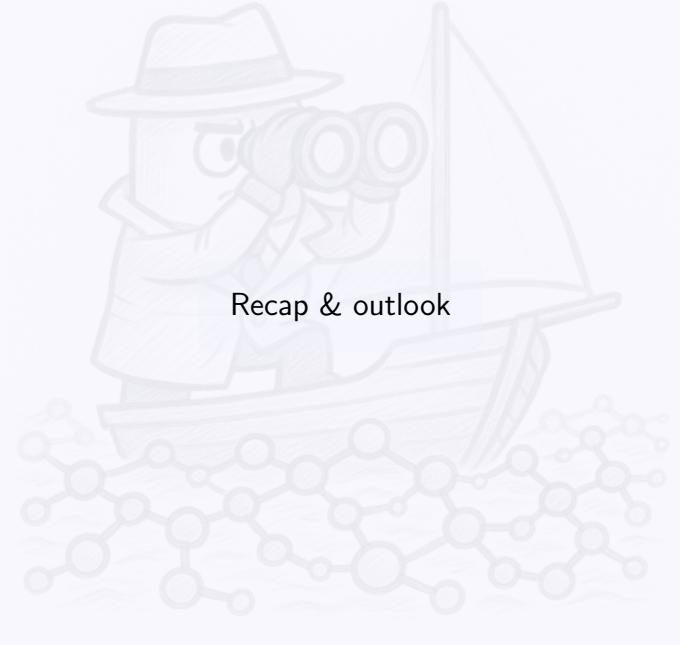
The molecule is reconstructed from the latent z with a custom Llama-like 17M° language transformer trained with GRIMACE supervision on the ~795k molecules from Alberts et al. [1].

Graph neural net encoder → latent → GRIMACE decoder [wip]



Graph neural net encoder → latent → GRIMACE decoder [wip]





Recap & outlook

Recap

Graph representation integrating multiple alternate chemical equivalents is a novel* way of teaching chemical structures to language transformers

It allows the model to express uncertainty

The multimodal NMR annotation → GRIMACE multi-task transformer achieves ~80% top–10 accuracy on ~80% of the synthetic dataset (and we can tell with ~90% confidence)

Outlook

Spectroscopy:

- A data-driven model of variability in experimental NMR spectra
- Cycle-consistent search with "NMR $\rightarrow$ GRIMACE" as a prior

GRIMACE:

- A spectrum-aware auto-encoder for molecules
- An efficient way to compute the reference GRIMACE

– Proompt-art: GPT-4o –

References I

[1] M Alberts et al. "Unraveling molecular structure: A multimodal spectroscopic dataset for chemistry". *NeurIPS 2024 Datasets and Benchmarks Track*. 2024.

[2] B Hong et al. "Biosynthesis of strychnine". *Nature* 607 (2022), pp. 617–622.

[3] D Lowe. *Chemical reactions from US patents (1976–Sep2016)*. figshare, 2017.

[4] M Alberts, F Zipoli, and AC Vaucher. "Learning the language of NMR: Structure elucidation from NMR spectra using transformer models". *ChemRxiv* (2023).

[5] M Alberts, N Hartrampf, and T Laino. "Automated structure elucidation at human-level accuracy via a multimodal multitask language model". *ChemRxiv* (2025).

[6] F Hu et al. "Accurate and efficient structure elucidation from routine one-dimensional NMR spectra using multitask machine learning". *ACS Central Science* 10.11 (2024), pp. 2162–2170.

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[7] S Kim et al. "PubChem 2025 update". *Nucleic Acids Research* 53.D1 (2025), pp. D1516–D1525.

[8] Z Xiong et al. "Atomic diffusion models for small molecule structure elucidation from NMR spectra". *arXiv* 2512.03127 (2025).

[9] EJ Bjerrum. "SMILES enumeration as data augmentation for neural network modeling of molecules". *arXiv* 1703.07076 (2017).

[10] W Ahmad et al. "ChemBERTa-2: Towards chemical foundation models". *arXiv* 2209.01712v1 (2022).

[11] E Jonas. "Deep imitation learning for molecular inverse problems". *Advances in Neural Information Processing Systems*. Vol. 32. 2019.

Appendix

The multi-task objective

$$\text{minimize} \quad \sum_{\text{task}} \left(\sigma_{\text{task}}^{-2}\,\mathrm{softplus}(\text{loss}_{\text{task}}) + \log \sigma_{\text{task}}^2\right)$$

with trainable σ_{task}, consists of the task-specific losses:

- for the "chembedding" head

$$\mathbf{e} \quad \mapsto \quad \tfrac{1}{n}\left(\tfrac{1}{2}\|T\mathbf{e}\|_2^2 - \log\det T + \tfrac{n}{2}\log 2\pi\right), \quad n = 384,$$

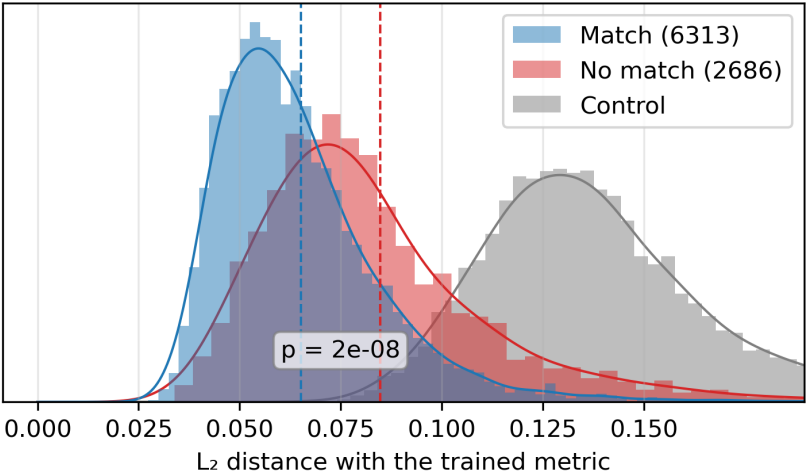
- for the "$\log(1 +$ functional group count$)$" head

$$\mathbf{f} \quad \mapsto \quad \tfrac{1}{m}\left(\|S\mathbf{f}\|_1 - \log\det S + m\log 2\right), \quad m = 289,$$

- average KL loss for the GRIMACE,
- cross-entropy loss for the end-of-sequence token,

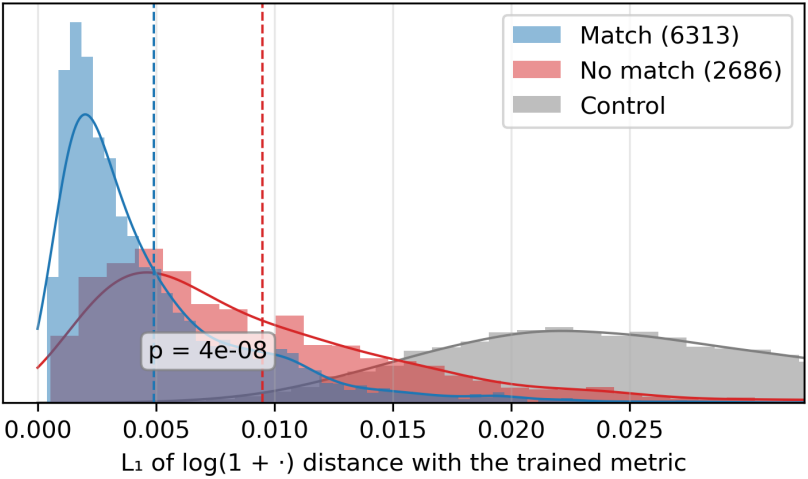
where T and S are trainable matrices.

“chembedding” head loss

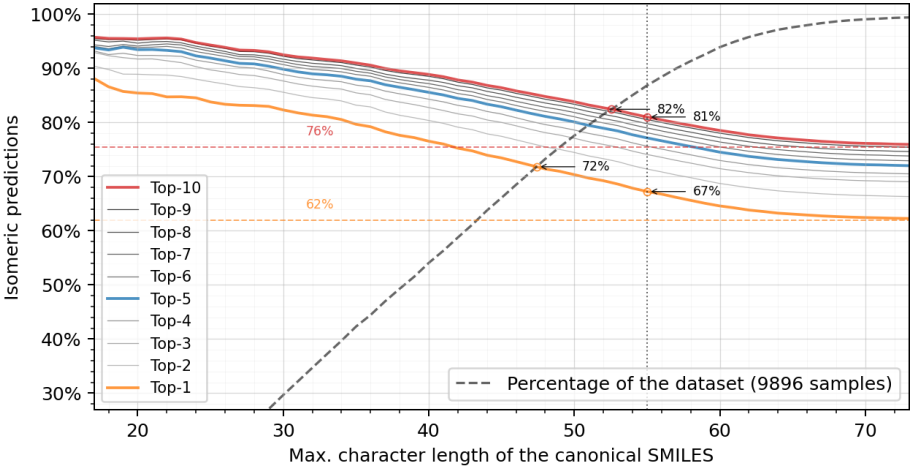


$\frac{1}{\sqrt{n}}\|T \cdot\|_2$-norm, stratified by whether there is a top–10 match

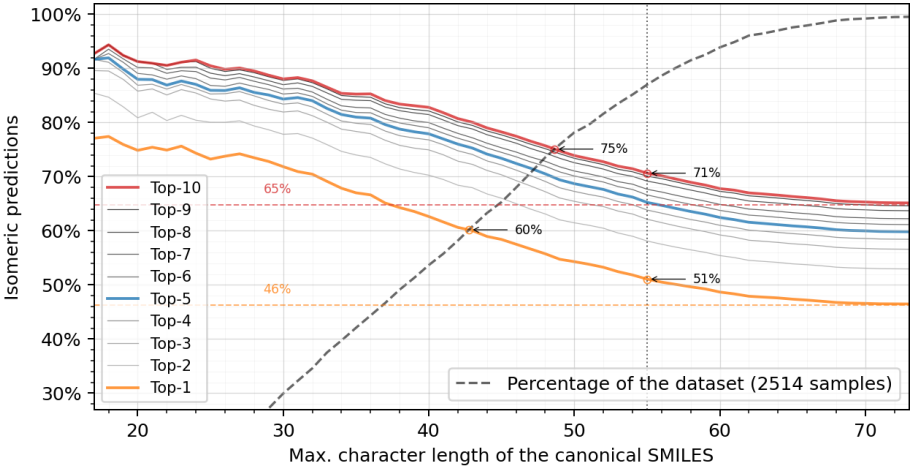
Functional group count loss



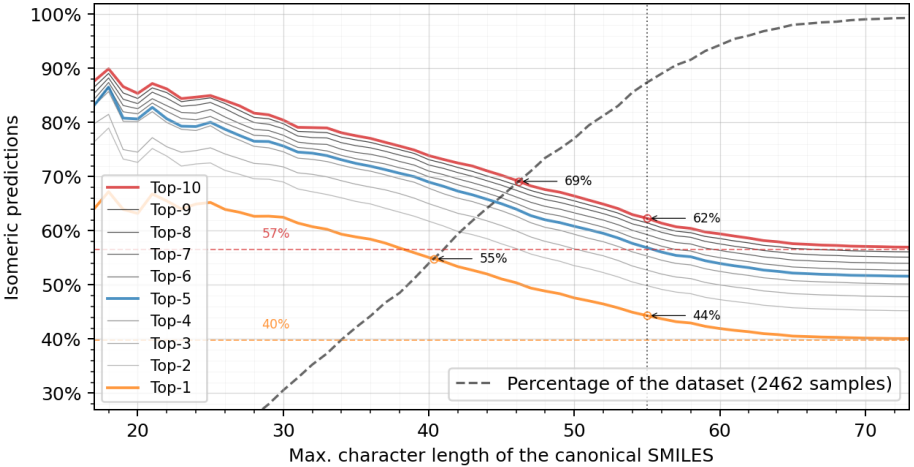
$\frac{1}{m}\|S \cdot\|_1$-norm, stratified by whether there is a top–10 match



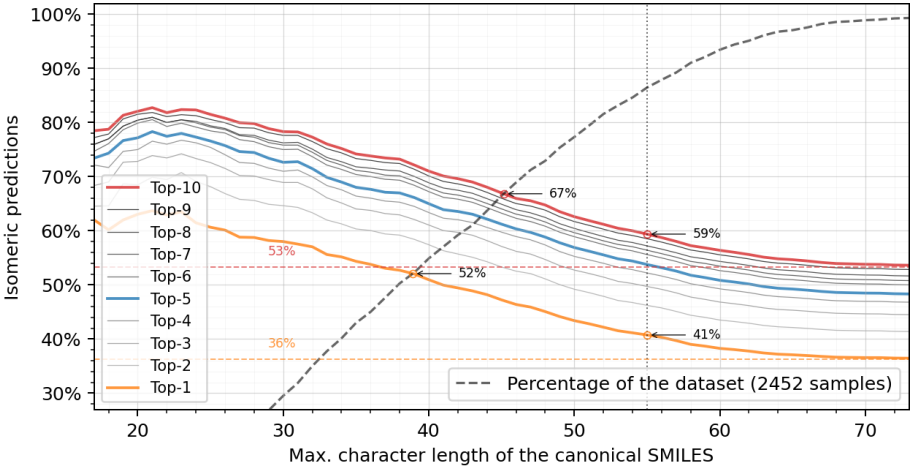
Original training



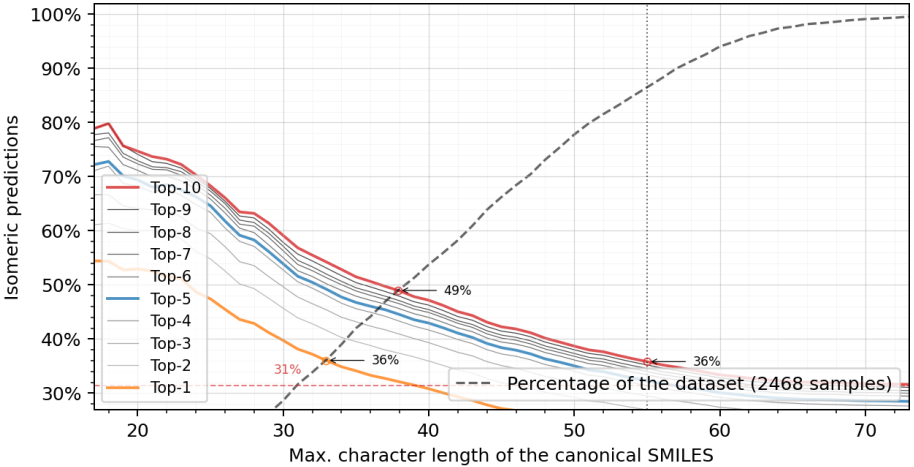
After fine-tuning on the validation set with HSQC / C-NMR dropout



After fine-tuning, evaluated on F + Q + ~~C~~ + H test set



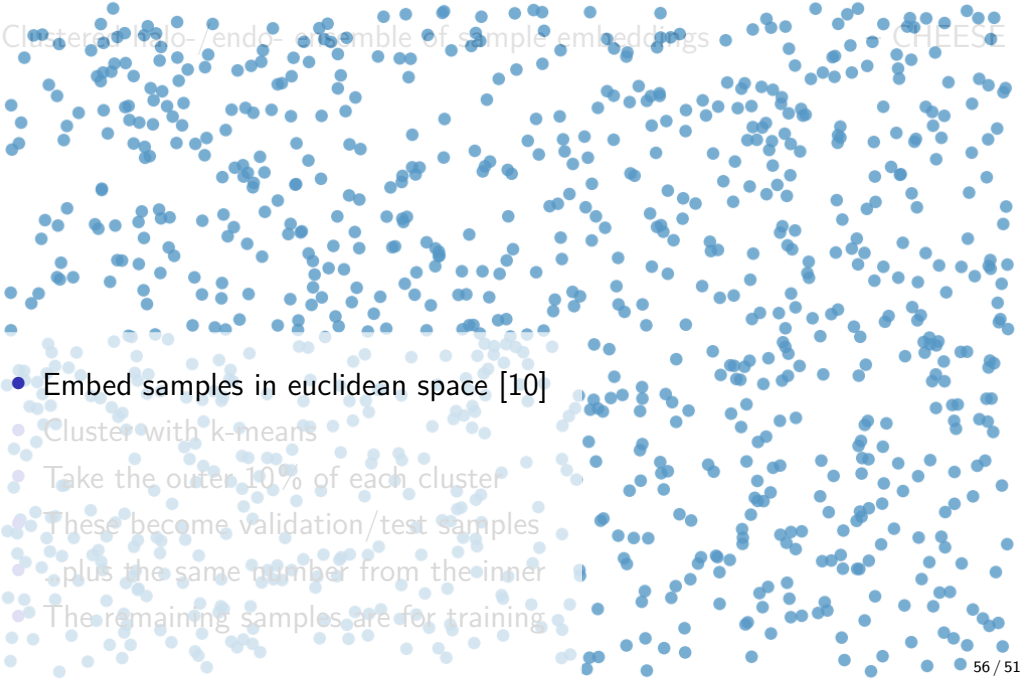
After fine-tuning, evaluated on $\mathrm{F} + \cancel{\mathrm{O}} + \mathrm{C} + \mathrm{H}$ test set



After fine-tuning, evaluated on $\mathrm{F} + \cancel{\mathrm{O}} + \cancel{\mathrm{C}} + \mathrm{H}$ test set

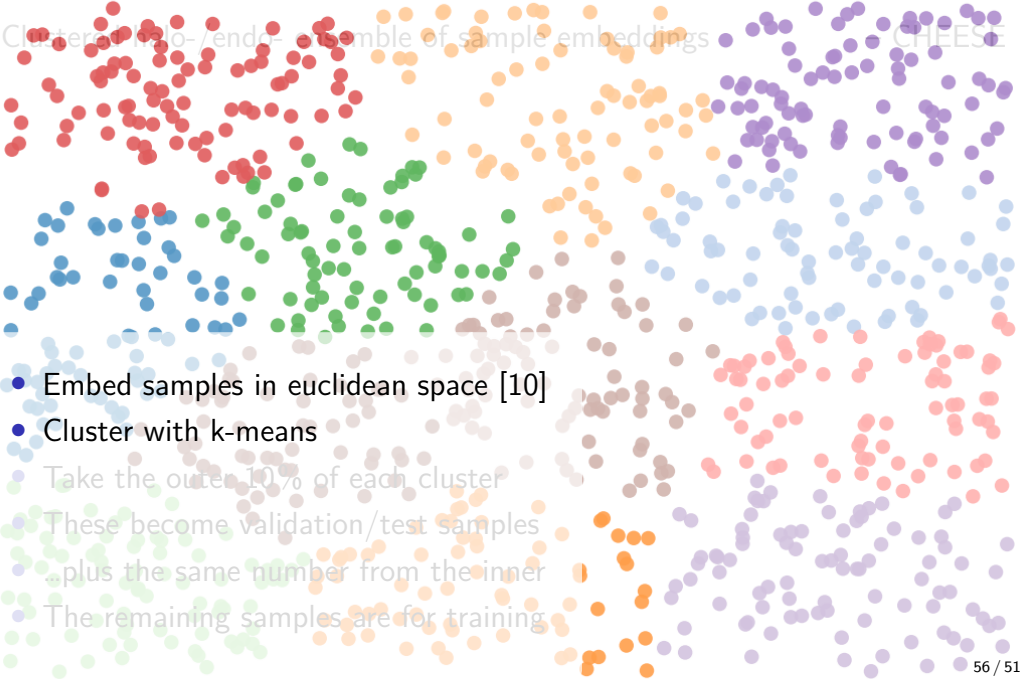
Clustered halo-/endo- ensemble of sample embeddings – CHEESE

- Embed samples in euclidean space [10]
- Cluster with k-means
- Take the outer 10% of each cluster
- These become validation/test samples
- ...plus the same number from the inner
- The remaining samples are for training



- Embed samples in euclidean space [10]
- Cluster with k-means
- Take the outer 10% of each cluster
- These become validation/test samples
- plus the same number from the inner
- The remaining samples are for training

Clustering-based hold-/end-out ensemble of sample embeddings — CHEESE



- Embed samples in euclidean space [10]
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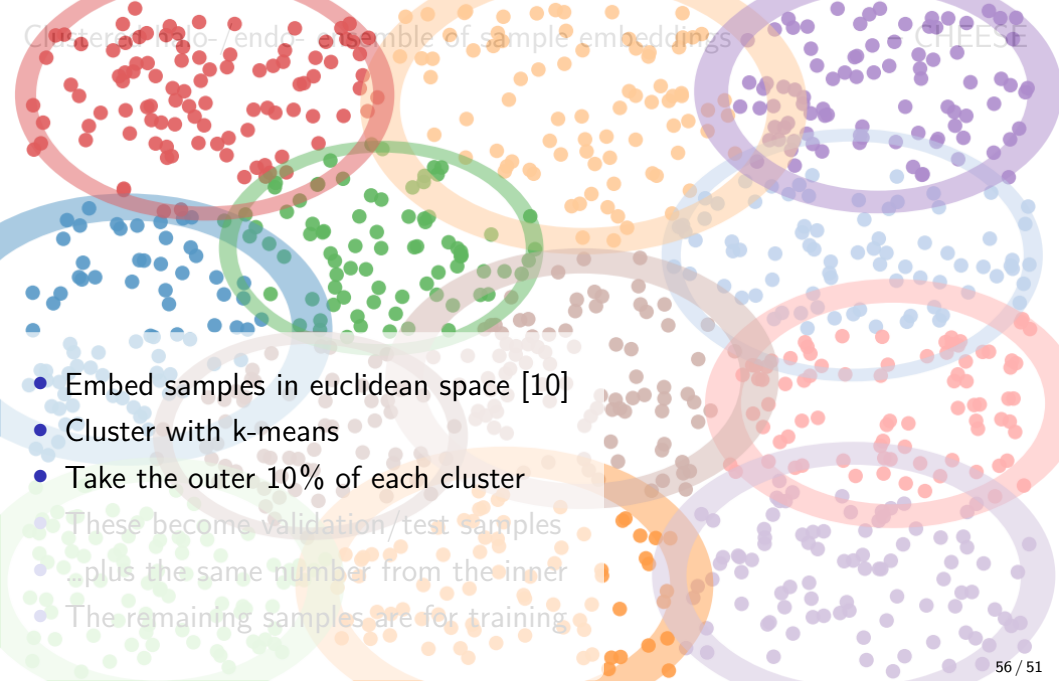
Clustered hold-/endo- ensemble of sample embeddings — CHEESE



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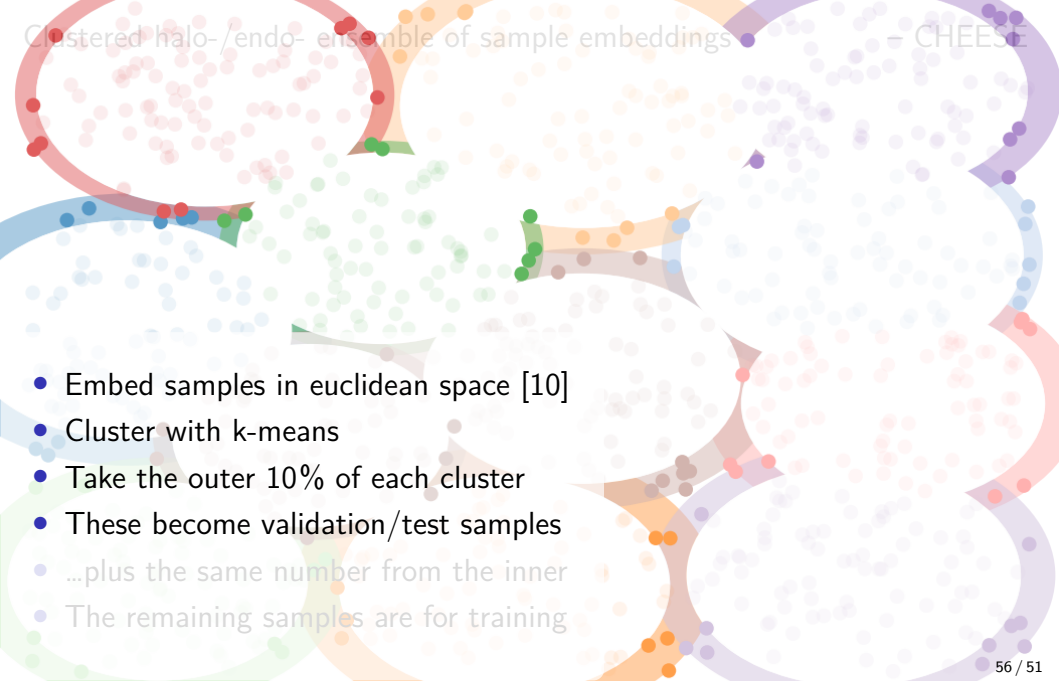
Clustered halo-/endo- ensemble of sample embeddings – CHEESE



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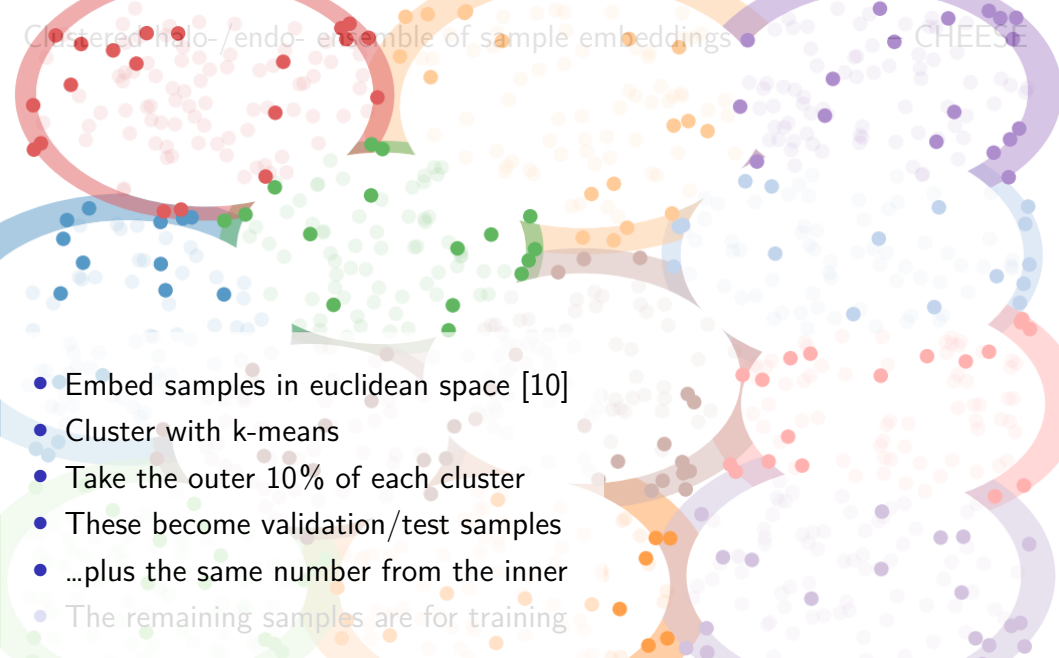
Clustered halo-/endo- ensemble of sample embeddings CHEESE



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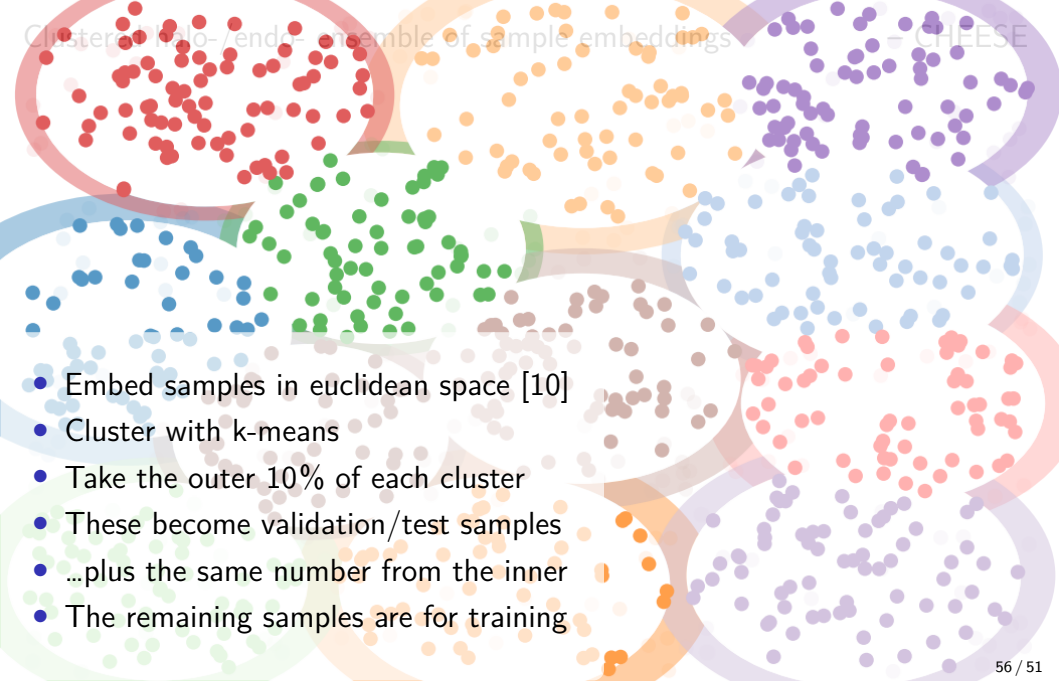

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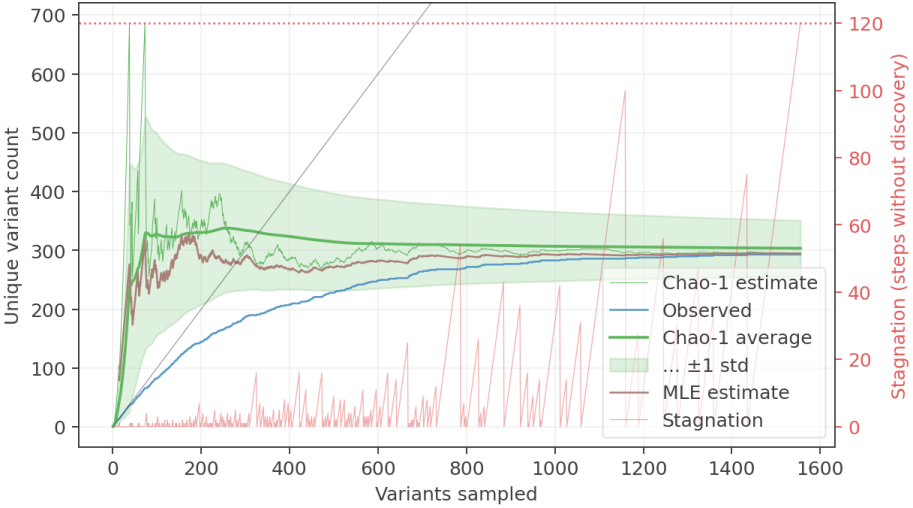
Collecting random serializations



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