Optimal transport for automatic alignment of untargeted metabolomic data

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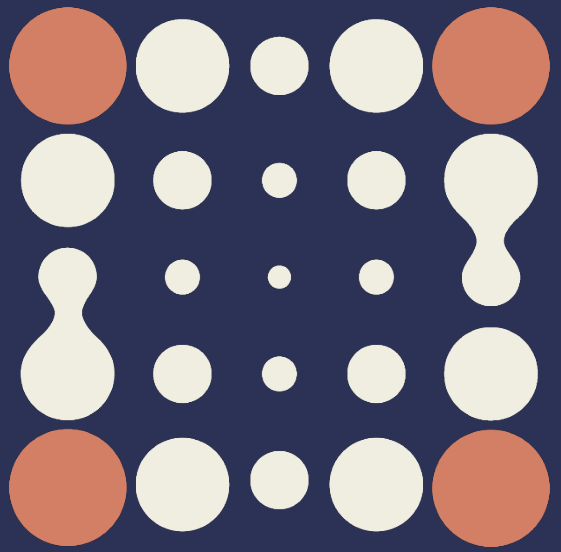
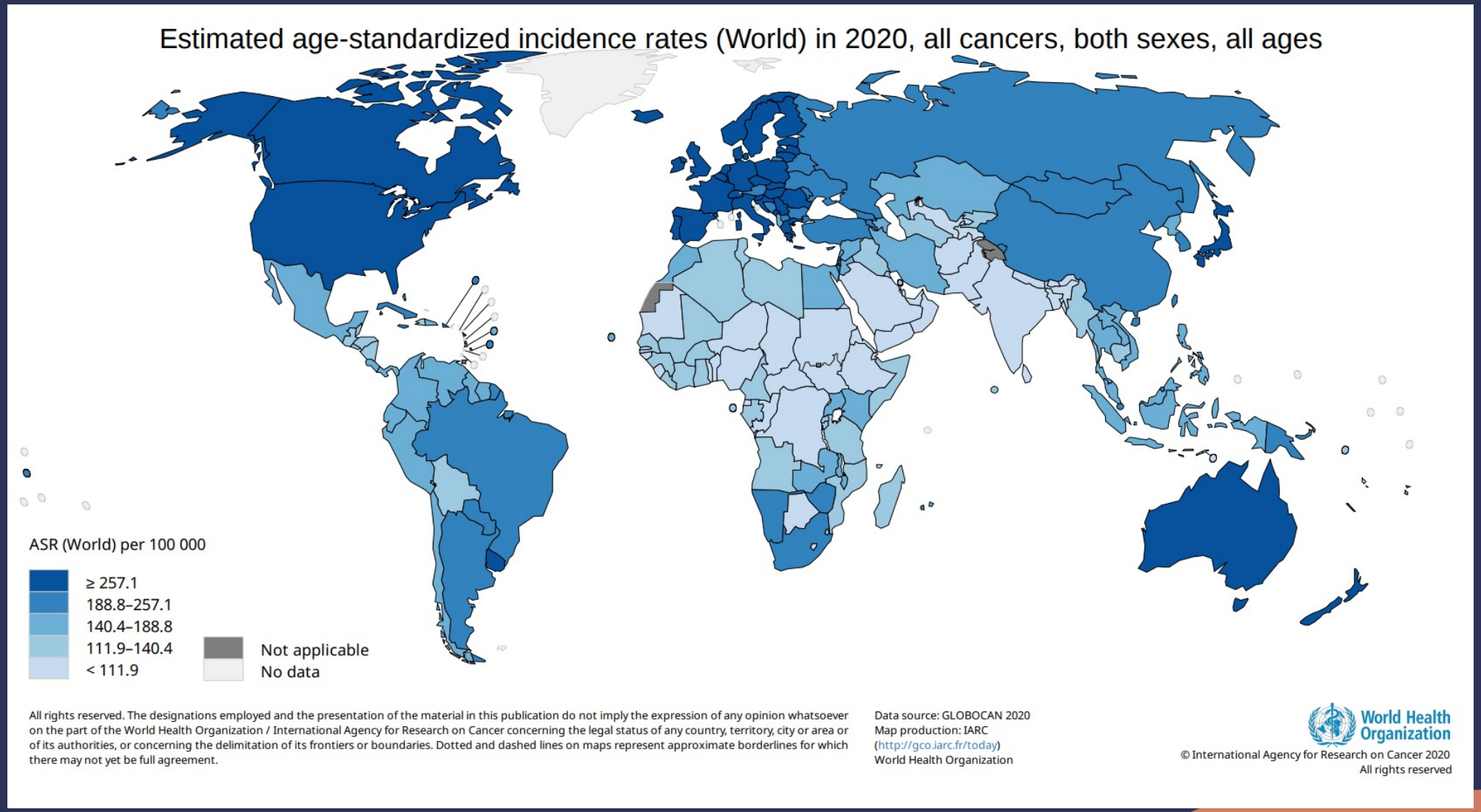


International Agency for Research on Cancer
World Health Organization

February 23th 2023

Cancer and lifestyle



Cancer and lifestyle

International Agency for Research on Cancer

- Better understand the causes and determinants of cancer, both endogenous and exogenous

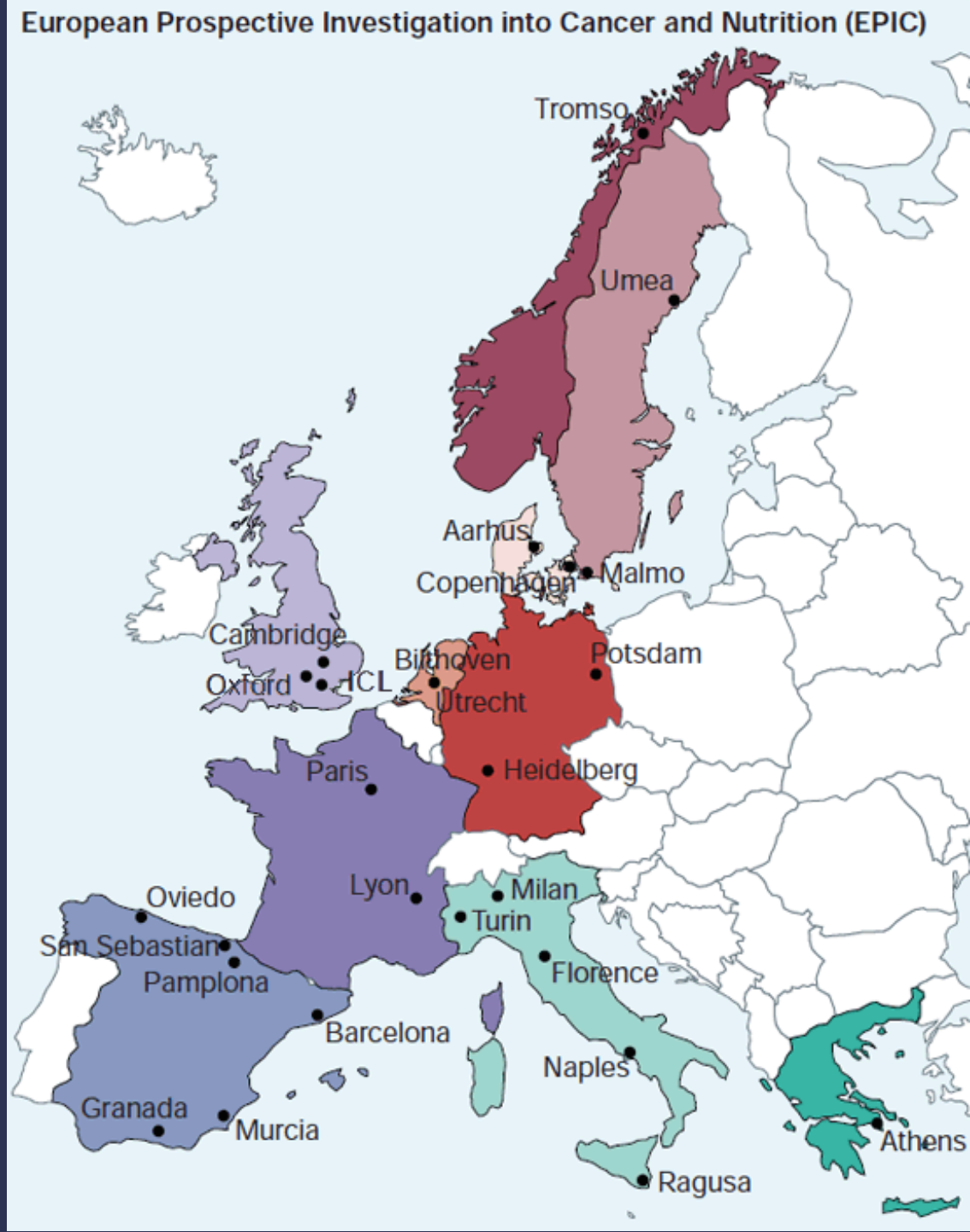
- Nutrition and Metabolism Branch (NME): focuses on lifestyle factors

Cancer and lifestyle

European Prospective Investigation into Cancer and nutrition cohort

- 10 European countries
- ~521K participants recruited around 1990
- Biological samples collected at inclusion

➢ Dietary, lifestyle, metabolomic, genetic data available



Cancer and lifestyle

- Study impact of alcohol on cancer

- Ask about study participants' alcohol intake

Cancer and lifestyle

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Cancer and lifestyle

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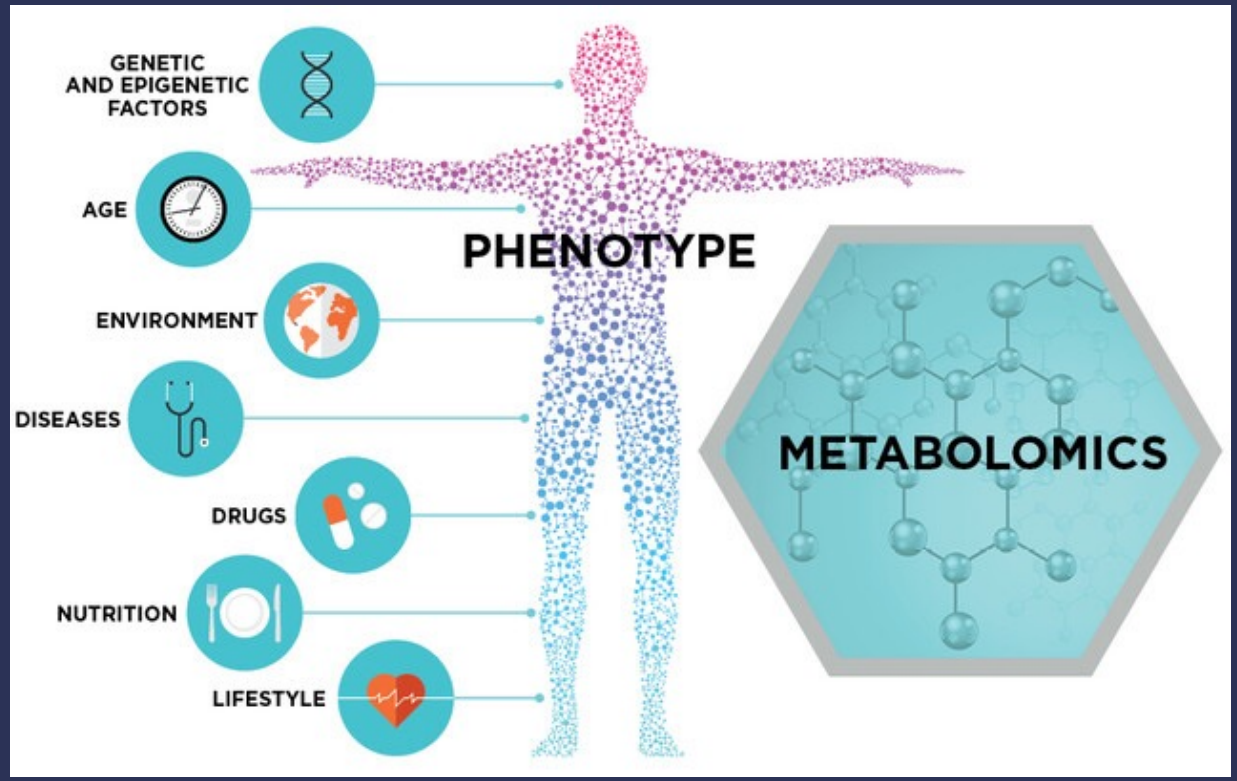
- **Biomarker (for alcohol)**

Biological molecule found in body that would accurately reflect alcohol intake

Cancer and lifestyle – Metabolomics

- Large-scale study of small molecules (metabolites) in a biological sample
- Reflects the metabolic health of an individual influenced by both genetic and environmental factors
- Untargeted approach: measure as many metabolites as possible in a sample



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✓ **Perfect for biomarker discovery**

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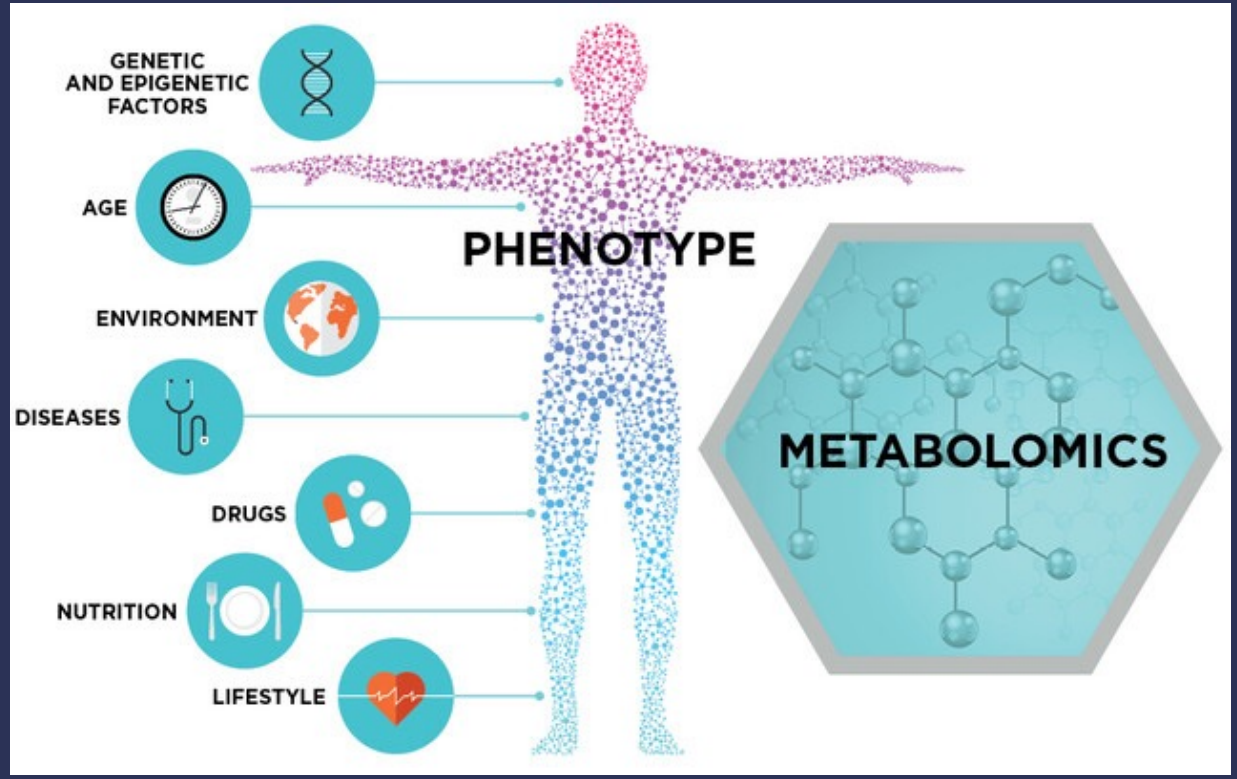

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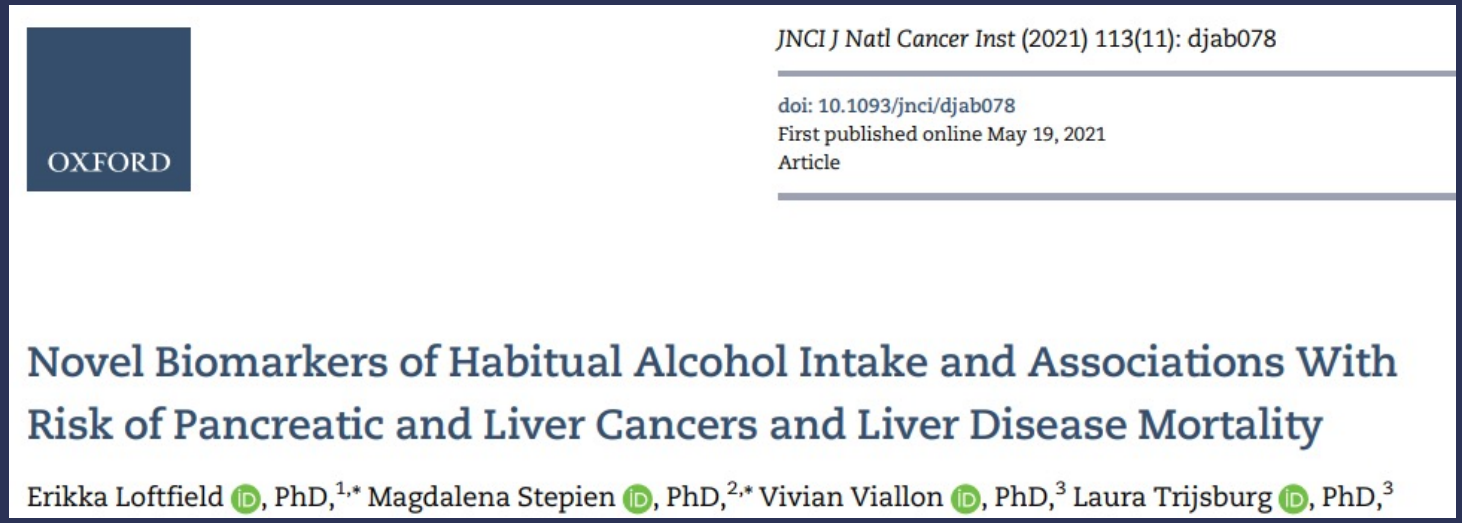
➢ **Pool/meta-analyse data from different sources ?**

Cancer and lifestyle – Metabolomics

Loftfield *et al.* 2021:

- Discover biomarkers associated with alcohol consumption, several features identified

- Untargeted metabolomic data from the EPIC cross-sectional calibration study, EPIC liver study, EPIC pancreas study, and two studies nested in the ATBC cohort



Cancer and lifestyle – Metabolomics

Untargeted metabolomics

- Measure every metabolite in a sample with LC-MS

- Features identified by
  - Mass-to-charge ratio (m/z)
  - Retention time (RT)

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Sample003	81951.95	33048.715
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- Possible by hand only on a restricted number of features

- Existing methods to align untargeted datasets: metabCombiner, M2S, PAIRUP-MS... Either require prior knowledge, overrely on hyperparameters, or make strict assumptions on the data

➢ **GromovMatcher**

Method overview

Study 1
n_1 samples, p_1 features

	Feat X_1	Feat X_2	Feat X_3	...	Feat X_{p_1}
m/z	743.8	231.1	189.7	...	435.4
RT	0.56	1.58	5.32	...	7.61
Feature intensities	10.6	12.1	8.4	...	9.2
	...	...	...	...	...
	9.5	9.1	13.6	...	10.8

Study 2
n_2 samples p_2 fatures

	Feat Y_1	Feat Y_2	...	Feat Y_{p_2}
m/z	349.0	233.0	...	528.1
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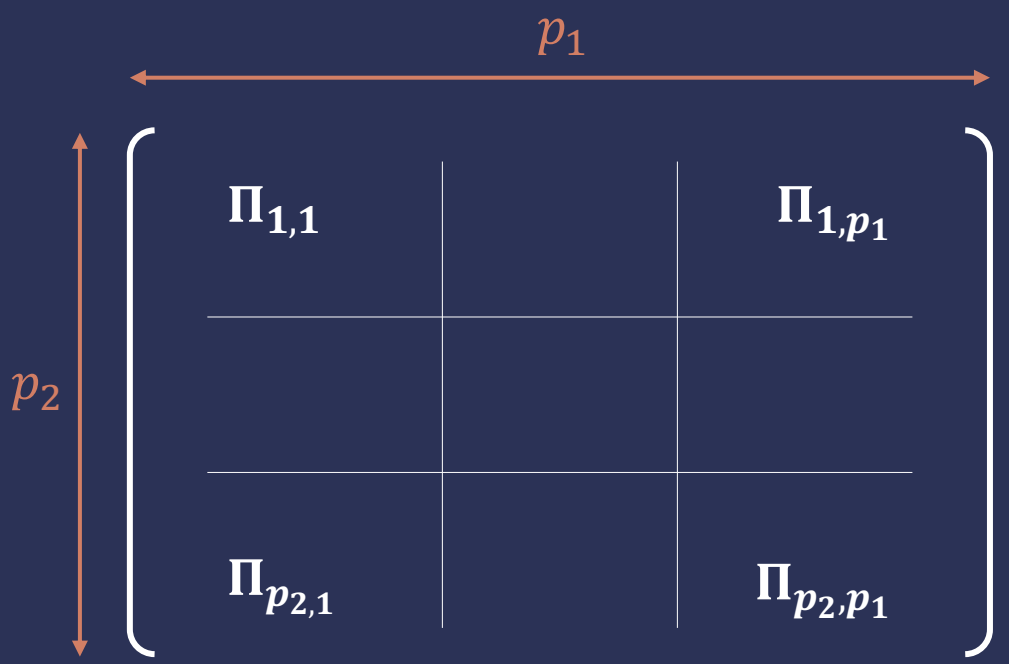

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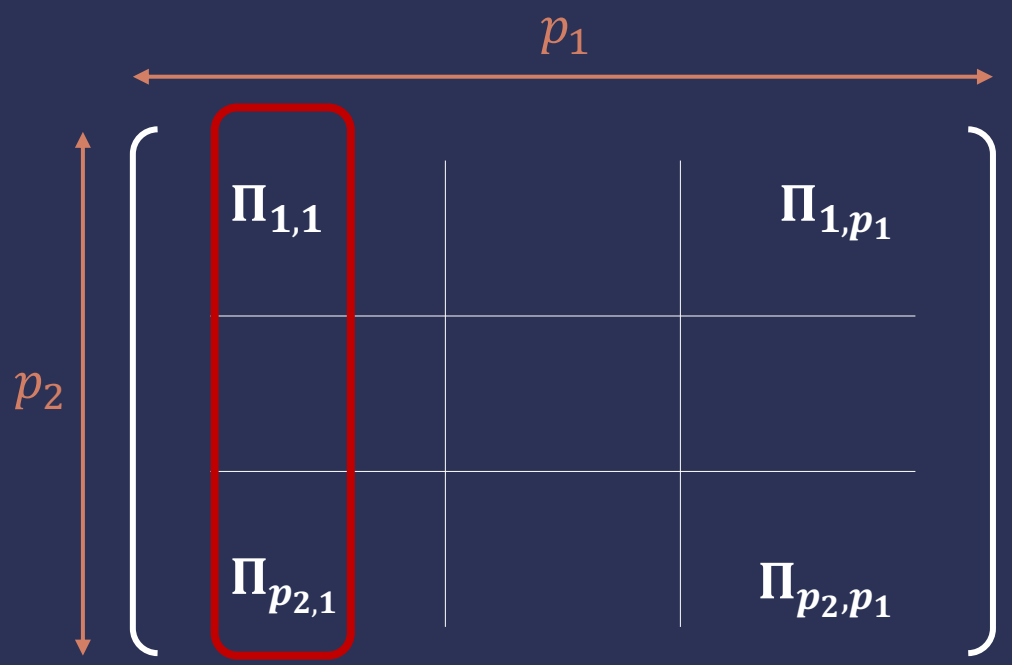

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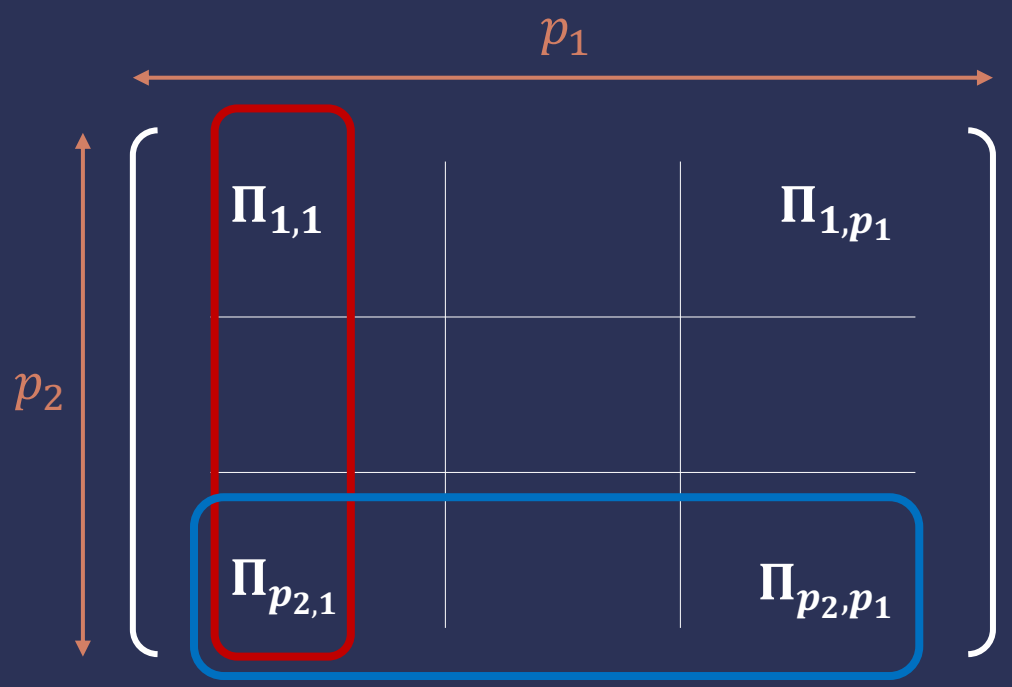
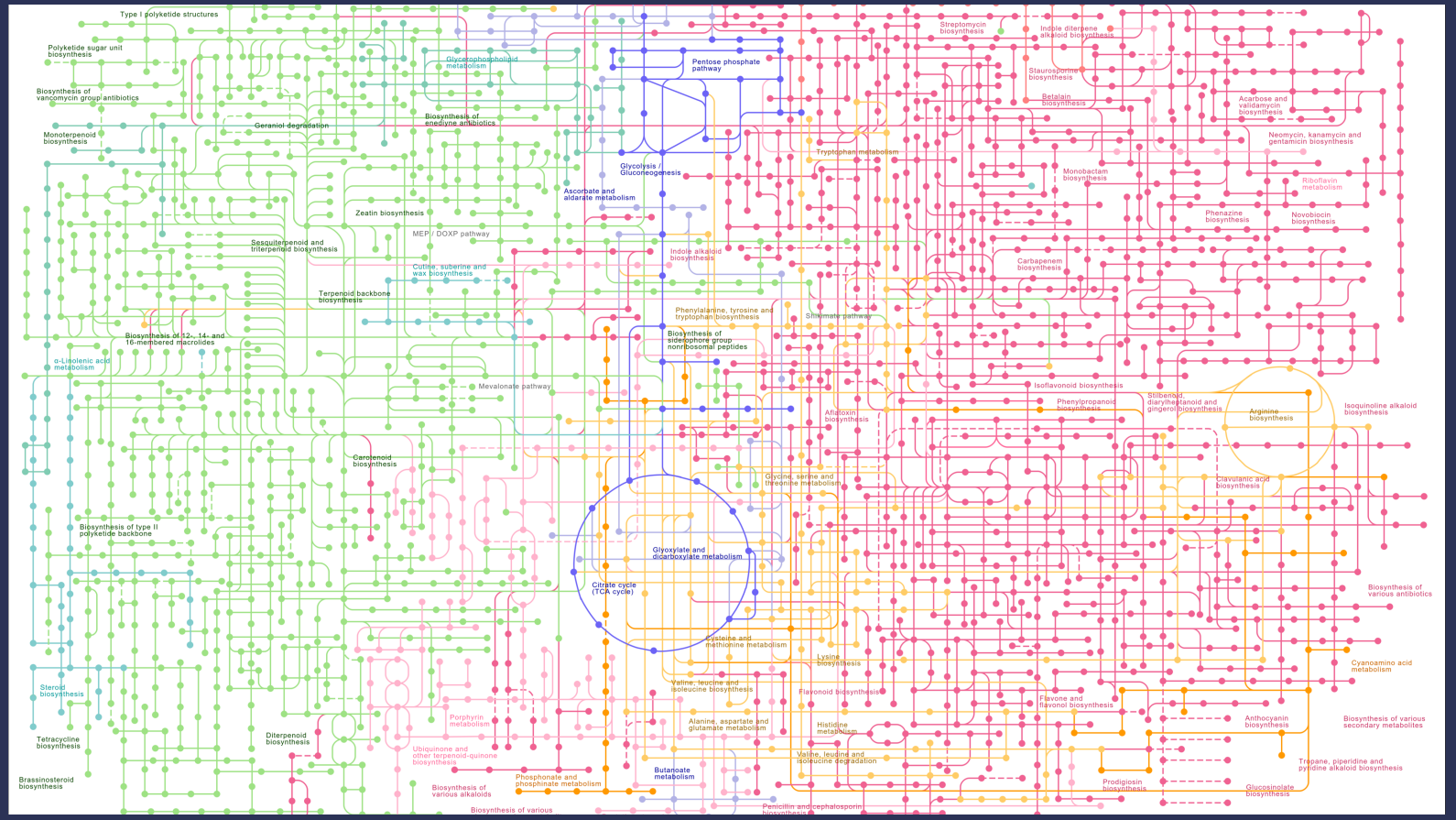


Method overview

m/z and RT are not stable enough, but similar correlation patterns can be expected



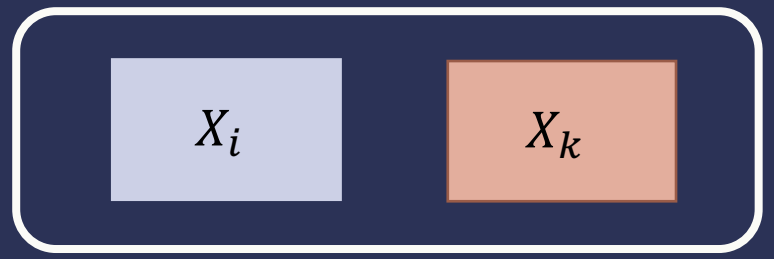
Kanehisa Lab.

Method overview

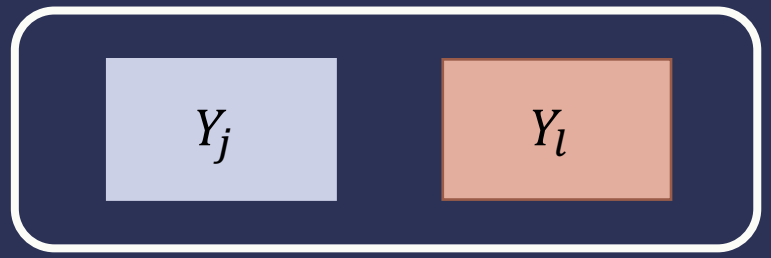
Metabolite A

Metabolite B

Study 1: n_1 samples, p_1 features



Study 2: n_2 samples, p_2 features



$$Corr(X_i, X_k) \approx Corr\ (Y_j, Y_l)$$

Method overview

Metabolite A

Metabolite B

- For $d_i(x, x') = \frac{1}{\sqrt{n_i}} \left|\left|x - x'\right|\right|_2$,

$$d_1(X_i, X_k) \approx d_2(Y_j, Y_l)$$

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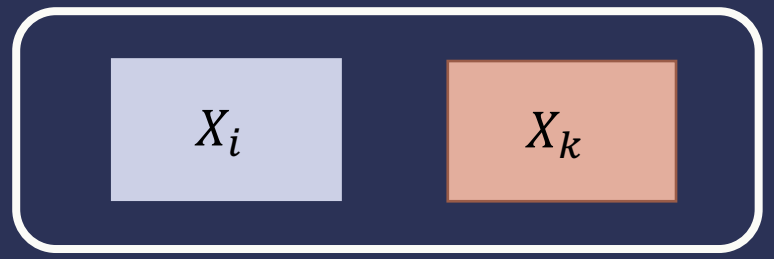

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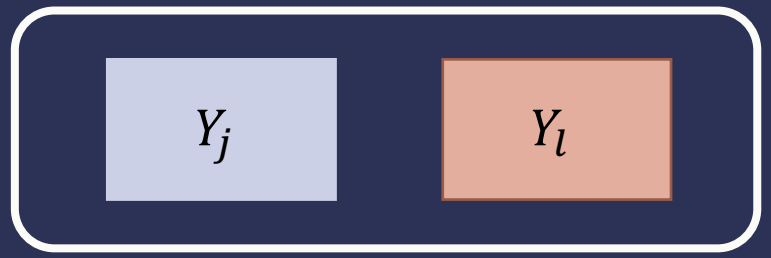

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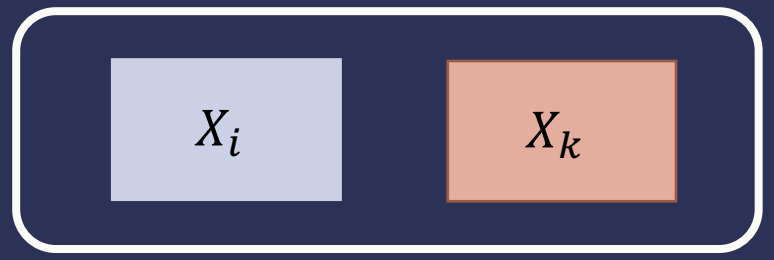

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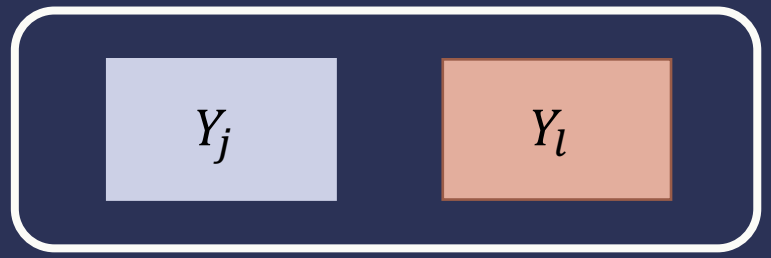

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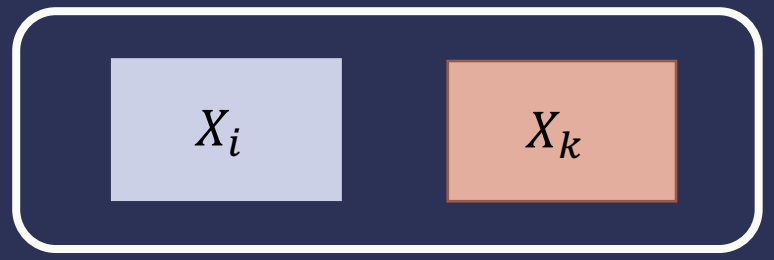

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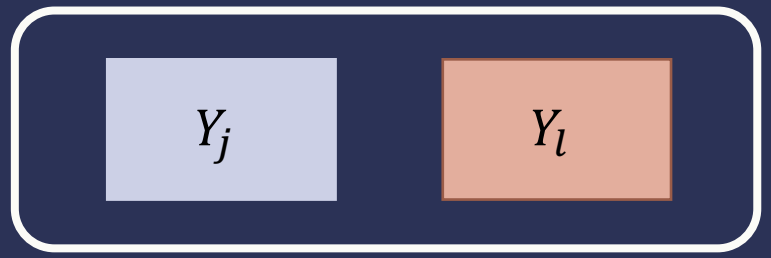

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- **Gromov-Wasserstein [Memoli, 2011]:**

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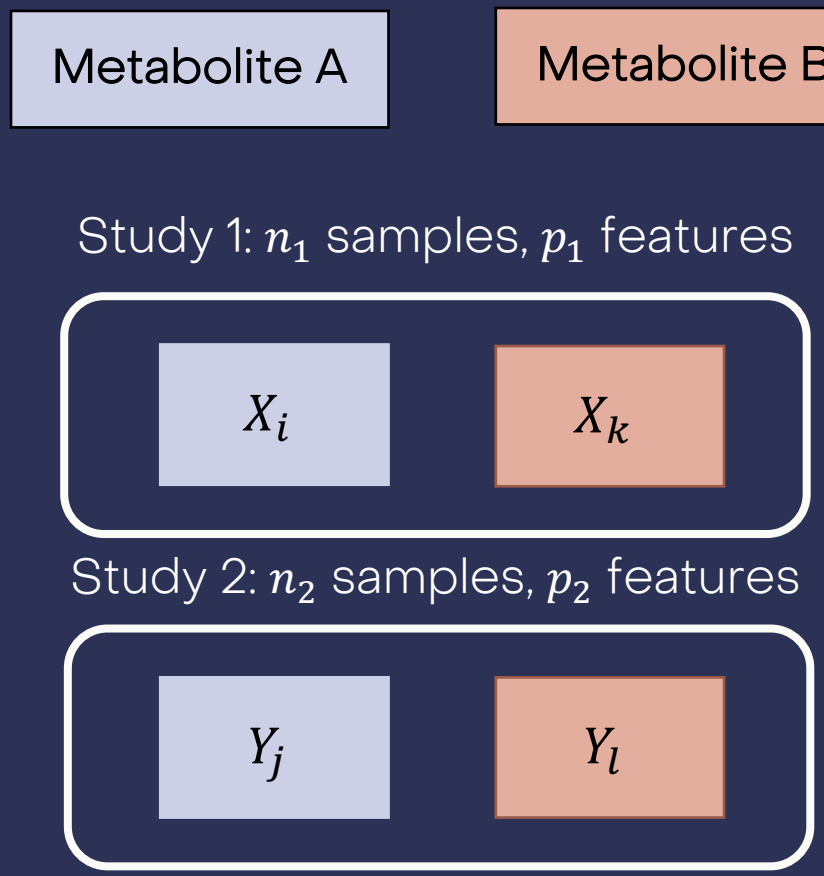

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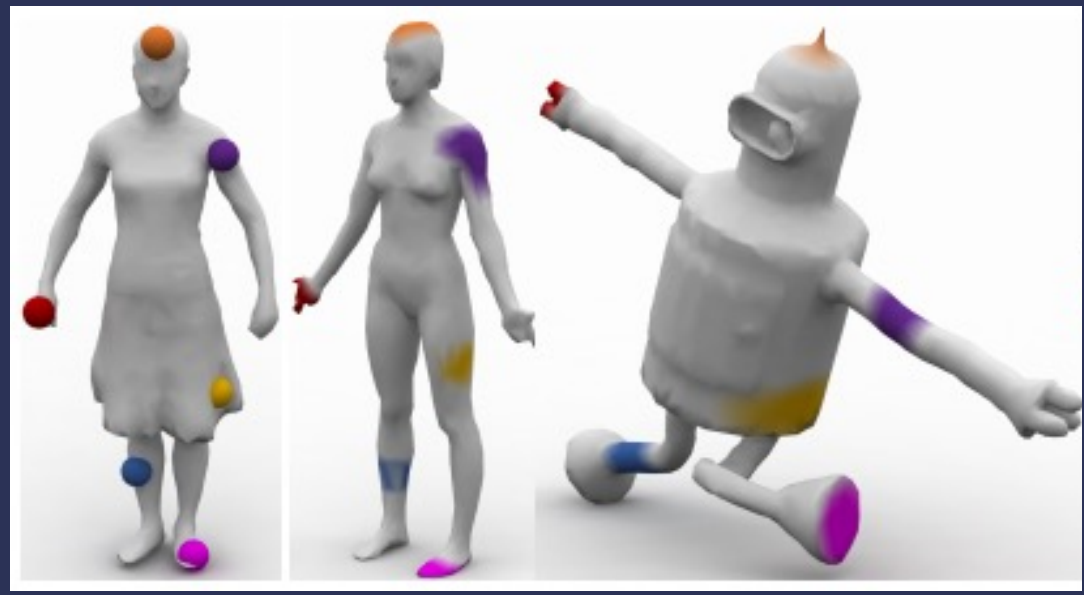
with $\mathbb{U} = \left\{\Pi \in \mathbb{R}_+^{p_1 \times p_2} : \Pi \mathbb{1}_{p_2} = \frac{1}{p_1} \mathbb{1}_{p_1} \text{ and } \Pi^T \mathbb{1}_{p_1} = \frac{1}{p_2} \mathbb{1}_{p_2}\right\}$

Method overview - Gromov-Wasserstein

- Expands optimal transport framework to sets living in different spaces: shape-wise matching

- ✓ Use distance profile to characterize the 'shape' of the sets
  - Versatile, adapts to every setting where a distance can be set between the points to match.



Solomon et al. 2016

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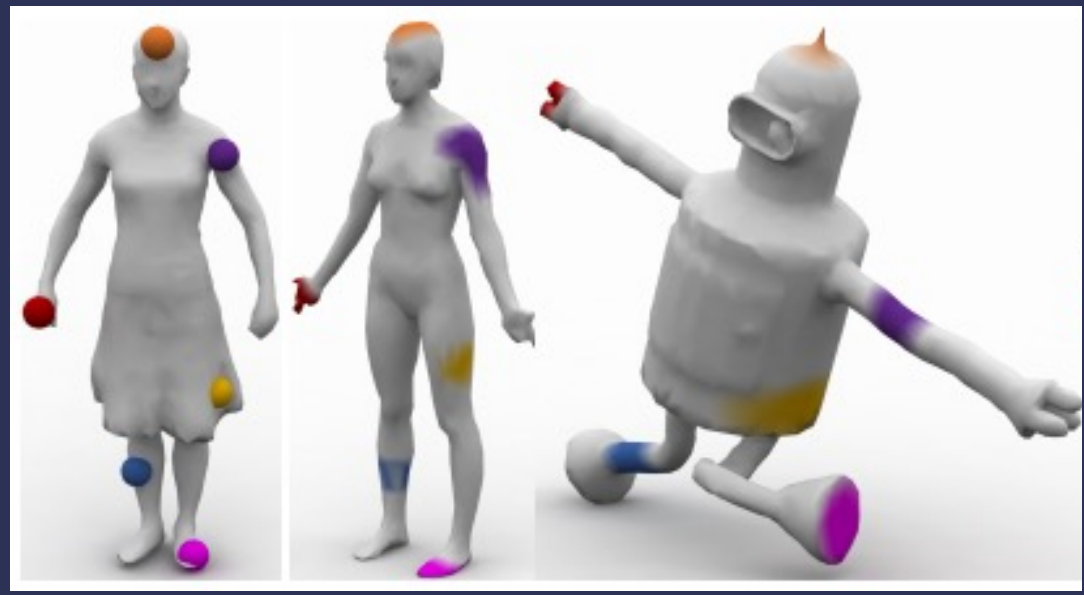
  - Versatile, adapts to every setting where a distance can be set between the points to match.

✗ Has a hard constraint ($\Pi \in \mathbb{U}$)
  - Will match every point in both sets

✗ Does not take into account additional knowledge on the points it's looking at
  - m/z and RT are not accounted for at all



Solomon et al. 2016

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Use the information contained in the feature tags:

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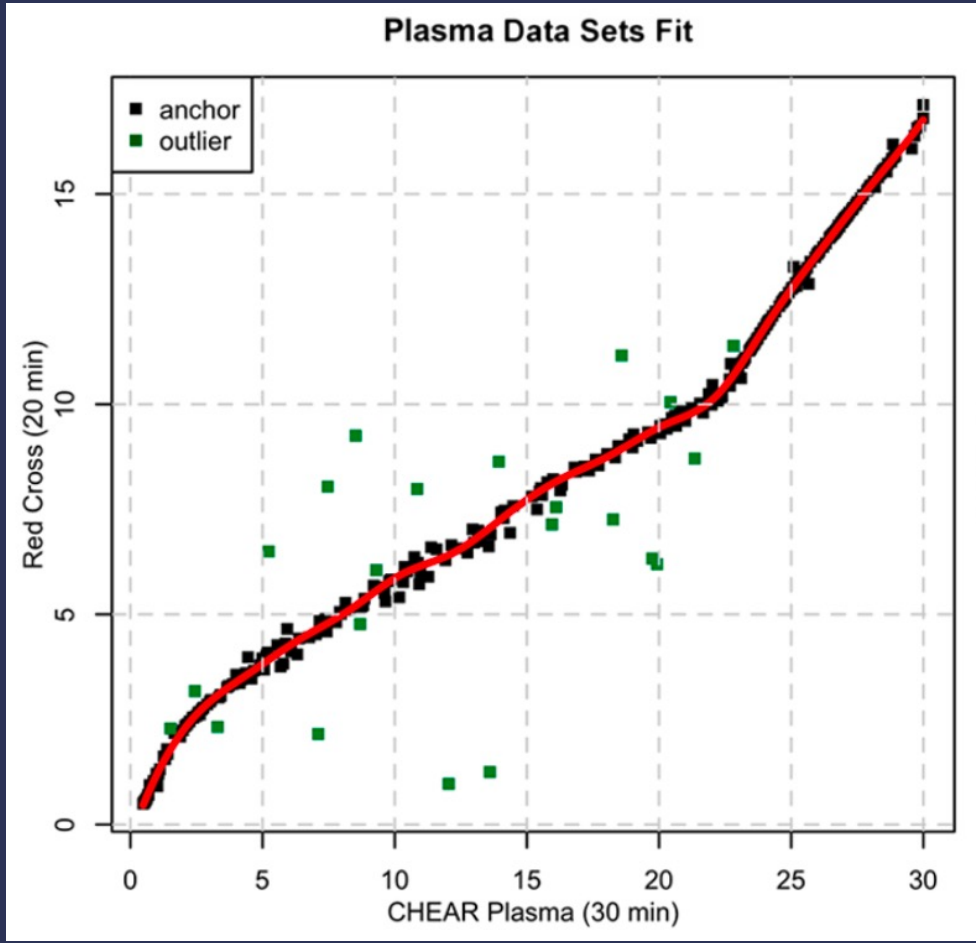
- RT vary way more, in a non-linear fashion

Method overview – RT drift

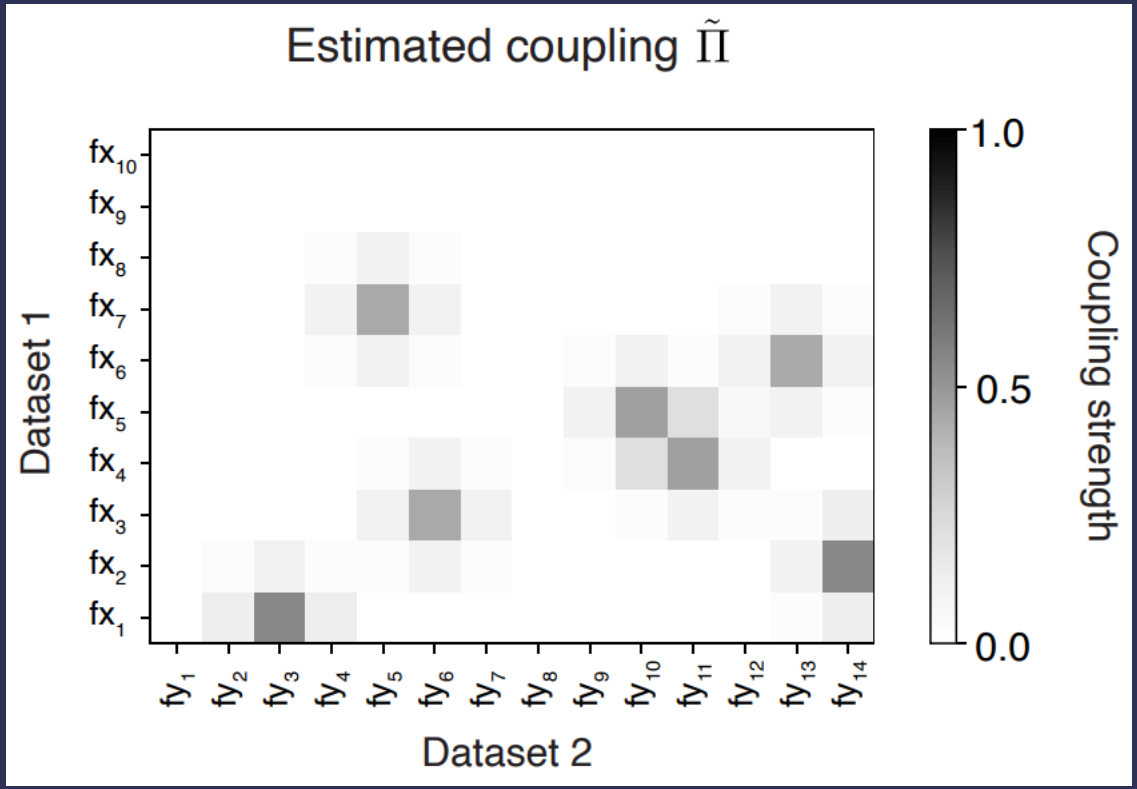


Habra et al. 2021

RT drift can be non-linear and of high amplitude

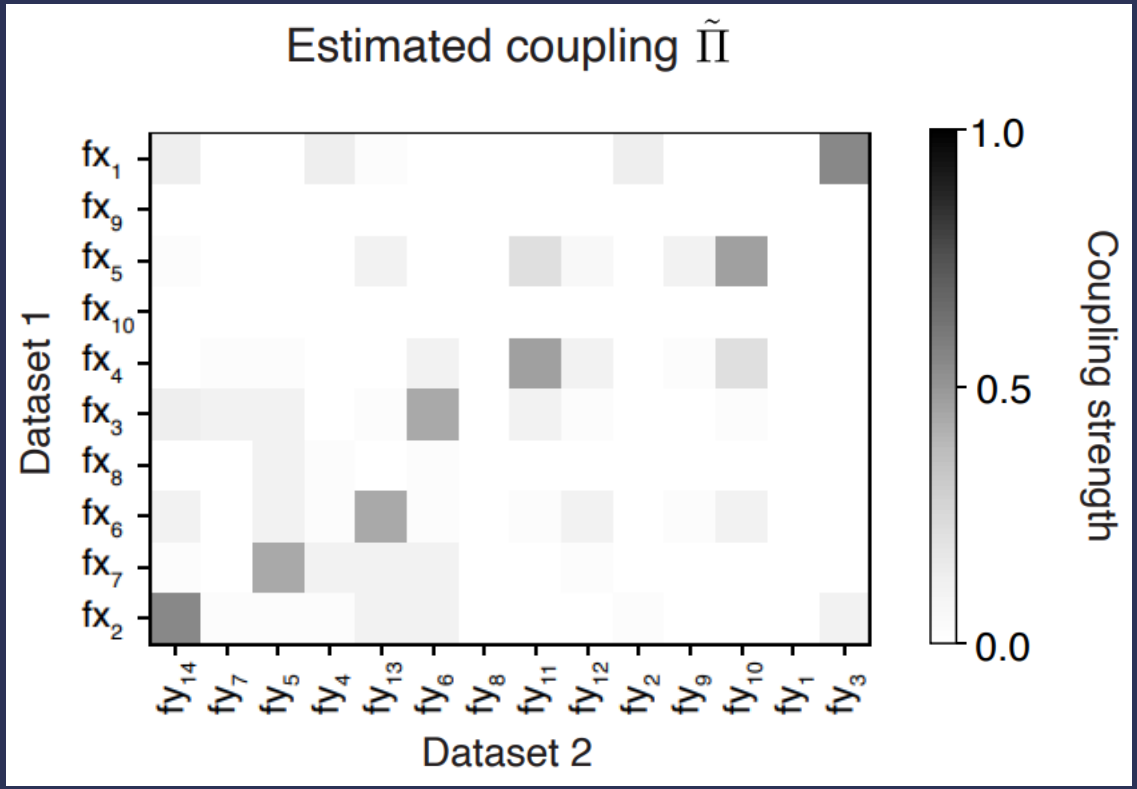
- Difficult to account for with an a priori constraint like the m/z
- Estimate the drift a posteriori and discard matched pairs that have incompatible RTs

Method overview – RT drift



1. Solve m/z constrained GW problem

Method overview – RT drift



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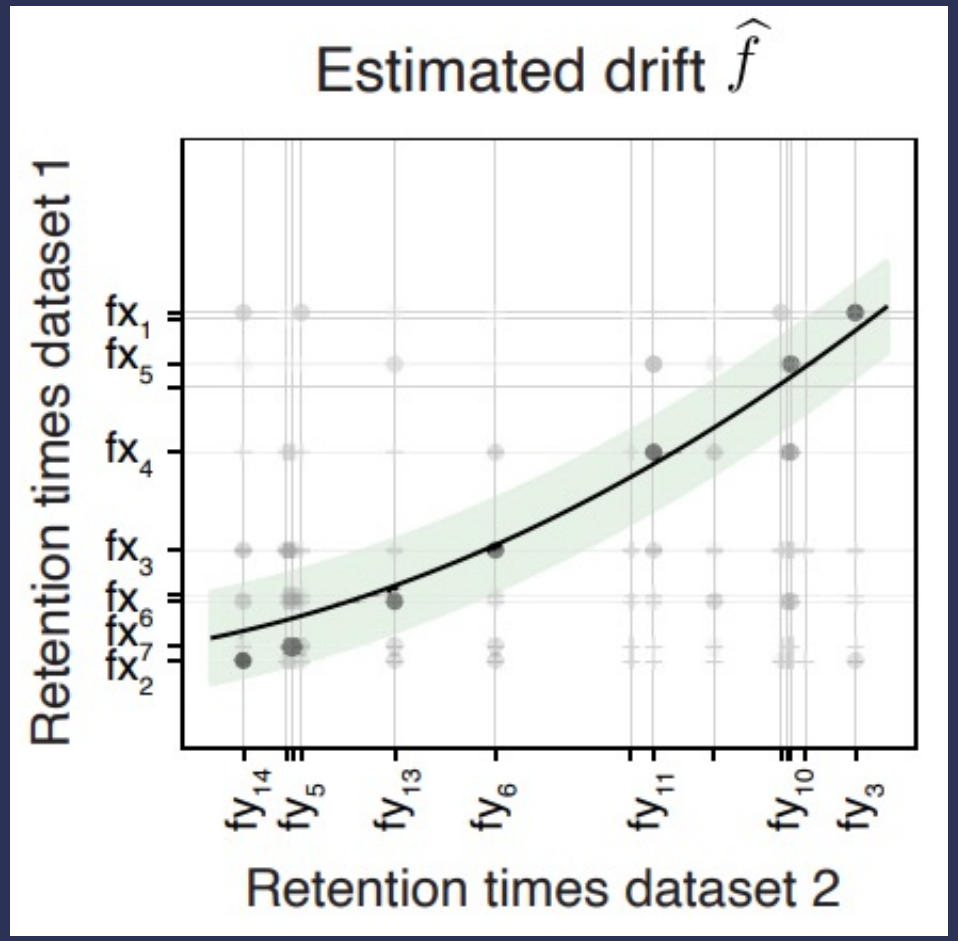

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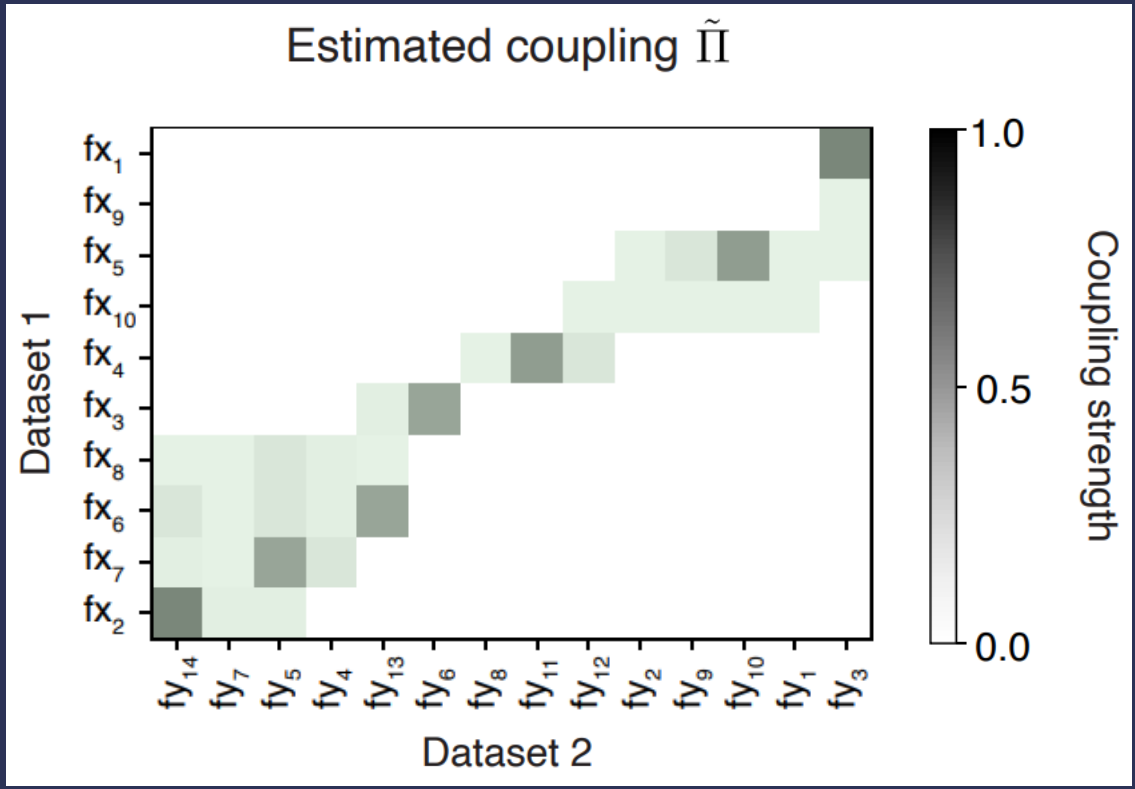

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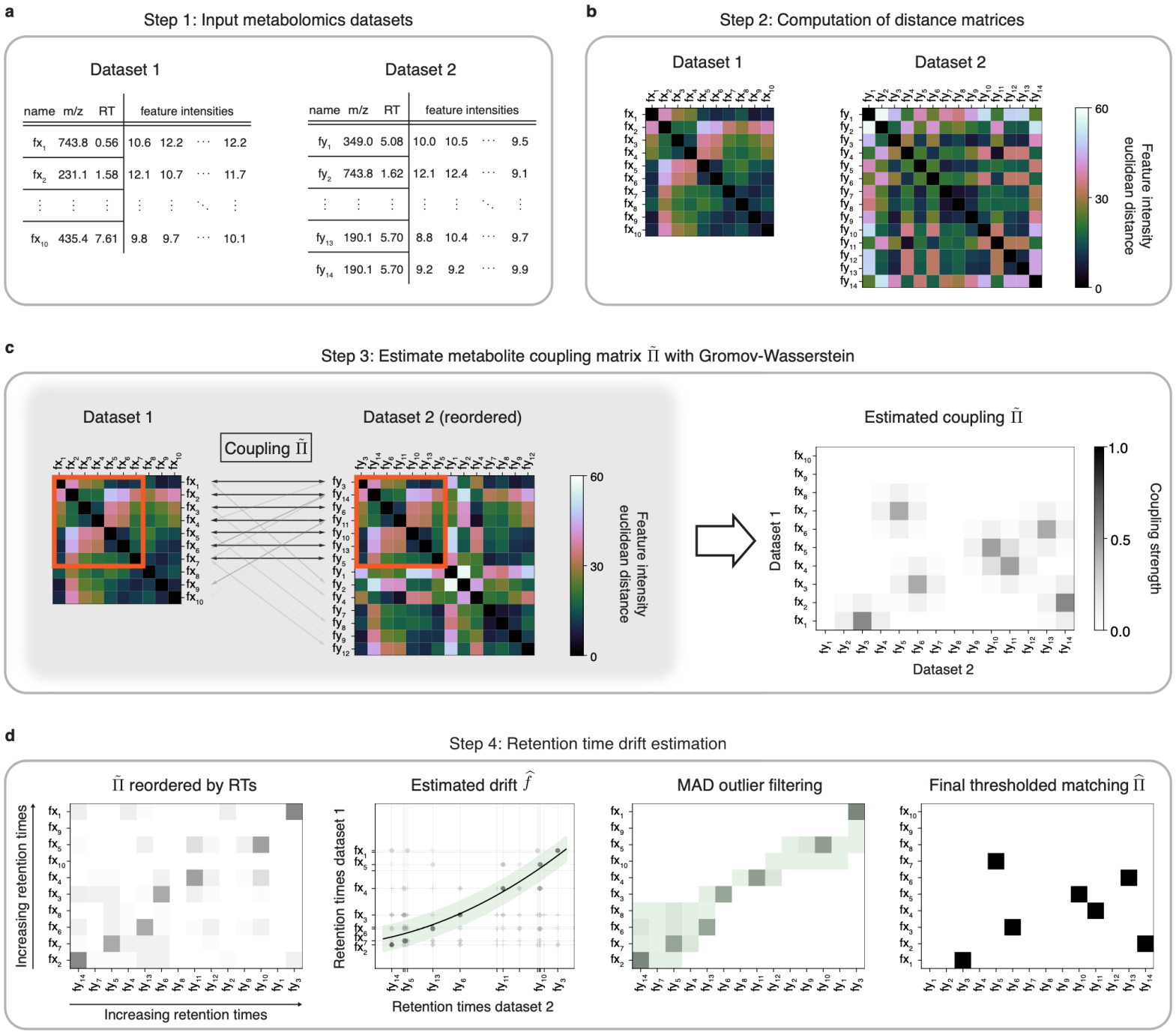
   - Discard pairs whose residual is higher than the MAD



GromovMatcher

Unbalanced Gromov-Wasserstein distance with entropic regularization [Séjourné et al. 2020]

- Allows for features to be dropped during the matching
- Computationally faster

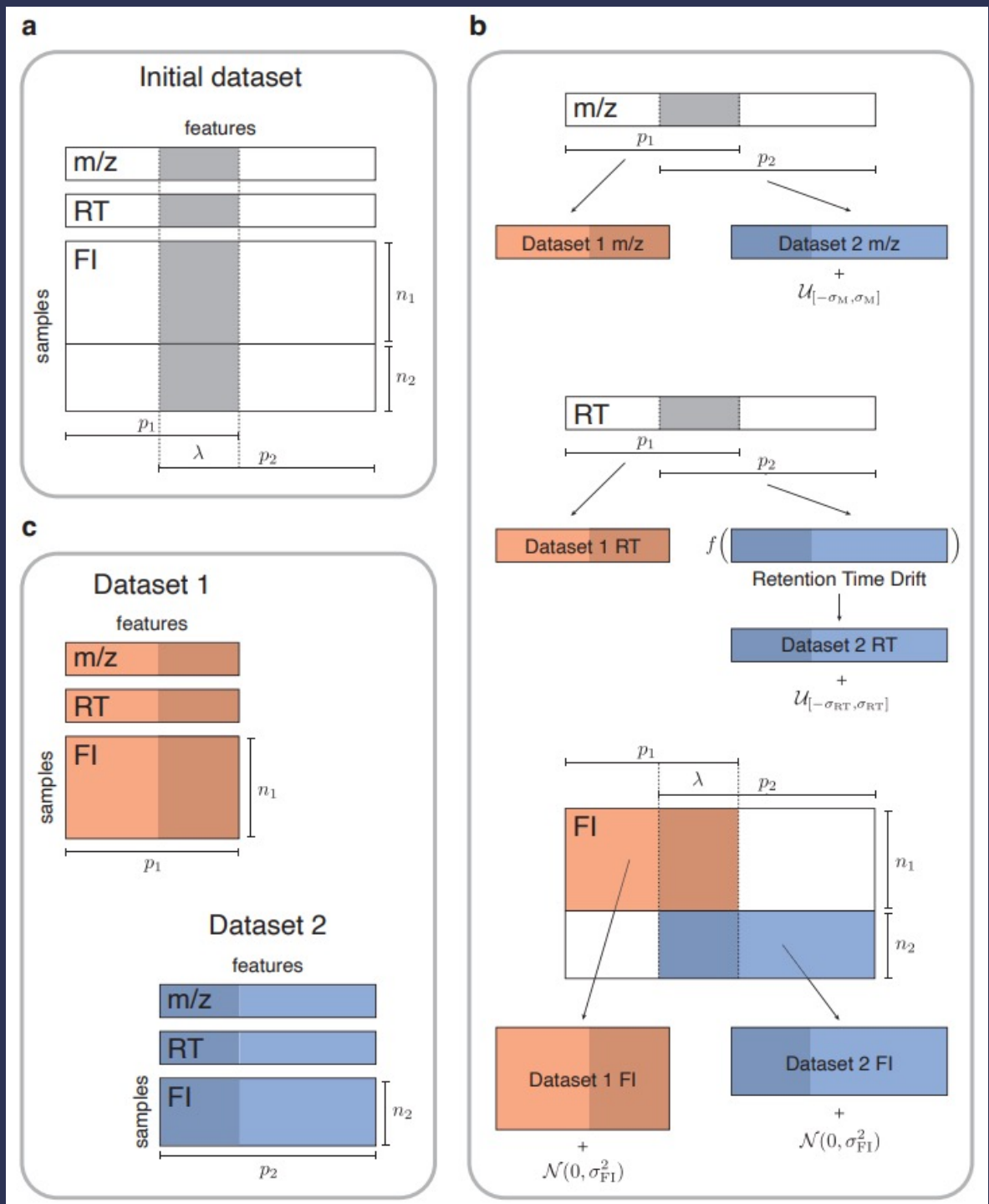
Implemented in Python

Runtime depends on the number of features. Typically less than 10 minutes for ~5000 features

Simulated data

Replicate a situation with 2 studies sharing a known set of features using an existing dataset of untargeted metabolomics on newborns

- Various setting investigated
- Compared with metabCombiner [Habra et al. 2021] and M2S [Pinto et al. 2022]

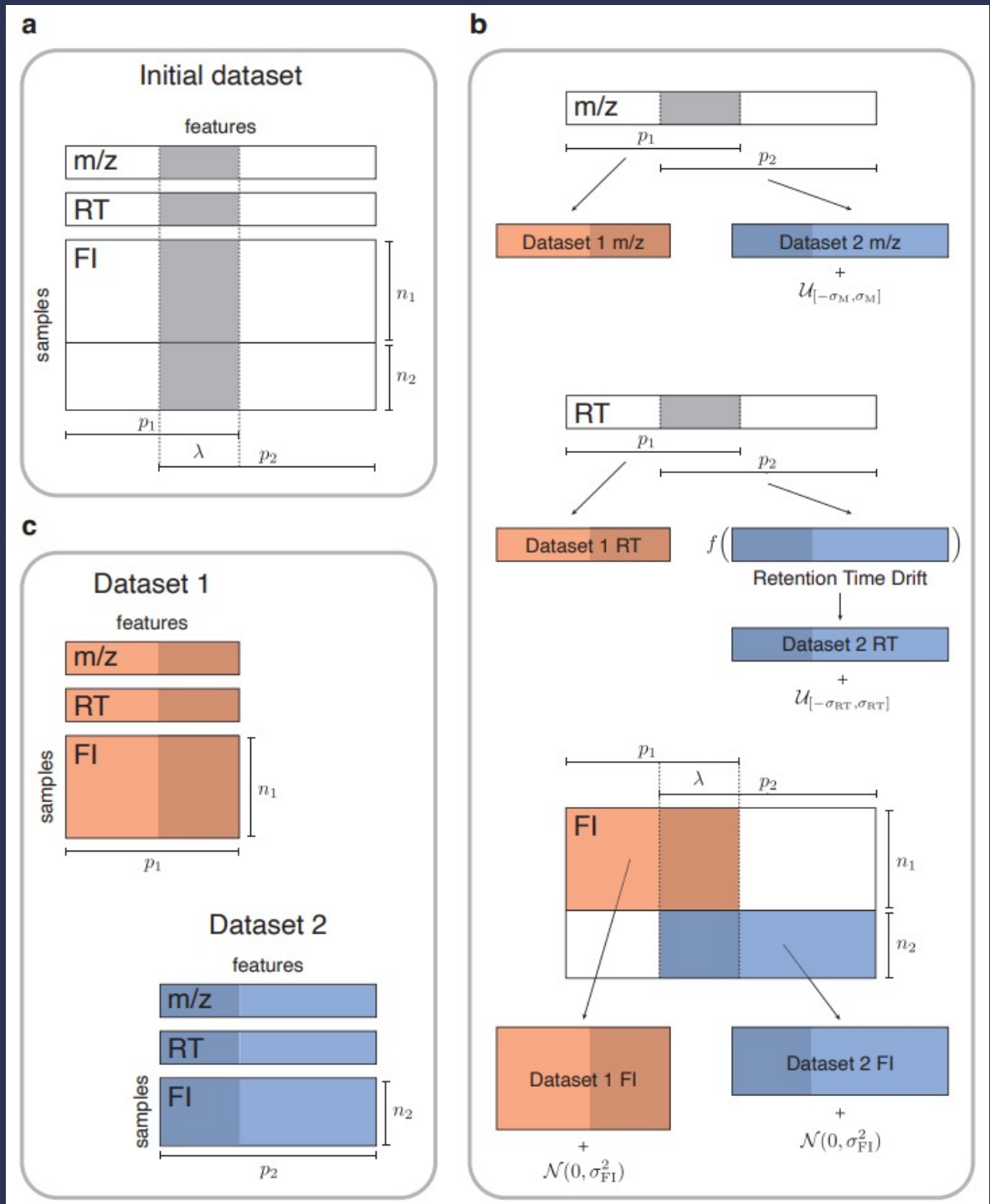


Simulated data

Replicate a situation with 2 studies sharing a known set of features using an existing dataset of untargeted metabolomics on newborns

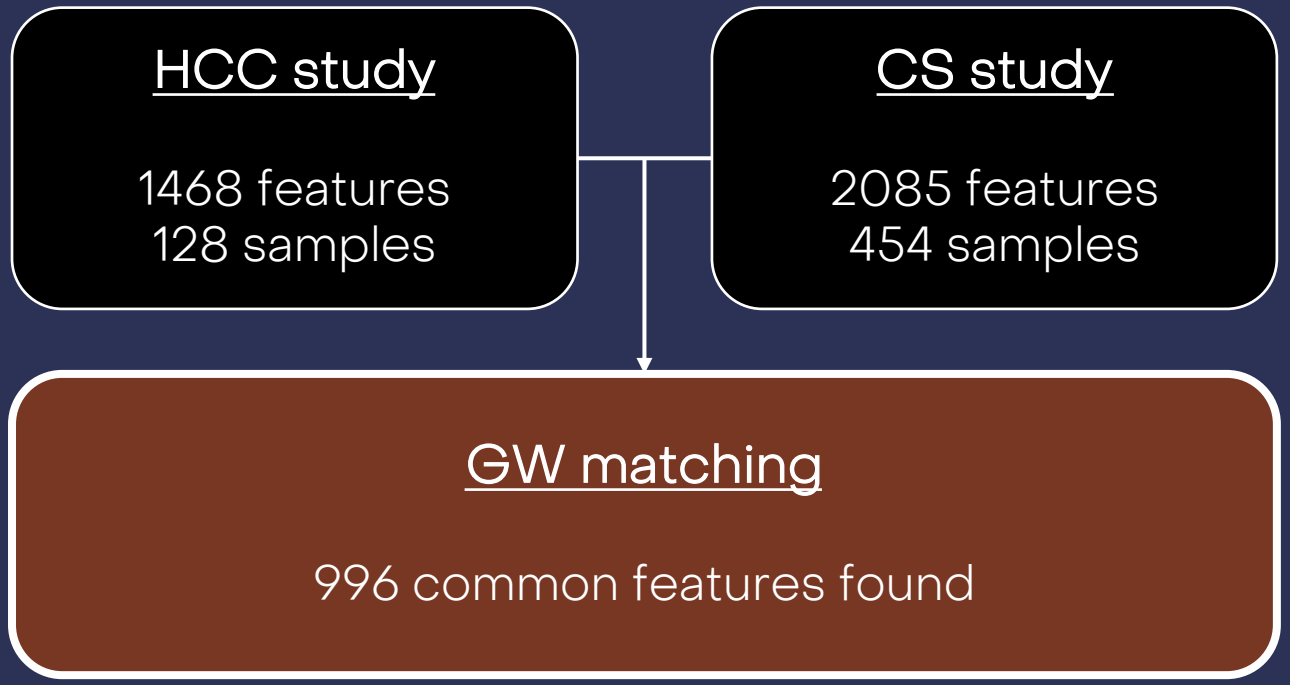
- Various setting investigated
- Compared with metabCombiner [Habra et al. 2021] and M2S [Pinto et al. 2022]

➢ Precision/recall were better in a majority of settings



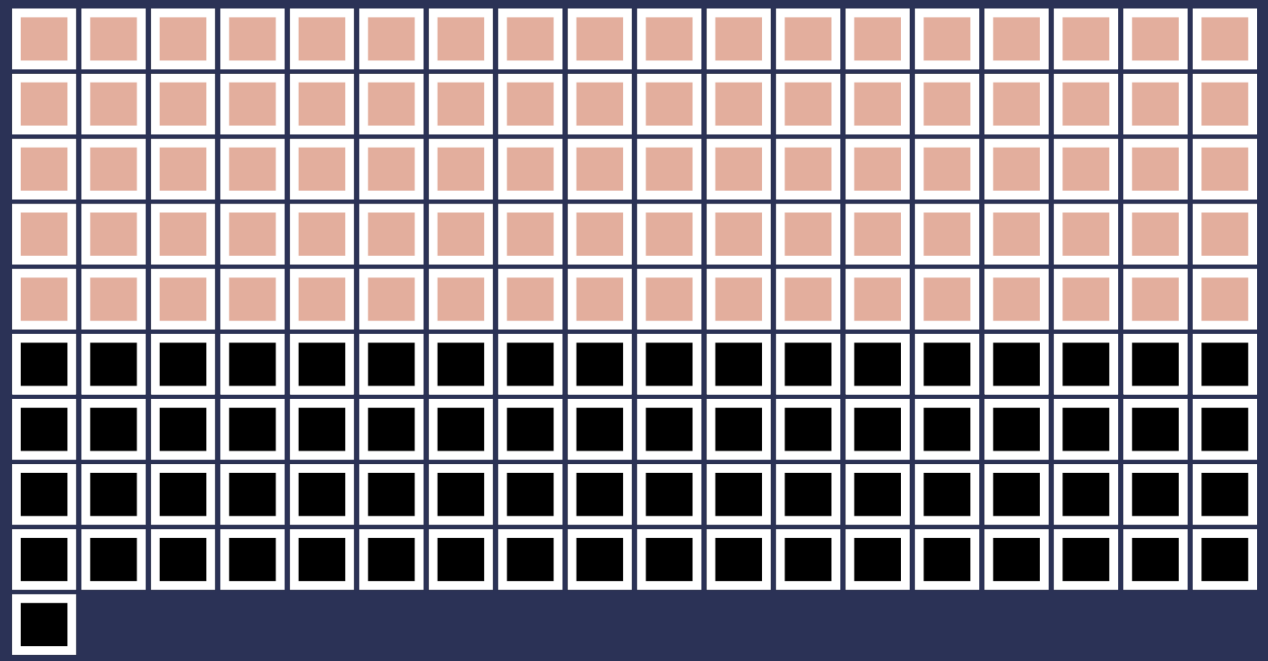
Application to EPIC data

Data from two EPIC studies used for alcohol biomarker discovery:
Cross-sectional (CS) study and hepatocellular carcinoma (HCC) study.



Application to EPIC data and validation

Data from two EPIC studies: Cross-sectional study and liver cancer study.

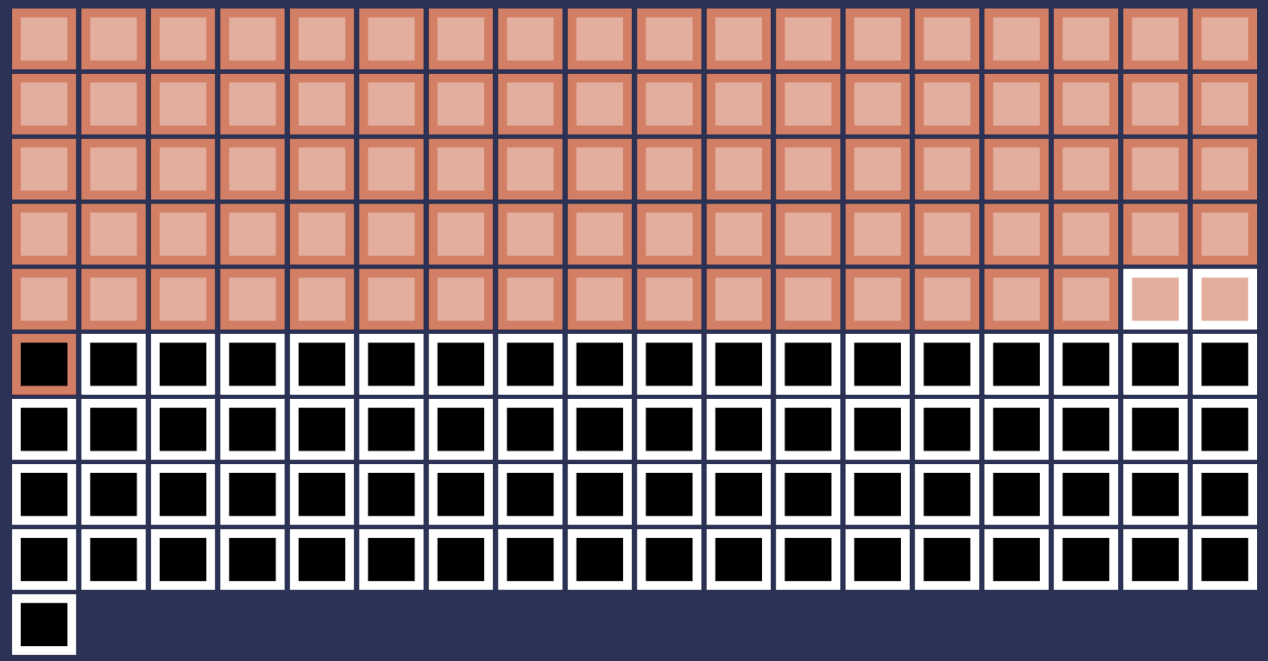


Manual examination (Loftfield *et al.*):
163 features from CS examined:

- 90 features also found in Liver
- 73 features unique to the CS study

Application to EPIC data and validation

Data from two EPIC studies: Cross-sectional study and liver cancer study.



Manual examination (Loftfield *et al.*):
163 features from CS examined:

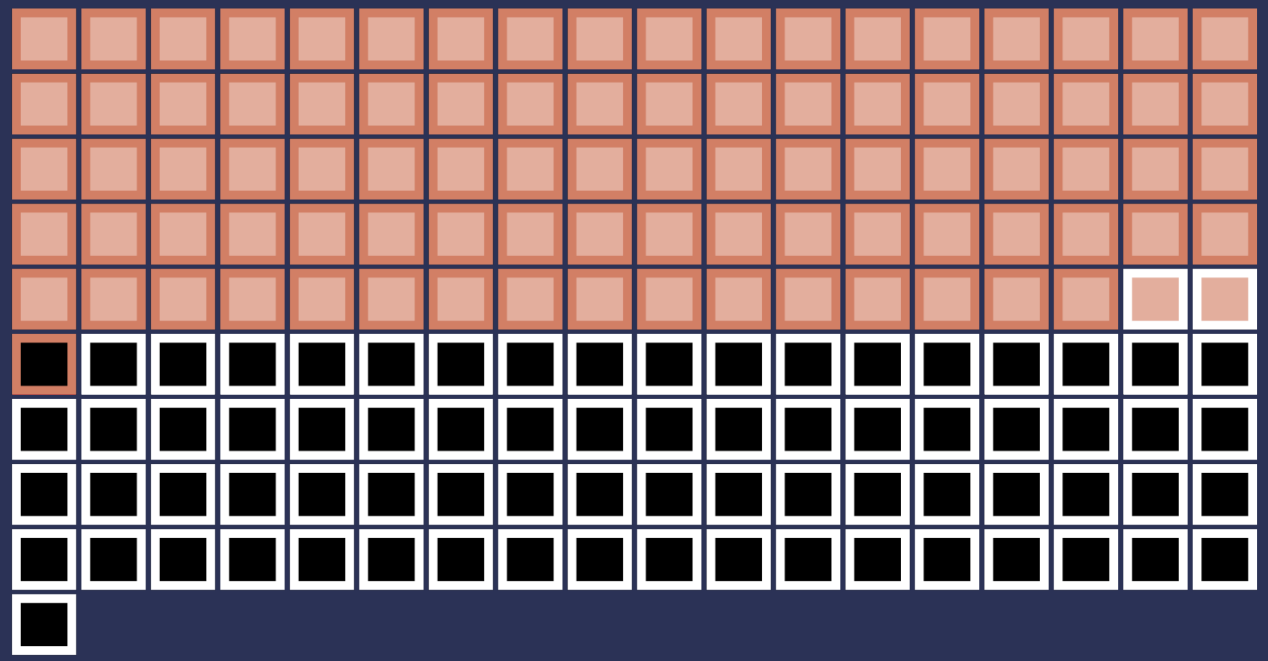
- 90 features also found in Liver
- 73 features unique to the CS study

- **89 common features found by GM**

(Recall: 0.98, precision: 0.99)

Application to EPIC data and validation

Data from two EPIC studies: Cross-sectional study and liver cancer study.



Manual examination (Loftfield *et al.*):
163 features from CS examined:

- 90 features also found in Liver
- 73 features unique to the CS study

- **89 common features found by GM**
- metabCombiner performed poorly (~20 matches recovered), M2S's optimal parameter combination was on par with GM

Application to EPIC data and validation

Data from two EPIC studies: Cross-sectional study and pancreatic cancer study.

- 987 common features found

- 65 out of 66 pairs recovered (same as M2S for optimal parameter tuning)
  - Recall: 0.98
- 7 additional pairs (11 for M2S)
  - Precision: 0.89

Application to EPIC data and validation

Data from two EPIC studies: Cross-sectional study and pancreatic cancer study.

- 987 common features found

- 65 out of 66 pairs recovered (same as M2S for optimal parameter tuning)
  - Recall: 0.98
- 7 additional pairs (11 for M2S)
  - Precision: 0.89

- Manual assessment found 2 good matches amongst the 7, the others were uncertain

Discussion

- Better performance than existing approaches
  - Compared with metabCombiner (Habra et al. 2021) and M2S (Pinto et al. 2022)
  - Better performance on simulated data and on EPIC data

- Perspectives
  - Extension to data where isotopic peaks/prior knowledge are available
  - Application to annotated data for EPIC Norfolk samples
  - Assess performance when data come from different studies, using different platforms

Acknowledgements

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References

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