Prediction of Metabolic Transformations using Cross Venn-ABERS Predictors

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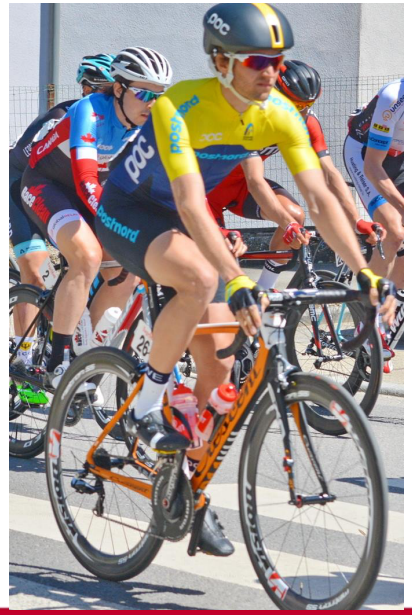
About me

- PhD student - supervisor Ola Spjuth
- Uppsala University
- Department of Pharmaceutical Biosciences
- Free time: Cyclist



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Presentation outline

1. Defining the problem setting
2. Describing reaction types using SMIRKS
3. Preprocessing
4. ML context
5. Results
6. Conclusions

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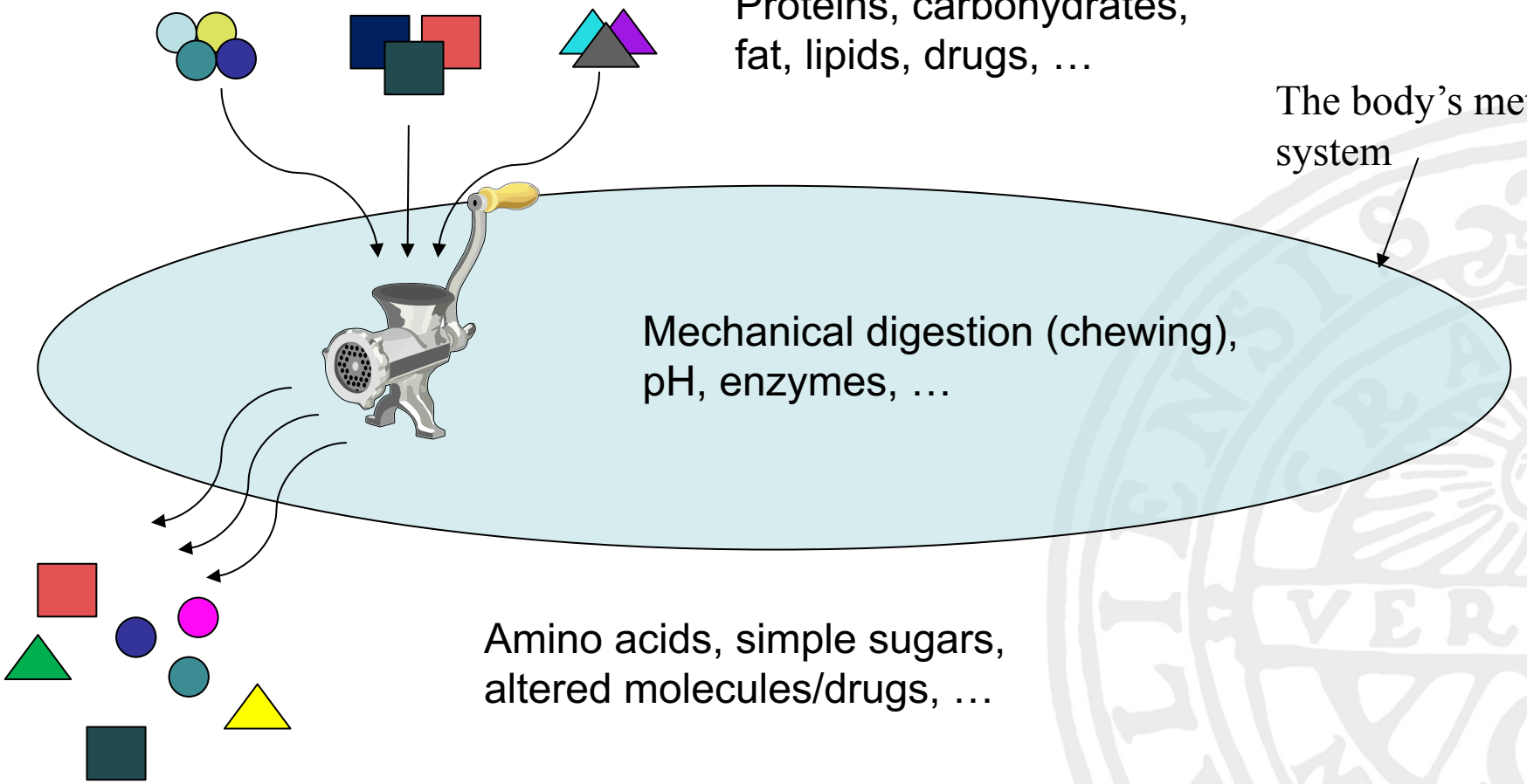
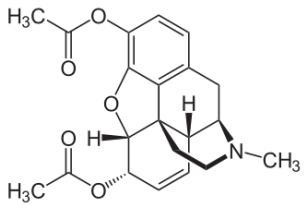
Problem setting – Metabolism

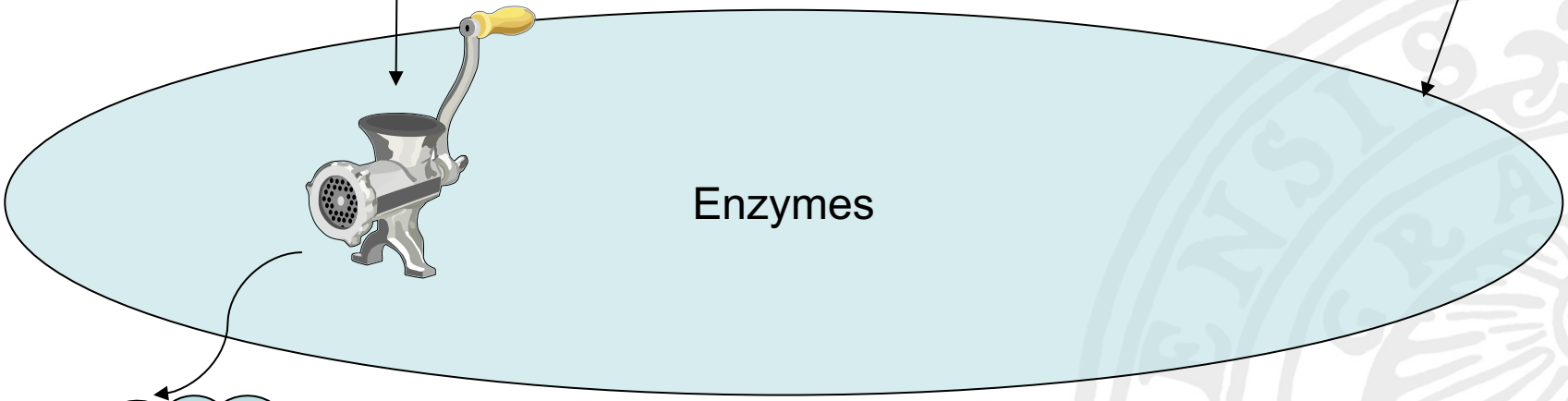


Problem setting – Drug Metabolism

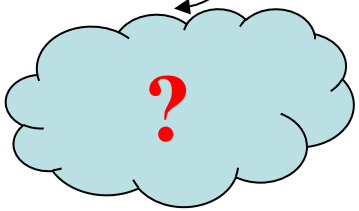


Drug candidate

The body's metabolic system



Enzymes



Same molecule? Altered?
How? Toxic? …

Predicting drug metabolism in drug discovery process

- Aid drug discovery process
  - Duration and intensity of pharmacological action
  - Metabolites might be biologically active
  - Provide early warnings → decrease costs
- Use known biotransformations
  - MDL Metabolite Database[1] 73599 recorded biotransformations
  - Use Machine Learning to predict metabolism for new drug candidates

[1]Elsevier MDL. Mdl metabolite database, 2005.
URL http://accelrys.com/products/ collaborative-science/databases/bioactivity-databases/biovia-metabolite.html.

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Describing reactions - SMIRKS

Definition

SMIRKS is a language used for describing chemical reaction transformations in a generic way[1]

Syntactic

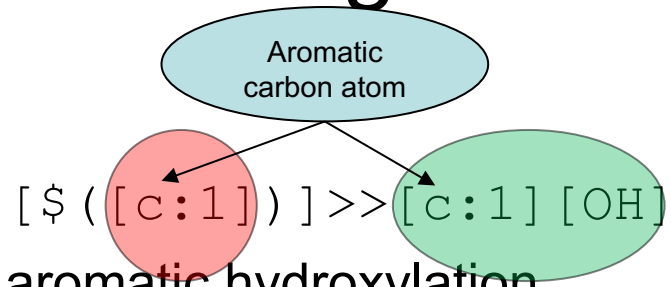
`[Reactant]>>[Product]`

Where `Reactant` and `Product` are represented as SMILES or reaction graphs

[1] Chemical Information Systems Inc. DAYLIGHT. Smirks - a reaction transform language, 2008. URL http://www.daylight.com/dayhtml/doc/theory/theory.smirks.html.

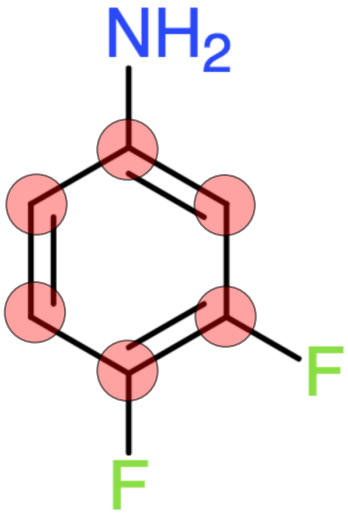
Describing reactions - SMIRKS

Example

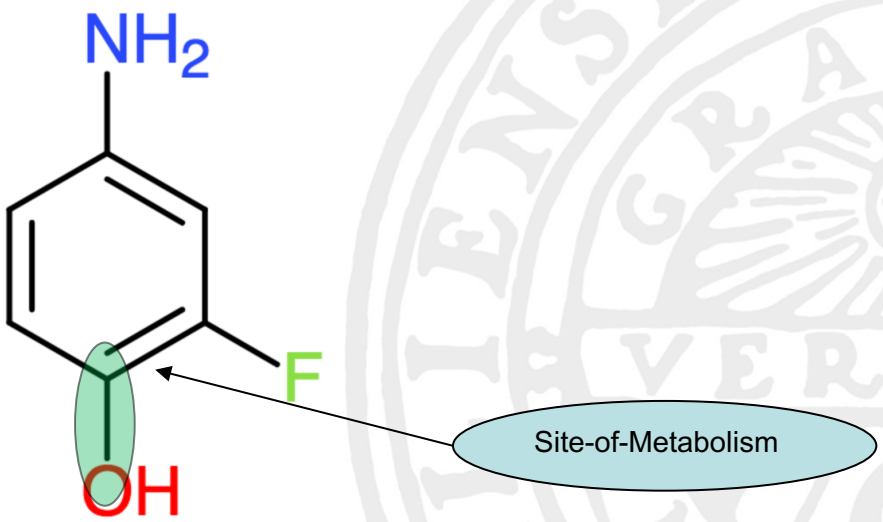


aromatic hydroxylation

Reactant



Product



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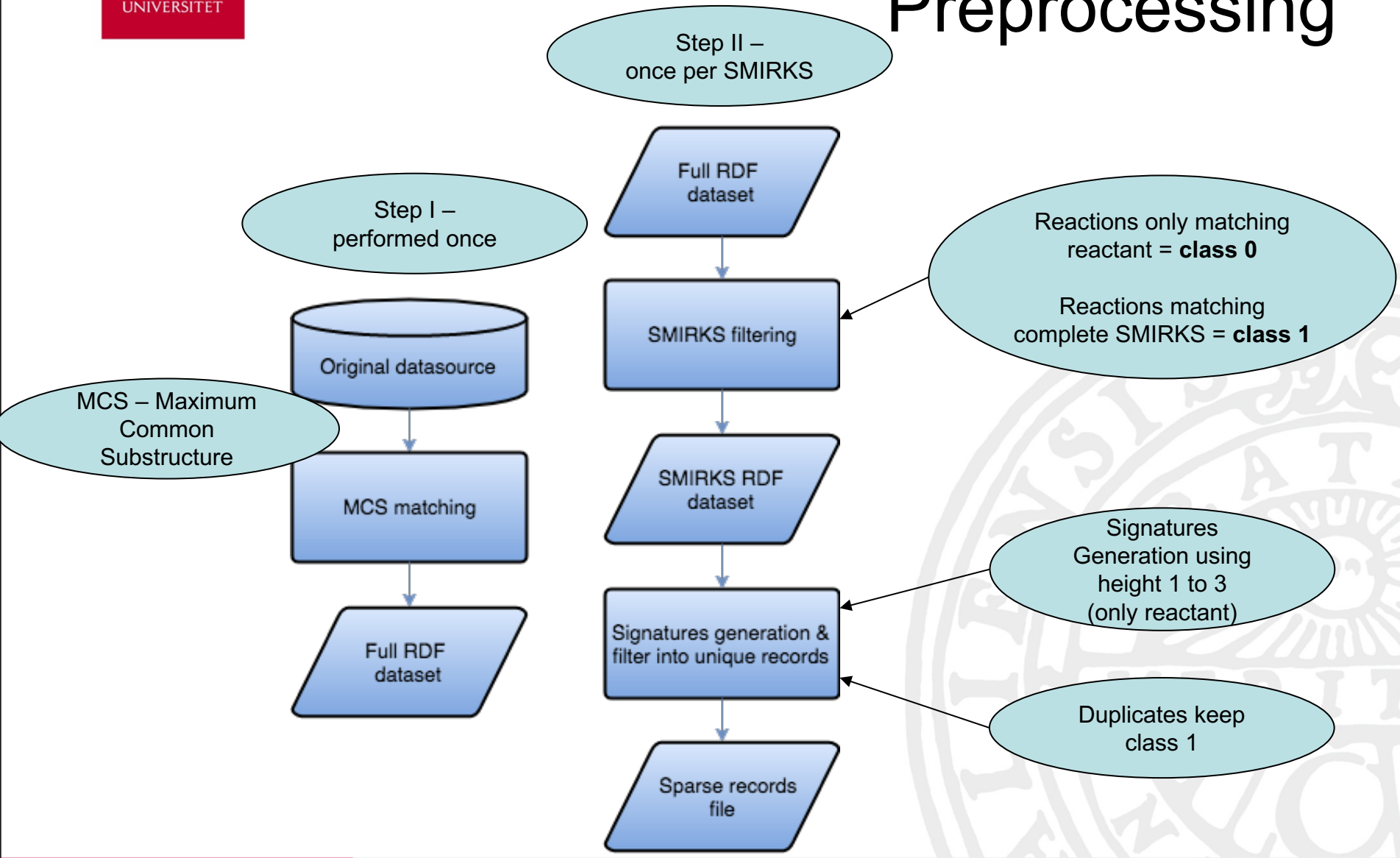
Preprocessing



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Derived datasets

Dataset name	SMIRKS	Biotrans-formations	Class 0
Alkyl hydroxylation	[$([C:1])]>>[C:1][OH]	17793	68%
Aromatic hydroxylation	[$([c:1])]>>[c:1][OH]	14691	85%
Carboxylation	[$([CH3:1])]>>[C:1](=O)O	12580	64%
Oxidation of tertiary amine	[$([N;X3:1])]>>[N+:1][O-]	11040	97%
Aromatization	[$([*;R;!a:1])]>>[a:1]	9518	25%

Skewed class distribution

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Machine learning context

- *Observations* $z = (x, y)$
  - x: Features derived using Signatures Descriptors[1] of height 1 to 3, total number of features was 112710
  - $y \in \{0, 1\}$, 0="no SMIRKS match", 1="SMIRKS match"
- Cross Venn-ABERS predictors
  - Using 10 Inductive Venn-ABERS predictors
  - Datasets taken fold-wise i.e. 10% in calibration set and 90% in proper training set

[1]Jean-Loup Faulon, et al. The signature molecular descriptor using extended valence sequences in qsar and qspr studies. Journal of chemical information and computer sciences, 43(3):707–720, 2003.

Machine learning context cont.

- Evaluation using outer *k*-fold cross validation, *k*=10
- Scoring algorithm: SVM in Python Scikit-learn[1]
  - RBF kernel
  - $C = 50$, $\gamma = 0.002$ previously found optimal values[2]
- Study both (p_0, p_1) interval and single prediction derived using: $p = \mathrm{GM}(p_1)/(\mathrm{GM}(1 - p_0) + \mathrm{GM}(p_1))$

[1]F. Pedregosa, et al. Scikit-learn: Machine learning in Python. Journal of Machine Learning Research, 12:2825–2830, 2011.
[2]J. Alvarsson, et al. Benchmarking study of parameter variation when using signature fingerprints together with support vector machines. Journal of chemical information and modeling, 54(11):3211–3217, 2014.

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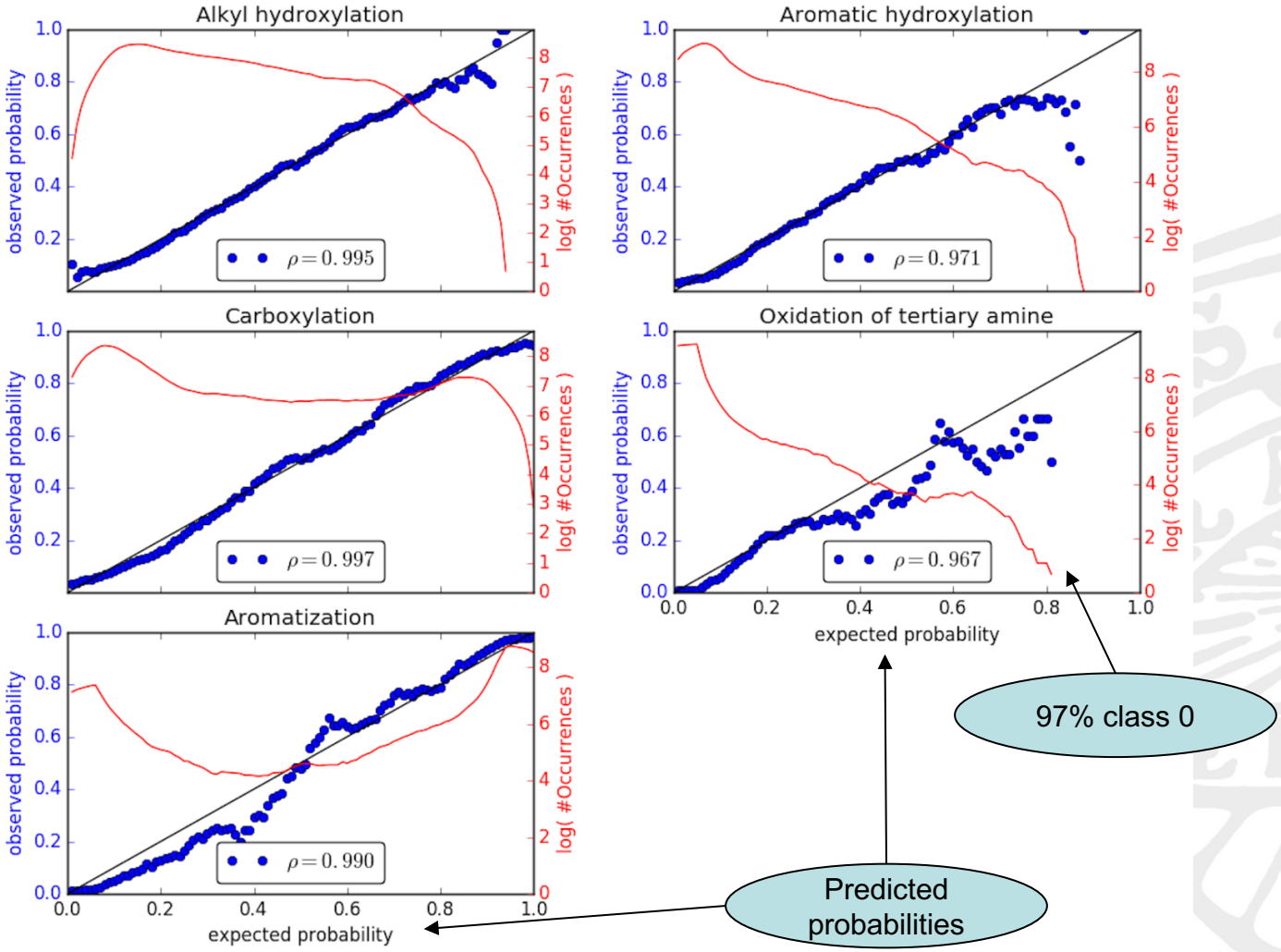
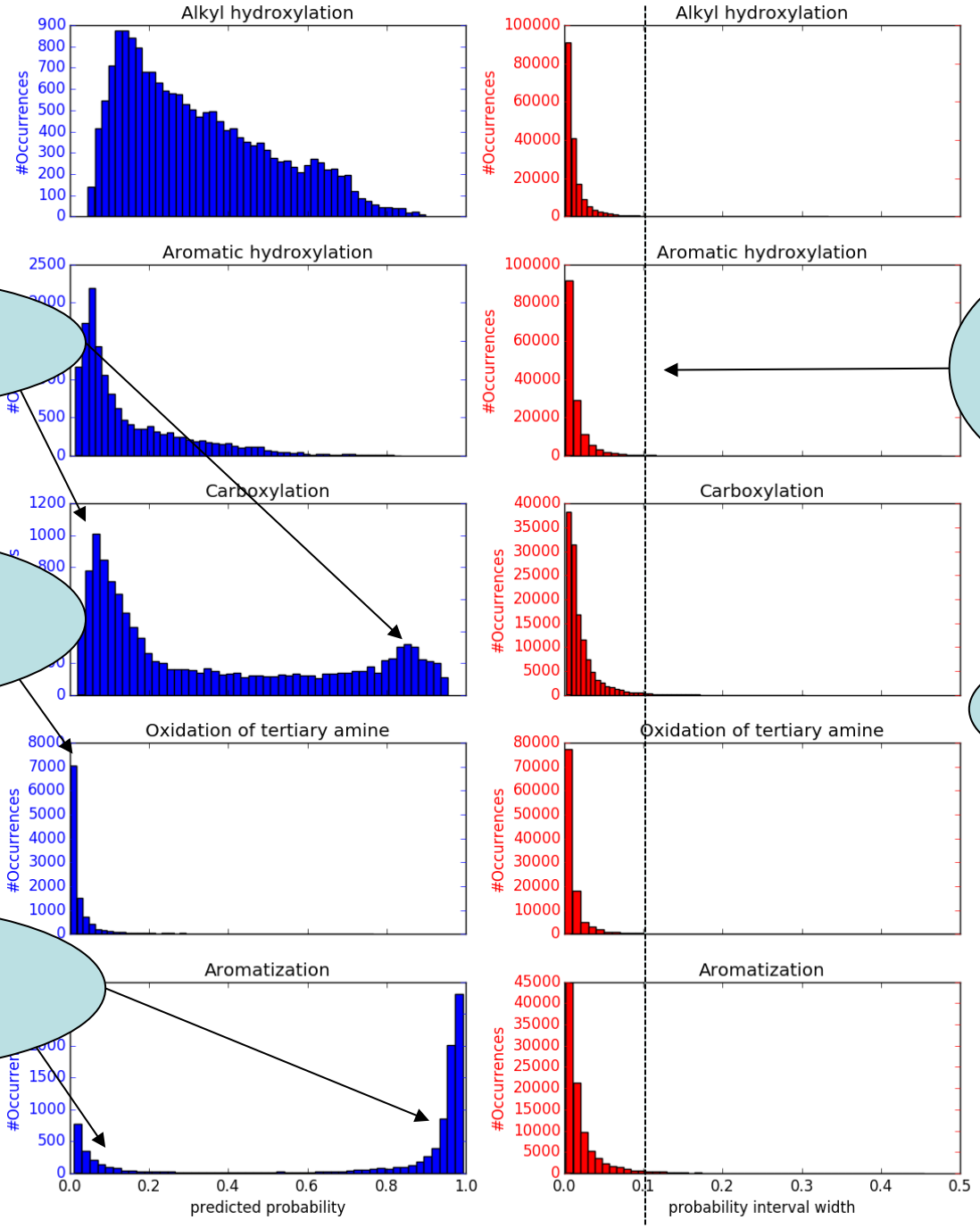
Calibration results



Observed frequencies of true label *y*=1 within bucket of size 0.1

97% class 0

Predicted probabilities



Peaks around desired prediction outcome

Almost only predicting class 0 – again due to skewed class distribution

High frequency of "informative predictions" – either class 0 or 1

Almost all objects probability intervals are less than 0.1 – median ranging between 0.006 to 0.013

Small intervals → High certainty in the predictions

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Performance metrics

Dataset name	Log Loss	AUC
Alkyl hydroxylation	0.538	0.753
Aromatic hydroxylation	0.348	0.793
Carboxylation	0.410	0.881
Oxidation of tertiary amine	0.093	0.904
Aromatization	0.173	0.964

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Conclusions

- Solve issue with skewed class distributions
  - Incorporate stratified sampling
  - Re-sampling of minority class
  - Mondrian classification in Conformal Prediction might be a better approach
- We achieve very good predictors in most of the datasets
  - Narrow prediction intervals for all datasets even though not always informative predictions

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Questions?