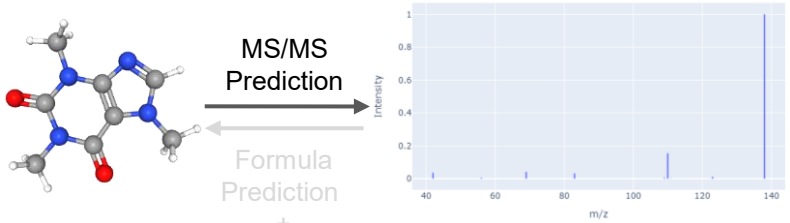
# A Machine Learning Model for Chemical Formula Prediction Using Tandem Mass Spectra of Compounds

Yuhui Hong, Haixu Tang
Luddy School of Informatics, Computing, and Engineering
Indiana University, Bloomington, IN 47408, USA

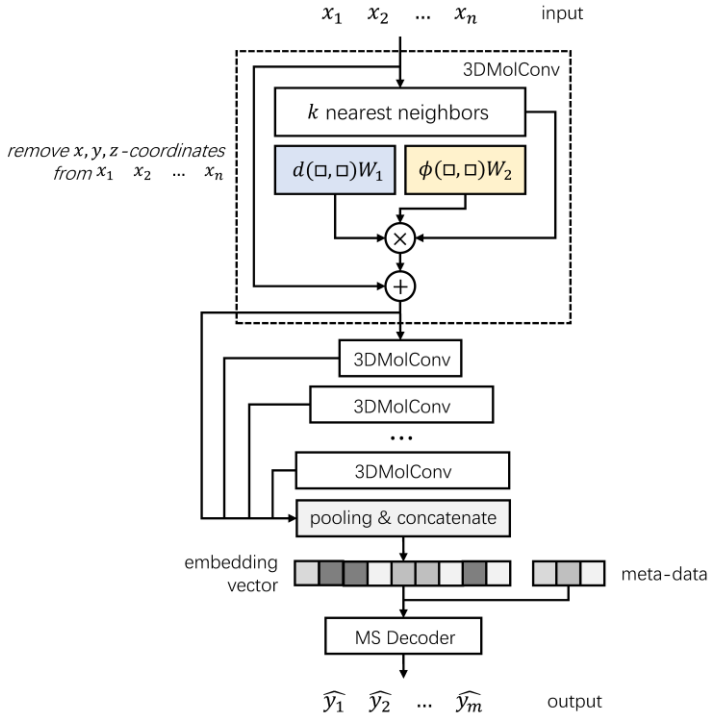
*The authors declare no competing financial interest.*

# From MS/MS Prediction to Formula Prediction




Codes are available on GitHub.

Online service are available on GNPS.



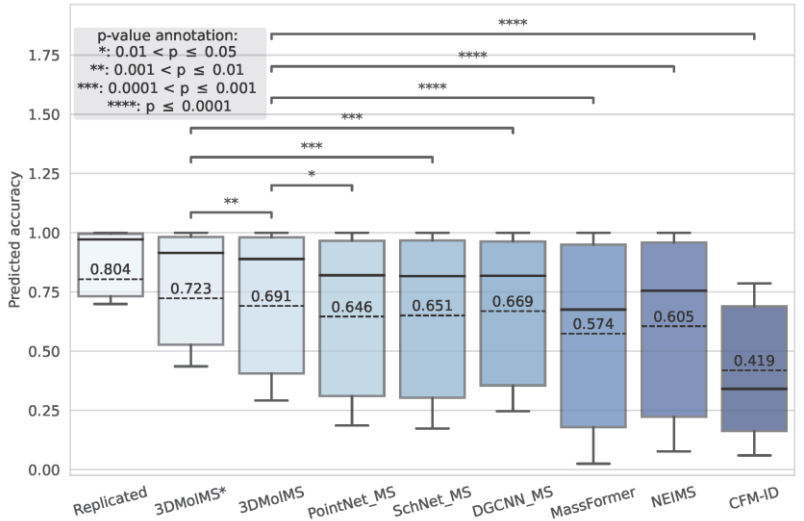

Architecture of 3DMolMS

[1] Hong, Yuhui, et al. "3DMolMS: prediction of tandem mass spectra from 3D molecular conformations." Bioinformatics 39.6 (2023): btad354.

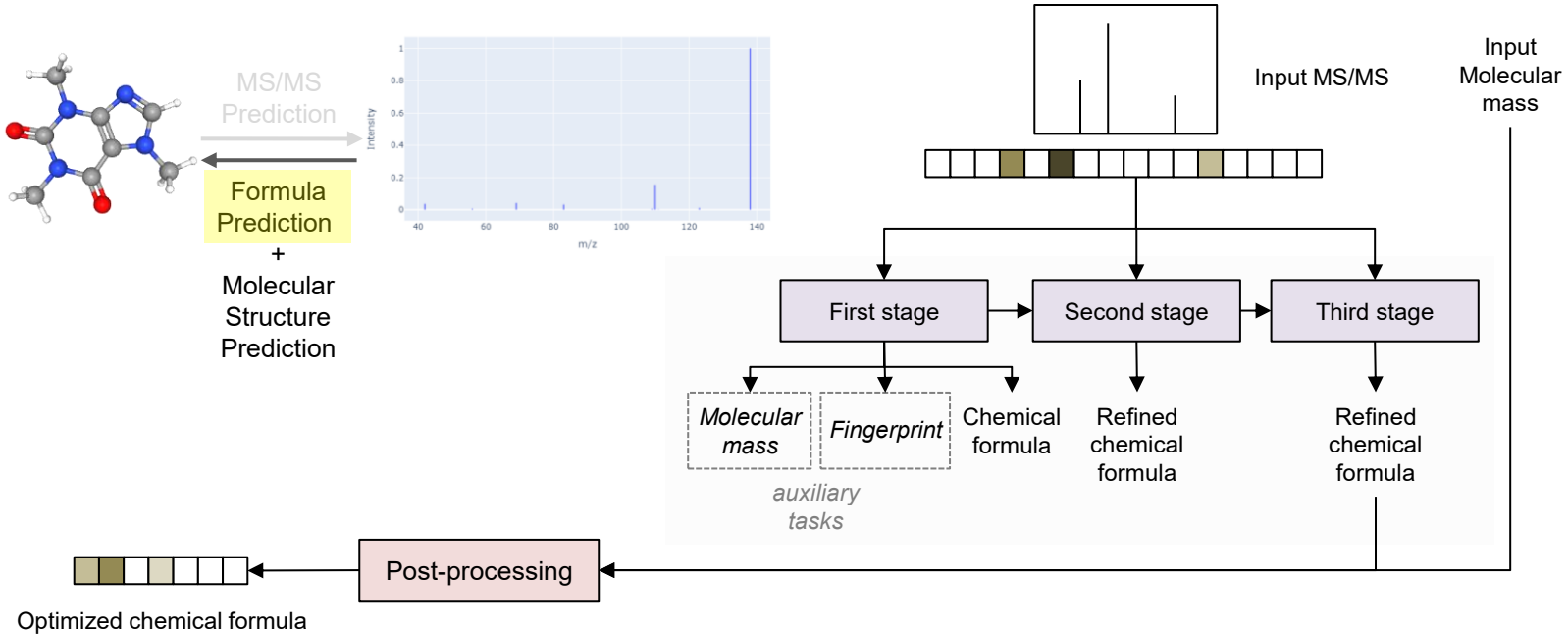
# From MS/MS Prediction to Formula Prediction

| | Positive ion mode | | Negative ion mode | |
|---|---|---|---|---|
| | # spectra | # compounds | # spectra | # compounds |
| NIST20 | 27085 | 2492 | 1749 | 193 |
| Agilent PCDL | 35373 | 11239 | 8362 | 2942 |
| Unique | 62458 | 13295 | 10111 | 3080 |

Performances of MS/MS Prediction on Agilent QTOF $[M+H]^+$



# From MS/MS Prediction to Formula Prediction



# Related Work: SIRIUS4

- Fragmentation tree[2][3] can only process single-charged MS/MS because it relies on the neutral loss, e.g., H2O.

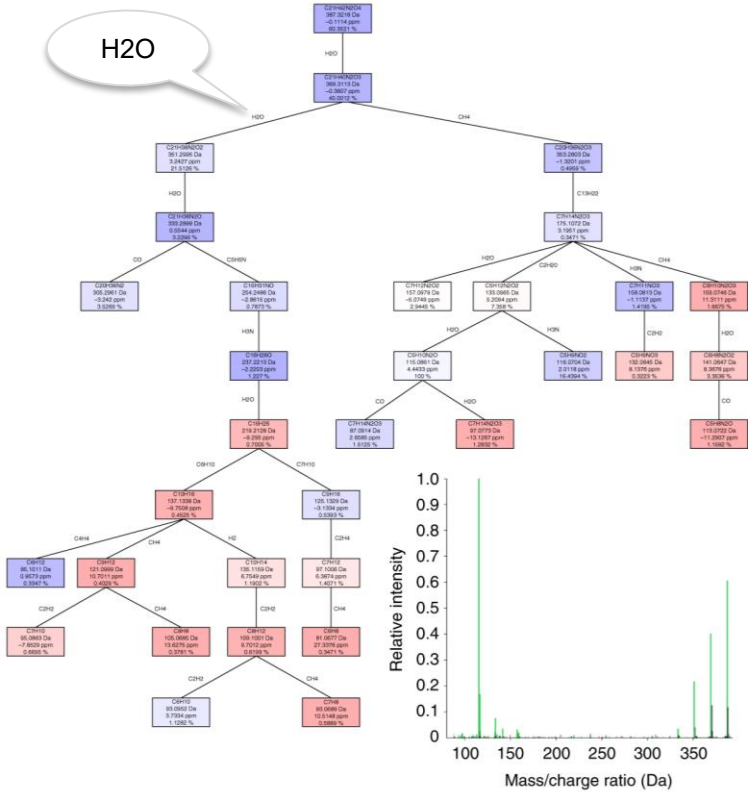
**Ion modes**

Whenever SIRIUS requires the ion mode, it should be given in the following format:

```
[M+ADDUCT]+ for positive ions
[M+ADDUCT]- for negative ions
[M-ADDUCT]- for losses
[M]+ for instrinsically charged compounds
```

ADDUCT is the molecular formula of the adduct. The most common ionization modes are `[M+H]+`, `[M+Na]+`, `[M-H]-`, `[M+Cl]-`. Currently, SIRIUS supports only single-charged compounds, so `[M+2H]2+` is not valid. For intrinsic charged compounds `[M]+` and `[M]-` should be used.

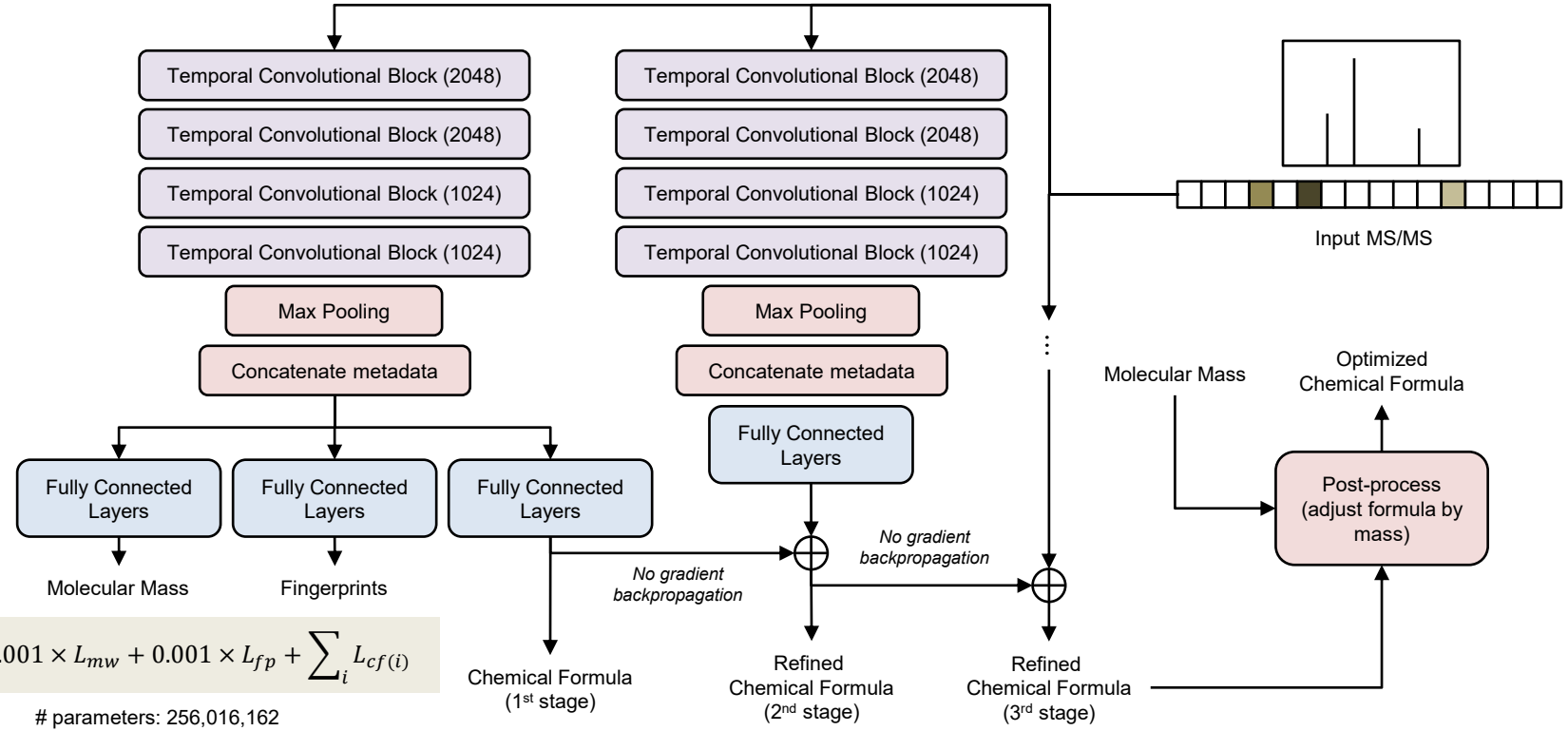
- Computations are time consuming.




Fragmentation tree that explains the experimentally observed MS/MS fragmentation pattern of the ion with *m/z* 387.322.


[2] Dührkop, Kai, et al. "SIRIUS 4: a rapid tool for turning tandem mass spectra into metabolite structure information." *Nature methods* 16.4 (2019): 299-302.
[3] Rasche, Florian, et al. "Computing fragmentation trees from tandem mass spectrometry data." Analytical Chemistry 83.4 (2011): 1243-1251.

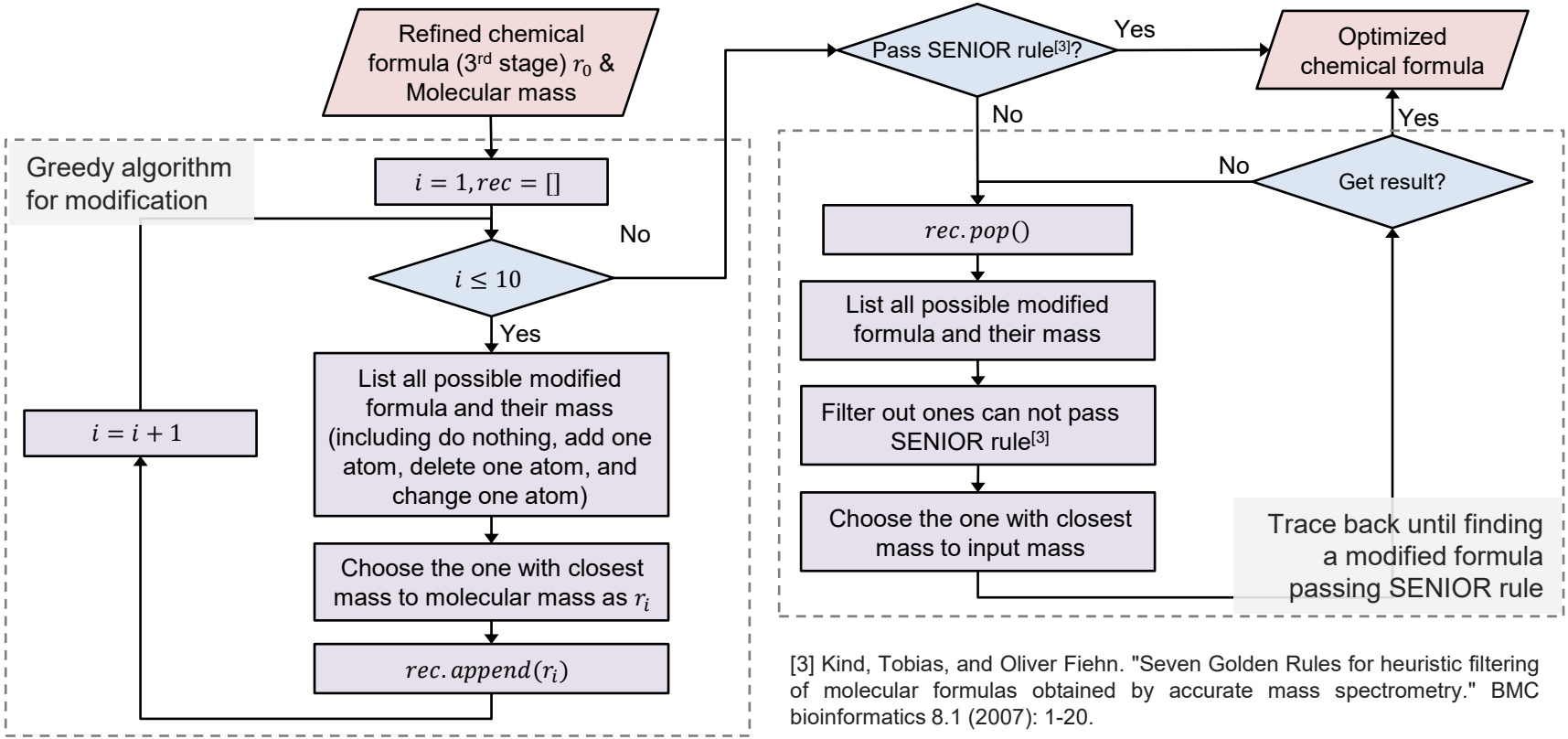
# Our Methods




$$\mathcal{L} = 0.001 \times L_{mw} + 0.001 \times L_{fp} + \sum_i L_{cf(i)}$$

# parameters: 256,016,162

# Our Methods (Post-processing)




[3] Kind, Tobias, and Oliver Fiehn. "Seven Golden Rules for heuristic filtering of molecular formulas obtained by accurate mass spectrometry." BMC bioinformatics 8.1 (2007): 1-20.

# Our Methods (SENIOR rule)

**SENIOR rule:**

1. The sum of valences or the total number of atoms having odd valences is even;
2. The sum of valences is greater than or equal to twice the maximum valence;
3. The sum of valences is greater than or equal to twice the number of atoms minus 1.

e.g., C9H14O3 passes SENIOR rule.

$4 \times 9 + 1 \times 14 + 2 \times 3 = 56$; The valences of C, H, and O are 4, 1, and 2, respectively.
$56 \geq 2 \times 4$;
$56 \geq 2 \times (9 + 14 + 3 - 1) = 50$;

[4] Kind, Tobias, and Oliver Fiehn. "Seven Golden Rules for heuristic filtering of molecular formulas obtained by accurate mass spectrometry." BMC bioinformatics 8.1 (2007): 1-20.

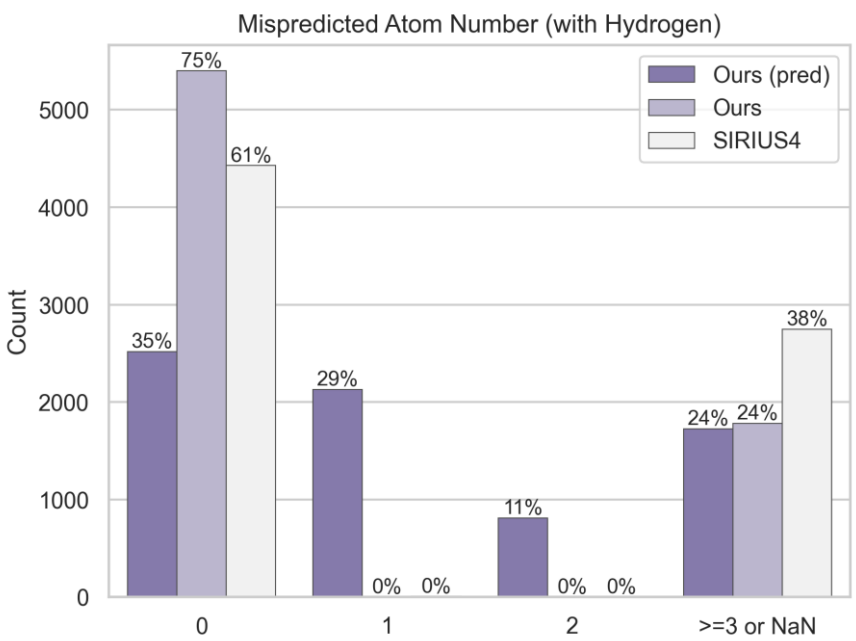
# Experiment Data Preprocessing

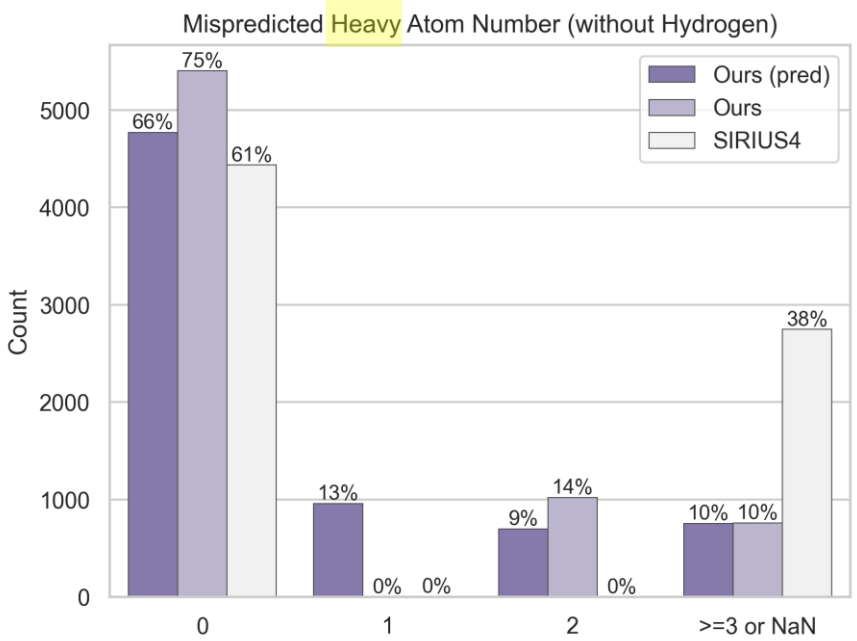
We collected **70,111** spectra of **14,376** compounds with masses from the Quadrupole Time-of-Flight (Q-TOF) MS/MS library of Agilent and NIST20.

The compounds are randomly split into training and test sets with a ratio of 9:1.

1. The spectra with less than 5 peaks are removed because they are typically unreliable;
2. The spectra with m/z greater than 1500 are discarded because only a few spectra are from such large molecules;
3. Only the spectra with the precursor types of M+H and M-H are retained;
4. Only the compounds with fewer than 300 atoms are retained because only a few compounds in the library have more than 300 atoms;
5. Only the molecules composed by the most common atoms (C, H, O, N, F, S, Cl, P, B, I and Br) are retained.

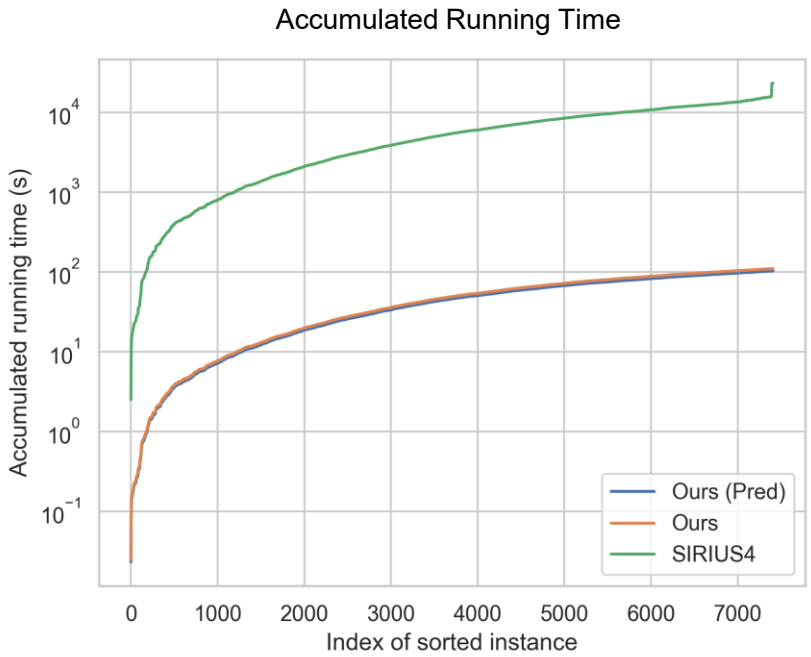
# Results on Single Charged MS/MS (accuracy)




Ours (pred) denotes the results from machine learning model without post-processing.

# Results on Single Charged MS/MS (speed)



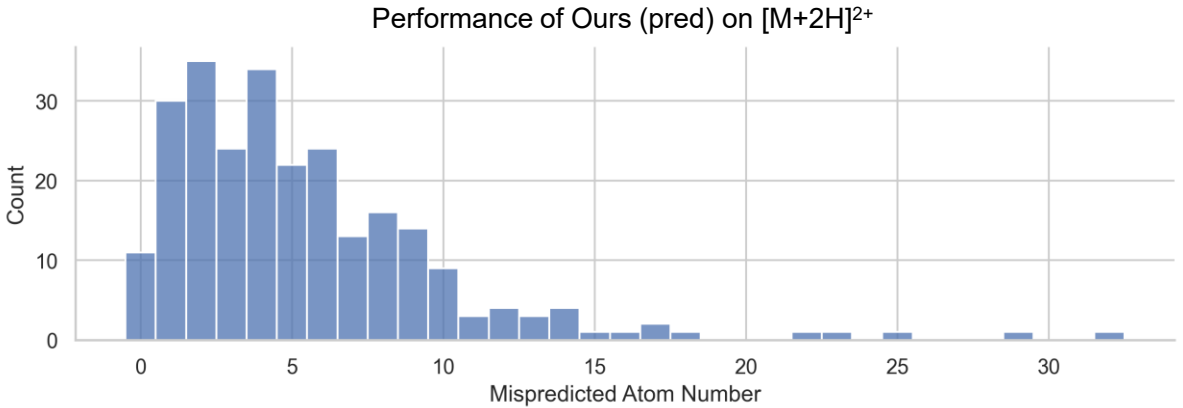

The compounds have been arranged in ascending order based on their mass.

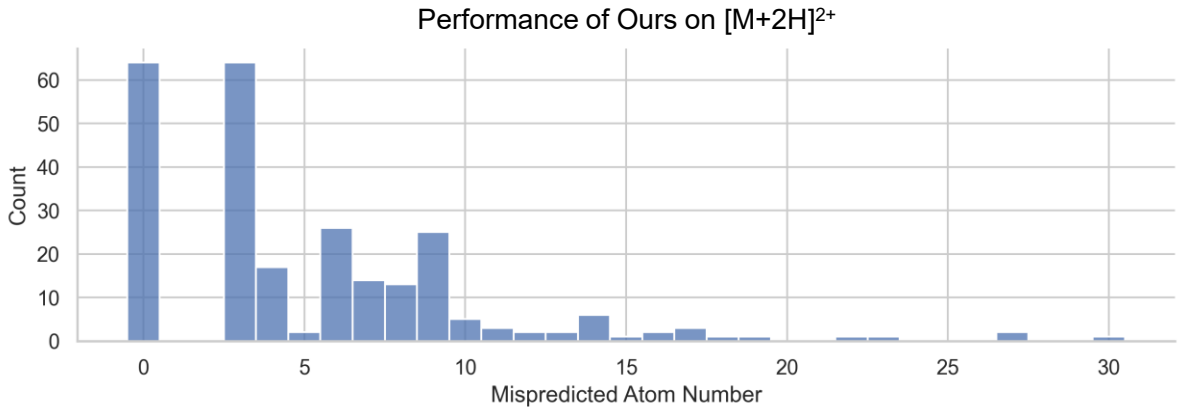
# Results on Double Charged MS/MS

The double charged MS/MS from Agilent PCDL and NIST20 are gathered as an additional test set.

The model trained on single charged MS/MS are applied directly to the double charged MS/MS.

| # Spectra | # Compound |
|---|---|
| 256 | 197 |



# Takeaways

- We presented a deep learning model with post-processing for chemical formula prediction achieving state-of-the-art performance on QTOF MS/MS.
- Our model is efficient, and it can be extended to MS/MS with different adducts.

Thank you!

Please find the codes of 3DMolMS on GitHub.

We will release the codes for chemical formula prediction soon!

# Acknowledgement

We appreciate Dr. Sujun Li, Dr. Christopher J. Welch, and Dr. Shane Tichy for their contribution of MS/MS data collection and invaluable advice on data preprocessing. We are indebted to Dr. Mingxun Wang for his invaluable advice and his effort to build the online service of 3DMolMS.

# Funding

We acknowledge the Center for Bioanalytical Metrology (CBM), an NSF Industry-University Cooperative Research Center, for providing funding under grant NSF IIP-1916645. This work was also partially supported by National Science Foundation grant DBI-2011271.

# References

[1] Hong, Yuhui, et al. "3DMolMS: prediction of tandem mass spectra from 3D molecular conformations." Bioinformatics 39.6 (2023): btad354.

[2] Dührkop, Kai, et al. "SIRIUS 4: a rapid tool for turning tandem mass spectra into metabolite structure information." Nature methods 16.4 (2019): 299-302.

[3] Rasche, Florian, et al. "Computing fragmentation trees from tandem mass spectrometry data." Analytical Chemistry 83.4 (2011): 1243-1251.

[4] Kind, Tobias, and Oliver Fiehn. "Seven Golden Rules for heuristic filtering of molecular formulas obtained by accurate mass spectrometry." BMC bioinformatics 8.1 (2007): 1-20.