Identifying sample mix-ups in eQTL data

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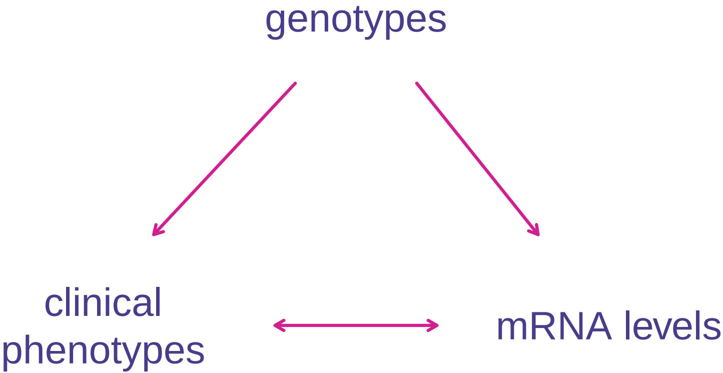
Associations in systems genetics

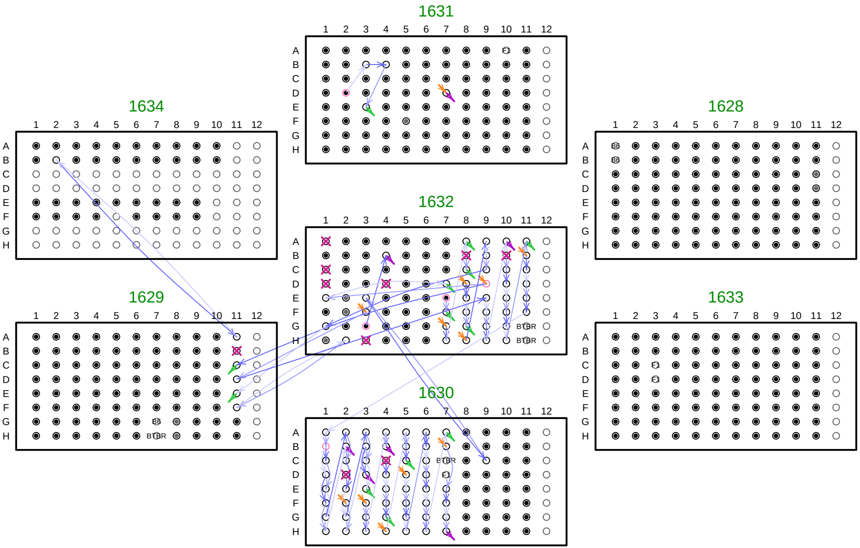


genotypes

clinical phenotypes

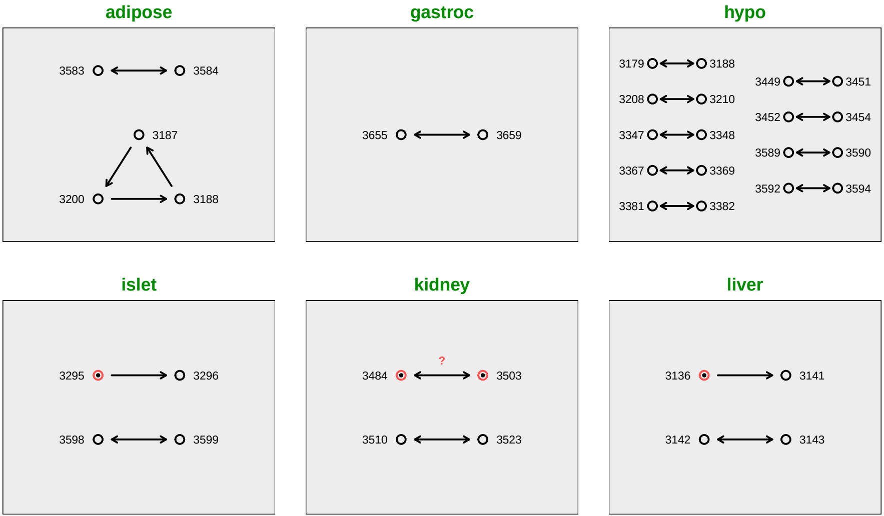
mRNA levels

Sample mix-ups



Broman et al. (2015) `doi:10.1534/g3.115.019778`

More sample mix-ups



Broman et al. (2015) `doi:10.1534/g3.115.019778`

Westra et al. (2011)

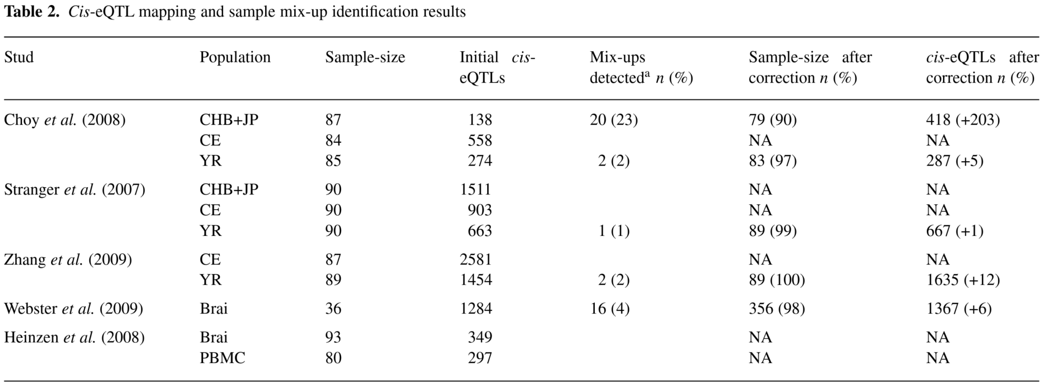


Table 2. *Cis*-eQTL mapping and sample mix-up identification results

Stud	Population	Sample-size	Initial *cis*-eQTLs	Mix-ups detected[a] n (%)	Sample-size after correction n (%)	*cis*-eQTLs after correction n (%)
Choy *et al.* (2008)	CHB+JP	87	138	20 (23)	79 (90)	418 (+203)
	CE	84	558		NA	NA
	YR	85	274	2 (2)	83 (97)	287 (+5)
Stranger *et al.* (2007)	CHB+JP	90	1511		NA	NA
	CE	90	903		NA	NA
	YR	90	663	1 (1)	89 (99)	667 (+1)
Zhang *et al.* (2009)	CE	87	2581		NA	NA
	YR	89	1454	2 (2)	89 (100)	1635 (+12)
Webster *et al.* (2009)	Brai	36	1284	16 (4)	356 (98)	1367 (+6)
Heinzen *et al.* (2008)	Brai	93	349		NA	NA
	PBMC	80	297		NA	NA

Westra et al. (2011) `doi:10.1093/bioinformatics/btr323`

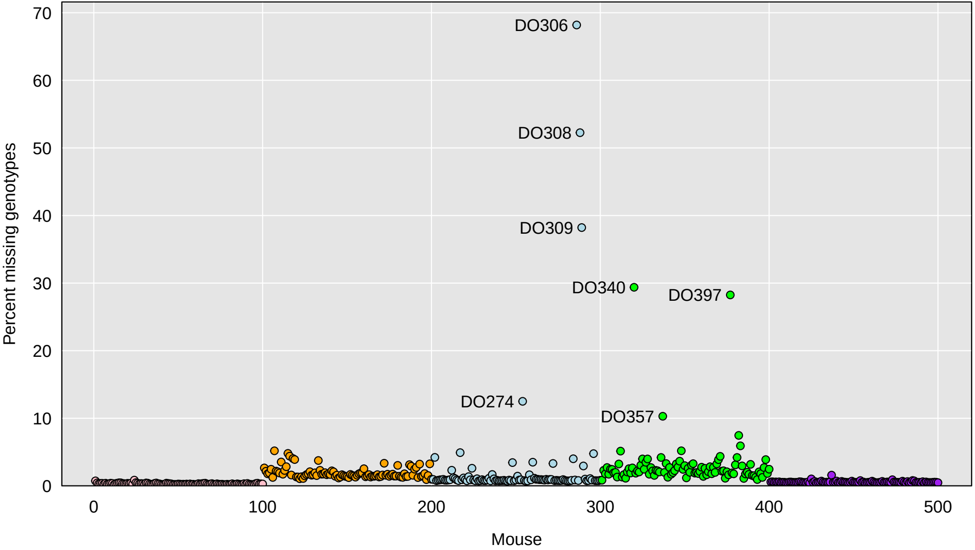
Outline

- Sample duplicates
- Sex verification
- Sample mix-ups:
  - mRNA ↔ protein
  - mRNA ↔ DNA
  - protein ↔ DNA

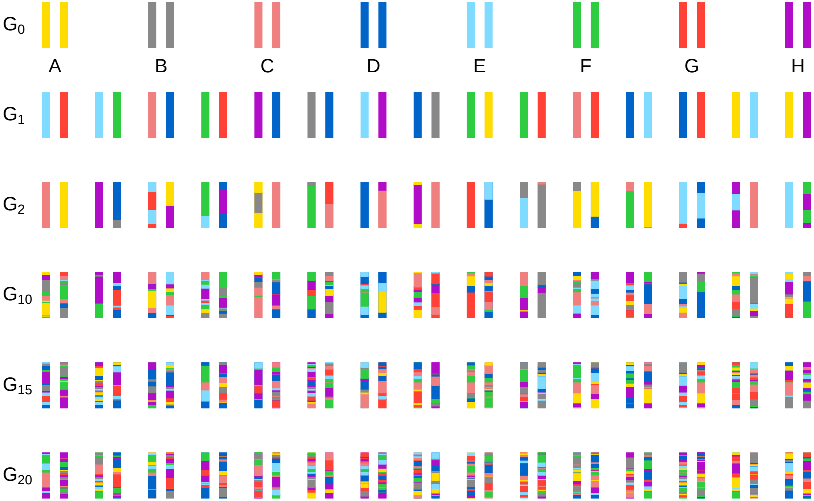
But first

Missing Data

Percent missing genotypes

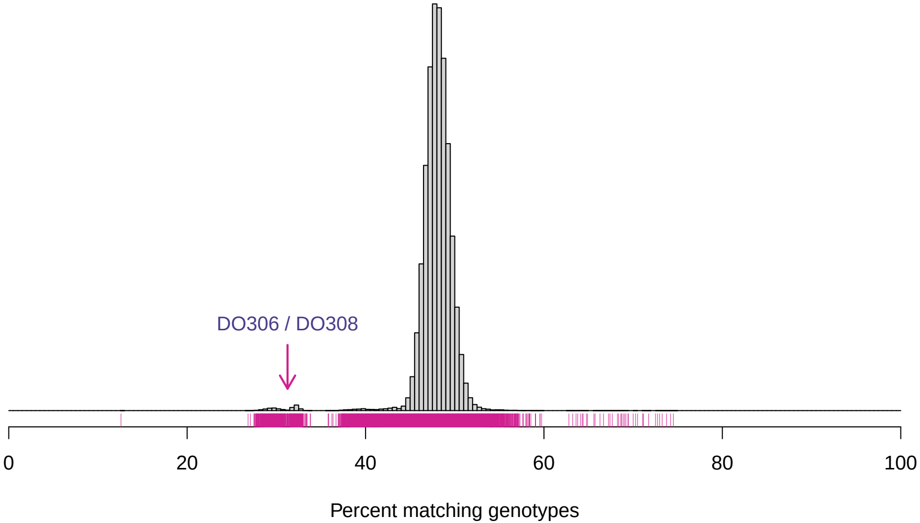


Heterogeneous Stock/Diversity Outbreds



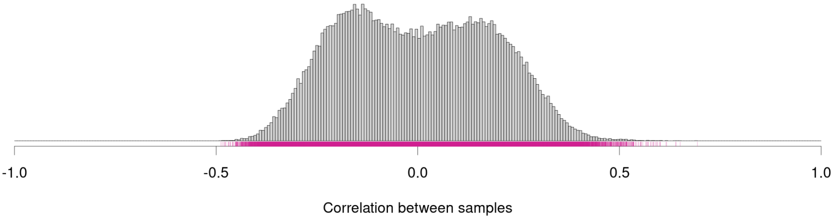
Sample duplicates

Percent matching genotypes

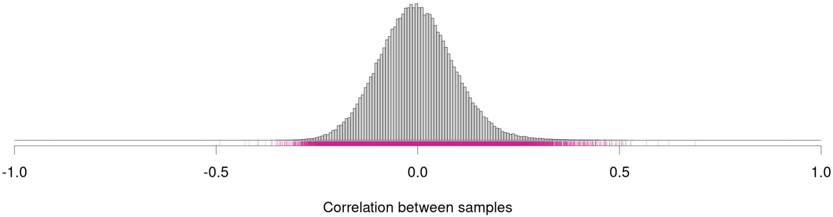


Correlation between mRNA samples

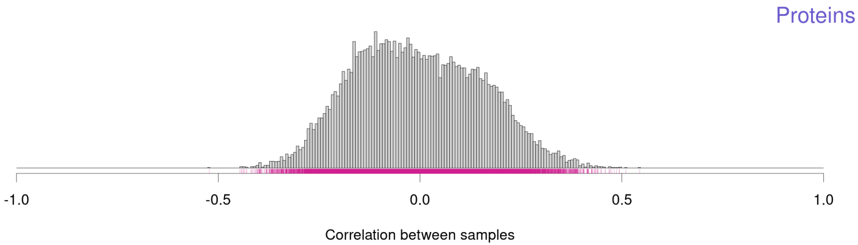
mRNAs

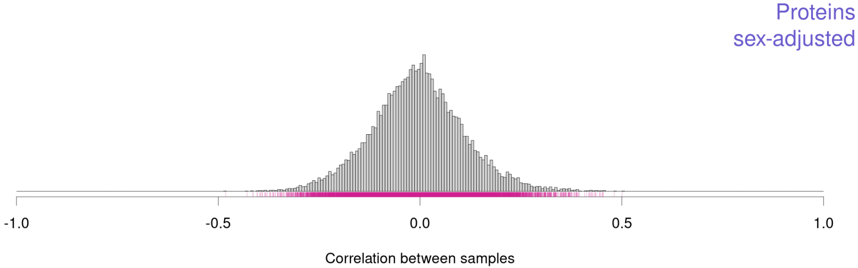


mRNAs
sex-adjusted



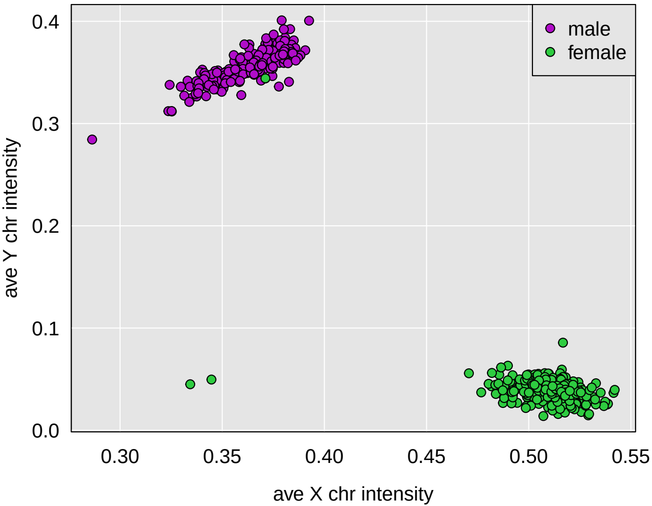
Correlation between protein samples



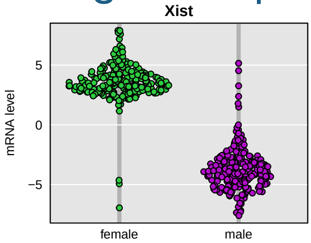


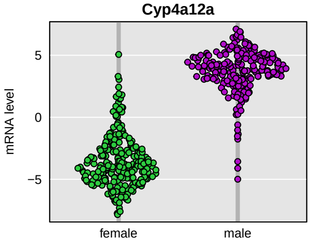
Sex verification

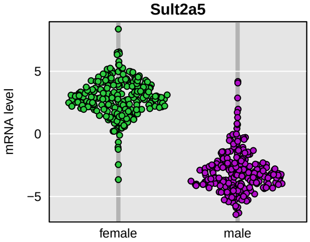
X and Y genotype dosage

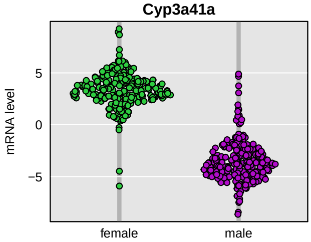


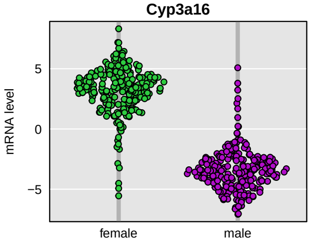
Sex and gene expression

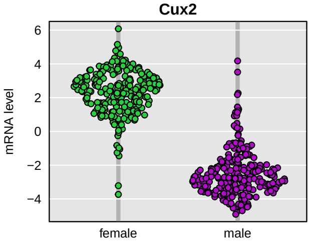

Xist


Cyp4a12a

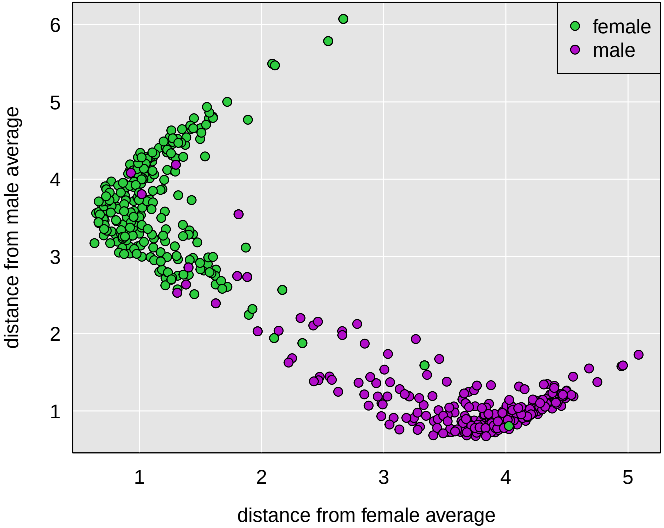

Sult2a5


Cyp3a41a

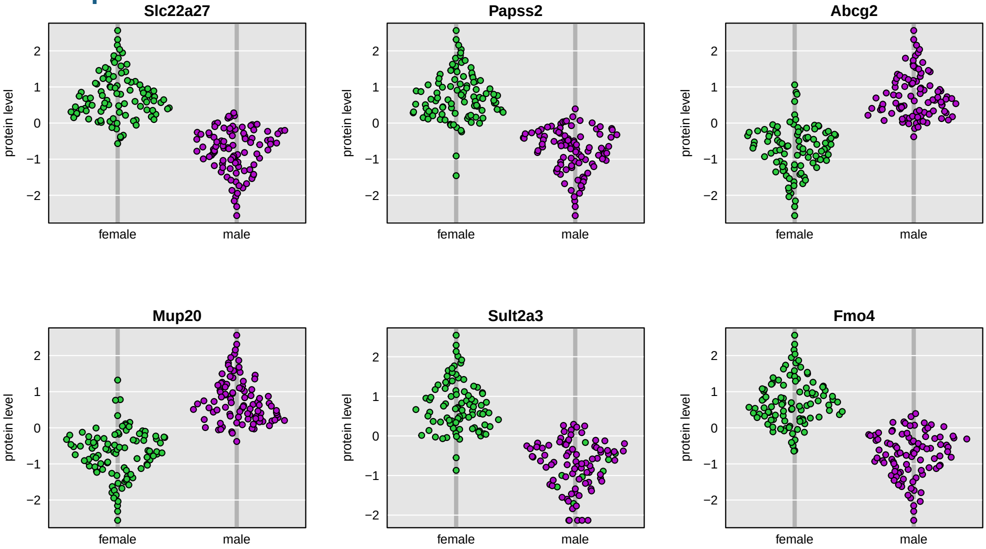

Cyp3a16


Cux2

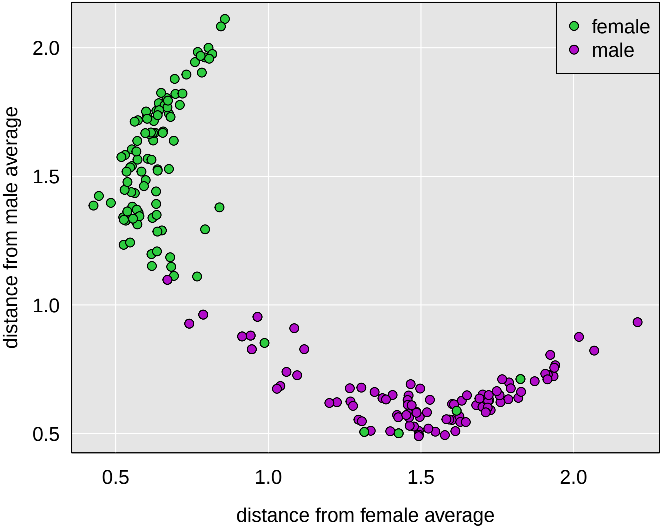
Sex and gene expression



Sex and proteins



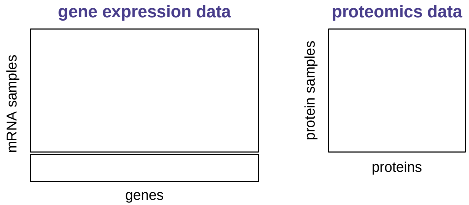
Sex and proteins



Sample mix-ups

mRNA ↔ protein

mRNA ↔ protein method



gene expression data

mRNA samples

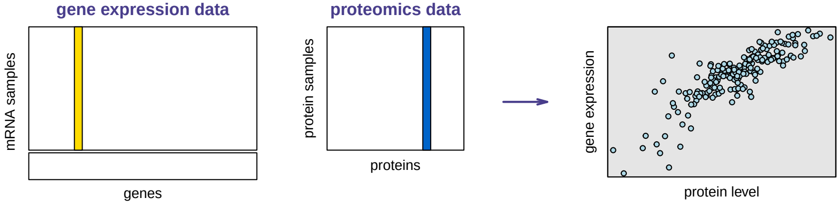
genes

proteomics data

protein samples

proteins

mRNA ↔ protein method



gene expression data

mRNA samples

genes

proteomics data

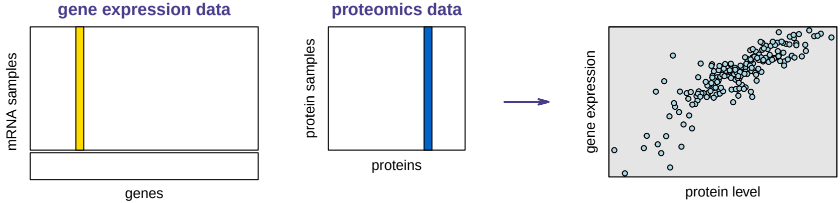
protein samples

proteins

gene expression

protein level

mRNA ↔ protein method



gene expression data

mRNA samples

genes

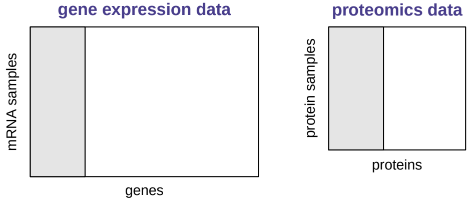
proteomics data

protein samples

proteins

gene expression

protein level



gene expression data

mRNA samples

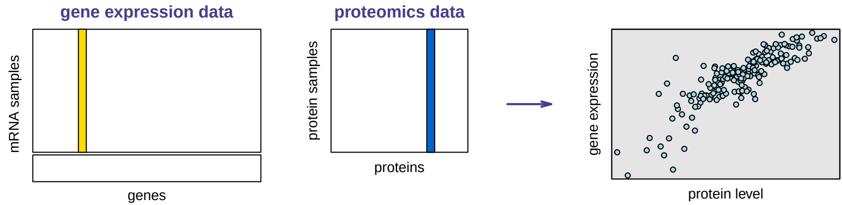
genes

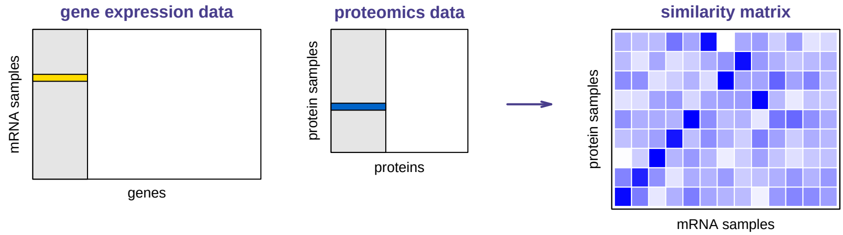
proteomics data

protein samples

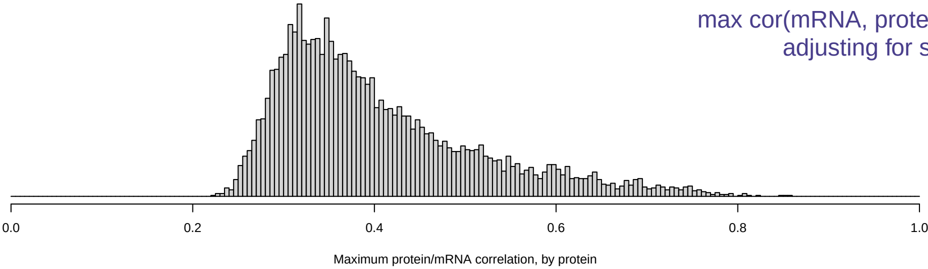
proteins

mRNA ↔ protein method

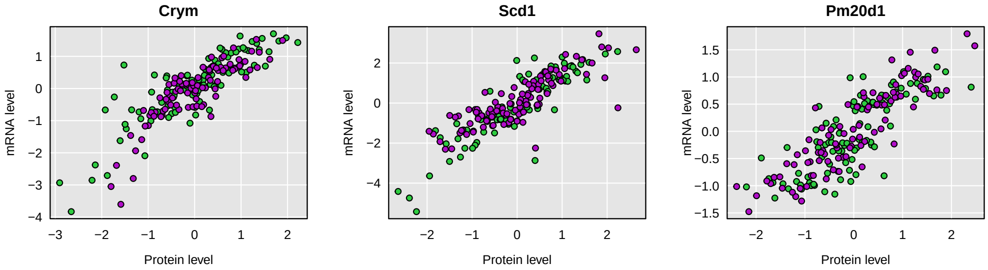




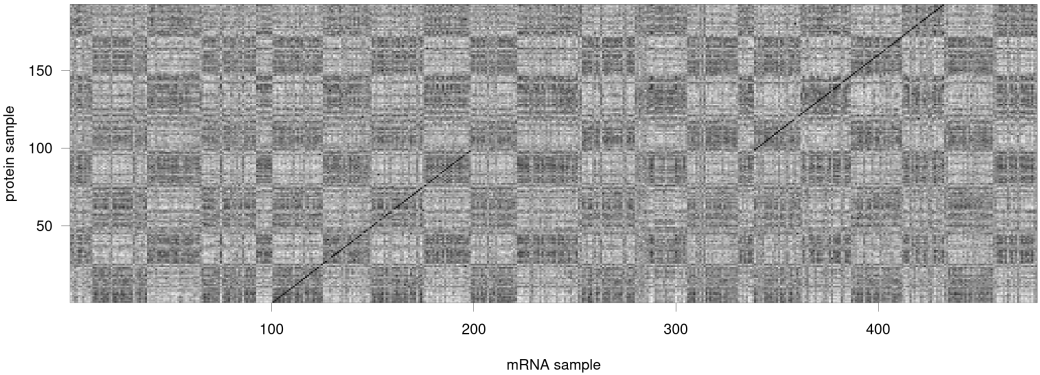
mRNA ↔ protein correlations



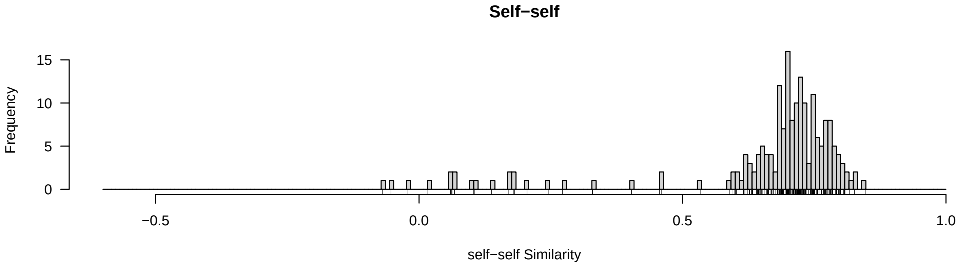
max cor(mRNA, protein)
adjusting for sex

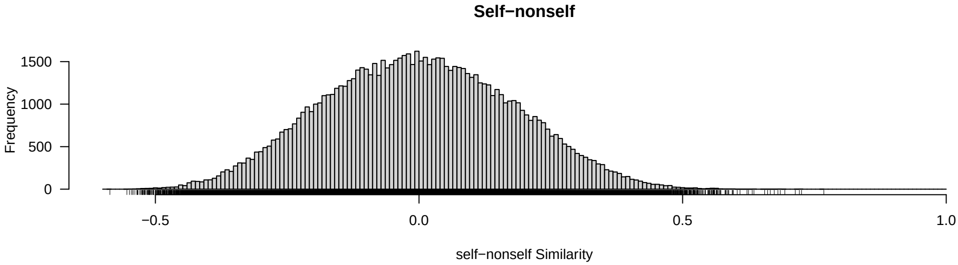


mRNA ↔ protein similarity matrix

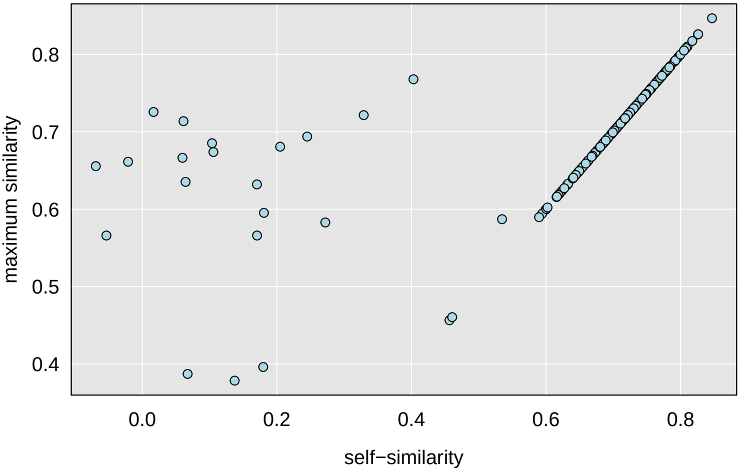


mRNA ↔ protein similarities

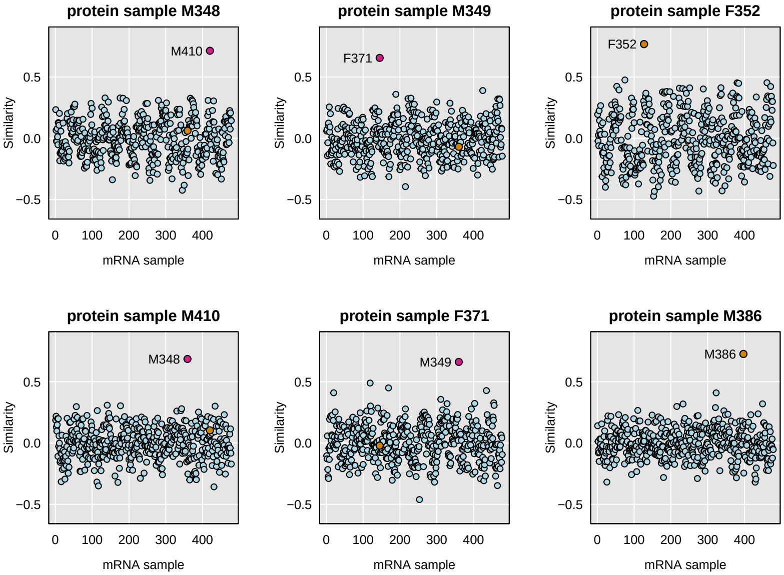




mRNA ↔ protein: closest vs self



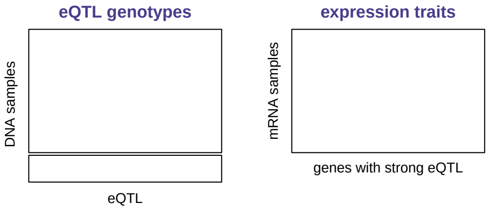
mRNA ↔ protein: selected samples



Sample mix-ups

DNA $\leftrightarrow$ mRNA

DNA ↔ mRNA method



eQTL genotypes

DNA samples

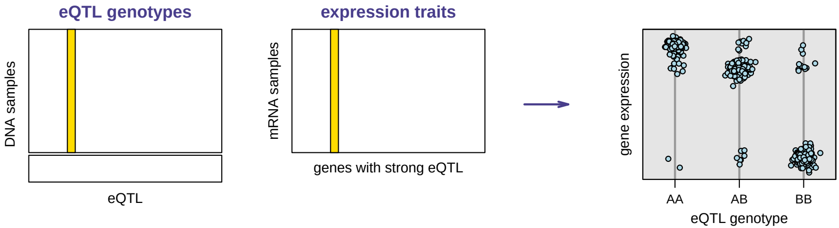
eQTL

expression traits

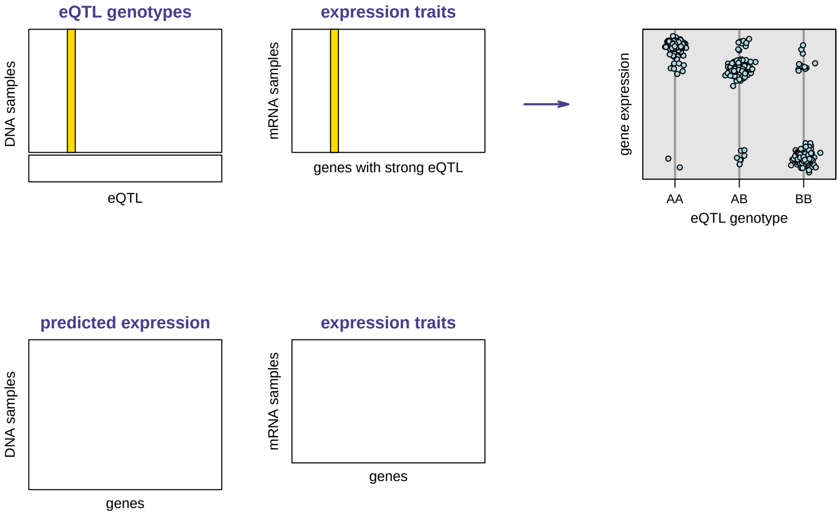
mRNA samples

genes with strong eQTL

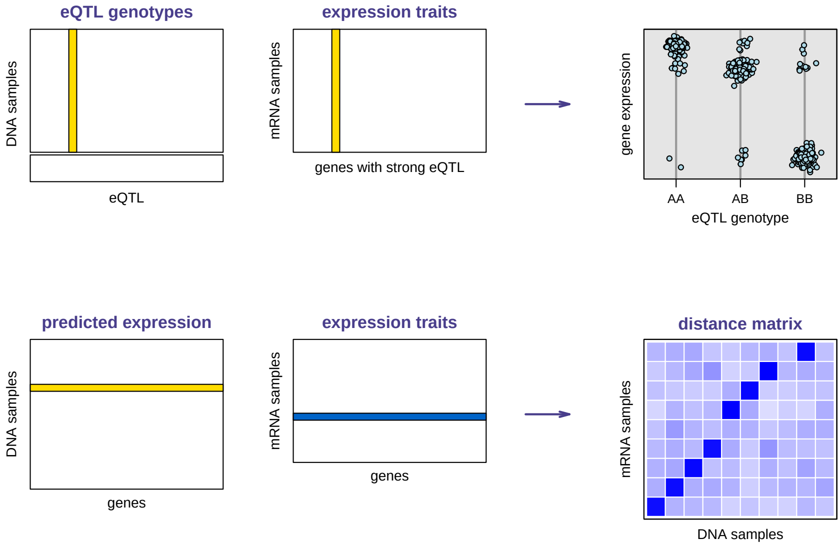
DNA ↔ mRNA method



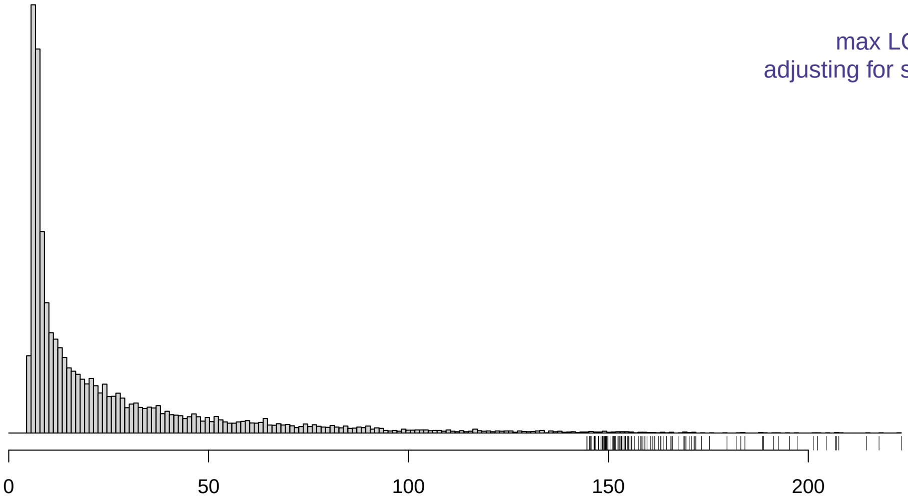
DNA ↔ mRNA method



DNA ↔ mRNA method

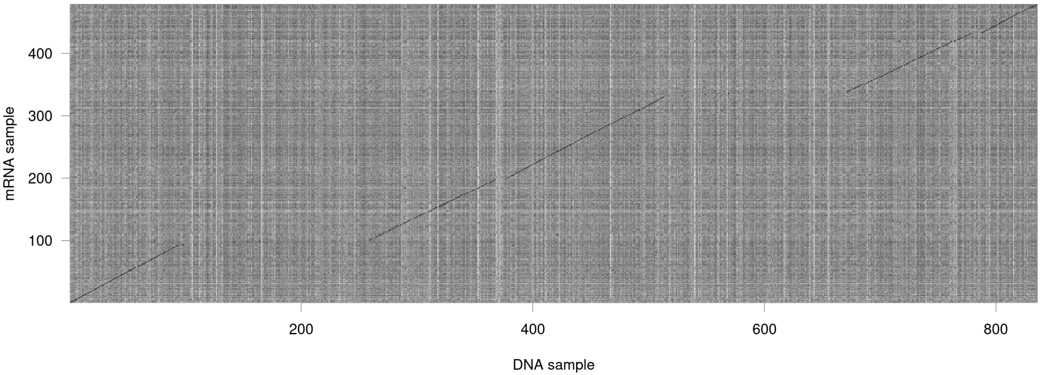


DNA ↔ mRNA LOD scores

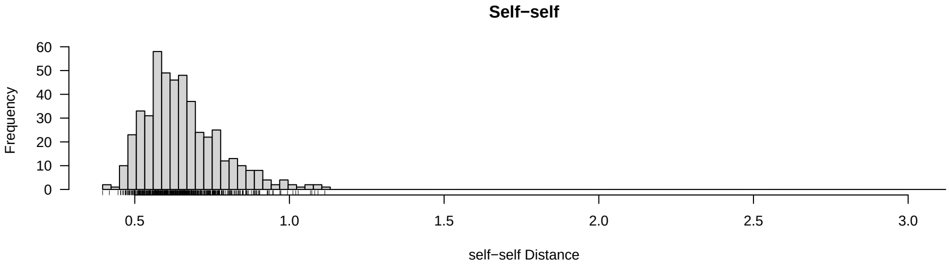


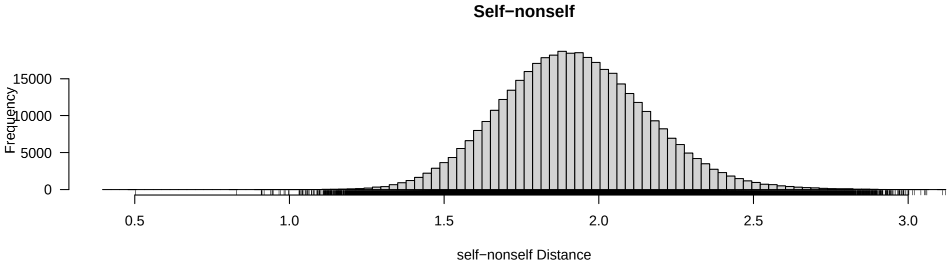
max LOD
adjusting for sex

DNA ↔ mRNA distance matrix

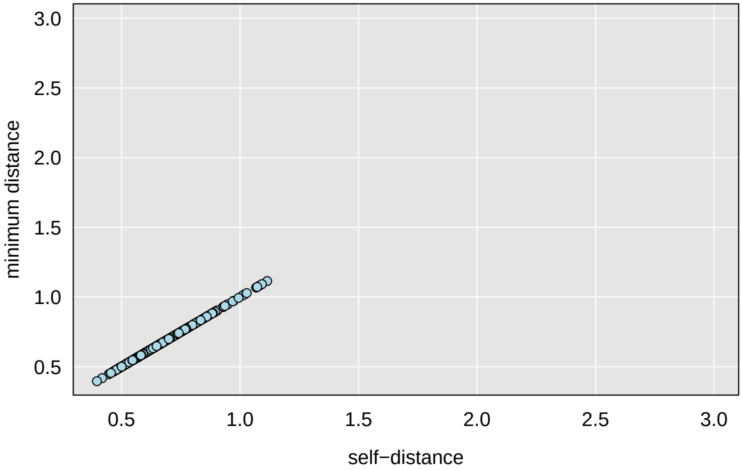


DNA ↔ mRNA distances

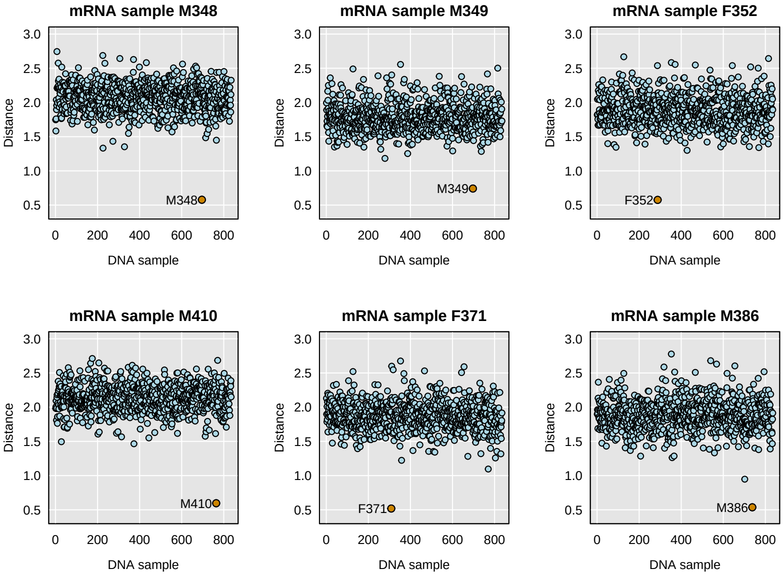




DNA ↔ mRNA: closest vs self



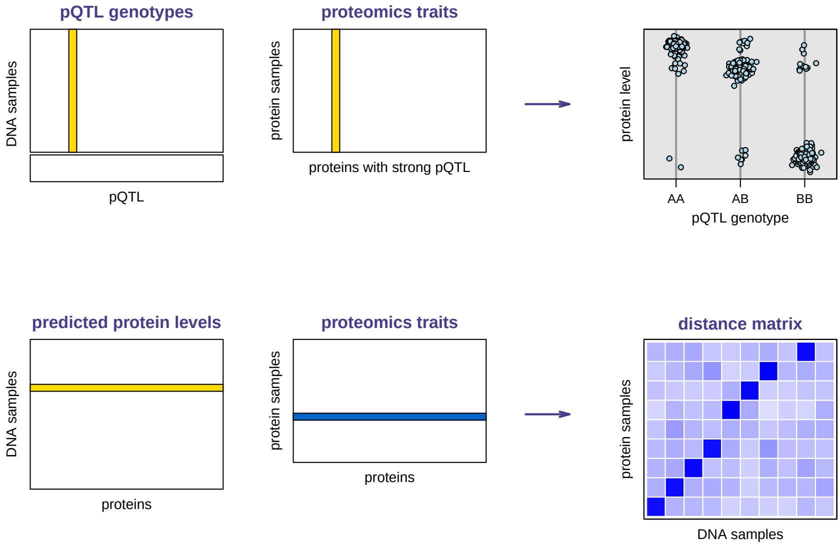
DNA ↔ mRNA: selected samples



Sample mix-ups

DNA ↔ protein

DNA ↔ protein method



pQTL genotypes

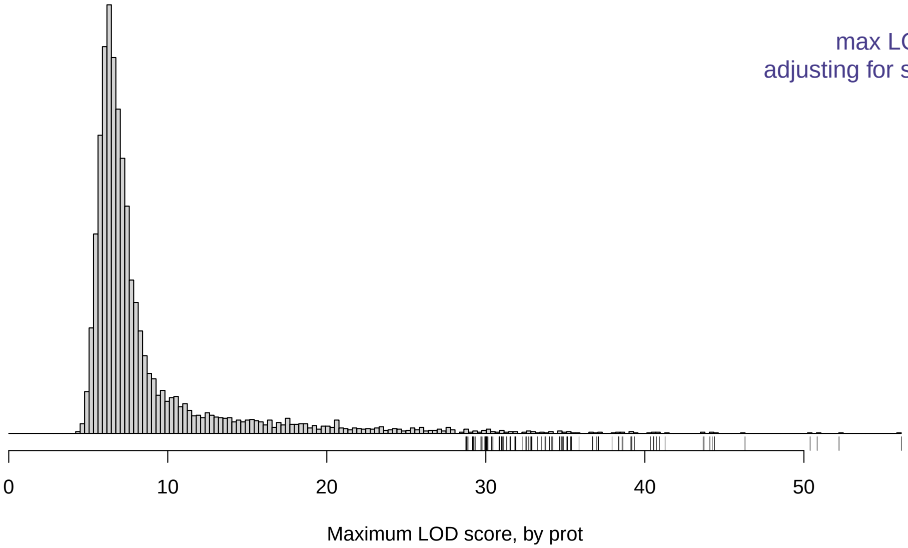
proteomics traits

predicted protein levels

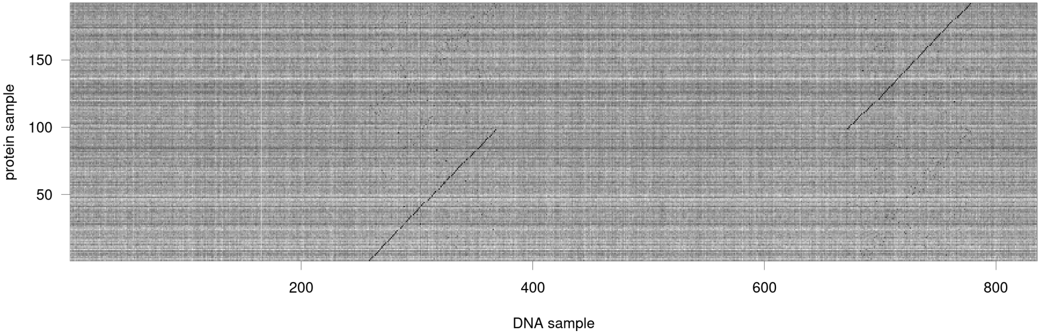
proteomics traits

distance matrix

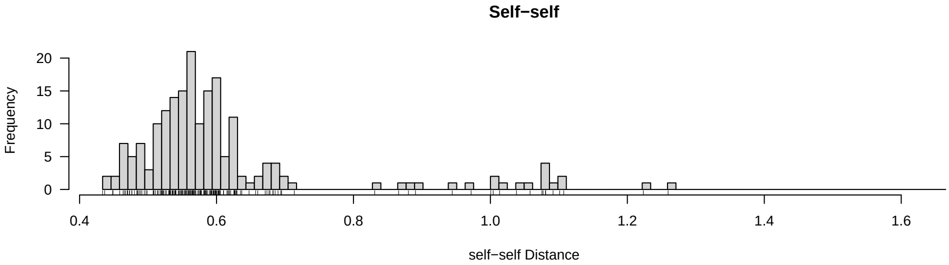
DNA ↔ protein correlations

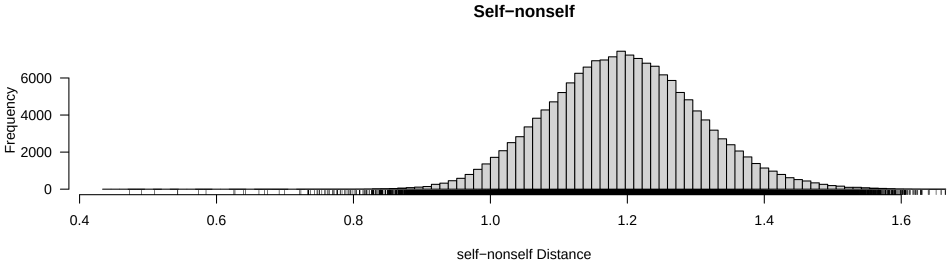


DNA ↔ protein distance matrix

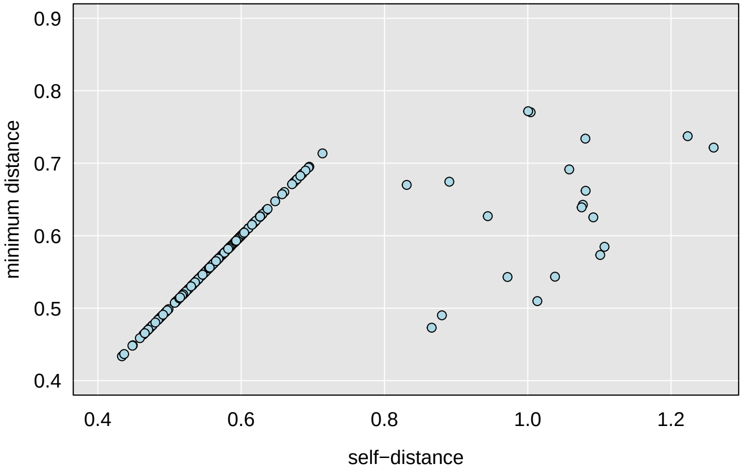


DNA ↔ protein distances

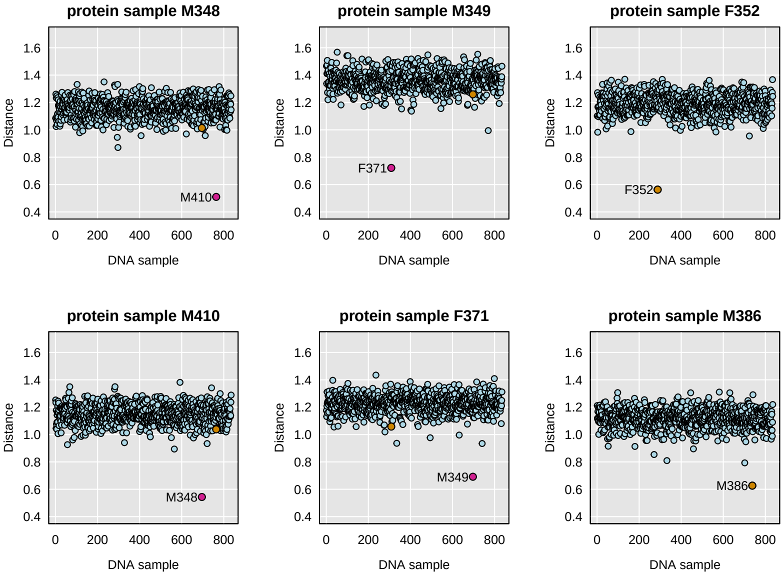




DNA ↔ protein: closest vs self

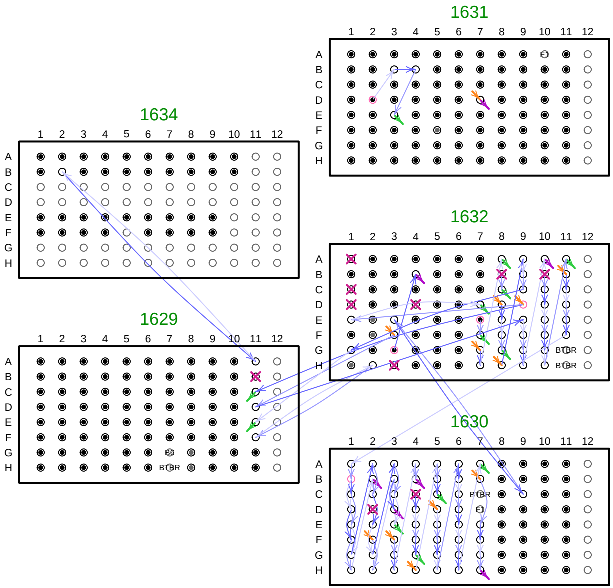


DNA ↔ protein: selected samples



Summary

- This shouldn't happen.
- But if it does, you should find it.
- If two data sets have rows that correspond, you should check that they do correspond.



References

- Westra et al. (2011) MixupMapper: correcting sample mix-ups in genome-wide datasets increases power to detect small genetic effects. Bioinformatics 15:2104–2111 doi:10.1093/bioinformatics/btr323

- Lynch et al (2012) Calling sample mix-ups in cancer population studies. PLOS One 7:e41815 doi:10.1371/journal.pone.0041815

- Broman et al. (2015) Identification and correction of sample mix-ups in expression genetic data: A case study. G3 (Bethesda) 5:2177–2186 doi:10.1534/g3.115.019778

- Broman et al. (2019) Cleaning genotype data from Diversity Outbred mice. G3 (Bethesda) 9:1571–1579 doi:10.1534/g3.119.400165

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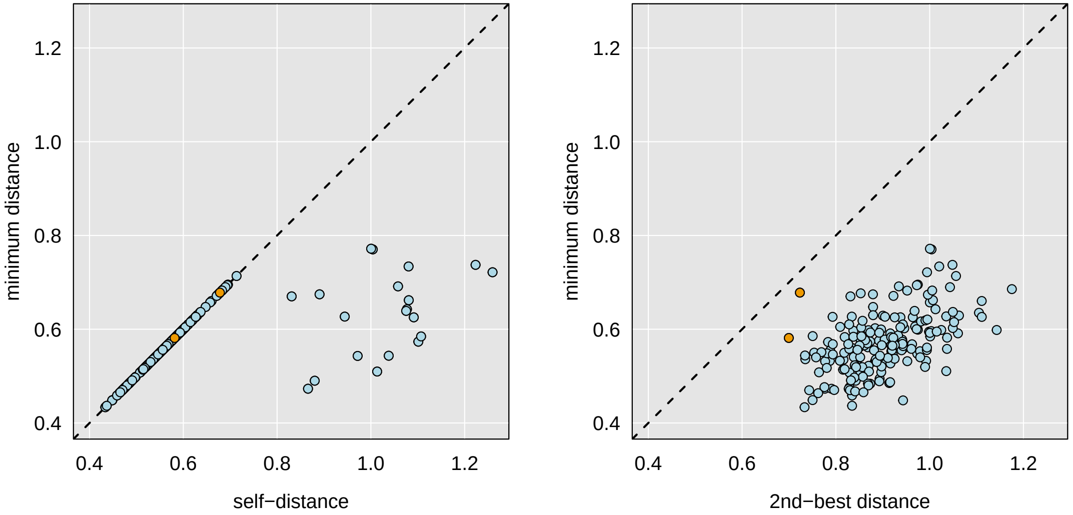
DNA ↔ protein: best vs 2nd-best


minimum distance
self−distance
minimum distance
2nd−best distance