semi-quantification in LC/HRMS non-targeted screening: the efforts of the community

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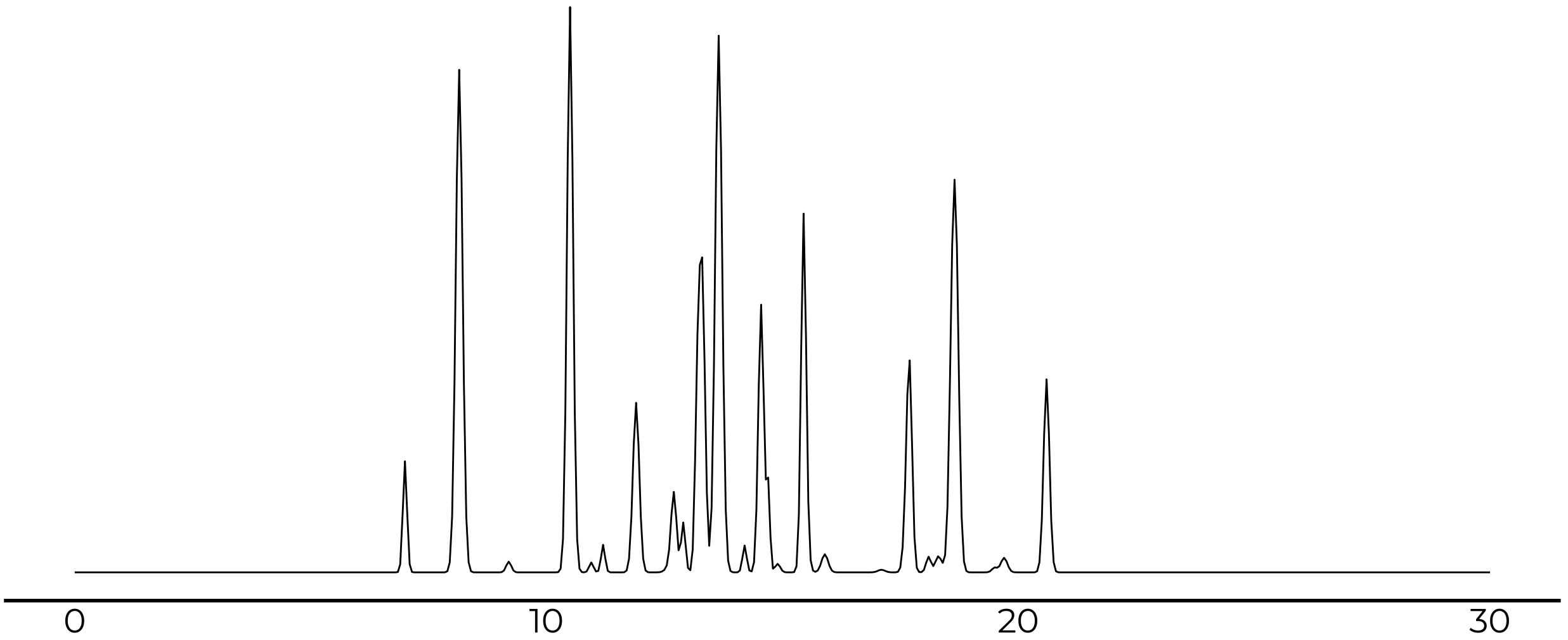
nontarget screening



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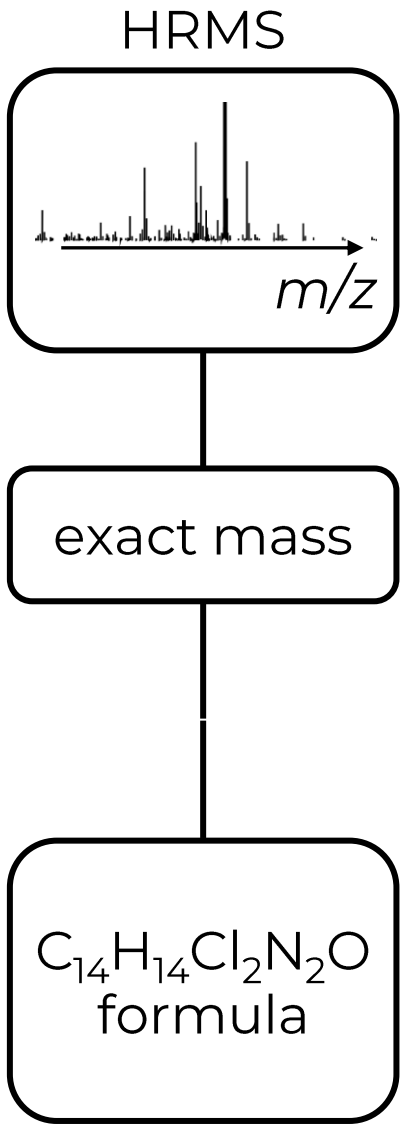
identification



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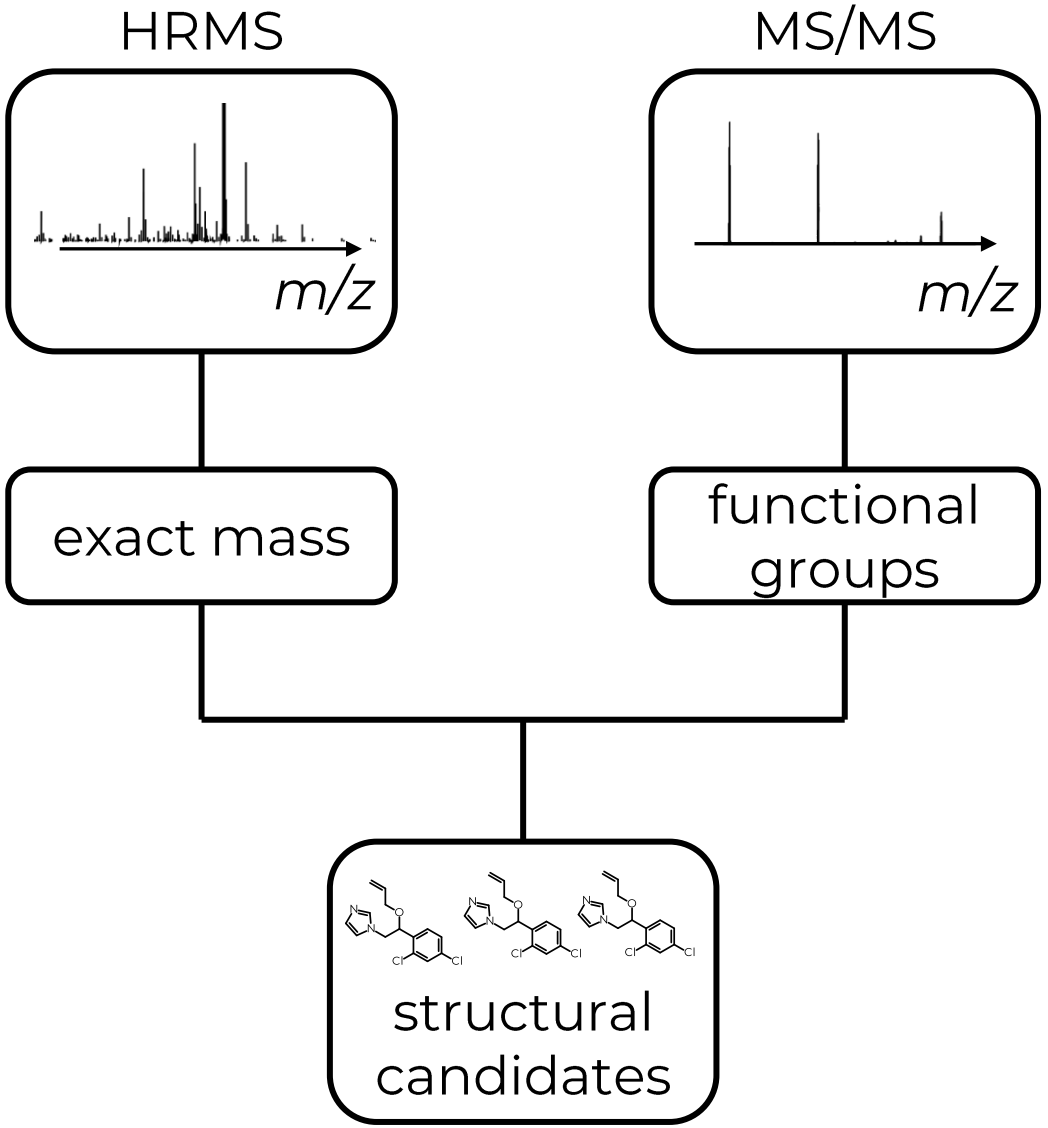
identification



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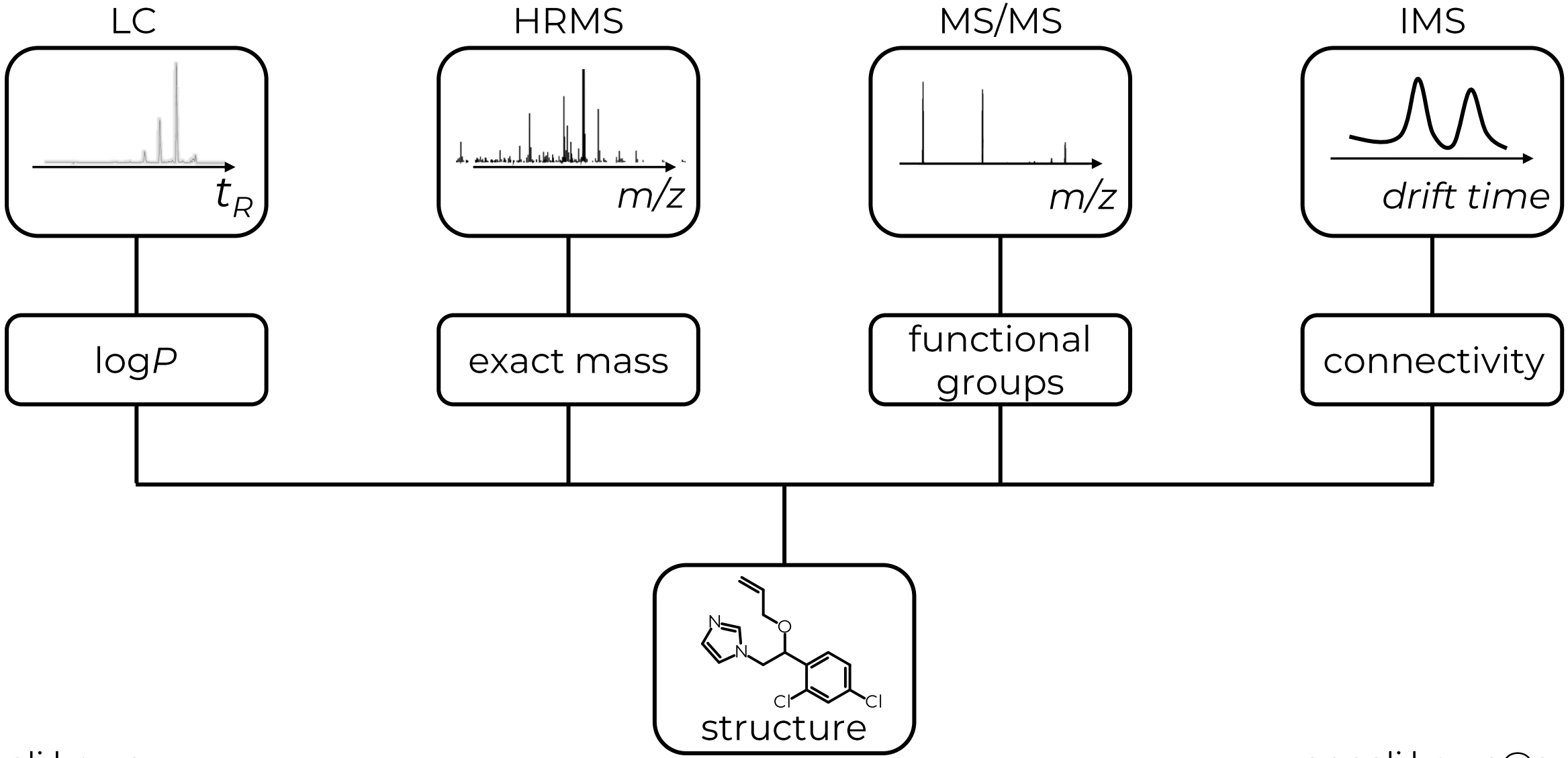

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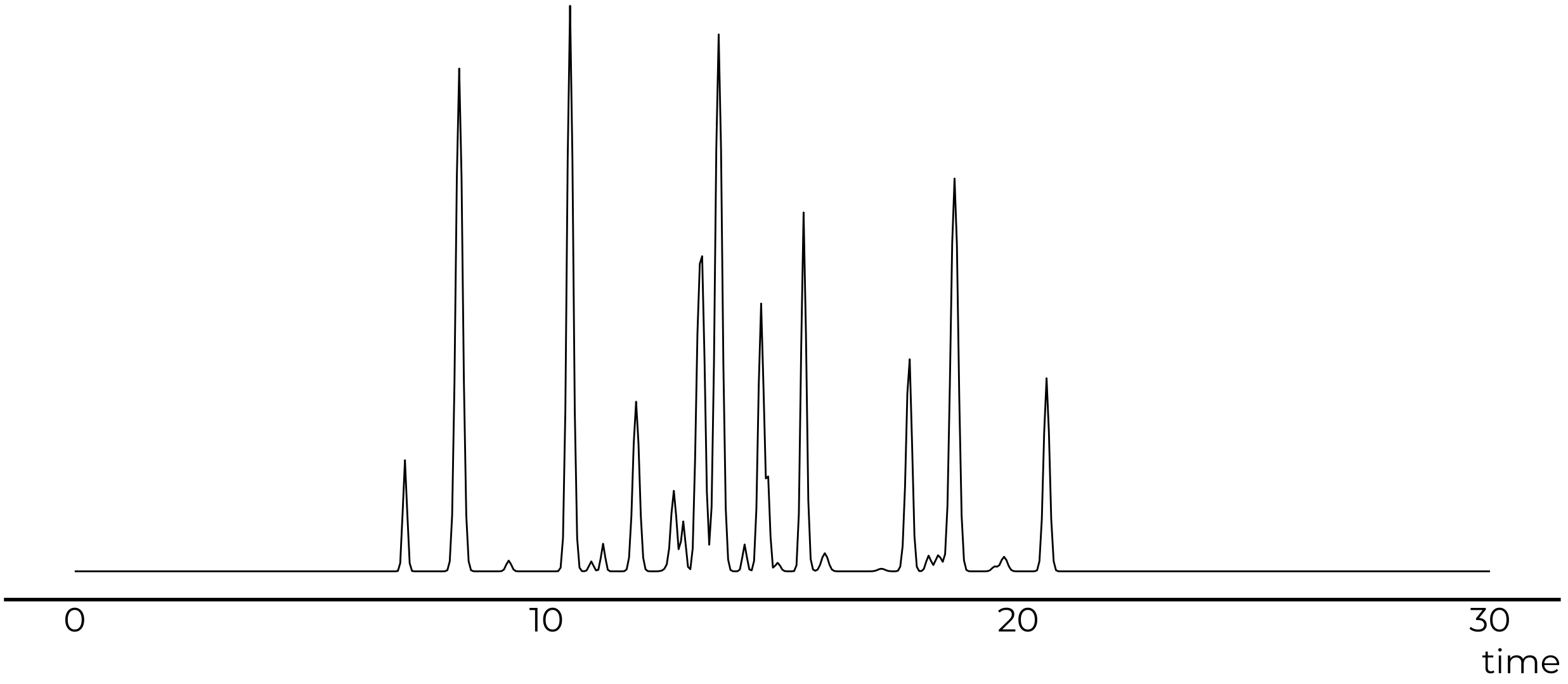
what next?



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prioritization

toxicity

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prioritization

toxicity

concentration

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prioritization

toxicity

concentration

risk

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prioritization

toxicity

concentration

risk

$$\text{PriorityScore} = \frac{C_{\text{predicted}}}{AC_{50}^{\text{5th percentile}}}$$

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quantification in ESI/HRMS

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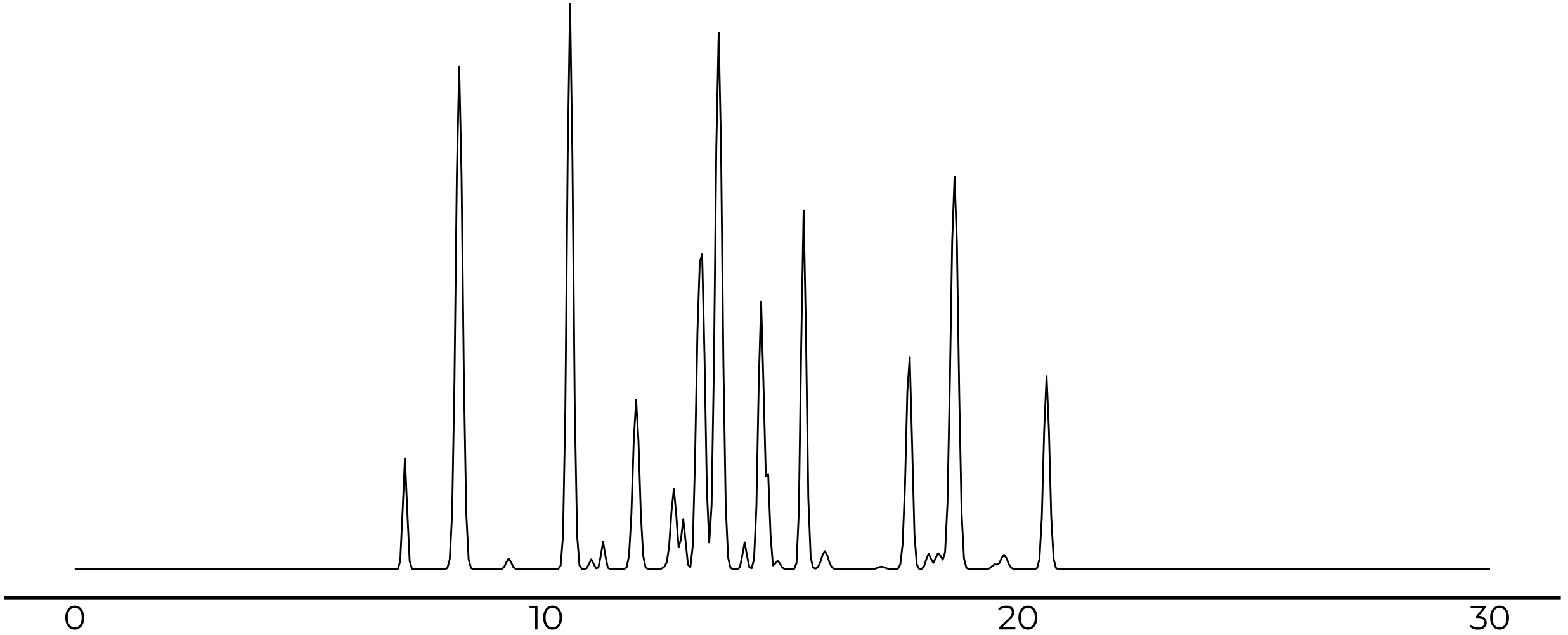
quantification in ESI/HRMS

Malm et al. Molecules 2021



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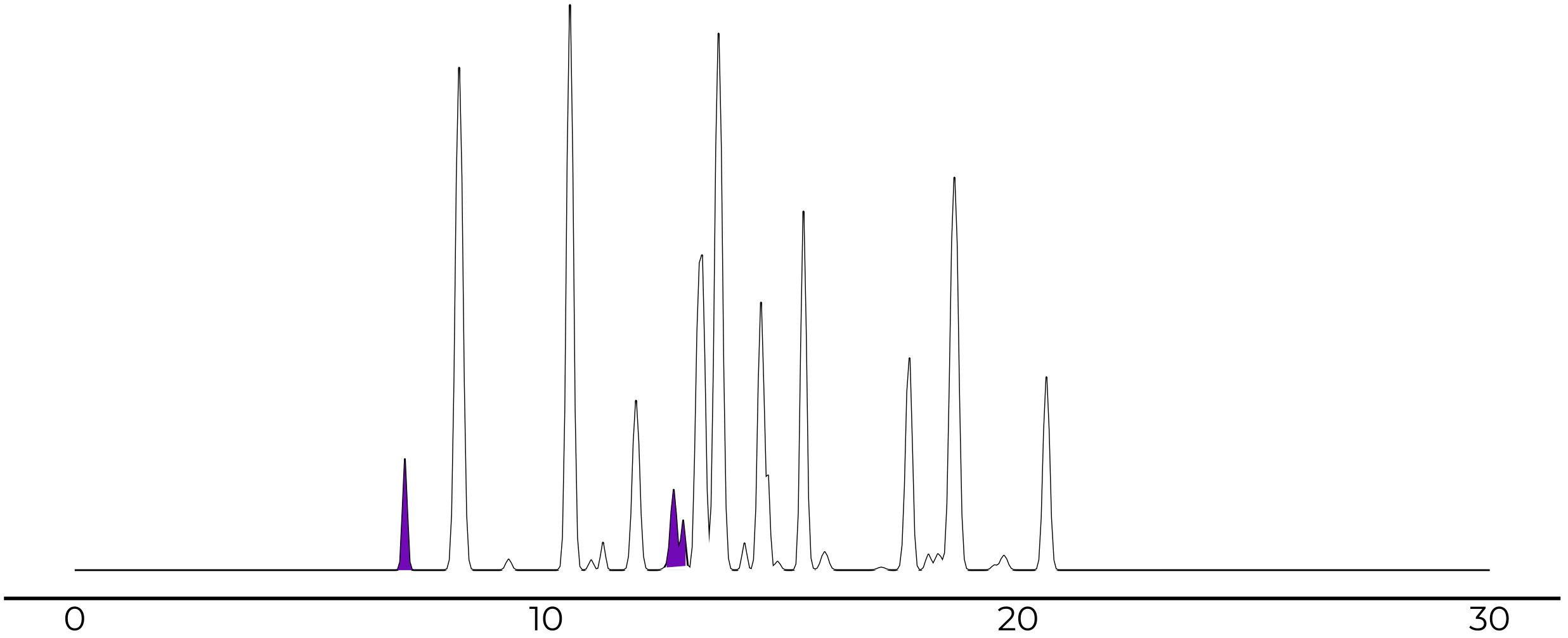
quantification in ESI/HRMS

Malm et al. Molecules 2021



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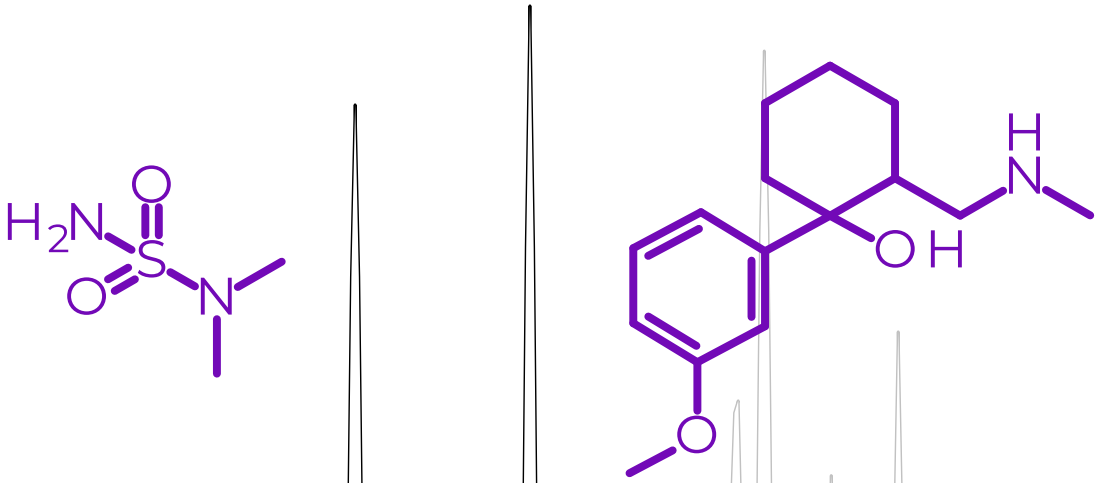
quantification in ESI/HRMS

Malm et al. Molecules 2021



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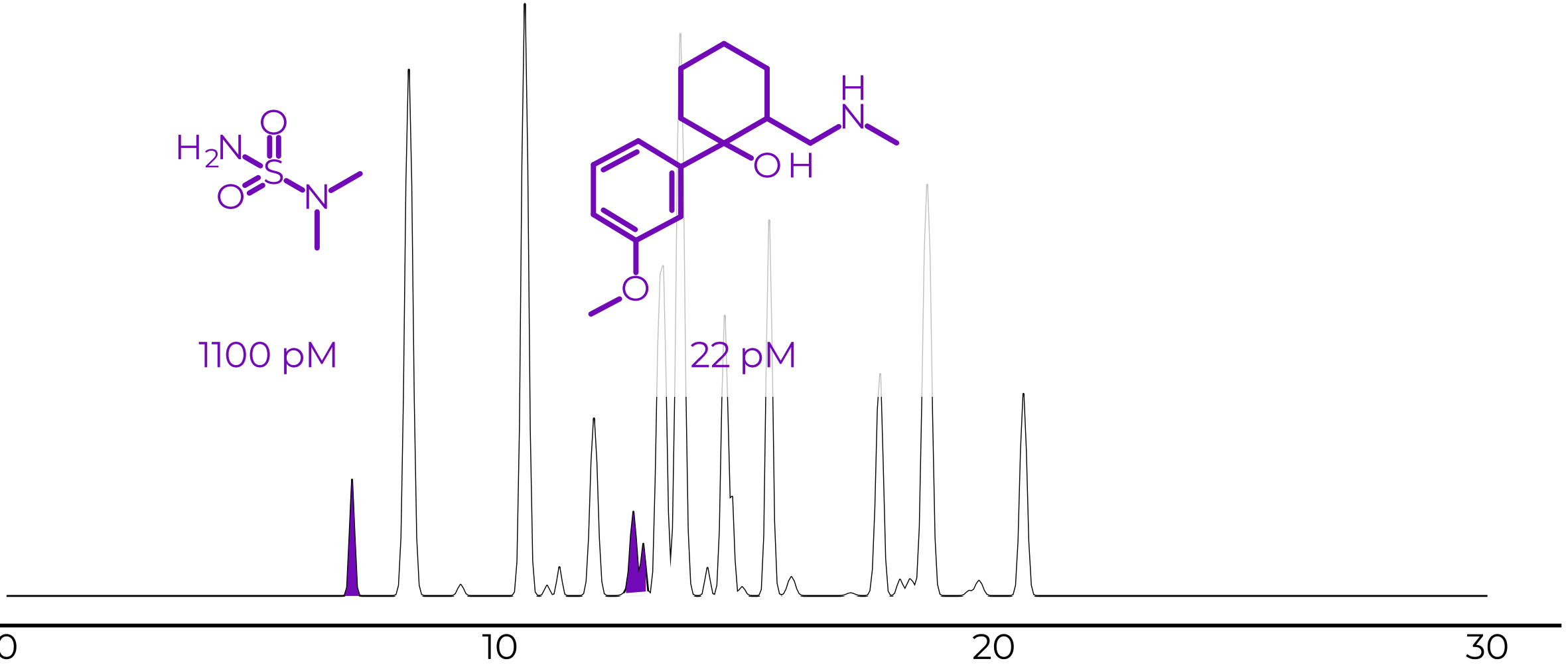
quantification in ESI/HRMS

Malm et al. Molecules 2021



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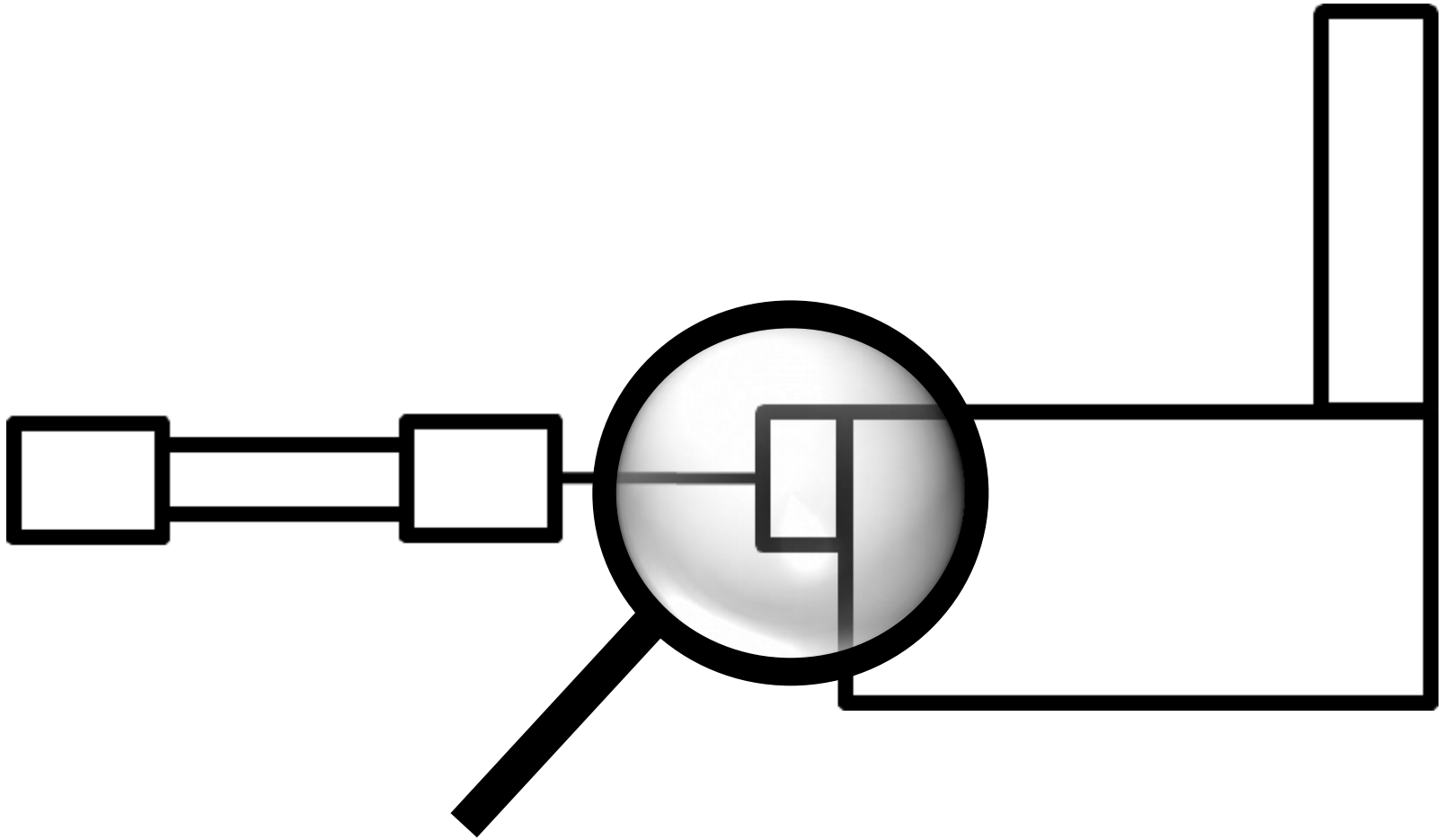
electrospray



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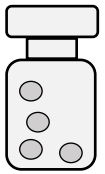
ionization efficiency

workflow



flow injections

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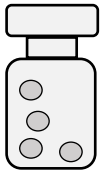
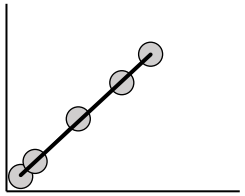
workflow



flow injections



calibration graph

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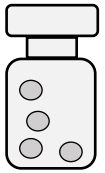
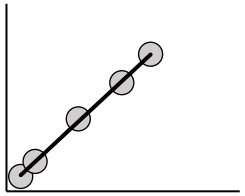
workflow



flow injections



calibration graph

$$\frac{slope_1}{slope_2} \rightarrow IE$$

relative measurements

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structure

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structure

one solvent, purely analyte properties

377 chemicals

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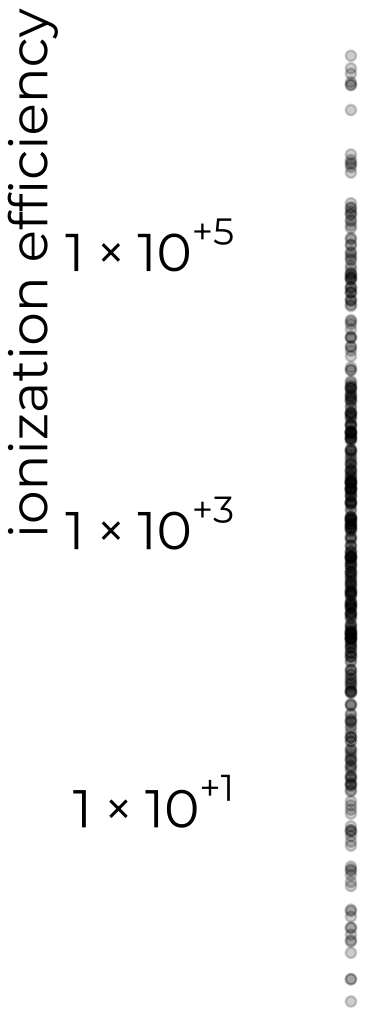
structure



one solvent, purely analyte properties

377 chemicals

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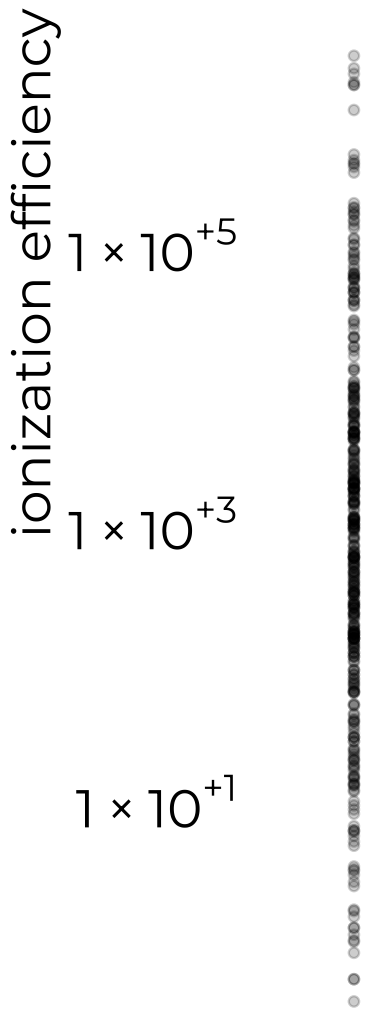
structure



one solvent, purely analyte properties

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10,000,000x difference in ionization efficiency

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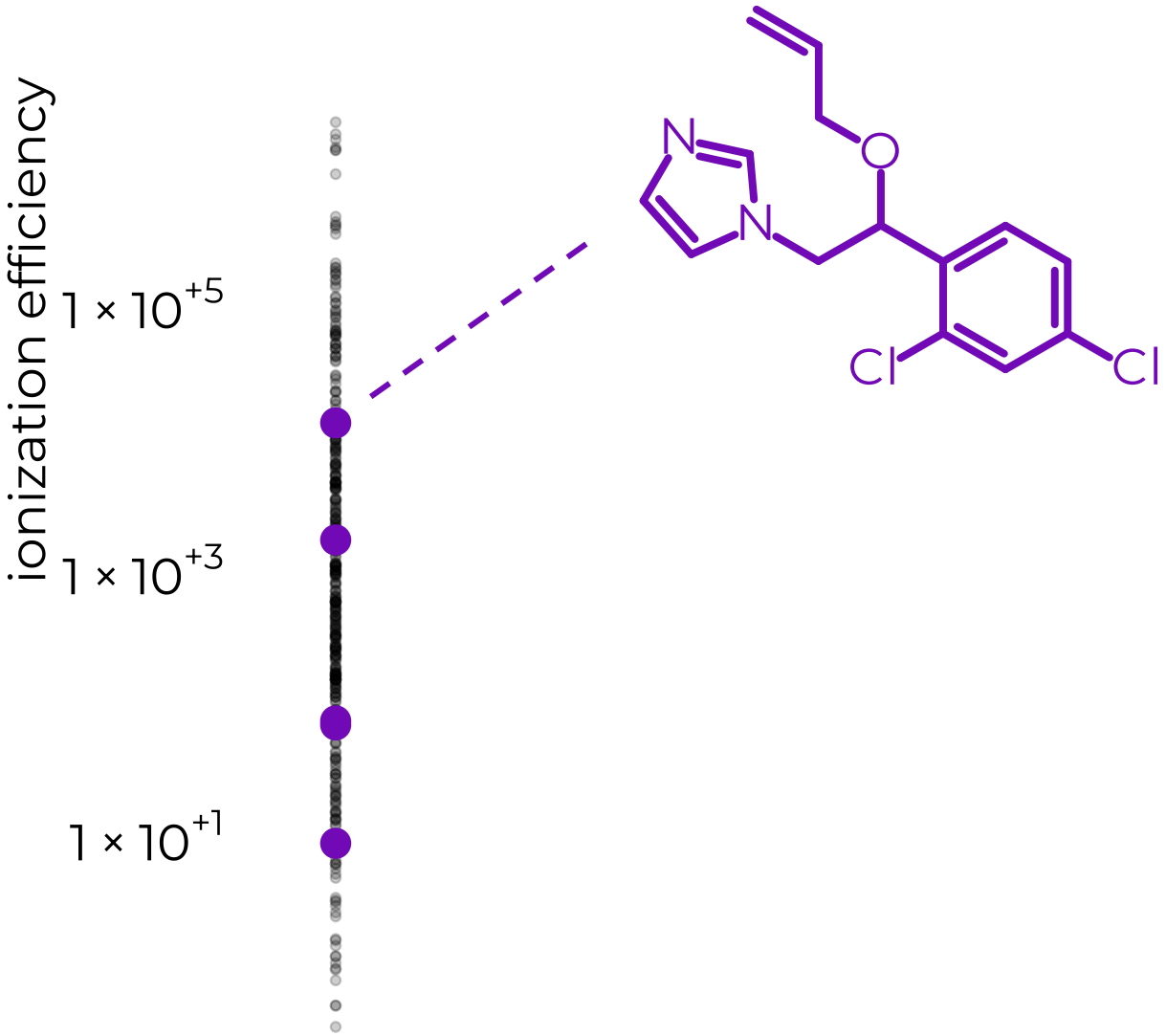
structure



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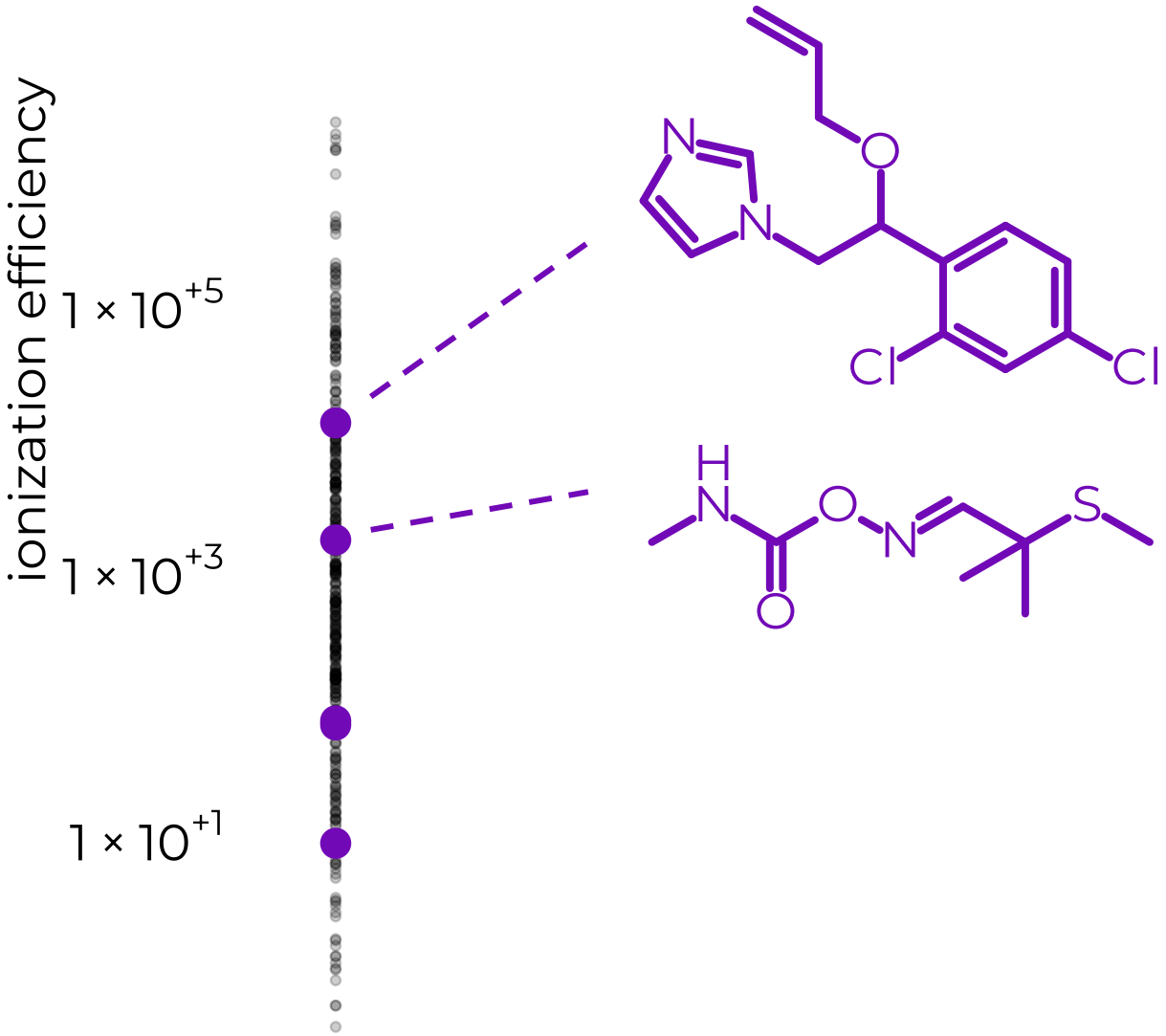
structure



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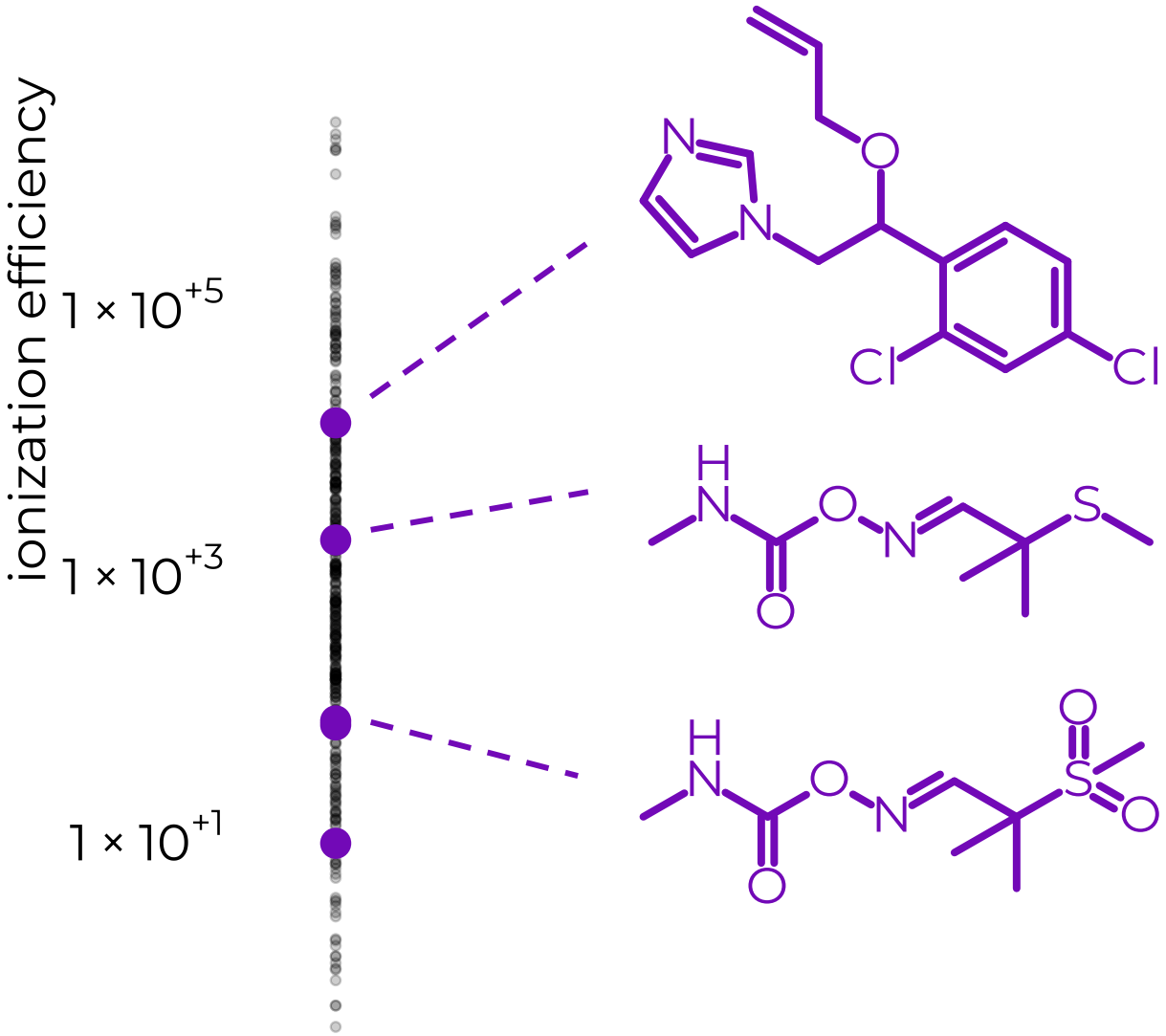
structure



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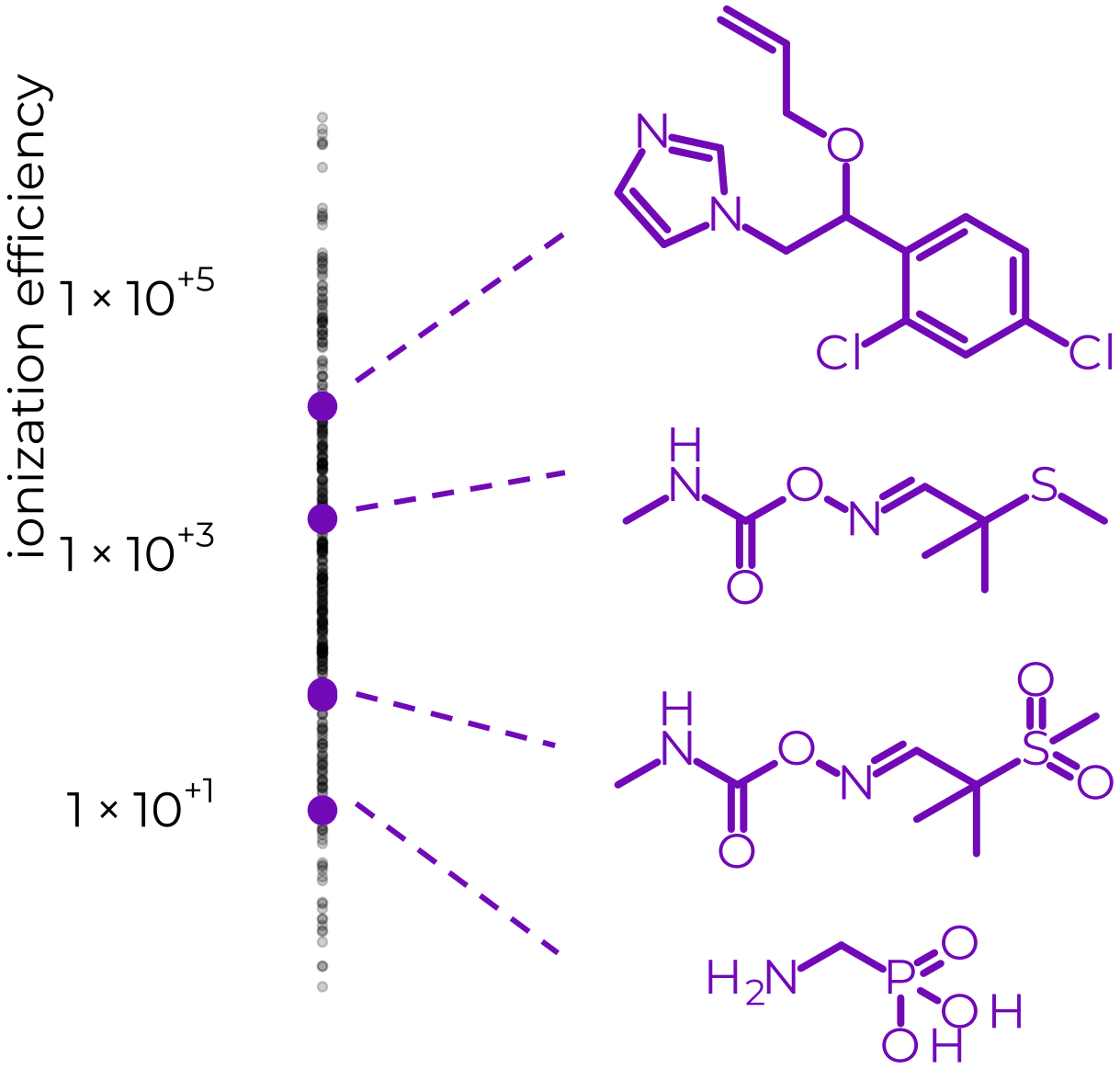
structure



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mobile phase: organic modifier

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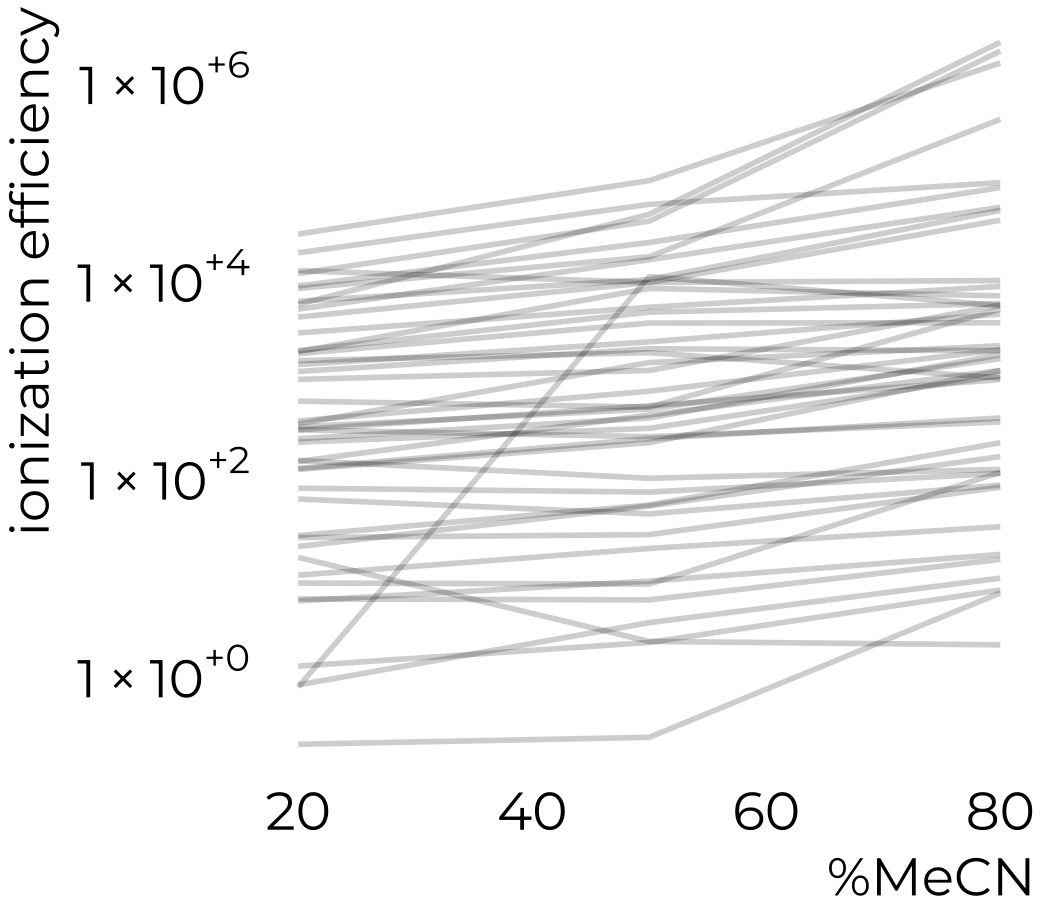
mobile phase: organic modifier

Liigand et al. JASMS 2014



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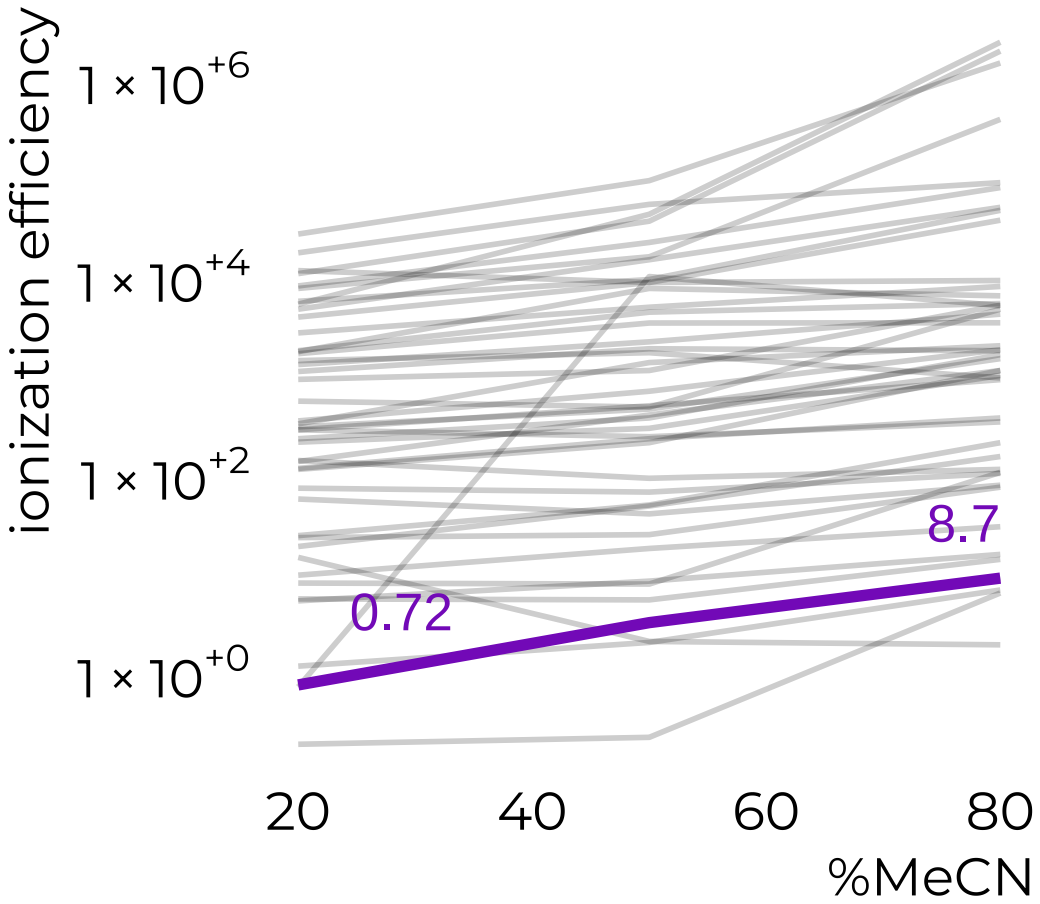
mobile phase: organic modifier

Liigand et al. JASMS 2014



%MeCN ↑ ~ ionization efficiency ↑

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mobile phase: pH

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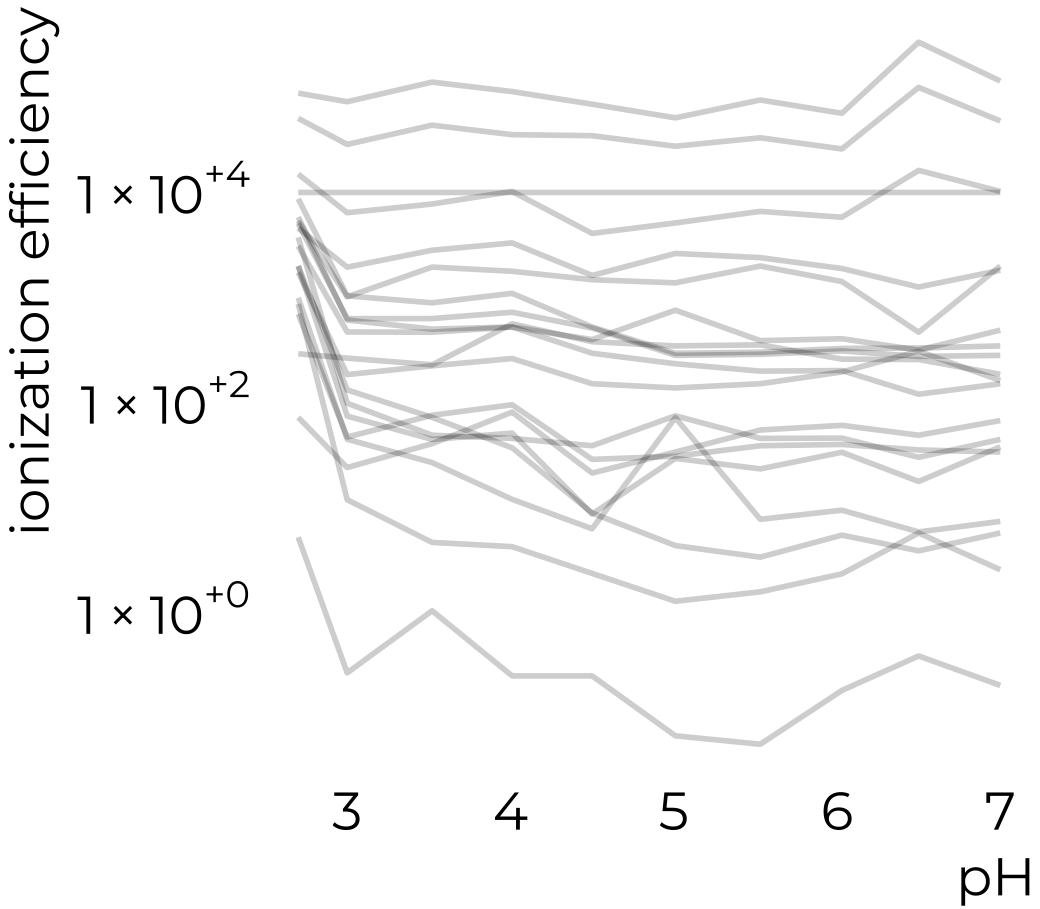
mobile phase: pH

Liigand et al. JASMS 2017

Kruve et al. Anal Chem 2017



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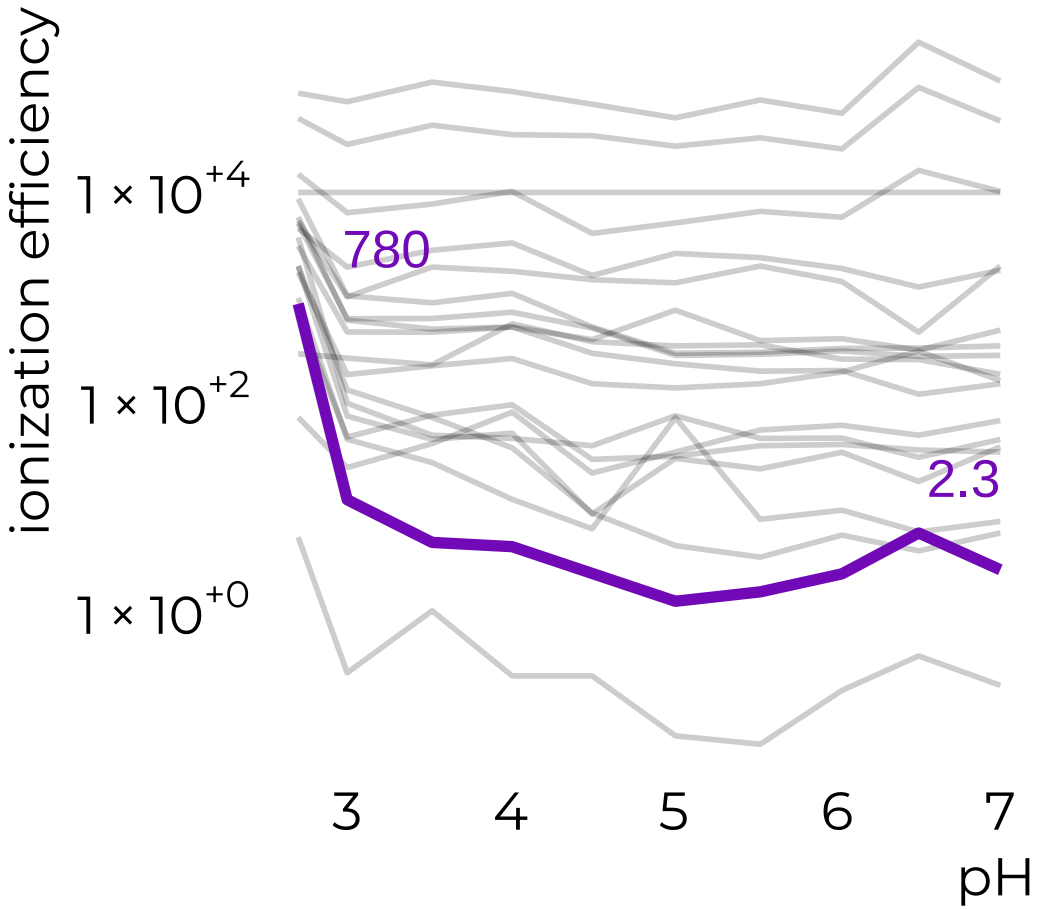
mobile phase: pH

Liigand et al. JASMS 2017

Kruve et al. Anal Chem 2017



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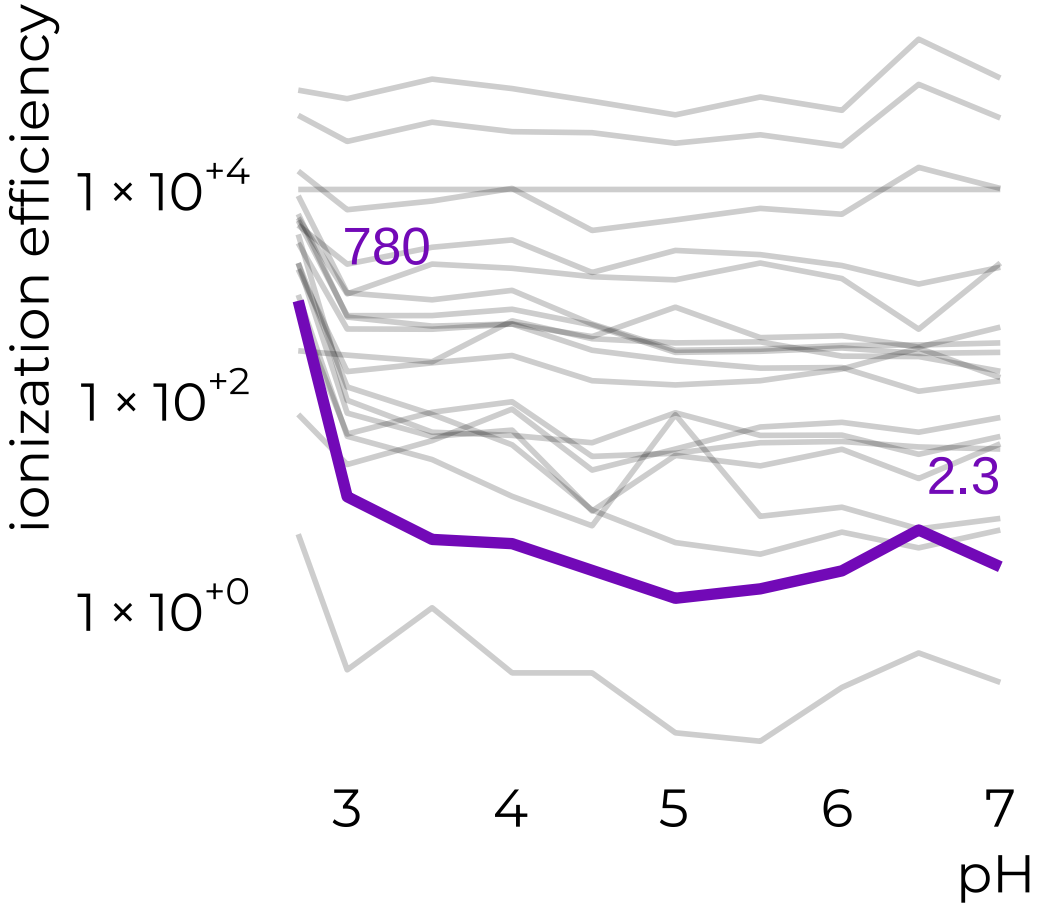
mobile phase: pH

Liigand et al. JASMS 2017

Kruve et al. Anal Chem 2017



pH & buffer type affect ionization efficiency

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instruments

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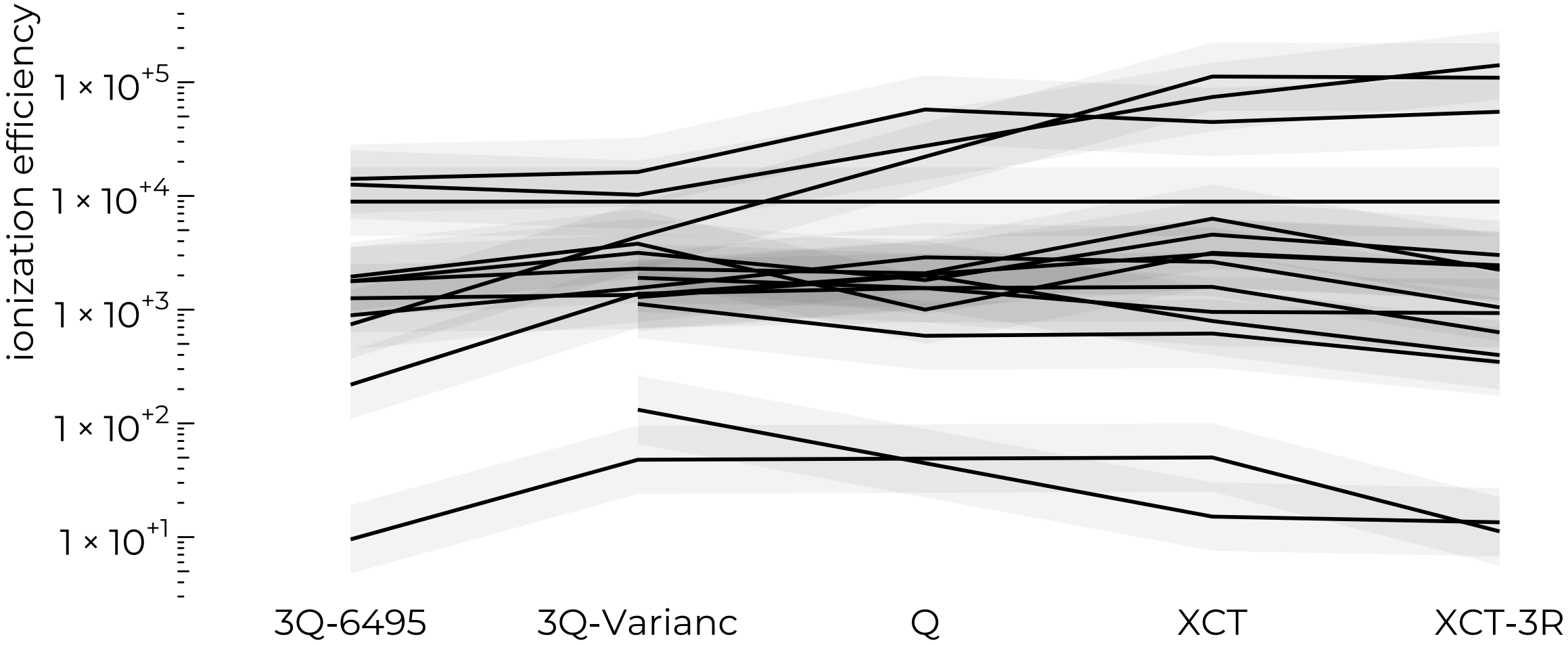
instruments

Liigand et al. JASMS 2015



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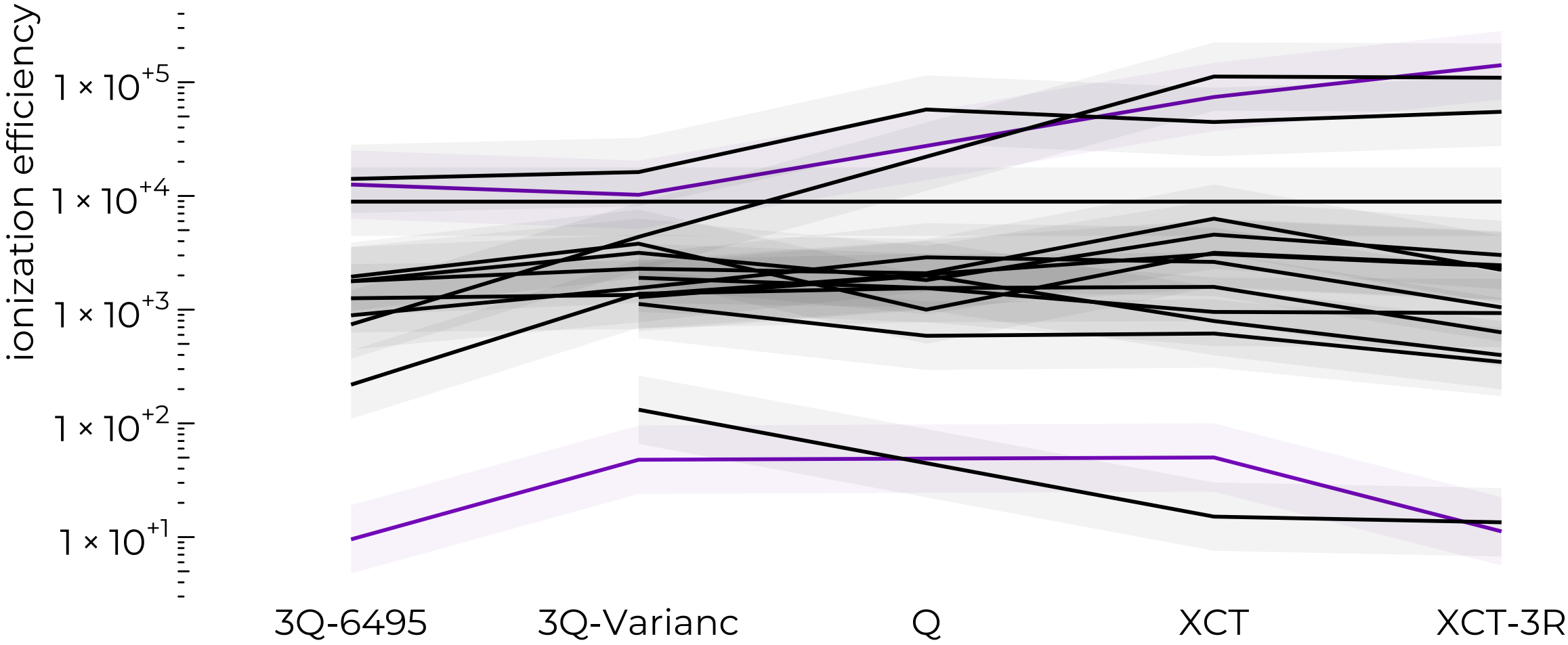
instruments

Liigand et al. JASMS 2015



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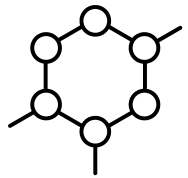
quantification

approaches

three common methods



structurally similar chemicals

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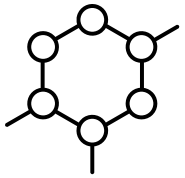
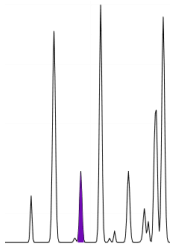
three common methods



structurally similar chemicals



close eluting chemicals

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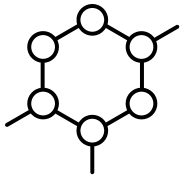
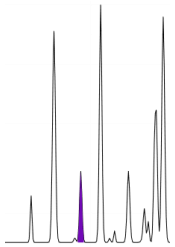
three common methods



structurally similar chemicals



close eluting chemicals

machine learning

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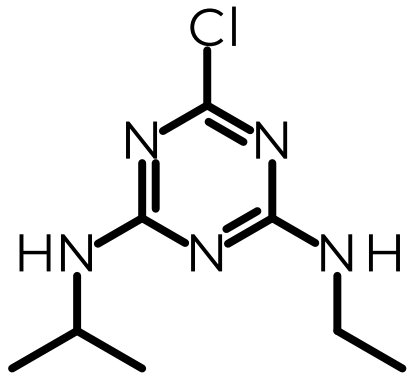
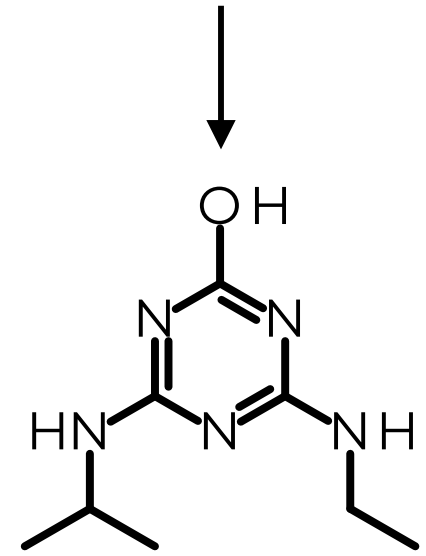
quantification

with structurally similar chemical

parent – transformation product

Malm et al. Molecules 2021





1x

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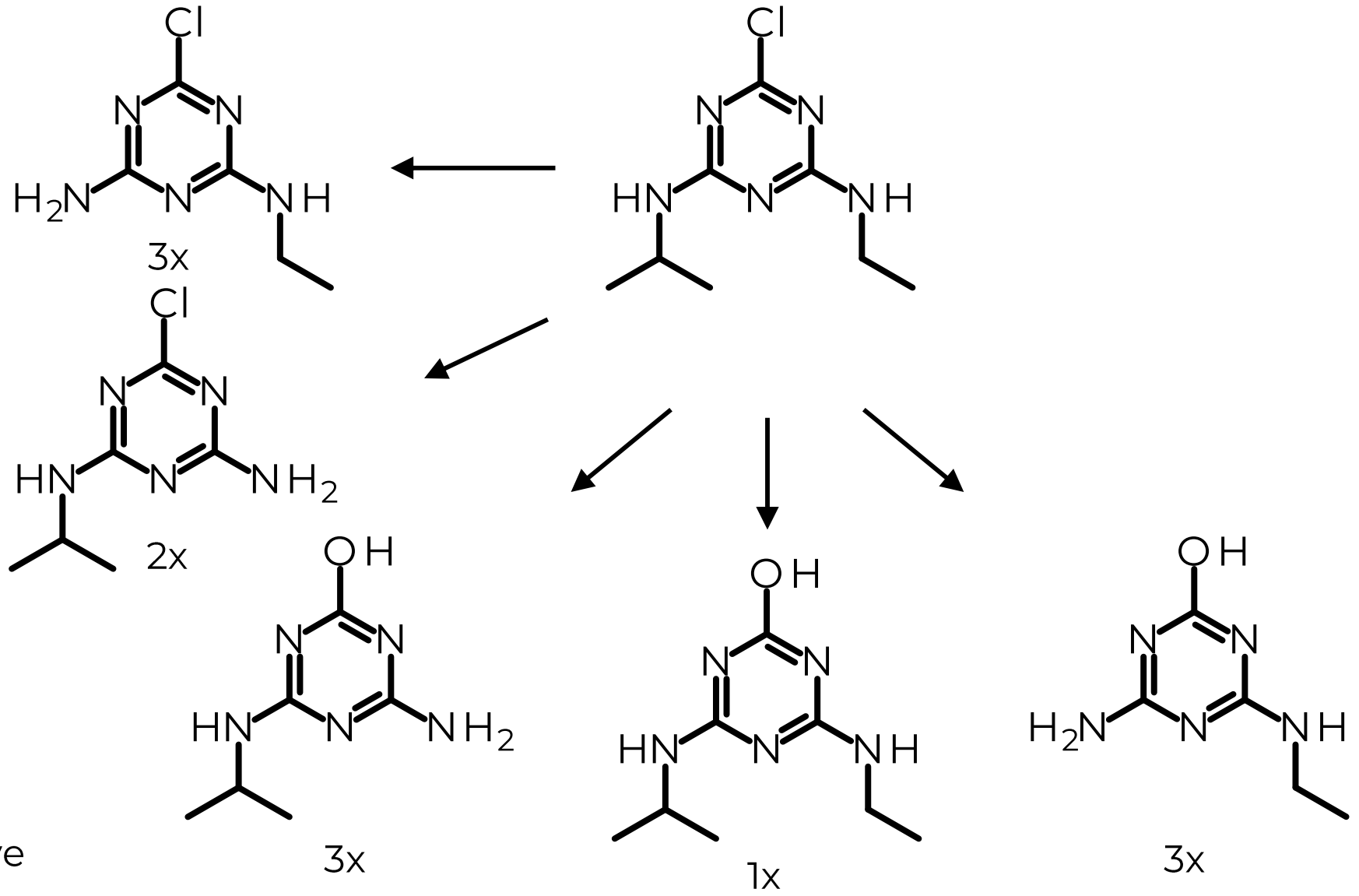
parent – transformation product

Malm et al. Molecules 2021



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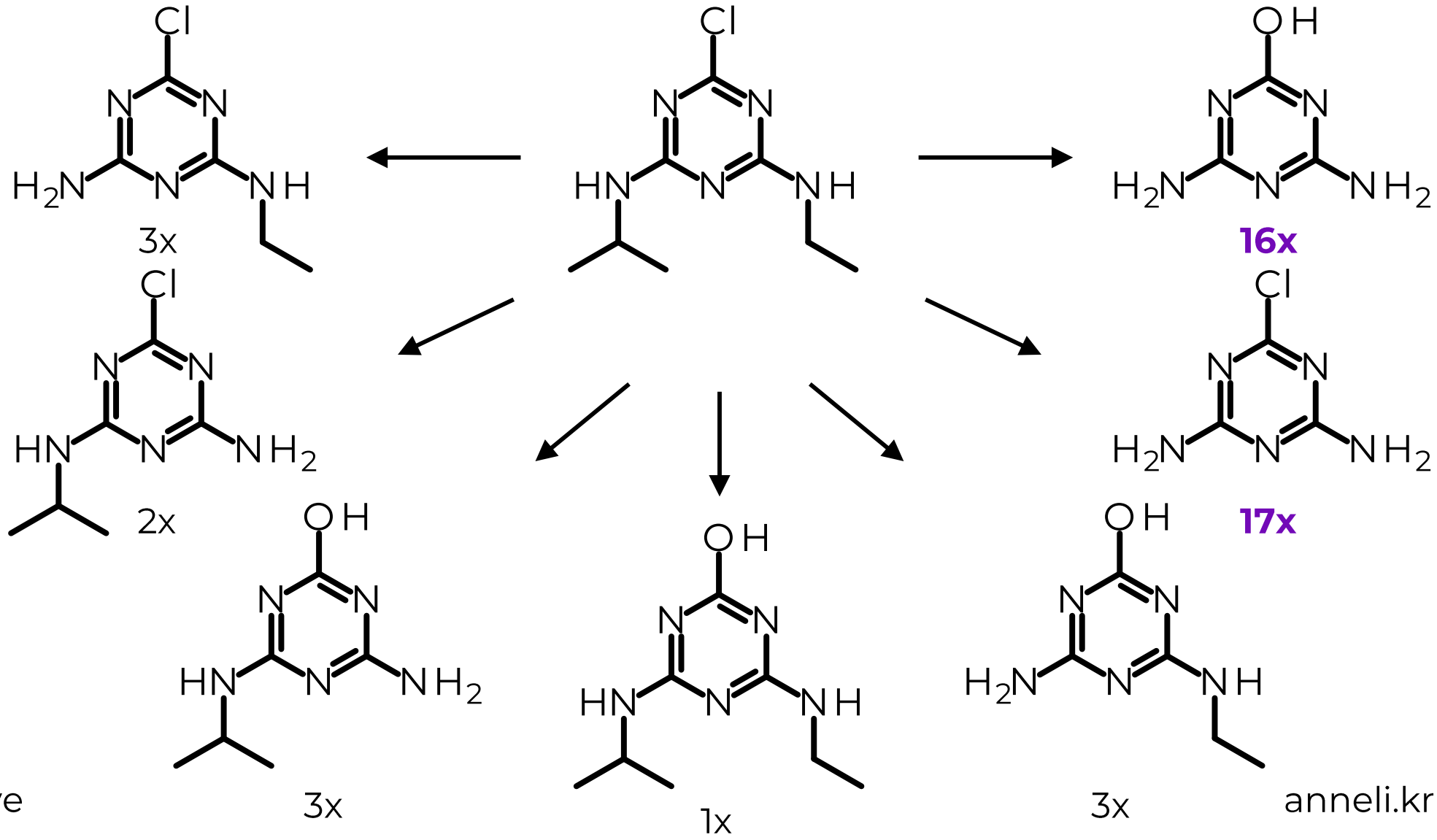
parent – transformation product

Malm et al. Molecules 2021



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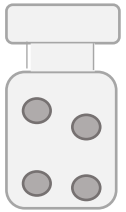
quantification

with close eluting chemical

compound eluting closest



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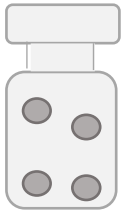
compound eluting closest



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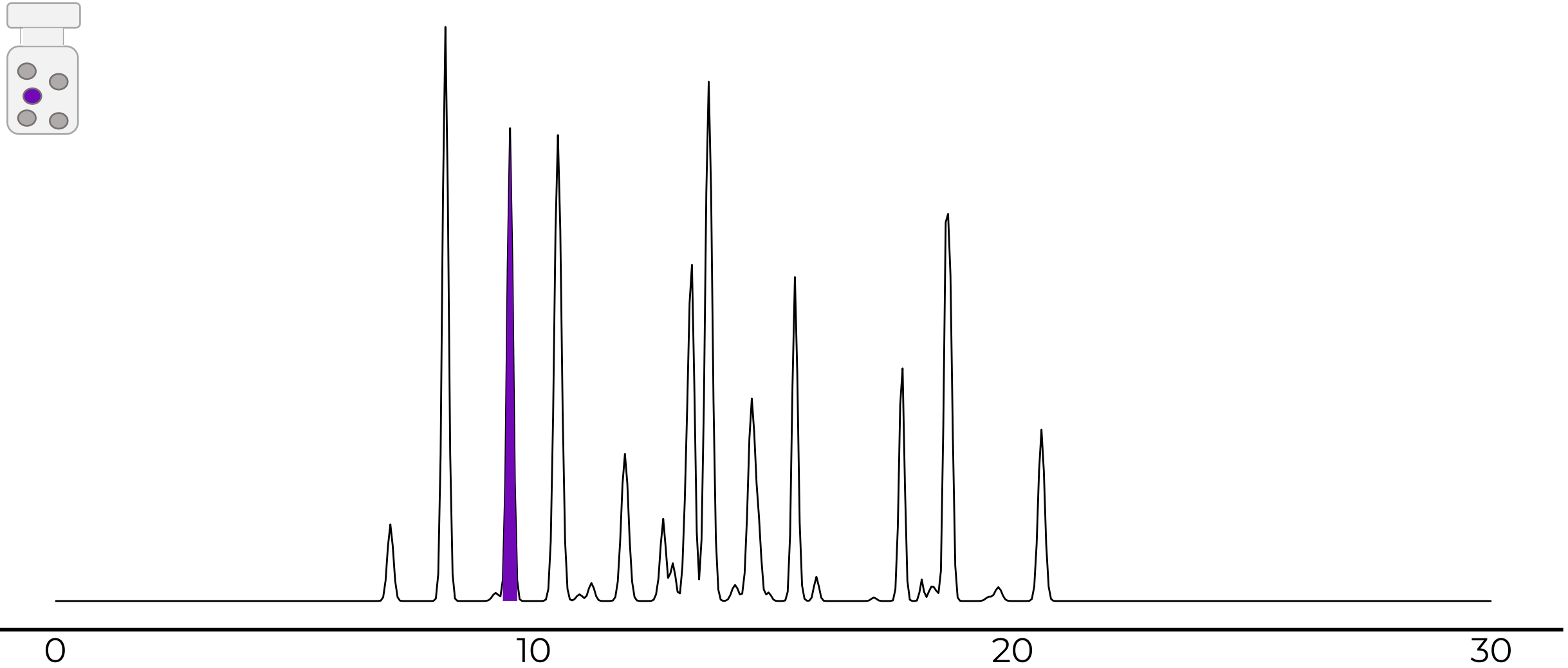
compound eluting closest



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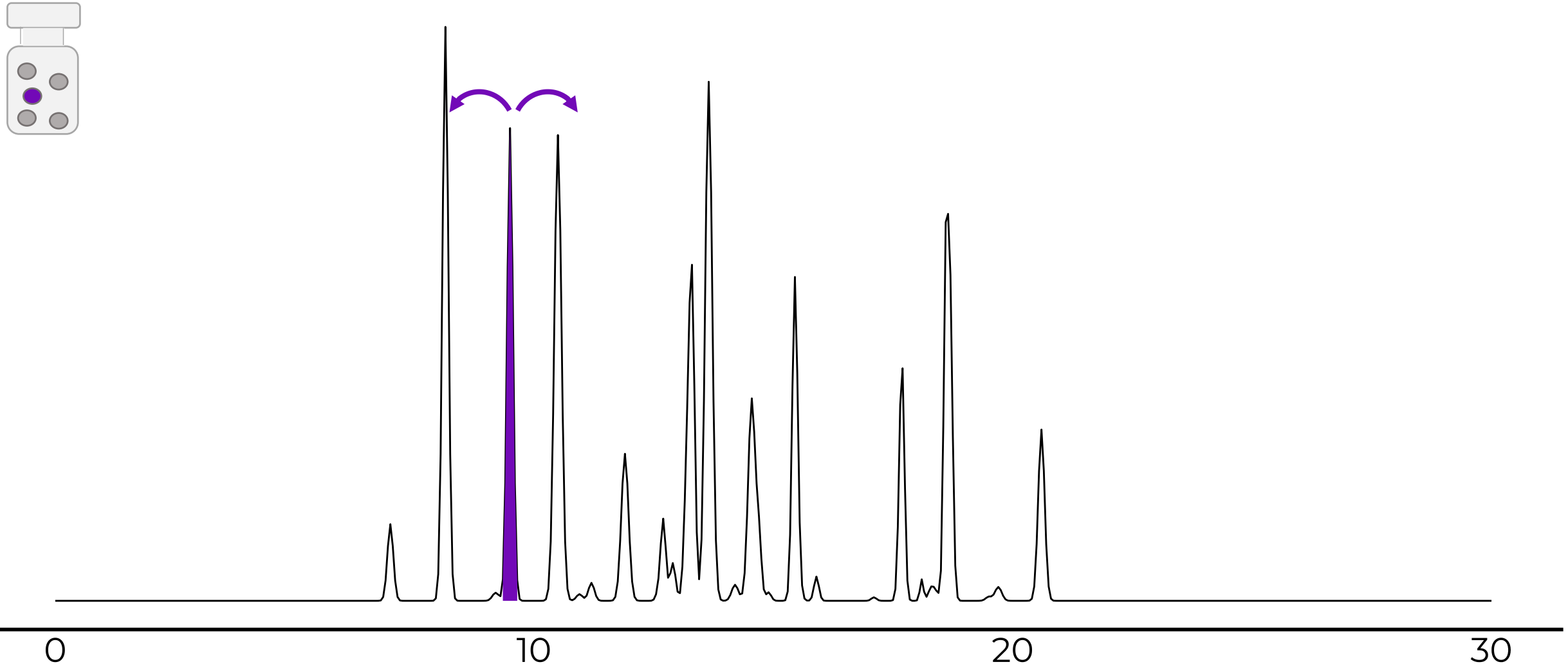
compound eluting closest



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pesticides and micropollutants

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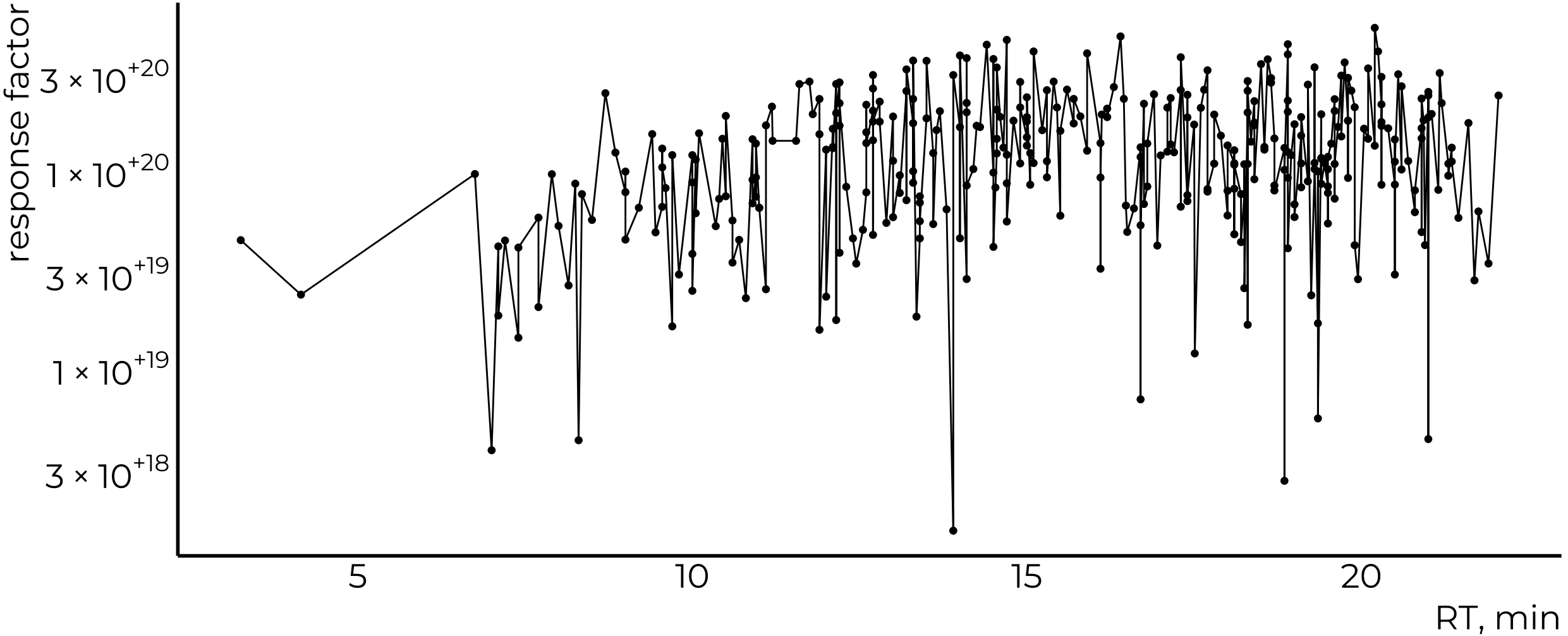
pesticides and micropollutants

Kruve et al. Anal Bioanal Chem 2021



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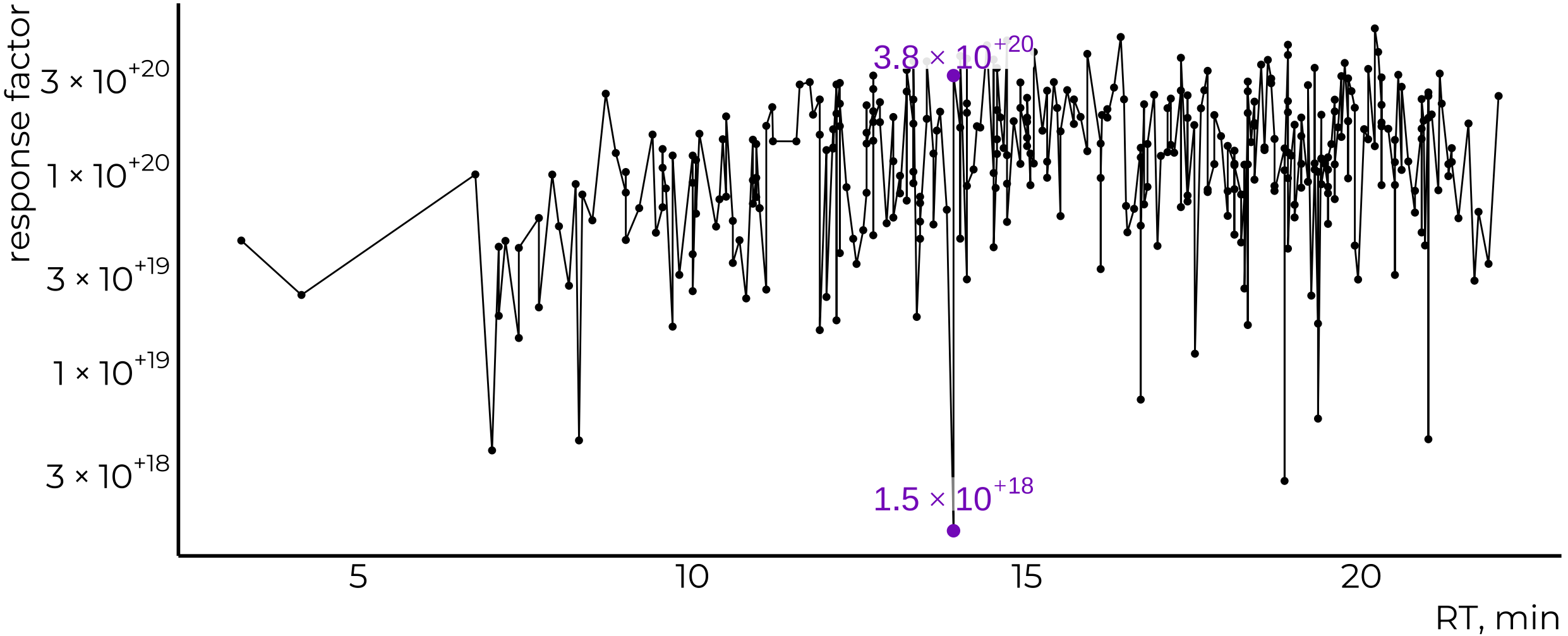
pesticides and micropollutants

Kruve et al. Anal Bioanal Chem 2021



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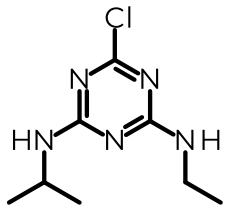
quantification

with machine learning

workflow



SMILES & solvent

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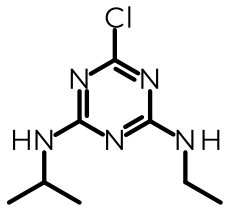
workflow



SMILES & solvent

molecular descriptors

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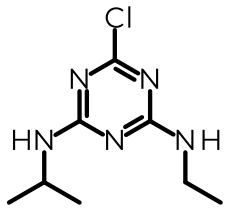
workflow



SMILES & solvent

molecular descriptors

training machine learning models

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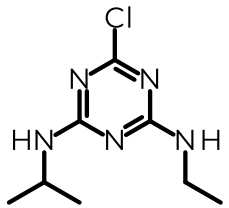
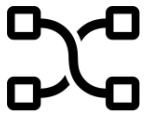
workflow



SMILES & solvent

molecular descriptors

training machine learning models



best model selection

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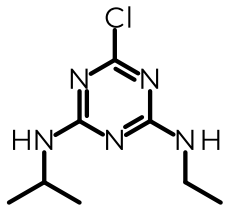
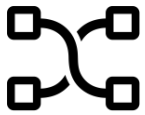
workflow



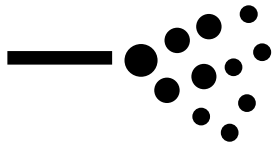
SMILES & solvent

molecular descriptors

training machine learning models



best model selection



predict ionization efficiency

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performance

Liigand et al. Sci Reports 2020

Sepman et al. under review

1403 chemicals

xlog*P* from -6.6 to 22.5

13 labs/methods

flow injections

RP & HILIC methods

MeCN & MeOH

0 – 100%

pH 2.1 – 10.8

different buffers

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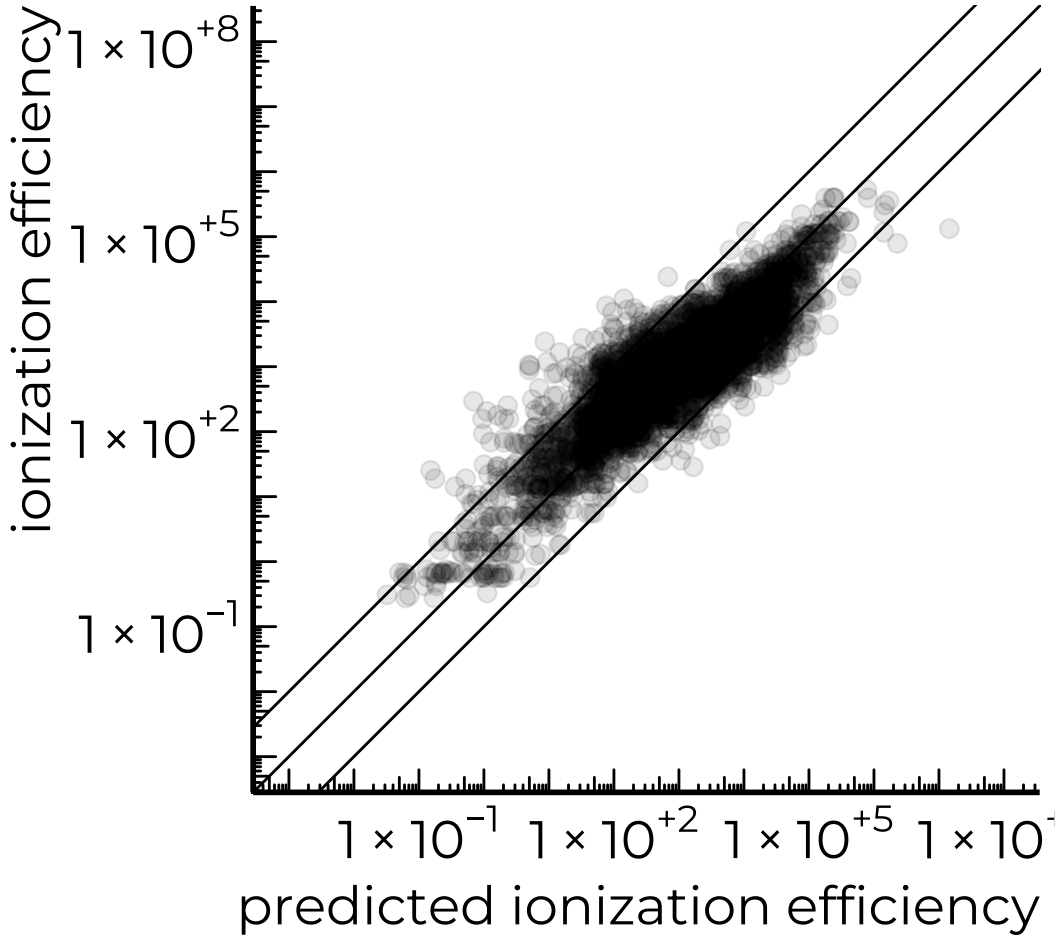
performance

Liigand et al. Sci Reports 2020

Sepman et al. under review



IE range

100,000,000

training set

RMSE 3.6x

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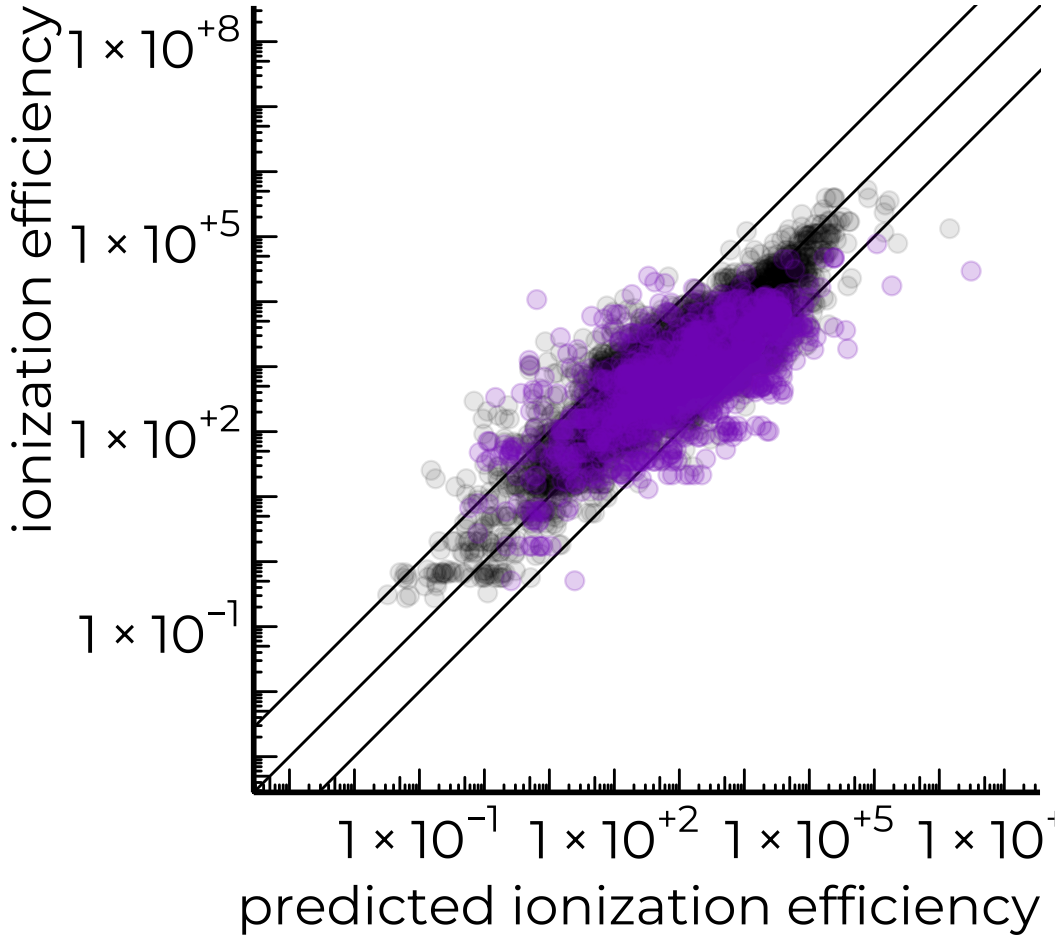
performance

Liigand et al. Sci Reports 2020

Sepman et al. under review



IE range

100,000,000

training set

RMSE 3.6x

test set

RMSE 5.6x

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application

compound	peak area
methiocarb sulfoxide	5,300
pyridaben	5,400
aldicarb-sulfone	70,800

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application

predict ionization efficiency

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application

compound	**peak area**	**log*IE*$_{pred}$**
methiocarb sulfoxide	5,300	2.57
pyridaben	5,400	3.78
aldicarb-sulfone	70,800	1.99

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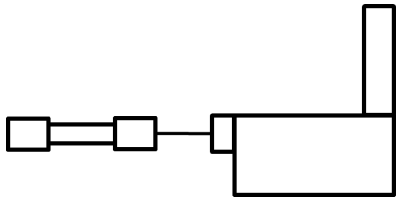
application

predict ionization efficiency



convert to instrument specific values

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application

compound	peak area	log*IE*$_{pred}$	c (nM)
methiocarb sulfoxide	5,300	2.57	
pyridaben	5,400	3.78	
aldicarb-sulfone	70,800	1.99	
atrazine-D5			4.5
gabapentin-lactam			0.35
sitagliptin			0.23
5-methyl-1H-benzotriazole			0.94
neburon			3.4
caffeine			0.50

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application

compound	peak area	log*IE*$_{pred}$	c (nM)
methiocarb sulfoxide	5,300	2.57	
pyridaben	5,400	3.78	
aldicarb-sulfone	70,800	1.99	
atrazine-D5	450,000		4.5
gabapentin-lactam	10,400		0.35
sitagliptin	8,100		0.23
5-methyl-1H-benzotriazole	27,000		0.94
neburon	243,000		3.4
caffeine	5,600		0.50

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application

$RF_{measured}$ = peak area /*c*

compound	peak area	log*IE*$_{pred}$	c (nM)	$RF_{meas} \cdot 10^{16}$
methiocarb sulfoxide	5,300	2.57		
pyridaben	5,400	3.78		
aldicarb-sulfone	70,800	1.99		
atrazine-D5	450,000		4.5	9.8
gabapentin-lactam	10,400		0.35	3.0
sitagliptin	8,100		0.23	3.5
5-methyl-1H-benzotriazole	27,000		0.94	2.9
neburon	243,000		3.4	7.2
caffeine	5,600		0.50	1.1

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application

compound	peak area	logIE_{pred}	c (nM)	RF_{meas}·10^{16}
methiocarb sulfoxide	5,300	2.57		
pyridaben	5,400	3.78		
aldicarb-sulfone	70,800	1.99		
atrazine-D5	450,000	3.46	4.5	9.8
gabapentin-lactam	10,400	2.66	0.35	3.0
sitagliptin	8,100	2.89	0.23	3.5
5-methyl-1H-benzotriazole	27,000	2.46	0.94	2.9
neburon	243,000	3.23	3.4	7.2
caffeine	5,600	2.30	0.50	1.1

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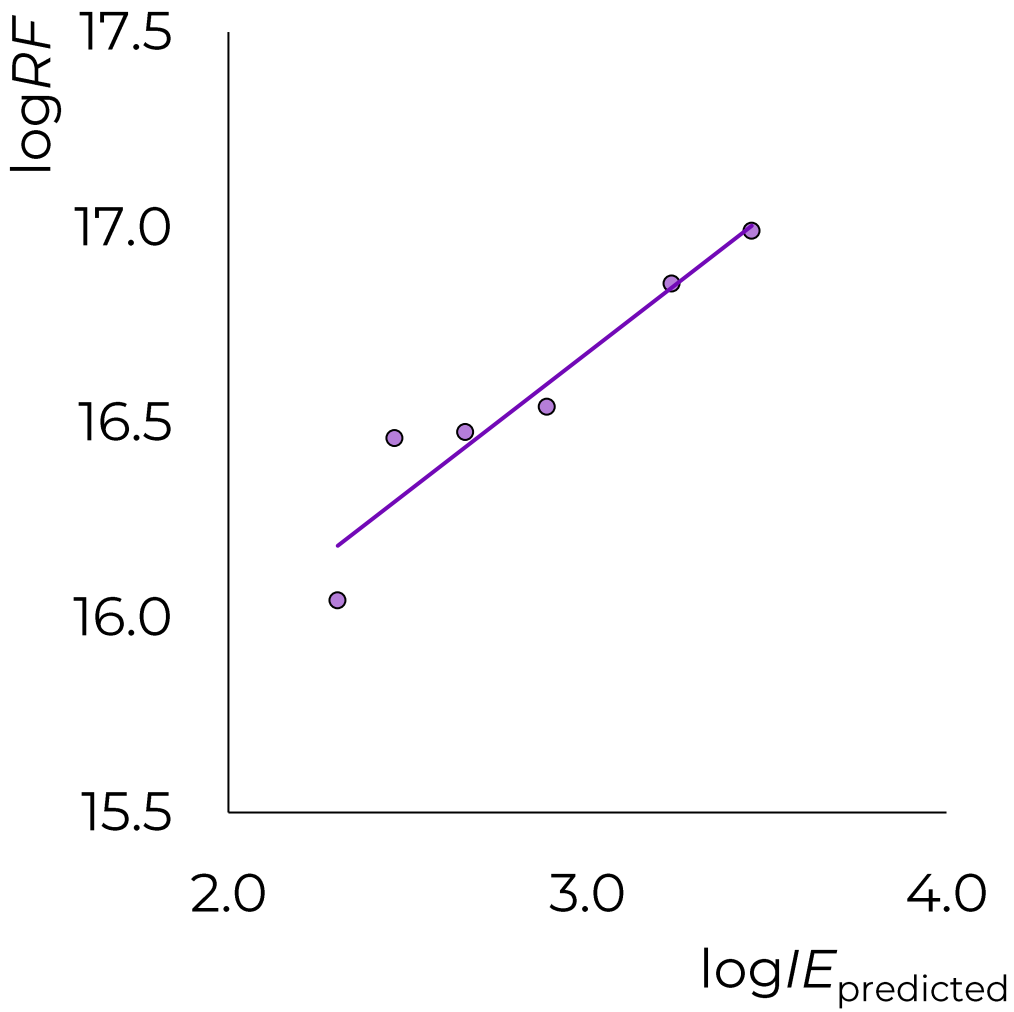
application

compound	peak area	log*IE*$_{pred}$
methiocarb sulfoxide	5,300	2.57
pyridaben	5,400	3.78
aldicarb-sulfone	70,800	1.99
atrazine-D5	450,000	3.46
gabapentin-lactam	10,400	2.66
sitagliptin	8,100	2.89
5-methyl-1H-benzotriazole	27,000	2.46
neburon	243,000	3.23
caffeine	5,600	2.30

log*RF* = slope·log*IE* + intercept



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application

$\log RF_{predicted} = slope \cdot \log IE_{predicted} + intercept$

compound	**peak area**	**logIE_{pred}**	**c (nM)**	**$RF_{meas} \cdot 10^{16}$**	**$RF_{pred} \cdot 10^{16}$**
methiocarb sulfoxide	5,300	2.57			2.6
pyridaben	5,400	3.78			15.5
aldicarb-sulfone	70,800	1.99			1.1
atrazine-D5	450,000	3.46	4.5	9.8	
gabapentin-lactam	10,400	2.66	0.35	3.0	
sitagliptin	8,100	2.89	0.23	3.5	
5-methyl-1H-benzotriazole	27,000	2.46	0.94	2.9	
neburon	243,000	3.23	3.4	7.2	
caffeine	5,600	2.30	0.50	1.1	

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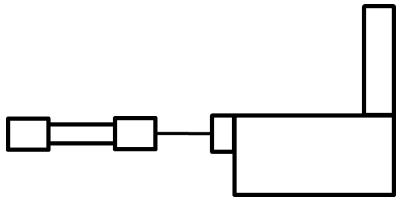
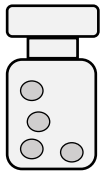
application

predict ionization efficiency



convert to instrument specific values



estimate concentration

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application

c = peak area / $RF_{predicted}$

compound	peak area	logIE_{pred}	c (nM)	RF_{meas}·10^{16}	RF_{pred}·10^{16}	c_{pred} (nM)
methiocarb sulfoxide	5,300	2.57			2.6	0.20
pyridaben	5,400	3.78			15.5	0.035
aldicarb-sulfone	70,800	1.99			1.1	6.3
atrazine-D5	450,000	3.46	4.5	9.8		
gabapentin-lactam	10,400	2.66	0.35	3.0		
sitagliptin	8,100	2.89	0.23	3.5		
5-methyl-1H-benzotriazole	27,000	2.46	0.94	2.9		
neburon	243,000	3.23	3.4	7.2		
caffeine	5,600	2.30	0.50	1.1		

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case studies

water

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chemicals in surface water

The Netherlands

Been et al. Water Research 2021

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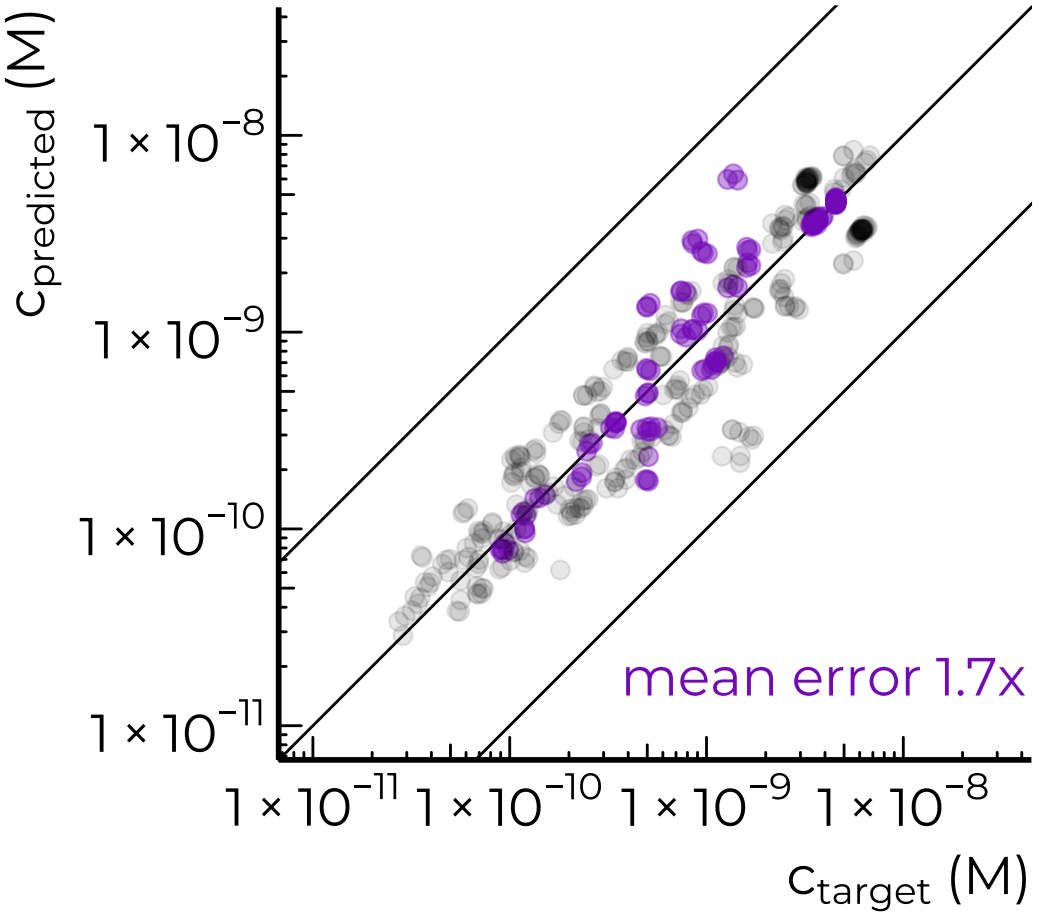
chemicals in surface water

The Netherlands

Been et al. Water Research 2021



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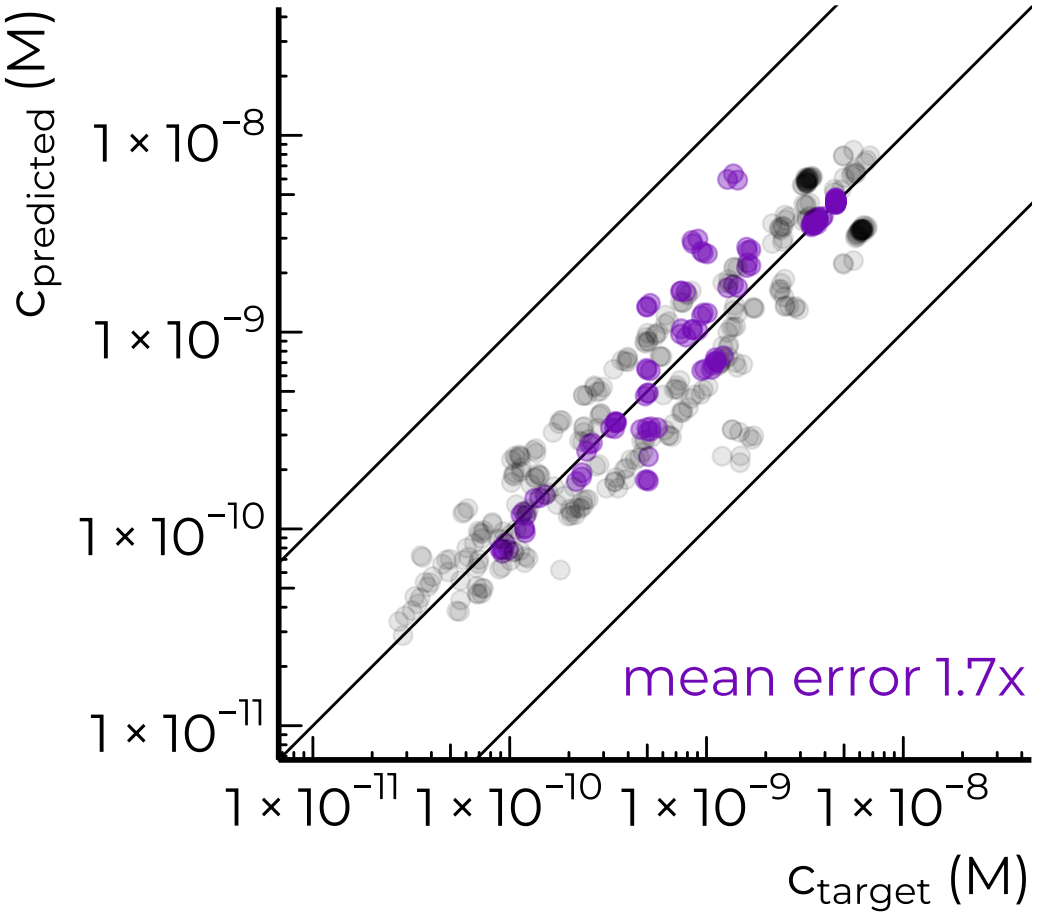
chemicals in surface water

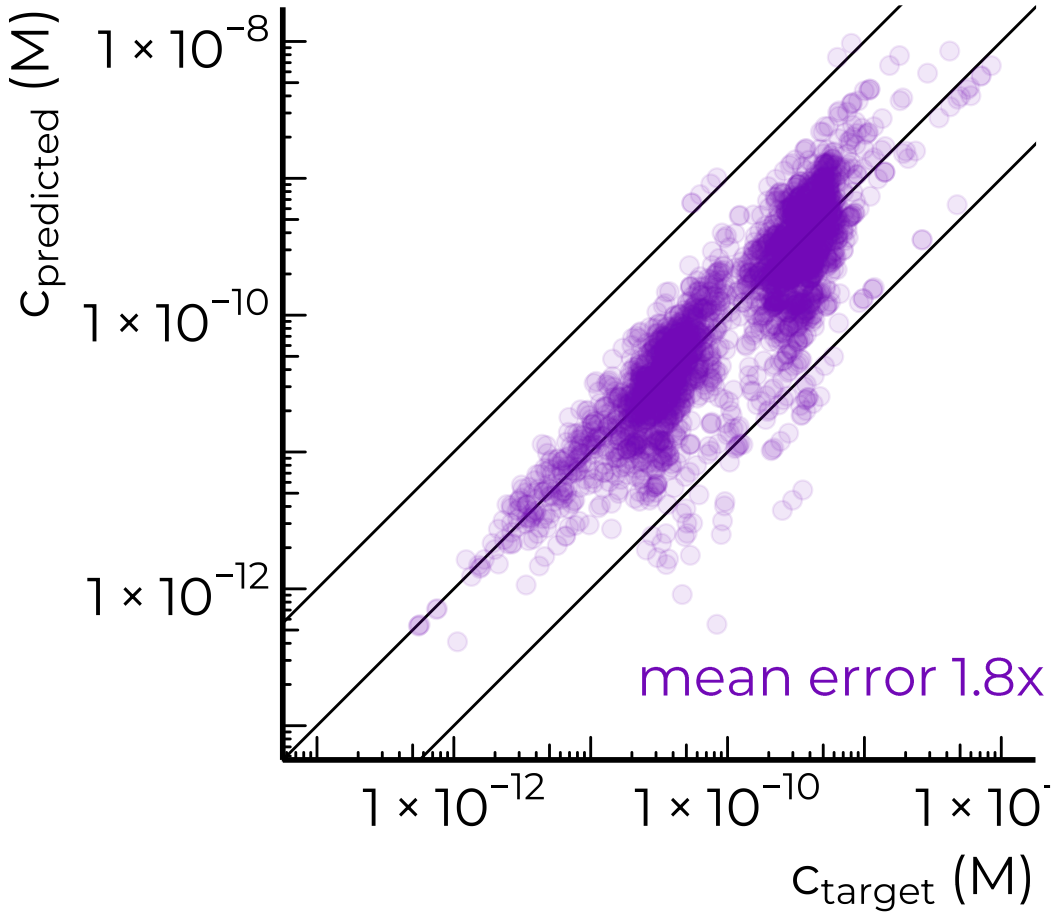
The Netherlands

Been et al. Water Research 2021



Switzerland

Kruve et al. Anal Bioanal Chem 2021



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case studies

water

blood

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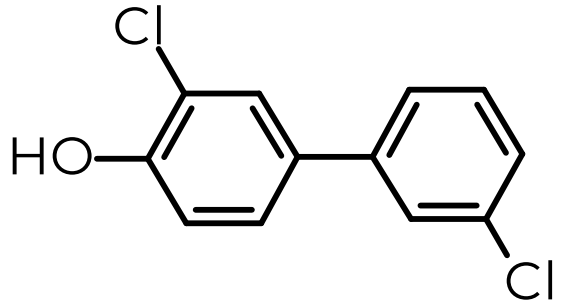
OH-PCBs in blood plasma

Khabazbashi et al. Anal Bioanal Chem 2022



retrained with small set of OH-PCBs

tested on 3 OH-PCBs

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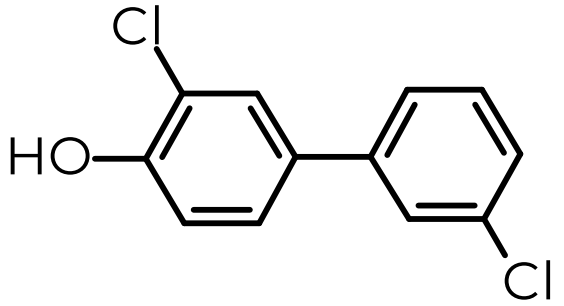
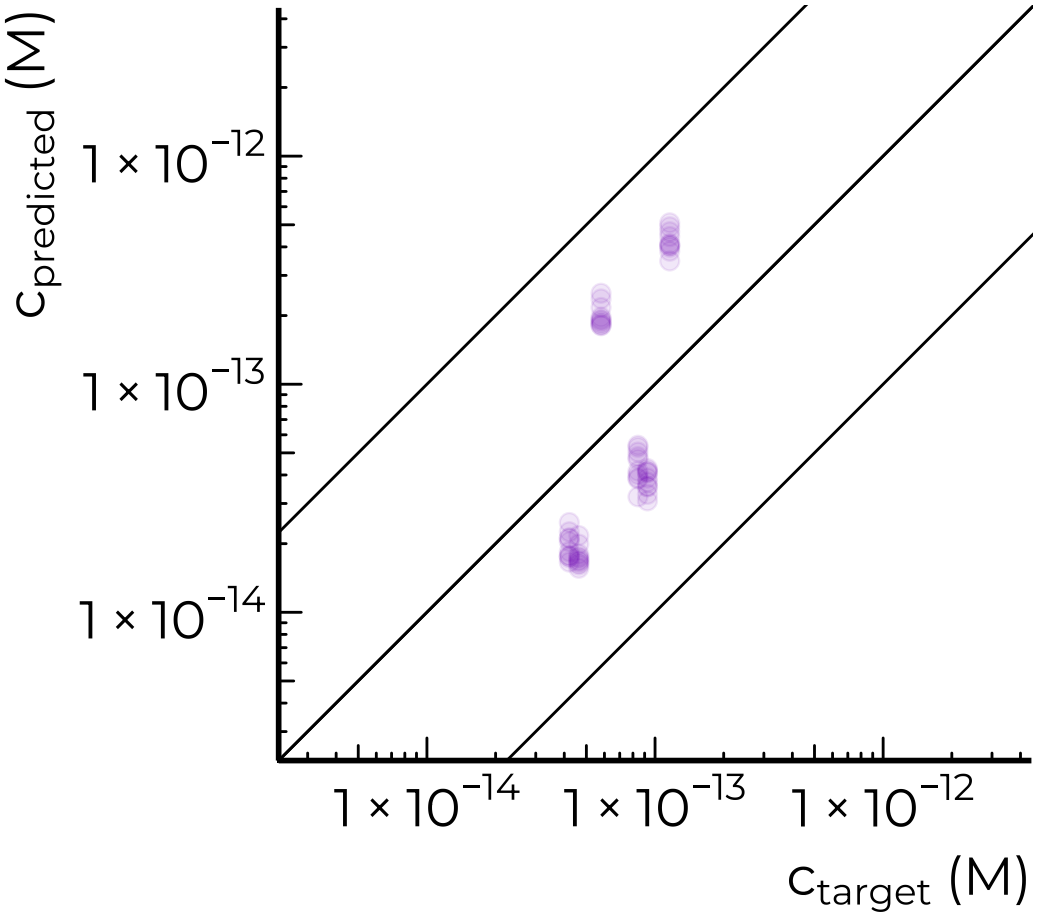
OH-PCBs in blood plasma

Khabazbashi et al. Anal Bioanal Chem 2022





retrained with small set of OH-PCBs

tested on 3 OH-PCBs

different matrixes

mean error 2.0x to 3.6x

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case studies

water

blood

food

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pesticides in food

Wang et al. Food Chem 2020

195 pesticides in 5 cereal matrices

11,500 data points

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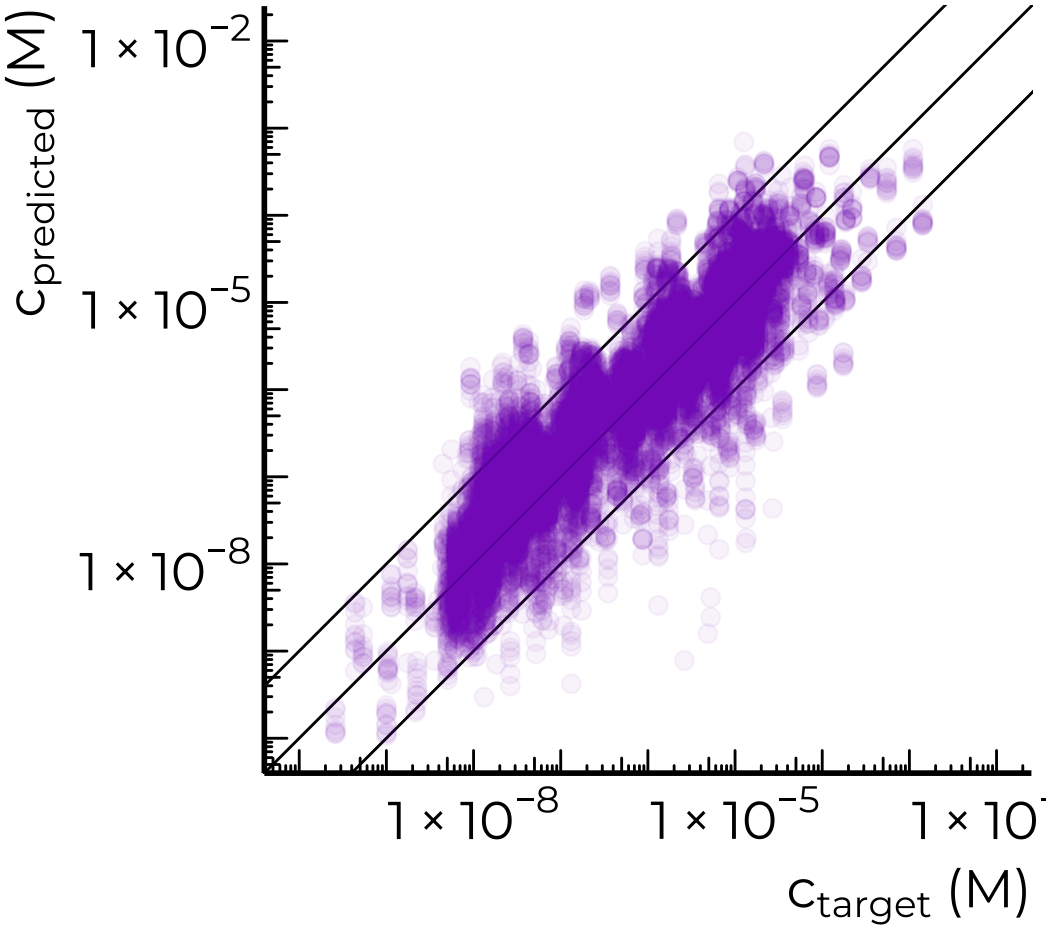
pesticides in food

Wang et al. Food Chem 2020



195 pesticides in 5 cereal matrices

11,500 data points

mean error 5.3x

89% of points with error <10x

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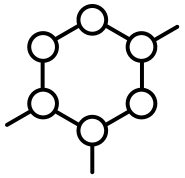
norman interlab

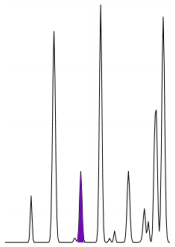
tested methods



structurally similar chemicals

transformation product - parent

Tanimoto similarity



close eluting chemicals

machine learning

Liigand et al.

Aalizadeh et al.

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participants

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sample

HPLC water

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sample

HPLC water

drinking water

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sample

HPLC water

drinking water

surface water

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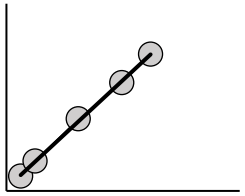
chemicals



36 calibration chemicals

known concentration

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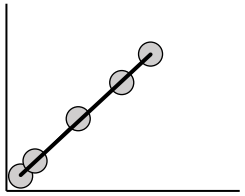
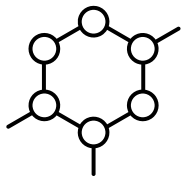
chemicals



36 calibration chemicals

known concentration



38 suspect chemicals

low and high concentration spike

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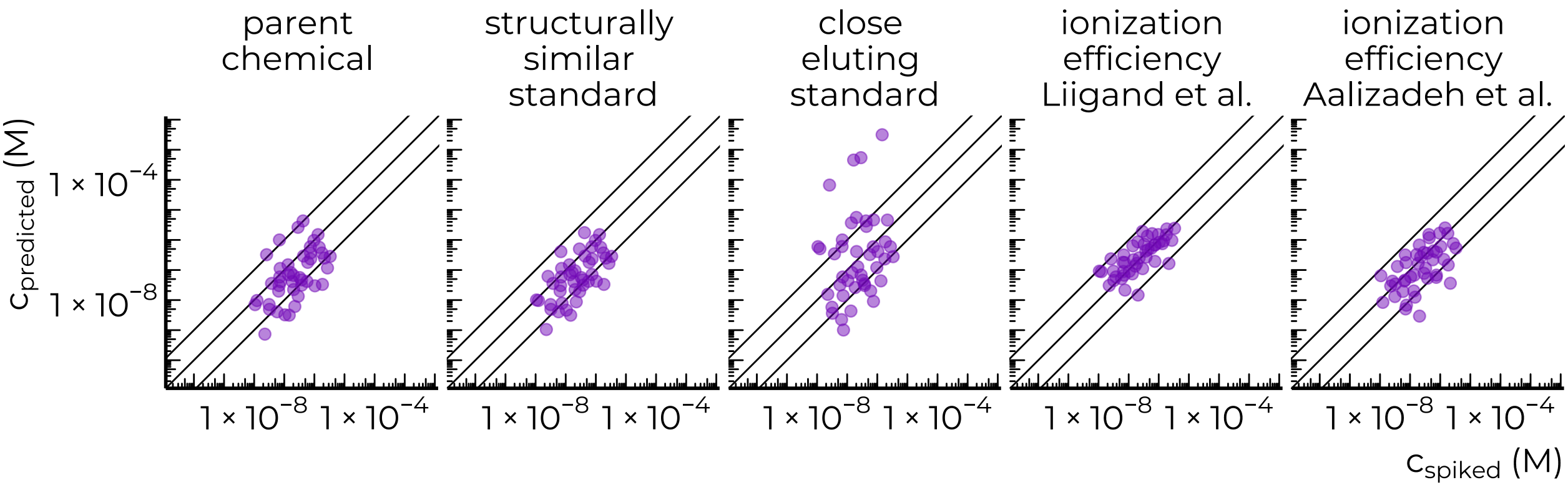
quantification accuracy TPs



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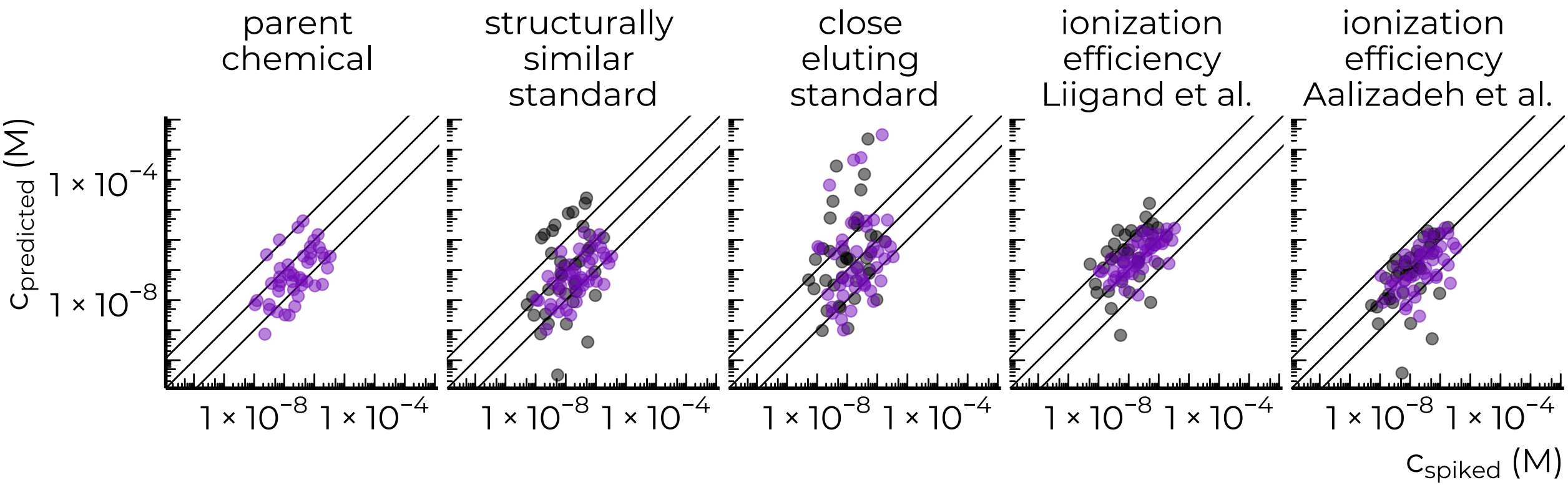
quantification accuracy



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prediction error

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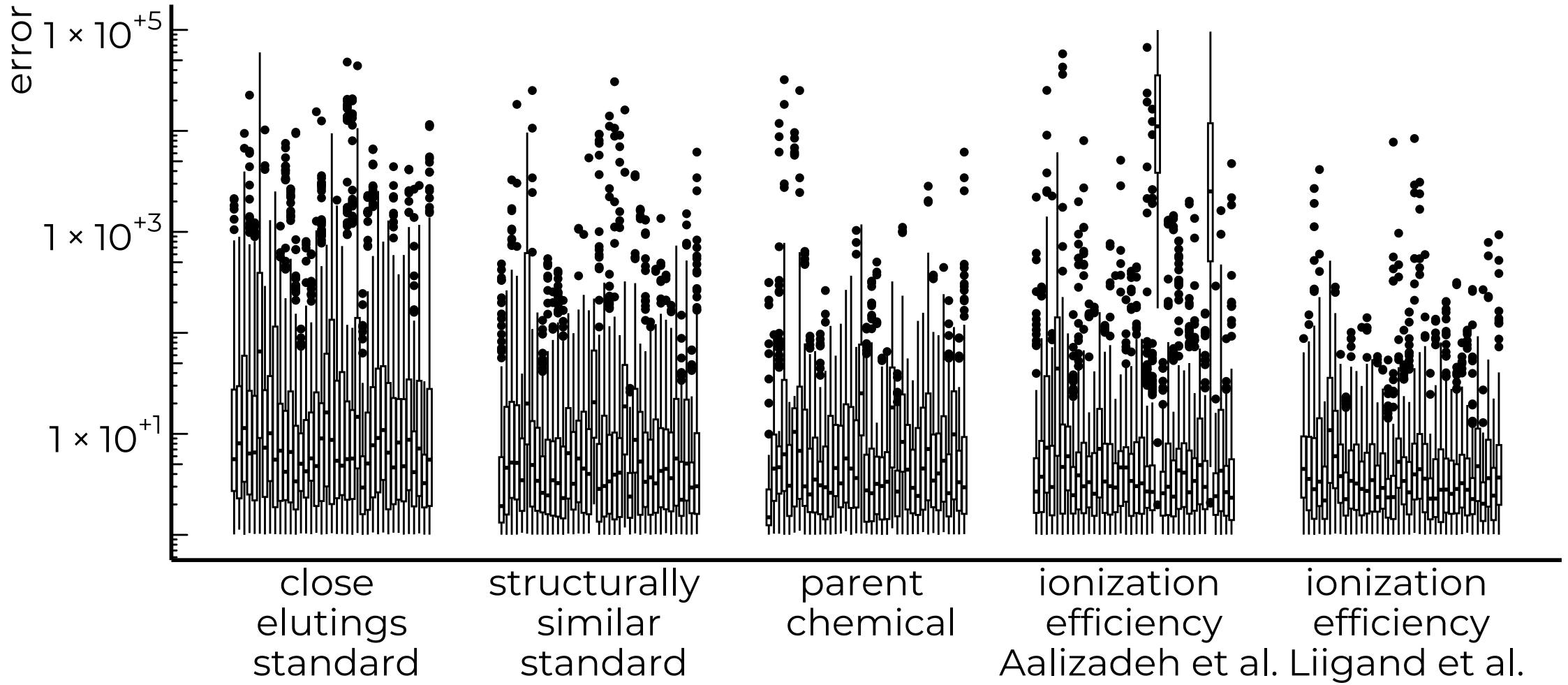
prediction error



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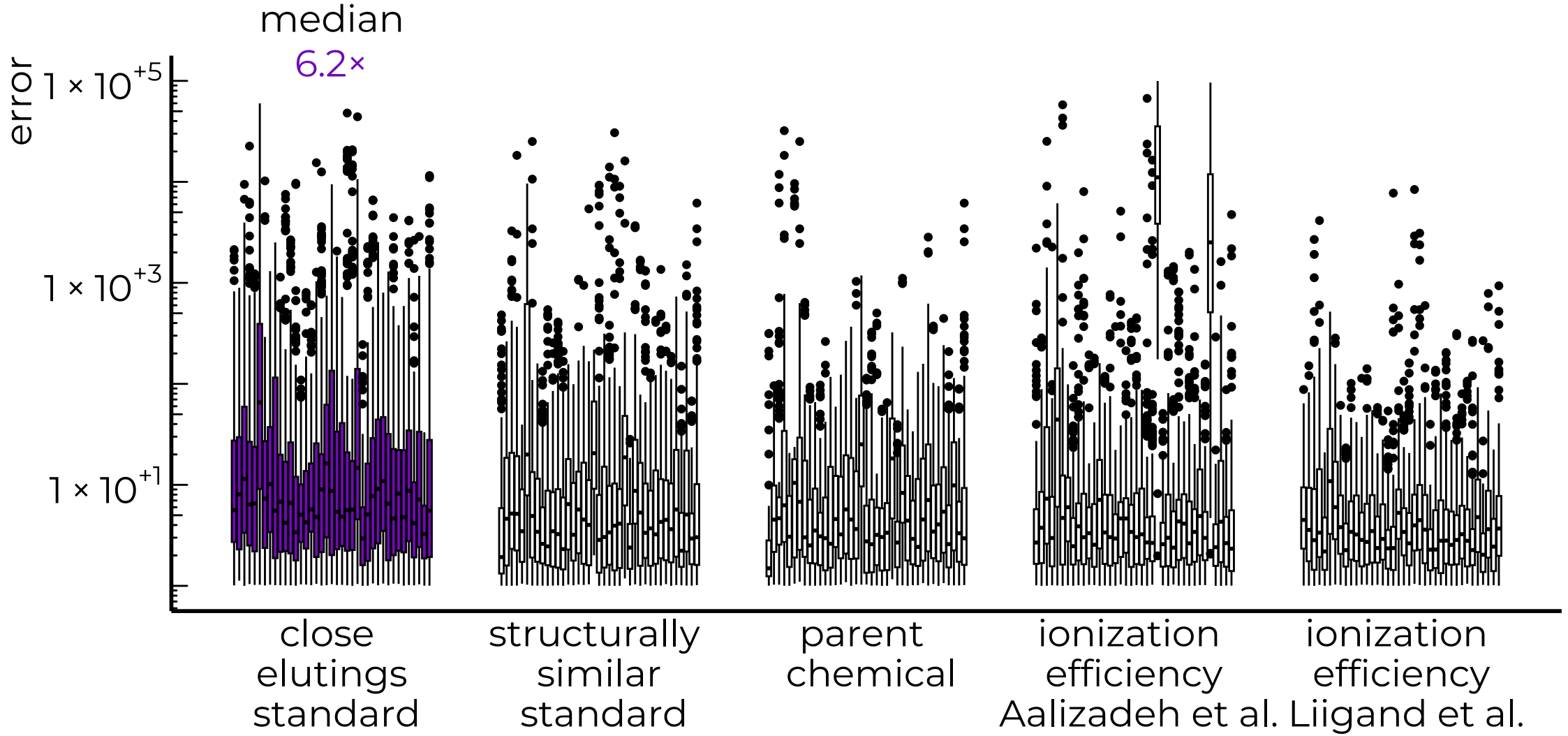
prediction error



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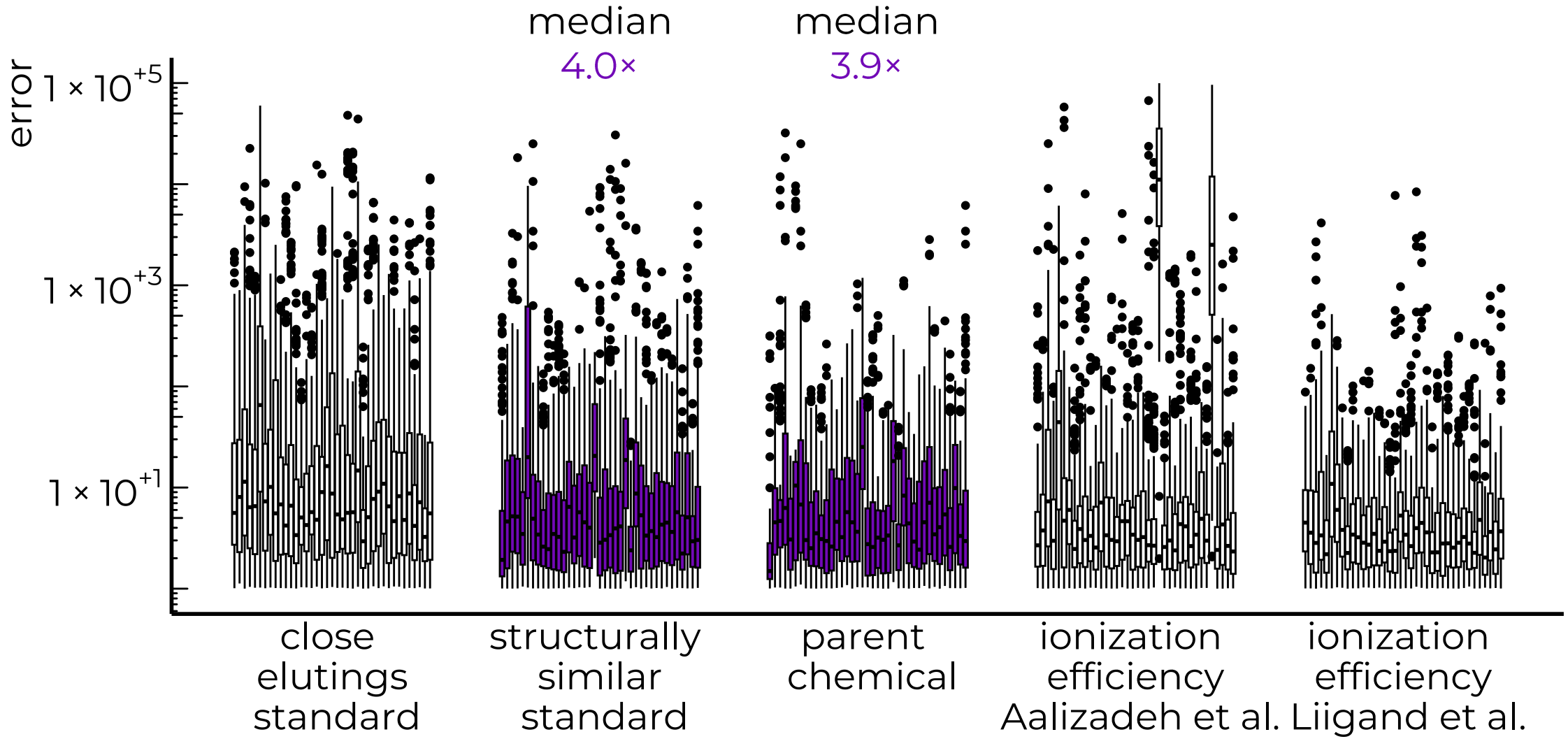
prediction error



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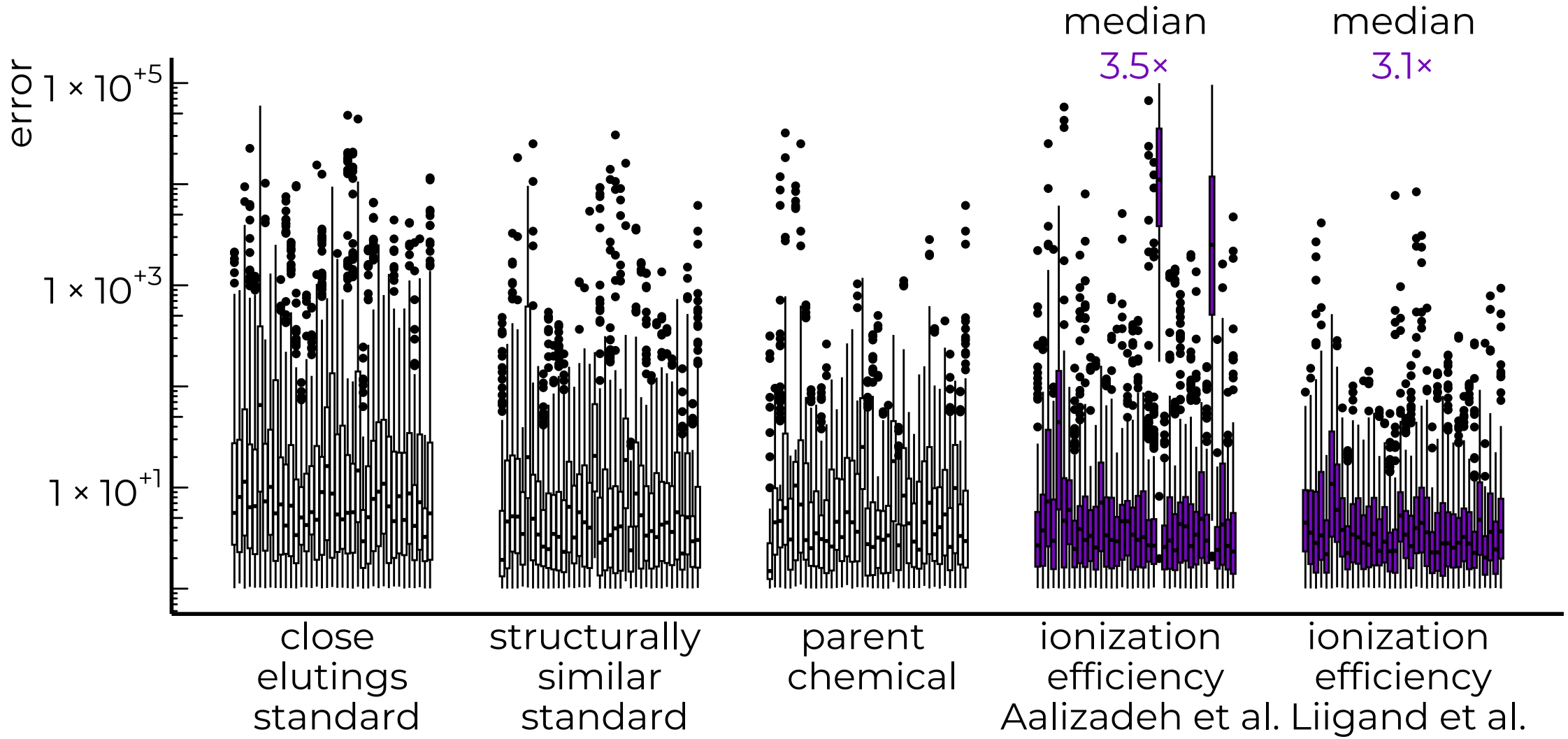
prediction error



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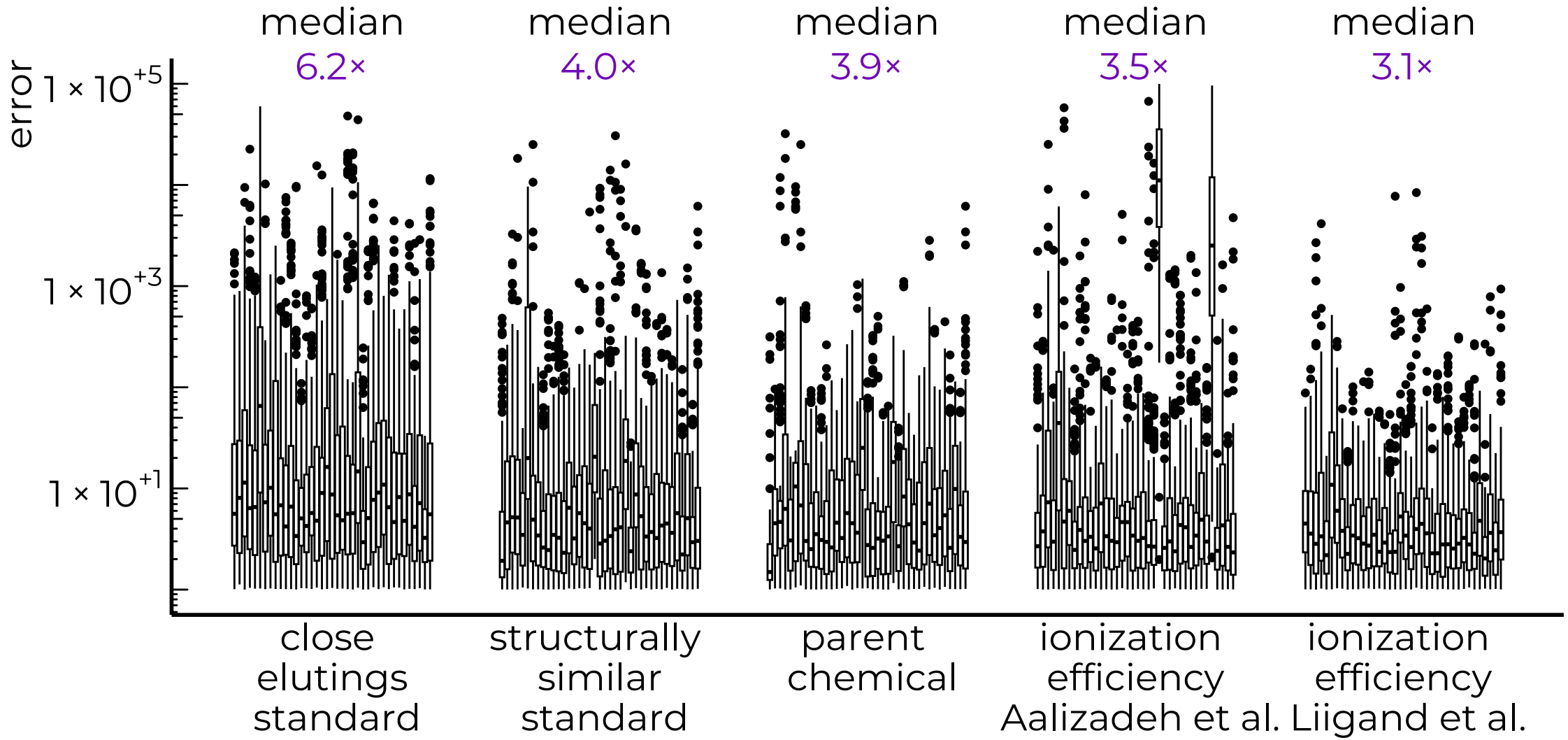
prediction error



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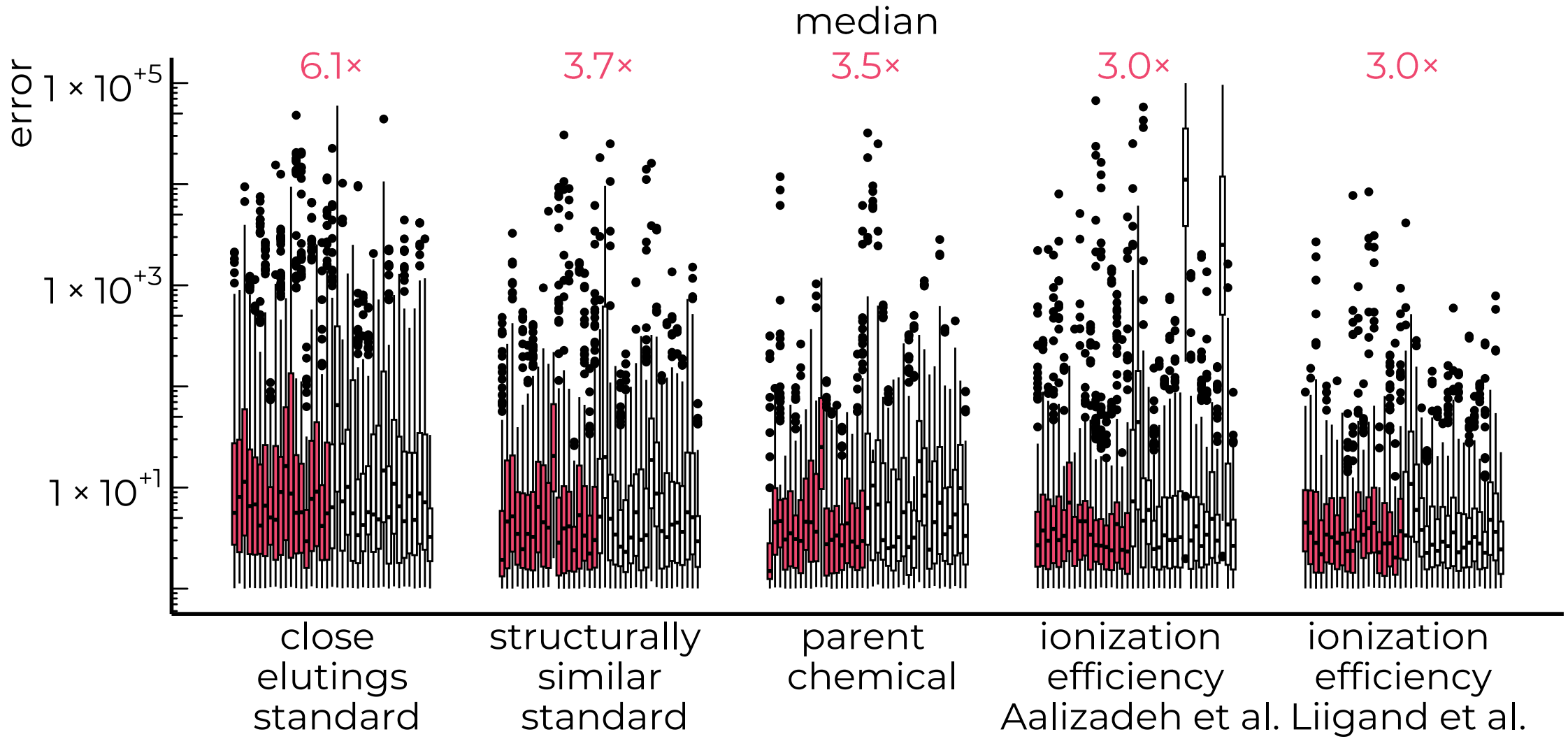
prediction error orbitrap



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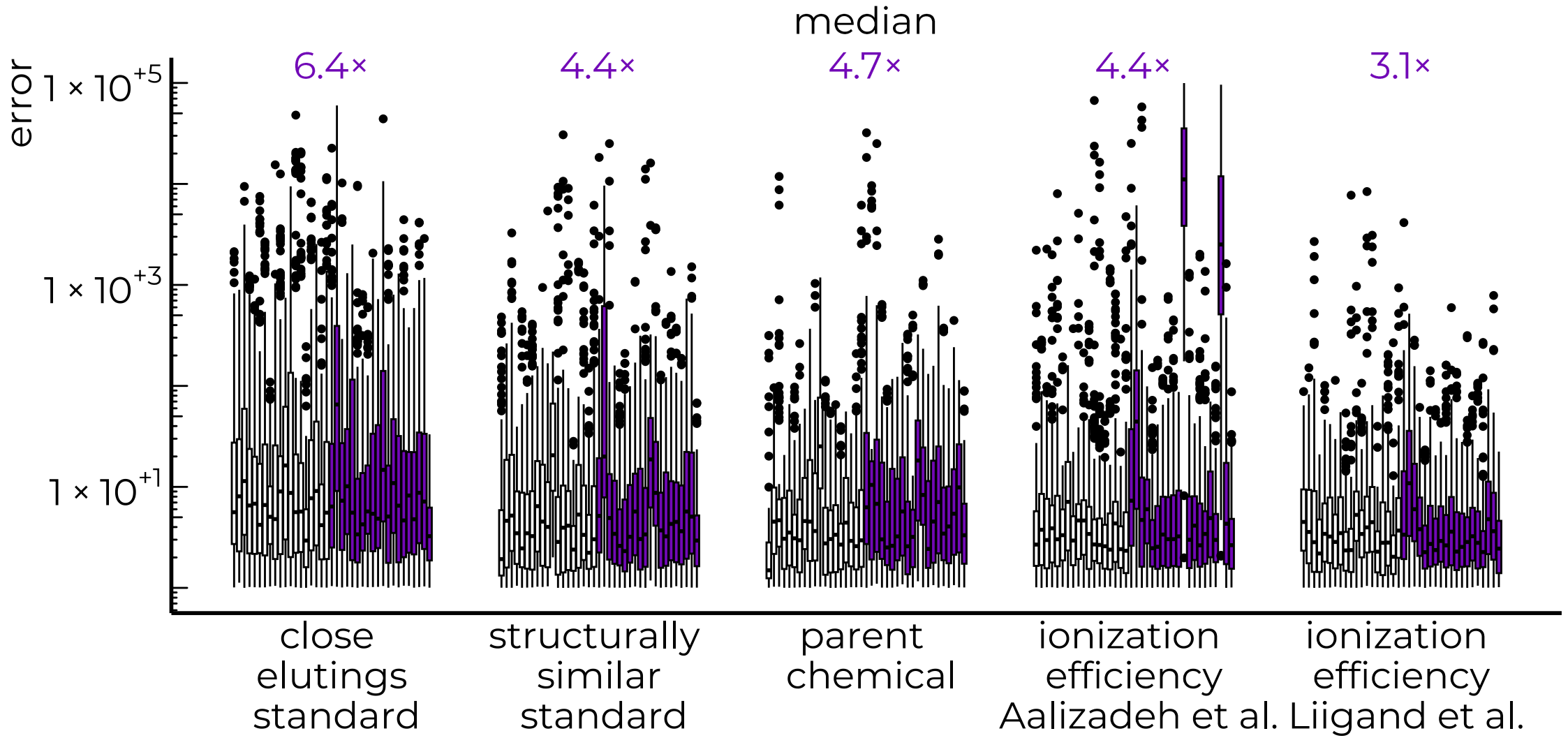
prediction error time-of-flight



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across samples

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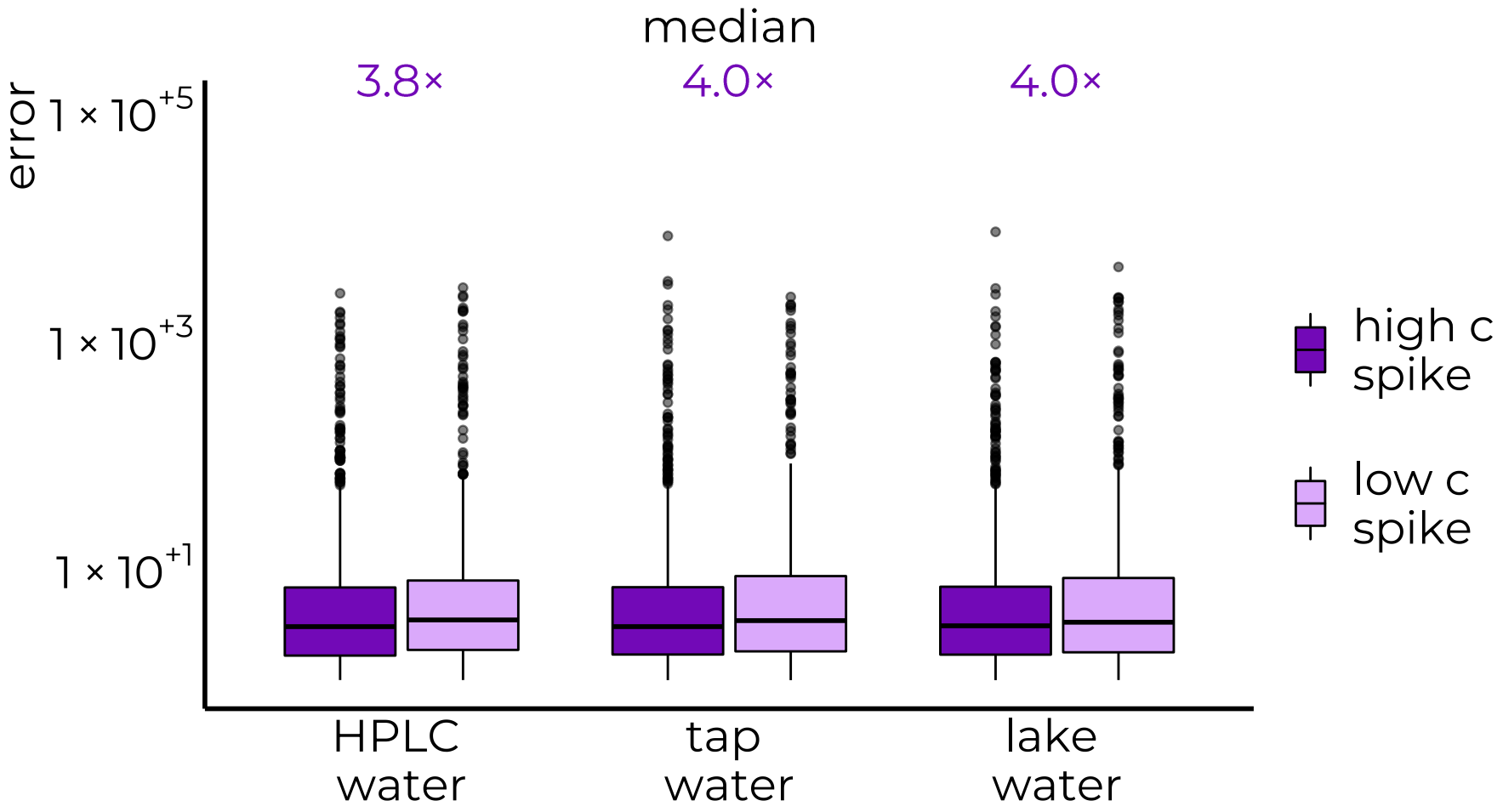
across samples



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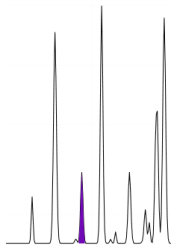
conclusions

close eluting



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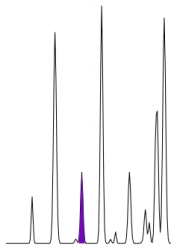
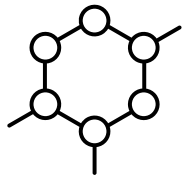
conclusions

close eluting



structurally similar



better

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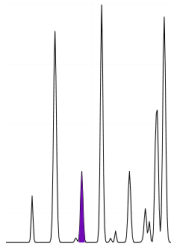
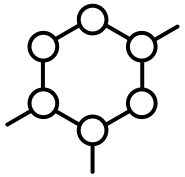
conclusions

close eluting



structurally similar



better

ionization efficiency

best

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unidentified chemicals

from MS^2 spectra

unidentified peaks

US EPA household dust study

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unidentified peaks

US EPA household dust study

3000 & 2000 features detected in ESI+ &ESI-

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unidentified peaks

US EPA household dust study

- 3000 & 2000 features detected in ESI+ &ESI-
- 978 formulas

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unidentified peaks

US EPA household dust study

3000 & 2000 features detected in ESI+ &ESI-

978 formulas → 3228 possible structures

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unidentified peaks

US EPA household dust study

- 3000 & 2000 features detected in ESI+ &ESI-
- 978 formulas → 3228 possible structures
- 33 identified

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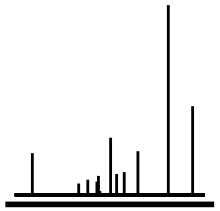
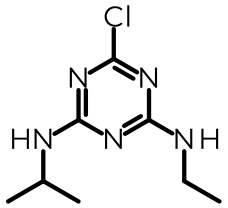
workflow



MS^2 spectra



structure as SMILES

molecular descriptors

predict toxicity and ionization efficiency

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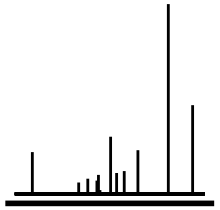
workflow



MS^2 spectra

molecular fingerprints

predict toxicity and ionization efficiency

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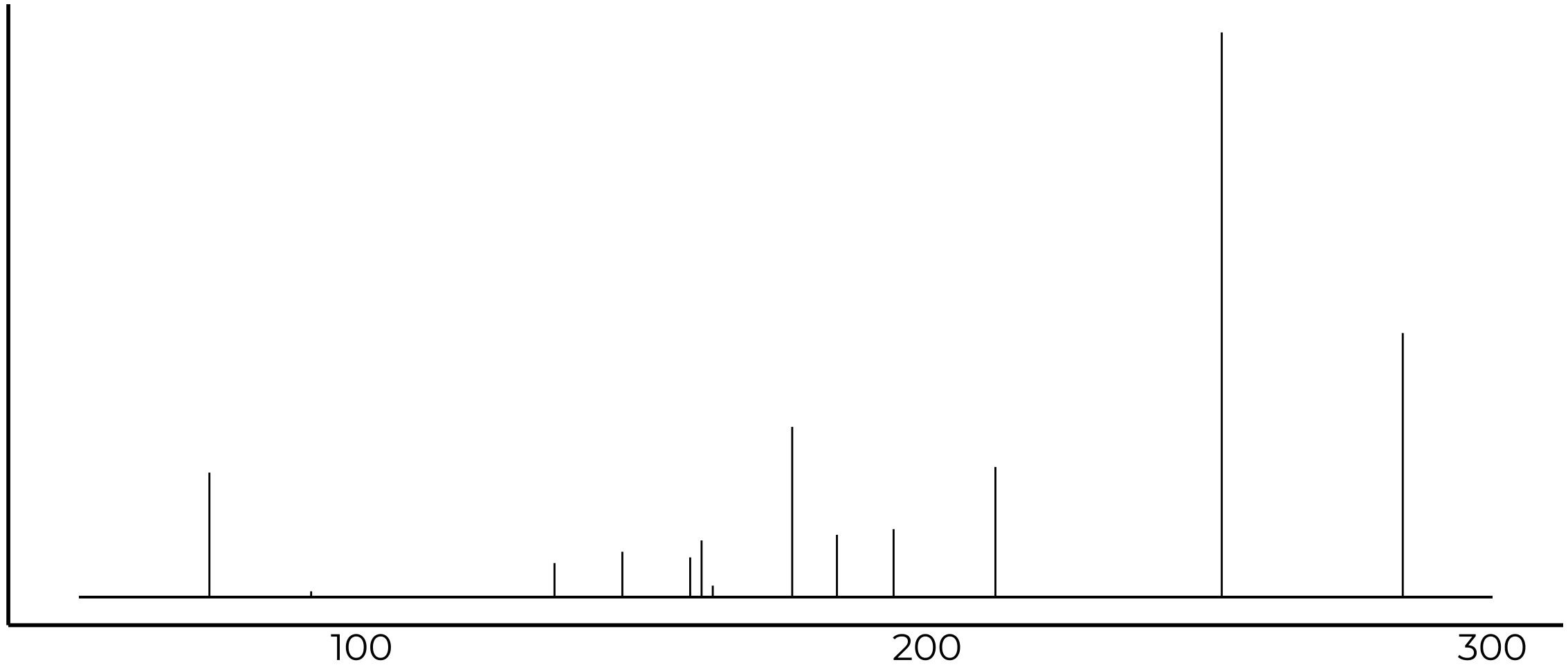
MS^2 spectra



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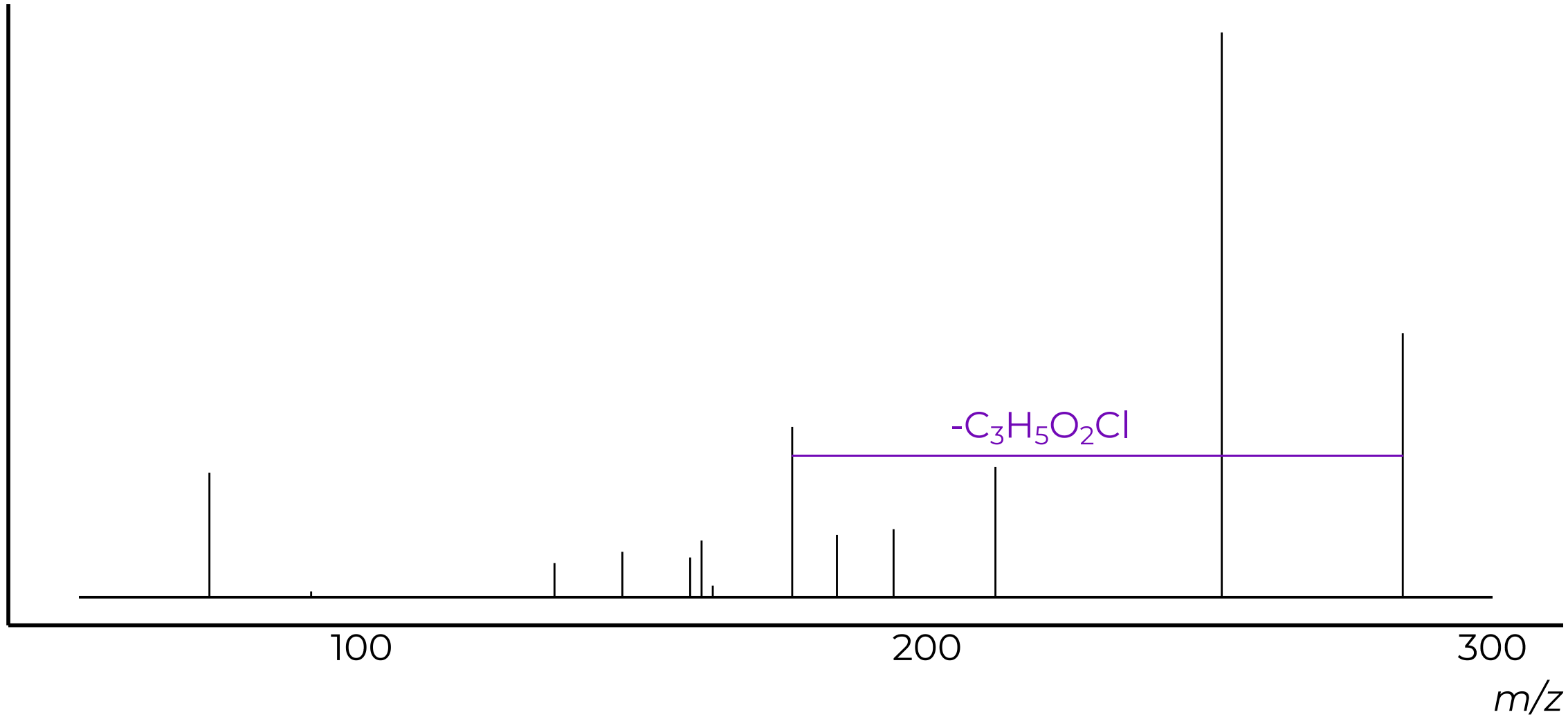
MS^2 spectra



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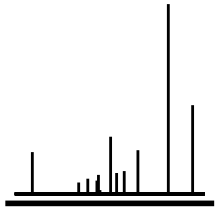
workflow



MS^2 spectra

molecular fingerprints with SIRIUS

predict toxicity and ionization efficiency

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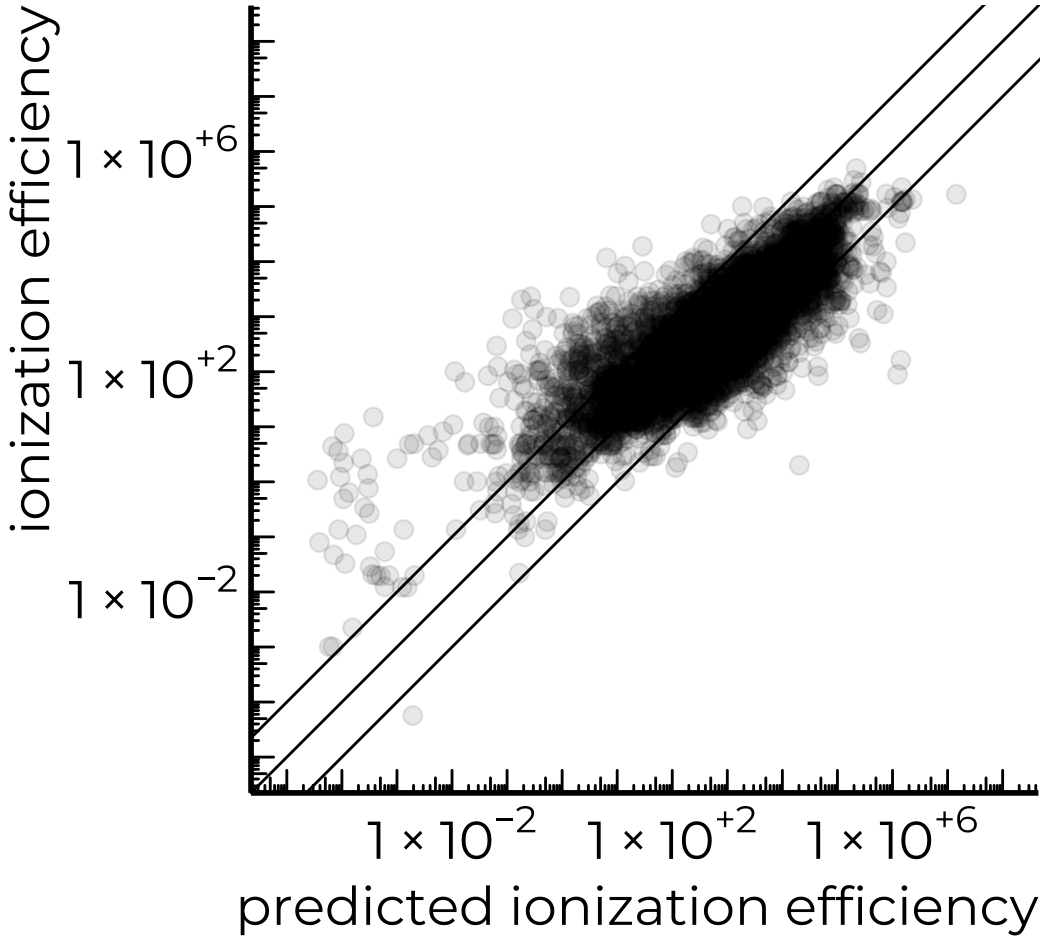
ionization efficiency

Sepman et al. in review



IE range

100,000,000

training set

RMSE 3.5x

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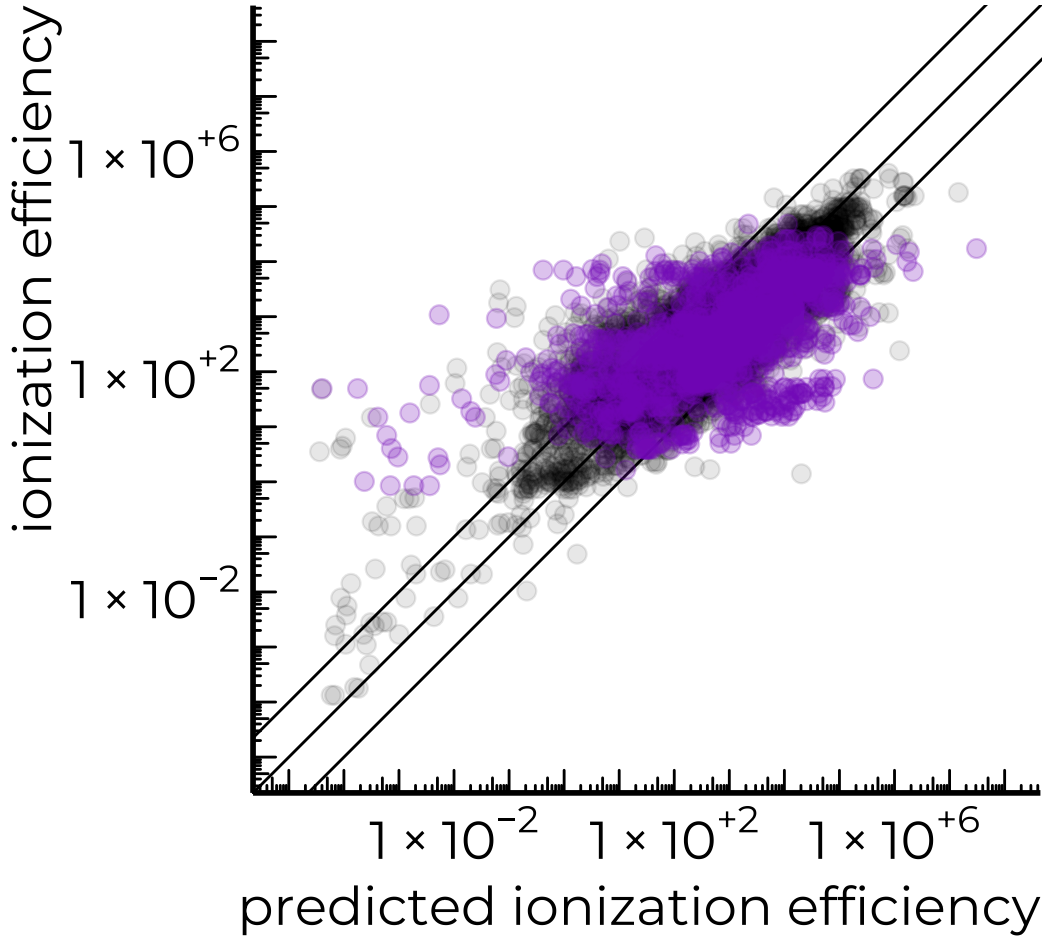
ionization efficiency

Sepman et al. in review



IE range

100,000,000

training set

RMSE 3.5x

test set

RMSE 6.3x

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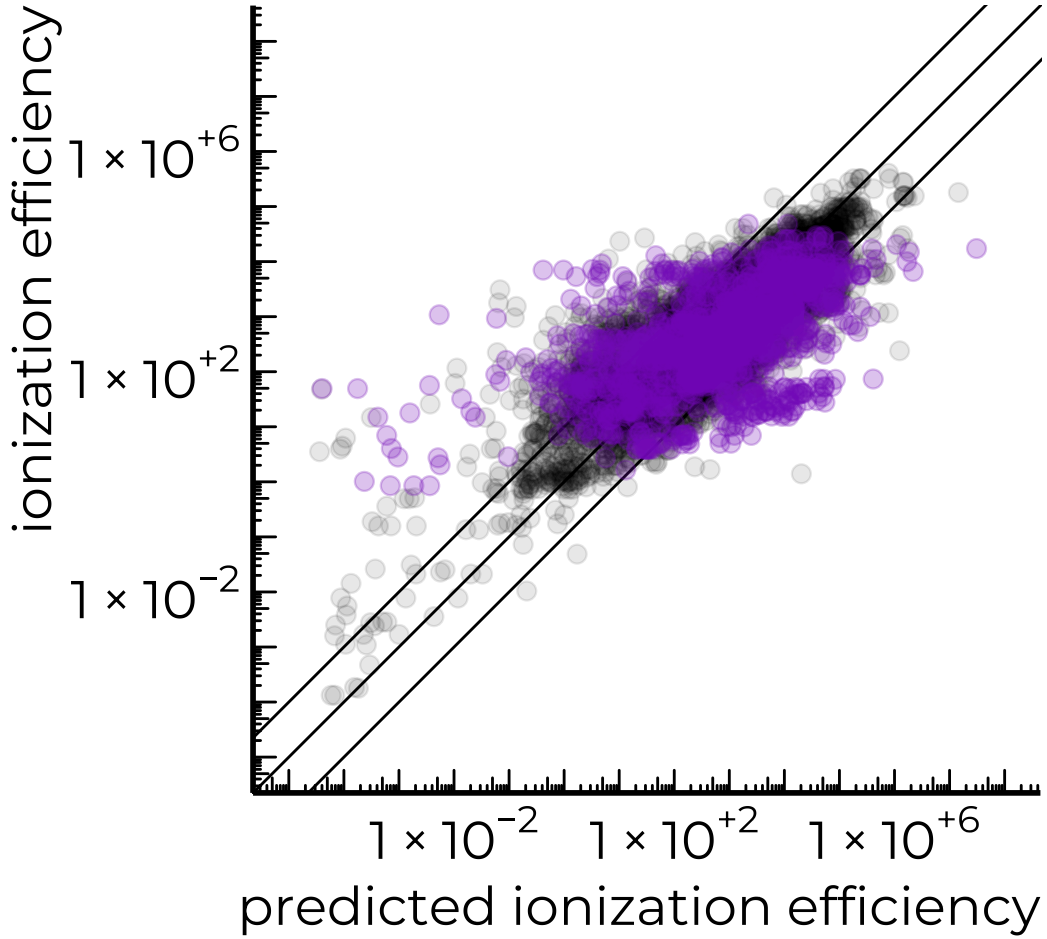
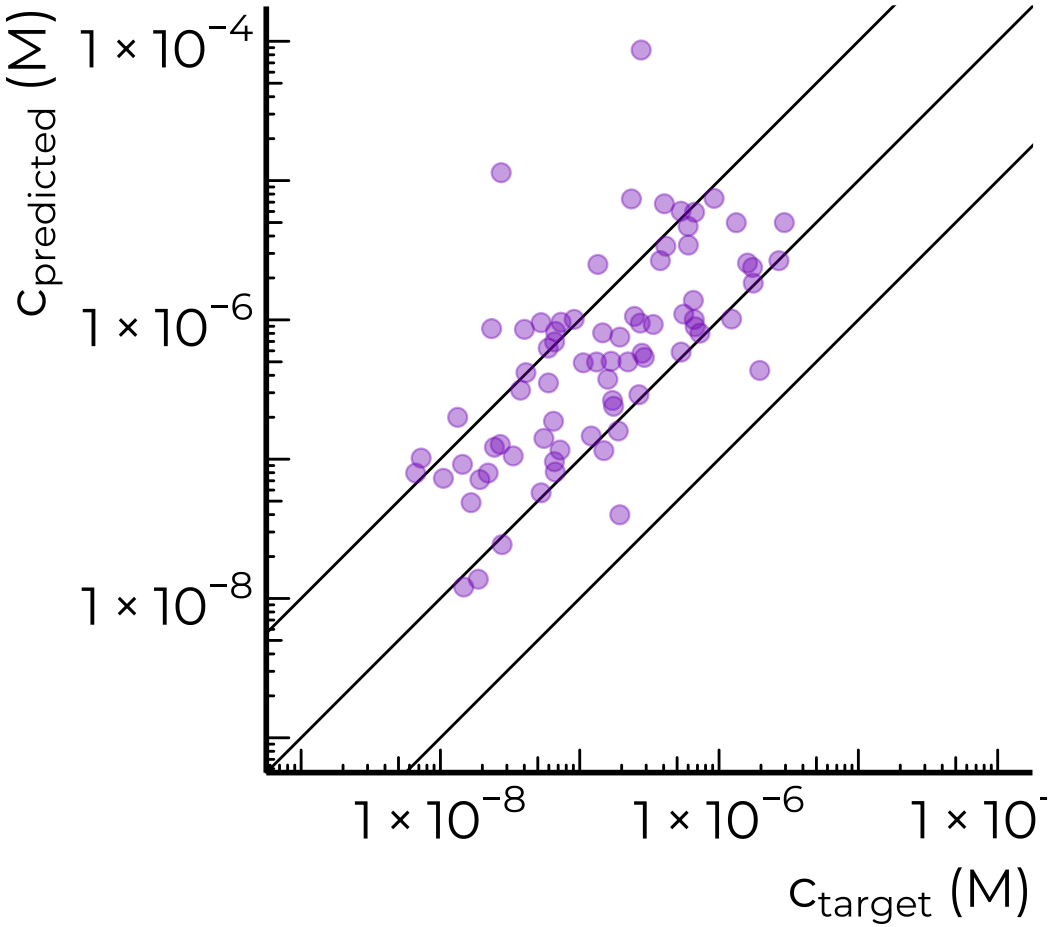
ionization efficiency

Sepman et al. in review





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ionization efficiency

Sepman et al. in review

mean prediction error

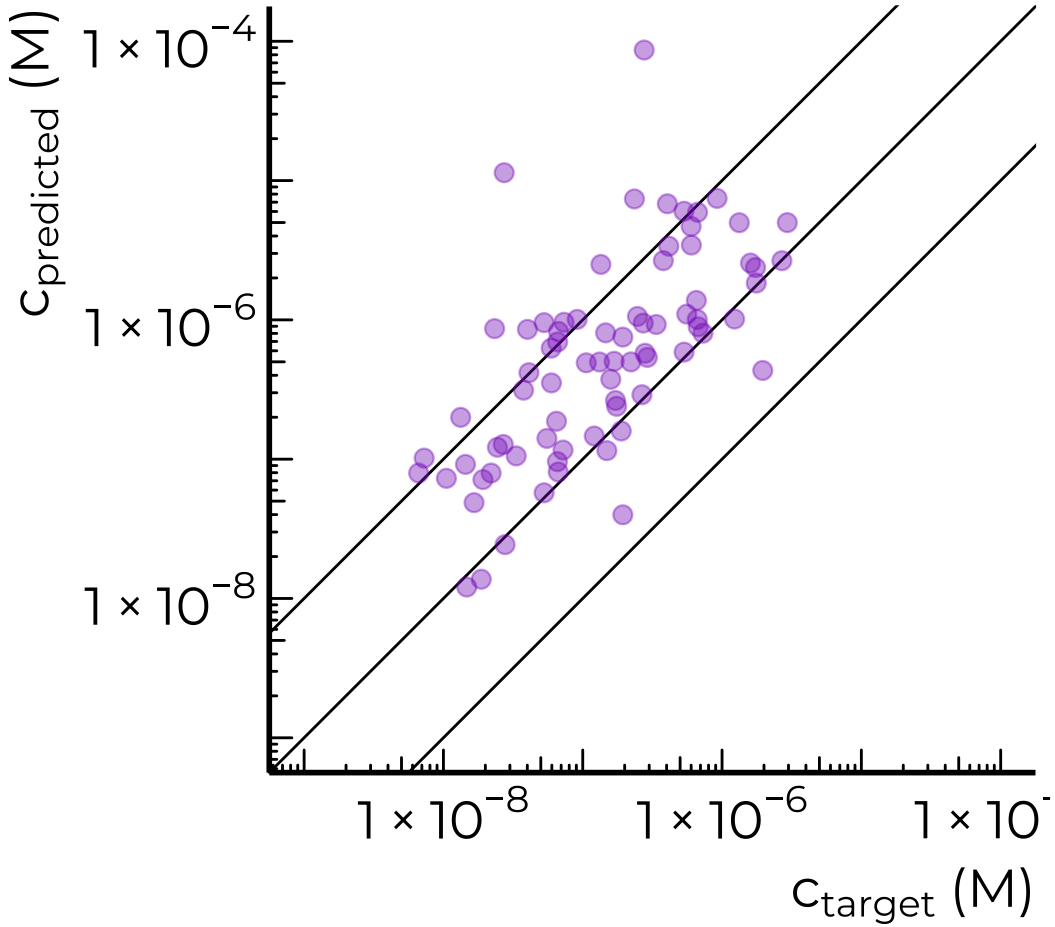
7.4x

geometric mean prediction error

4.5x

median prediction error

4.0x



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summary

prioritization in NTS

toxicity

concentration

risk

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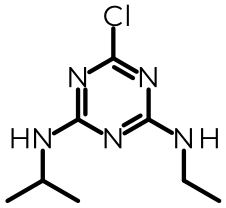
prioritization in NTS

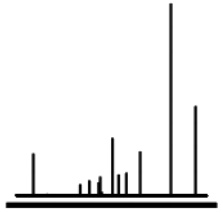
toxicity

concentration

risk



structure



MS^2 spectrum

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