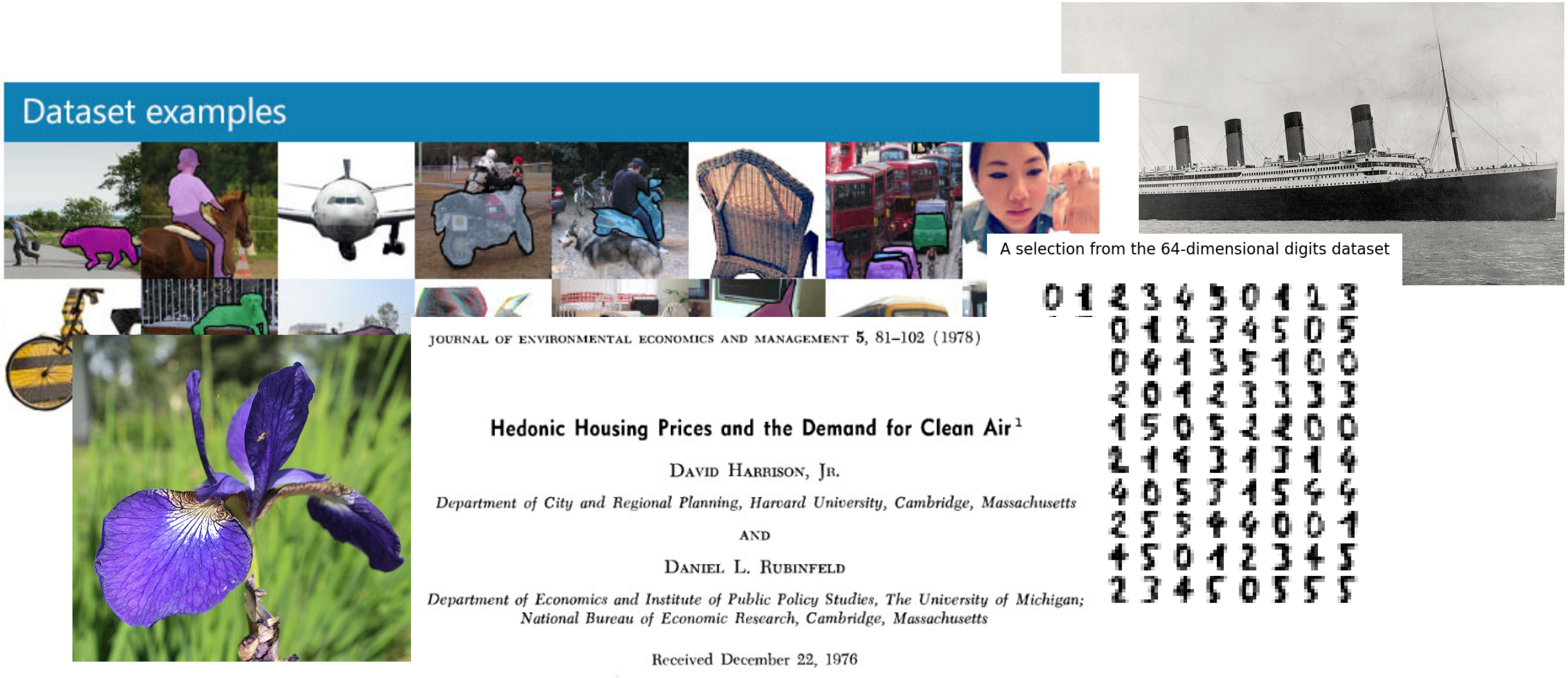
Using multiple data modalities for brain tumor diagnostics and treatment

Sören Lukassen
BIH Digital Health Center
02/02/2023

Berlin Institute of Health @Charité



Dataset examples

A selection from the 64-dimensional digits dataset

JOURNAL OF ENVIRONMENTAL ECONOMICS AND MANAGEMENT 5, 81–102 (1978)

Hedonic Housing Prices and the Demand for Clean Air[1]

DAVID HARRISON, JR.

Department of City and Regional Planning, Harvard University, Cambridge, Massachusetts

AND

DANIEL L. RUBINFELD

Department of Economics and Institute of Public Policy Studies, The University of Michigan; National Bureau of Economic Research, Cambridge, Massachusetts

Received December 22, 1976

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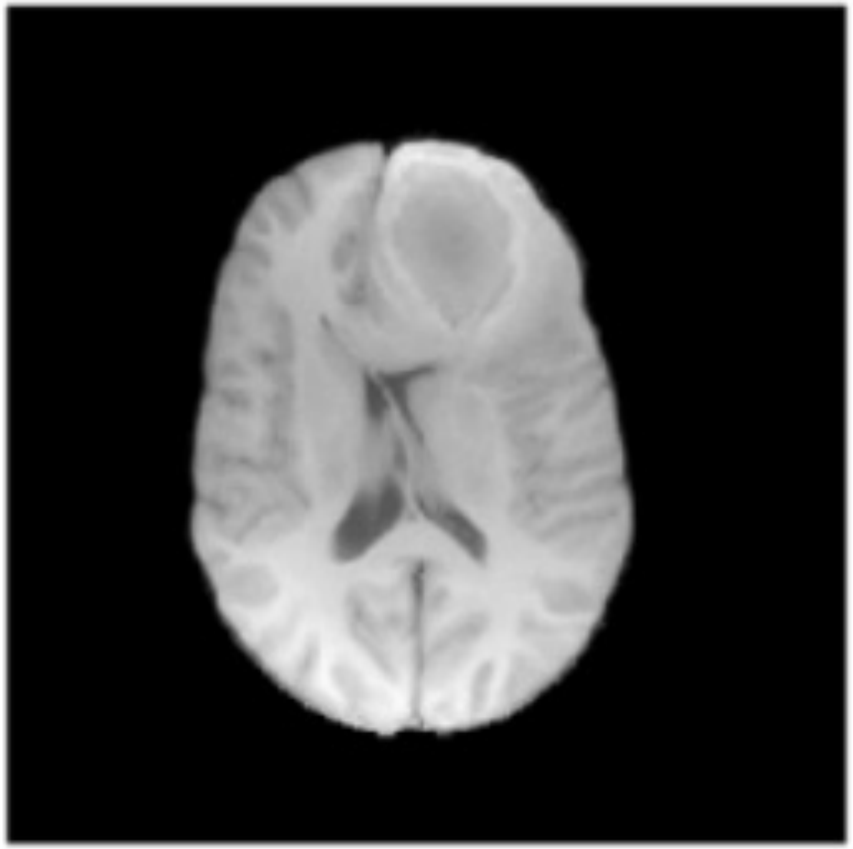
Our application: brain tumor diagnostics and treatment



Jabareen & Lukassen, 2022

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Tumor diagnostics – common workflow

Step 0: Indication for diagnostics (screening, symptoms, etc.)

Step 1: Imaging

Step 2: Biopsy

Step 3: Surgery + immediate frozen section

Step 4: Histopathology

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Tumor diagnostics – common workflow

Step 0: Indication for diagnostics (screening, symptoms, etc.)

Unilateral loss of vision

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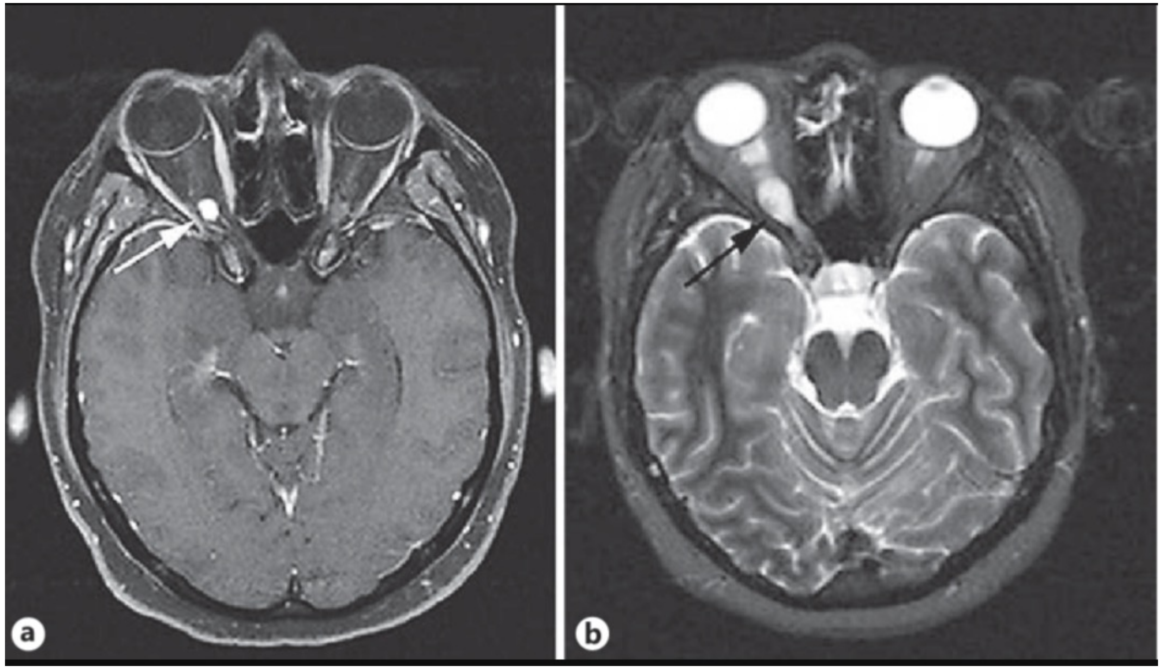
Tumor diagnostics – common workflow

Step 0: Indication for diagnostics (screening, symptoms, etc.)

Unilateral loss of vision

Step 1: Imaging



McGrath et al., 2018

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Tumor diagnostics – common workflow

Step 0: Indication for diagnostics (screening, symptoms, etc.)

Unilateral loss of vision

Step 1: Imaging

Lesion at the optic nerve

Step 2: Biopsy

Difficult to reach location, risk of permanent damage to optic nerve

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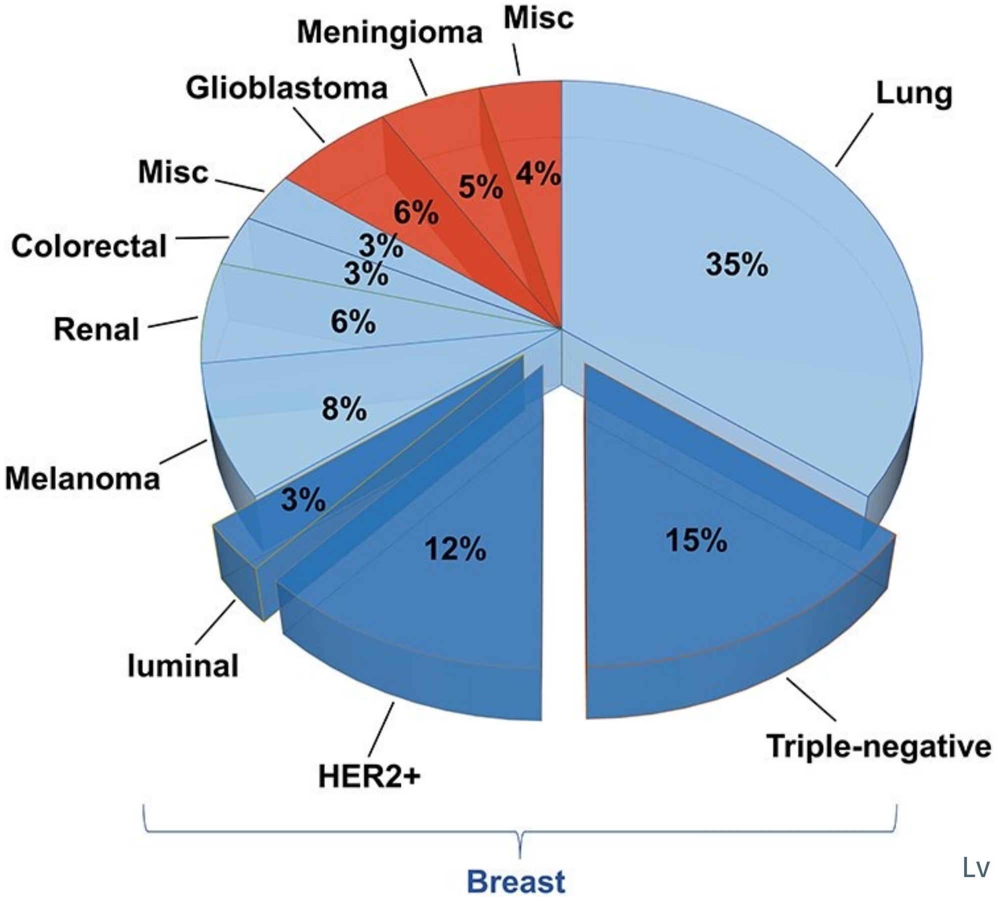
Problem 1: we don‘t know what we‘re looking at



Lv et al., 2021

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Problem 2: no fine-needle biopsies

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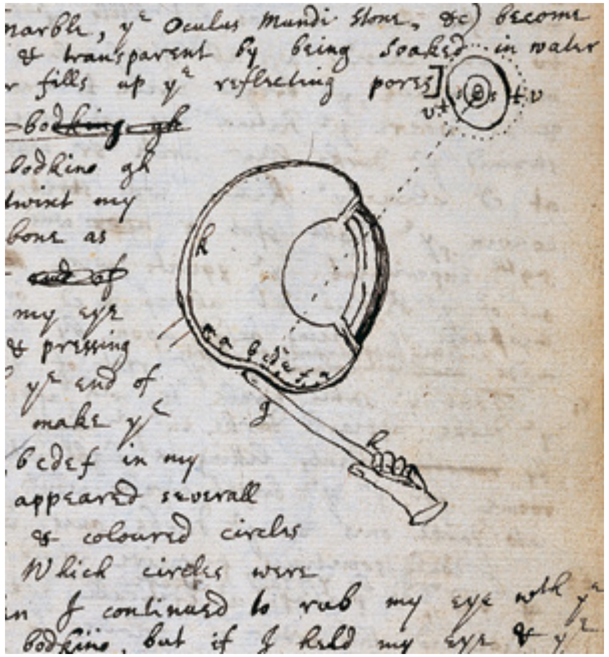
Problem 2: no fine-needle biopsies



marble, y^e Oculus Mundi Stone, &c) become
& transparent by being soaked in water
r fills up y^e reflecting pores]
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Isaac Newton

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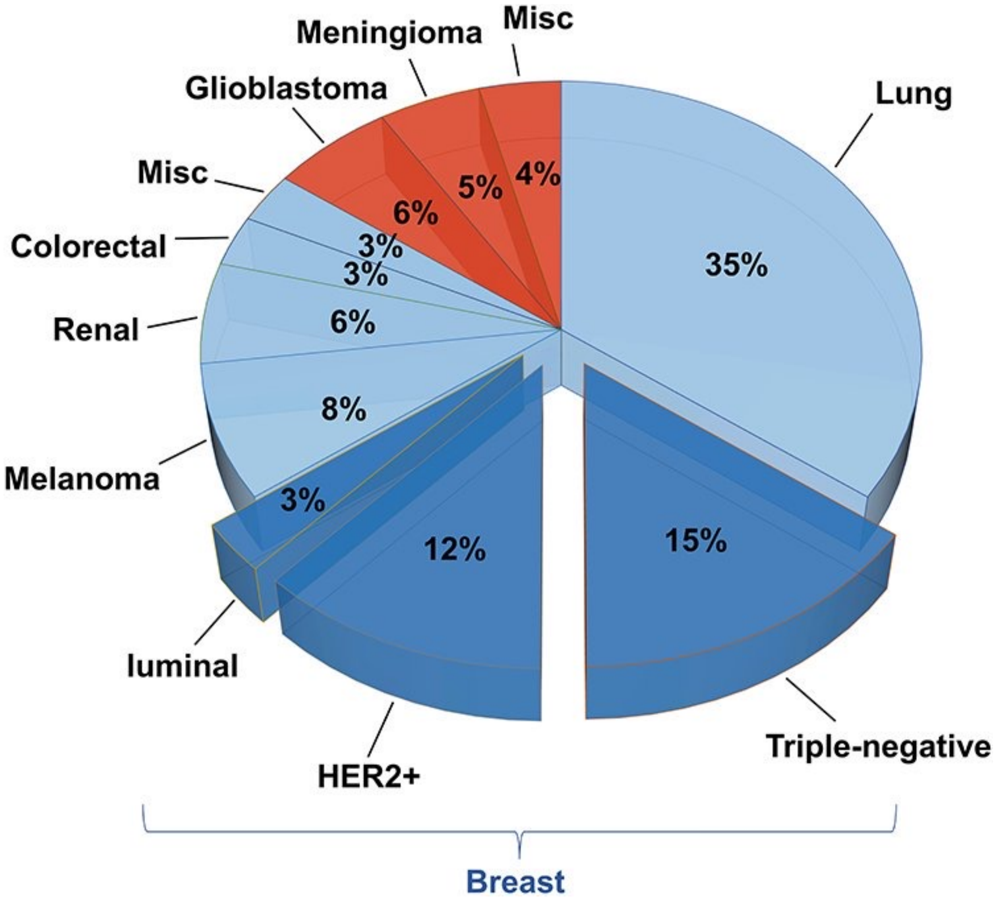

Lv et al., 2021

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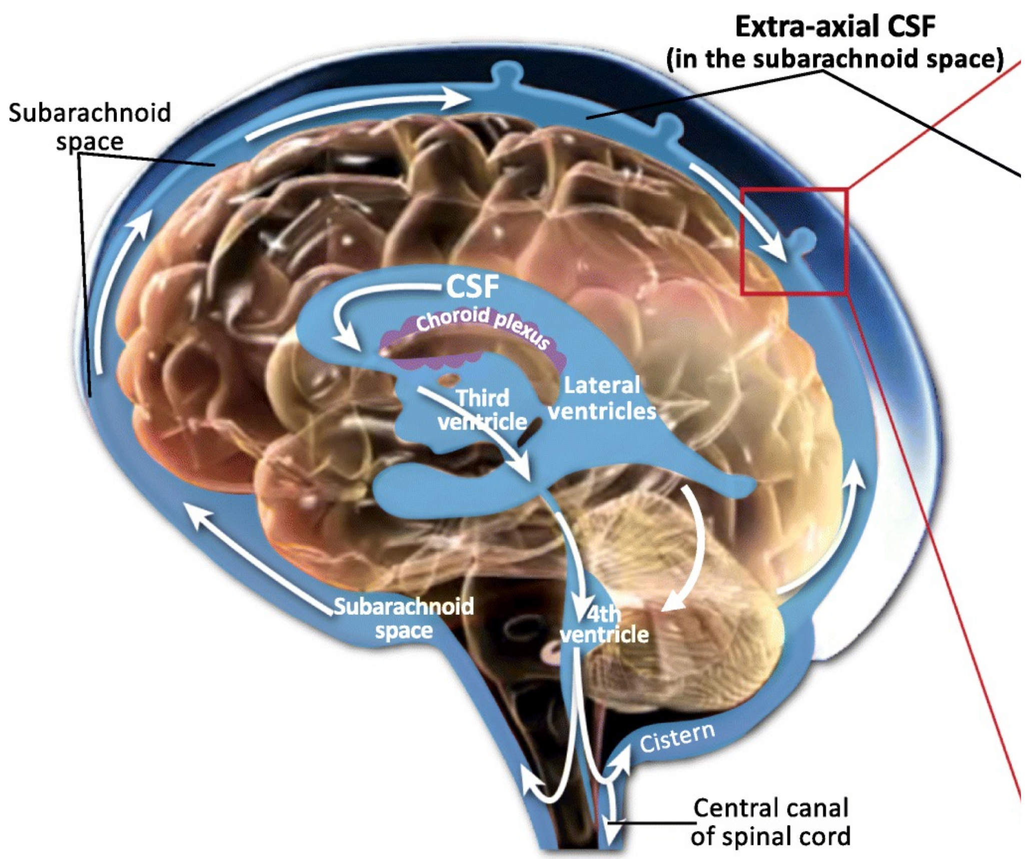
We can‘t reach the tumor directly, but...



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What can we do with CSF?

1. Cytology (stain, identify & count cells)
2. Proteomics
3. Metabolomics
4. Cell-free DNA analysis

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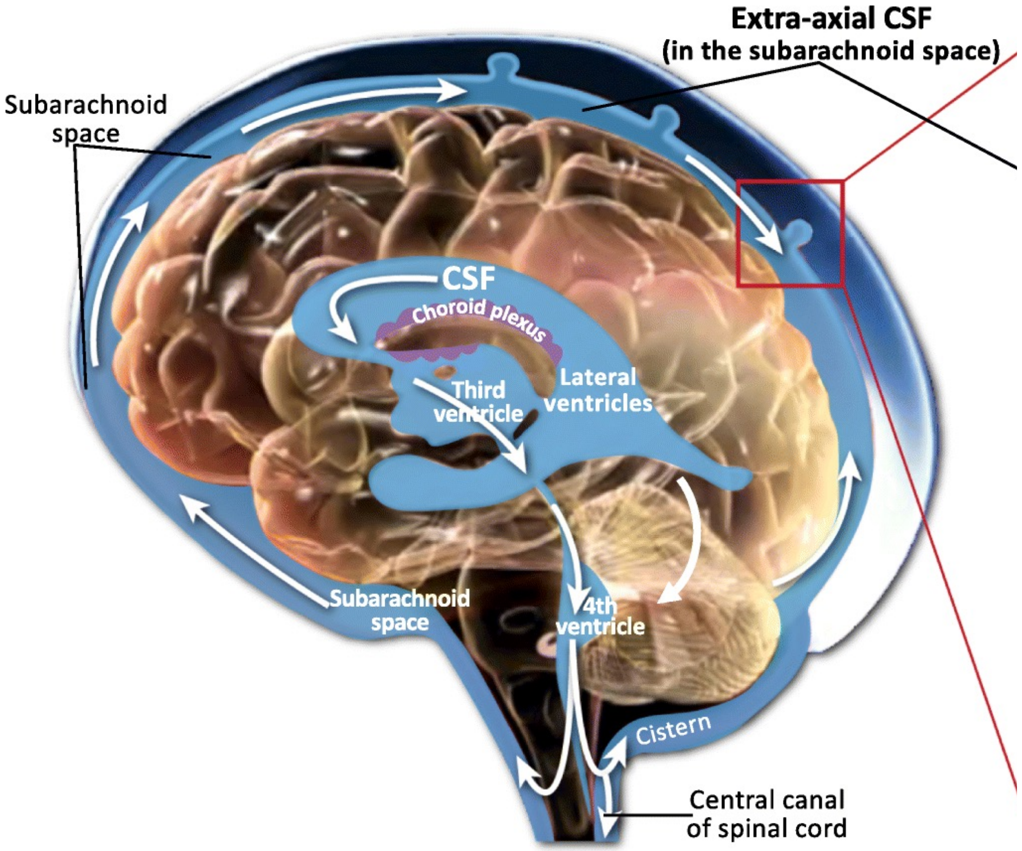

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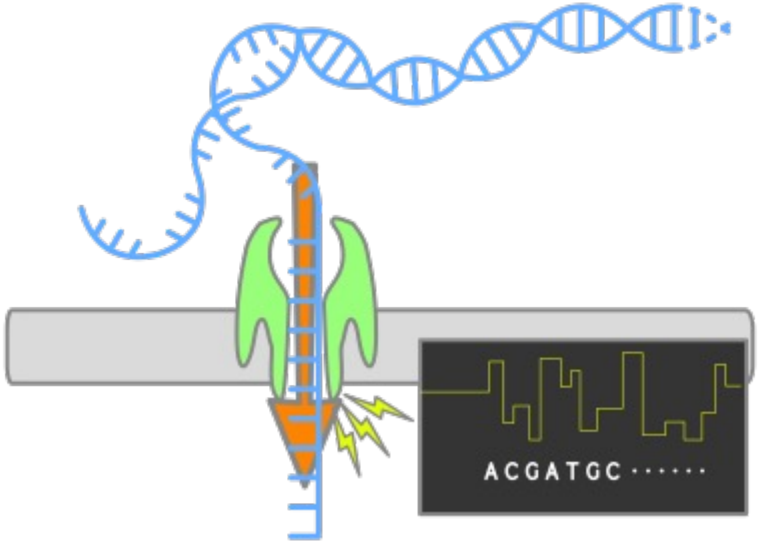

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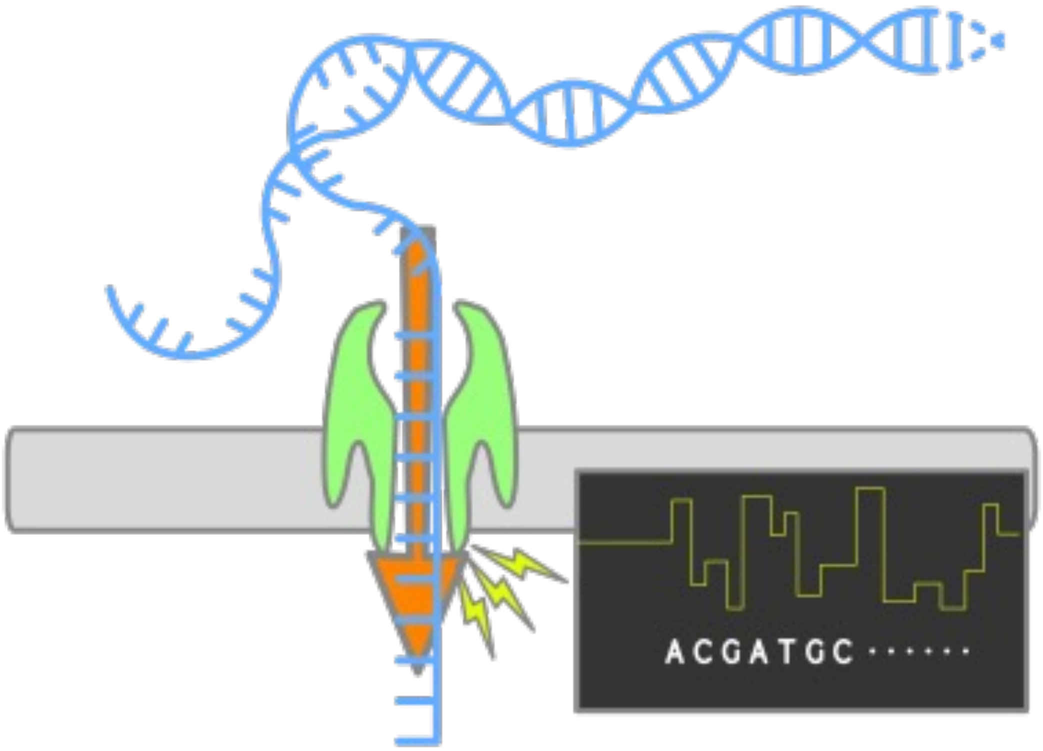
Nanopore sequencing

- Very fast (initial results within minutes)
- Read length can be hundreds of kb
- Produces reads sequentially
- Not very accurate
- Can detect DNA modifications



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Nanopore sequencing

- Very fast (initial results within minutes)
- Read length can be hundreds of kb
- Produces reads sequentially
- Not very accurate
- Can detect DNA modifications

Good:

- We can process while we sequence
- We can stop sequencing once we have enough data
- Read length means we can distinguish cellular/cell-free DNA

Bad:

- Few training data (but we can use microarrays)
- Very shallow coverage
- Mutation calling is hard

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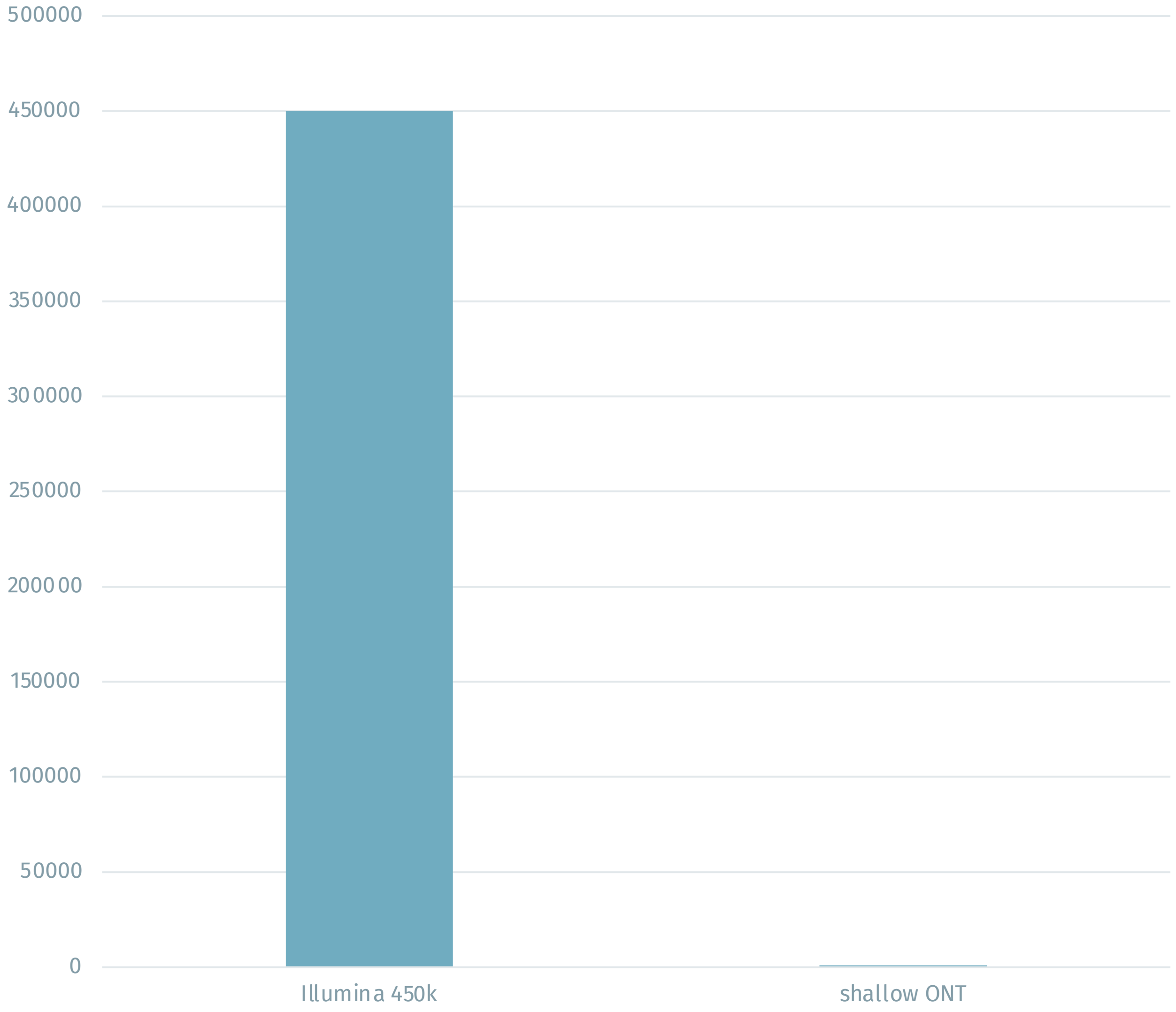
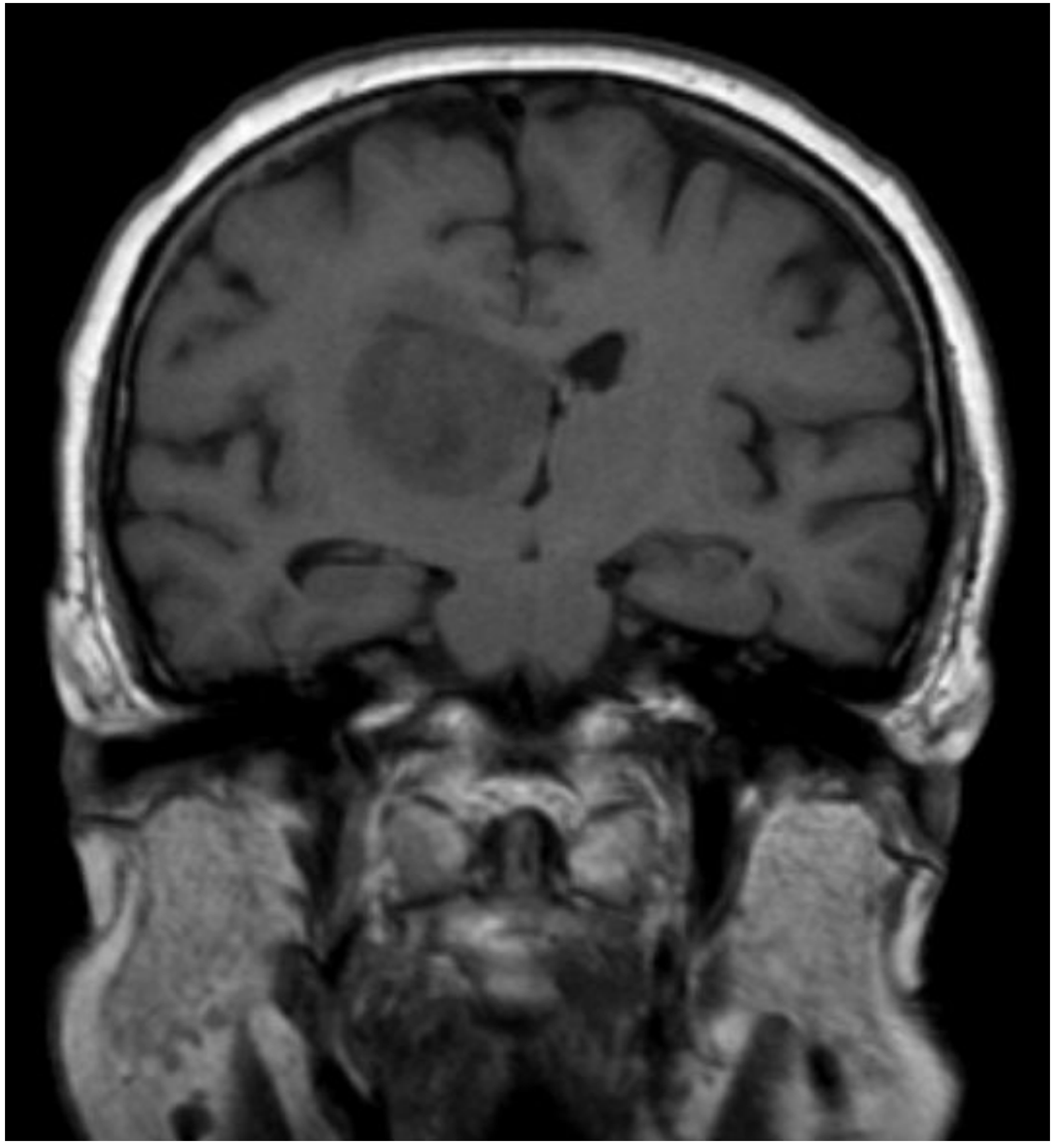
So what‘s shallow?



- Of the 450,000 sites in our microarray training data, as little as 1,000 are covered

So what‘s shallow?



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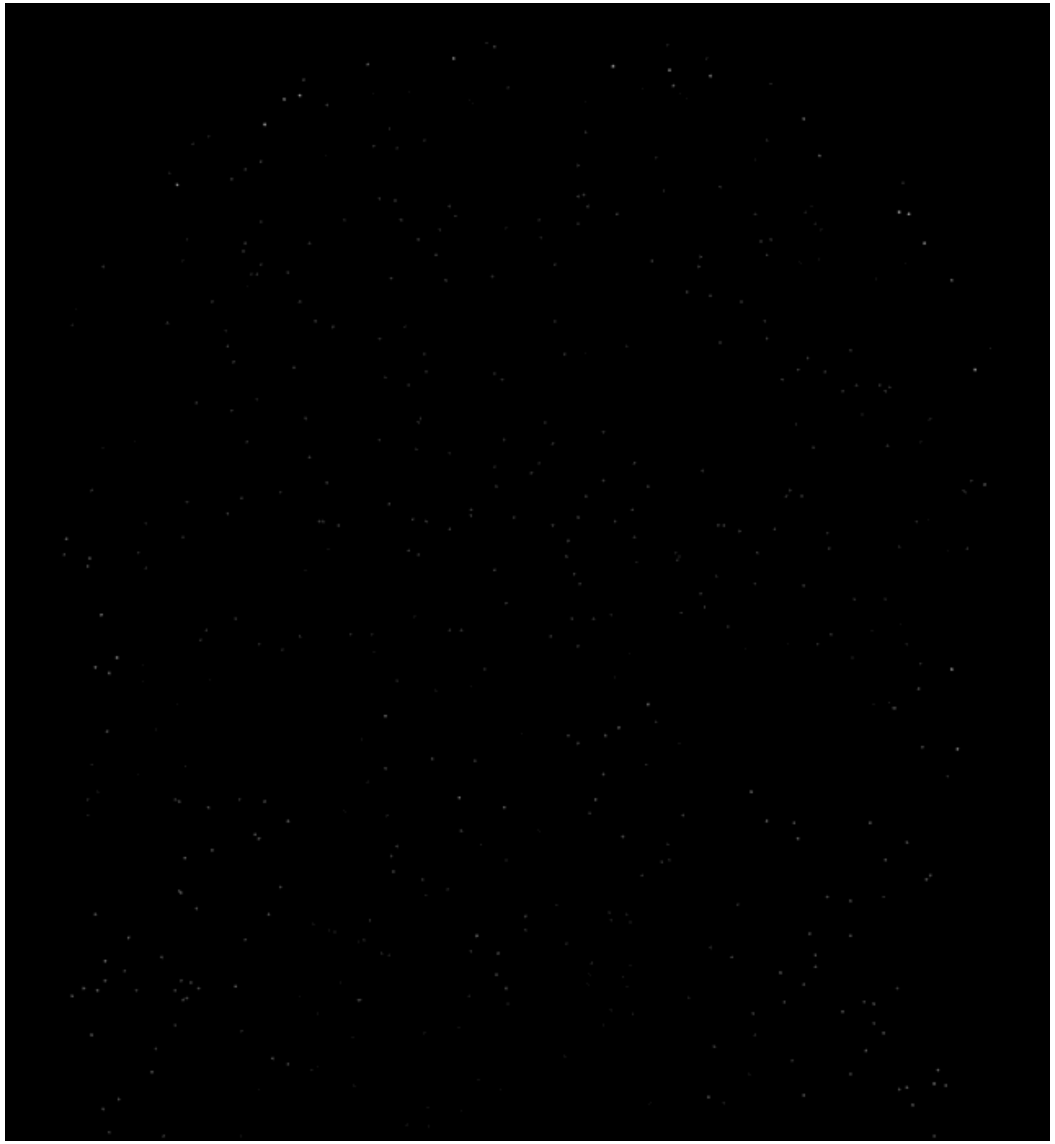

- Of the 450,000 sites in our microarray training data, as little as 1,000 are covered

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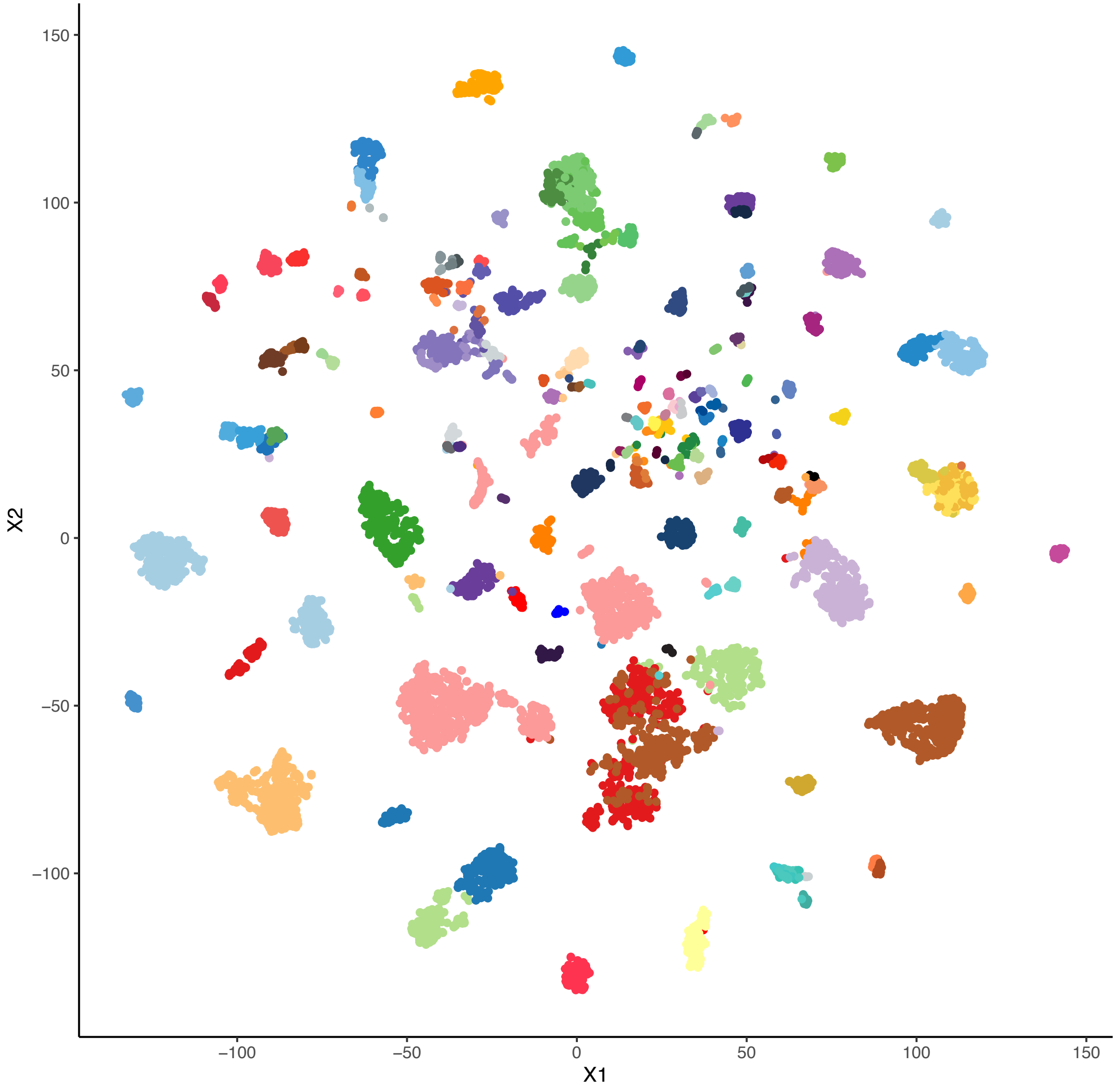
Main problems with our project

t−SNE, perplexity = 30



- Predictor missingness
- Relatively few training samples (~8000)
- n << p
- Many classes (~180)
- Severe class imbalance

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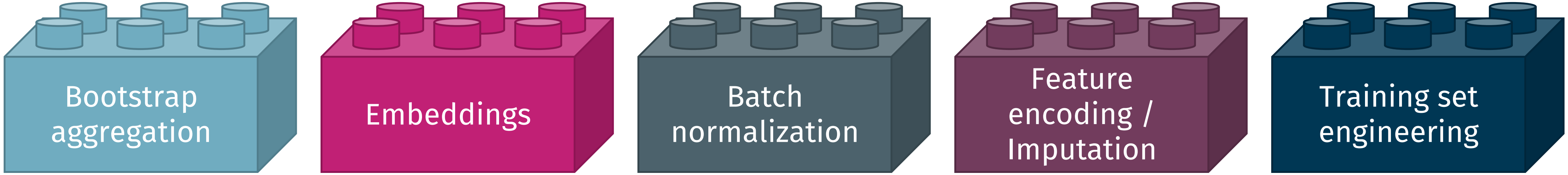
Building blocks for n << p; predictor missingness



Bootstrap aggregation

To prevent overfitting

Embeddings

Reduces number of predictors

Ideally helps to minimize differences between predictor sets

Batch normalization

Keeps activations in deep neural networks constant when input activation varies

Feature encoding / Imputation

What to do with missing values? Mean? 0.5?

Could make predictor missingness informative

Training set engineering

Reduction of training set features to observed features

Needs repeated training

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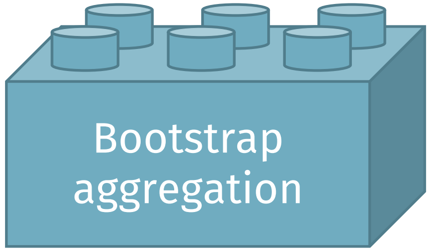
Our journey through algorithms, part I: baseline



- Random forest: ~ 85% accuracy on tissue samples

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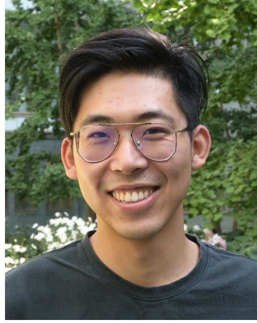
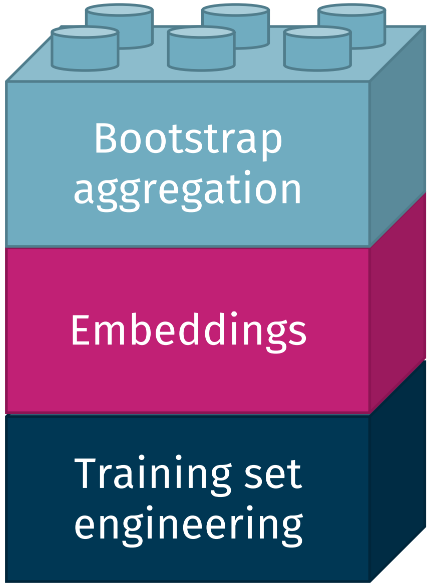
Our journey through algorithms, part II: multi-step



Dongsheng Yuan



- Multi-step model
- Only uses CpGs from the sample to be classified
- Joint embedding of sample and training set; selection of most similar classes

  → retraining for every sample
- Second step: random forest classifier

➔ Accuracy on tissue samples: > 90% (Top1)

➔ with < 1000 CpGs: > 60%

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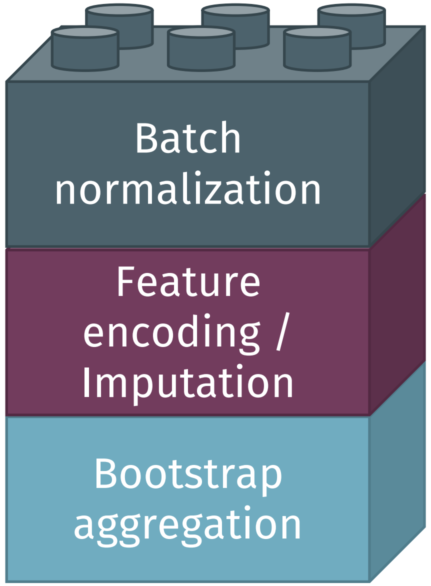
Our journey through algorithms, part III: train once



- Multilayer Perceptron
- Full training set with random feature selection each epoch
- Data encoded as: methylated(1)/unmethylated(-1)/missing(0)

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Short reminder: neural networks and encoding

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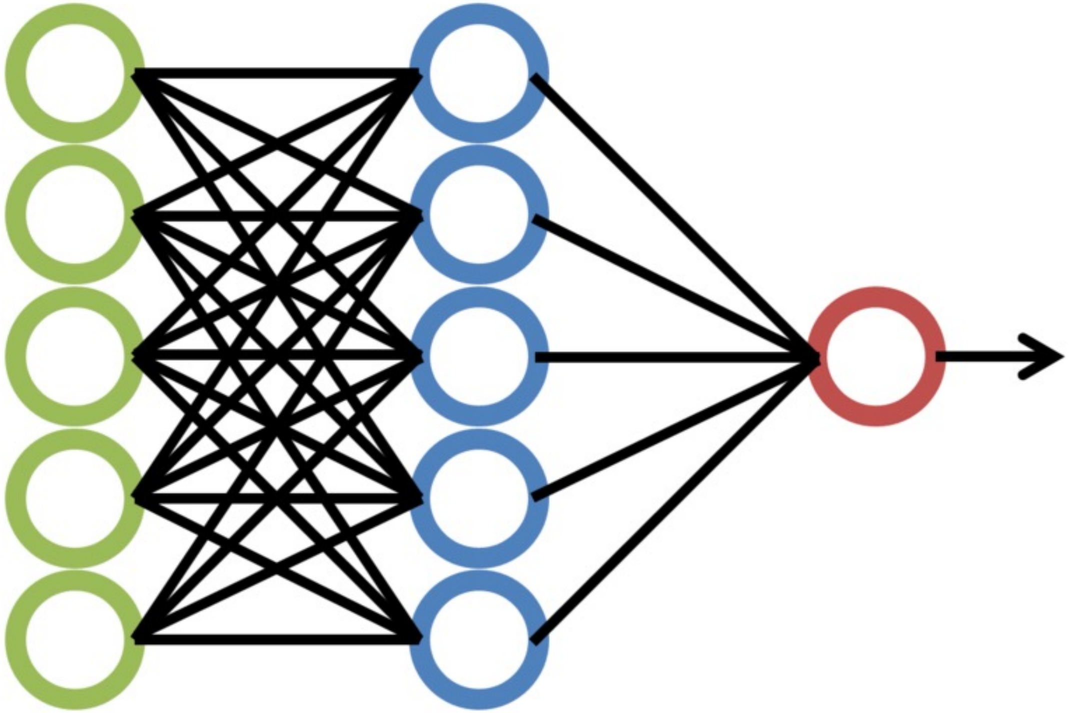
$$y = mx + n$$



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Short reminder: neural networks and encoding

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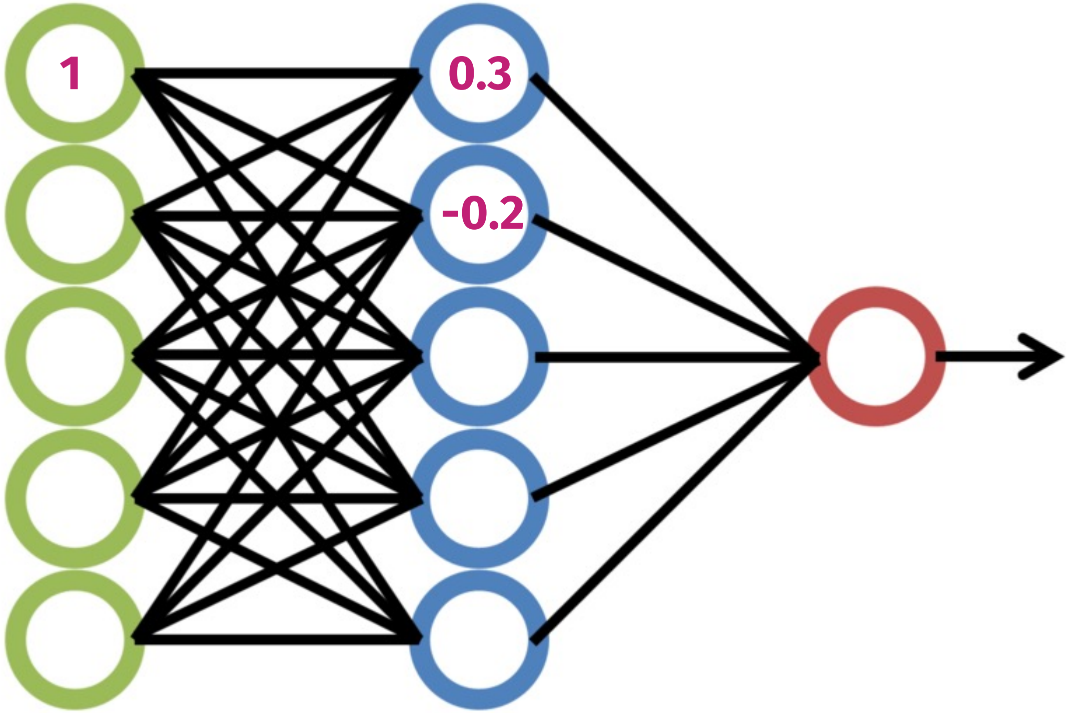
$$y = m * 1 + 0 = m$$



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Short reminder: neural networks and encoding

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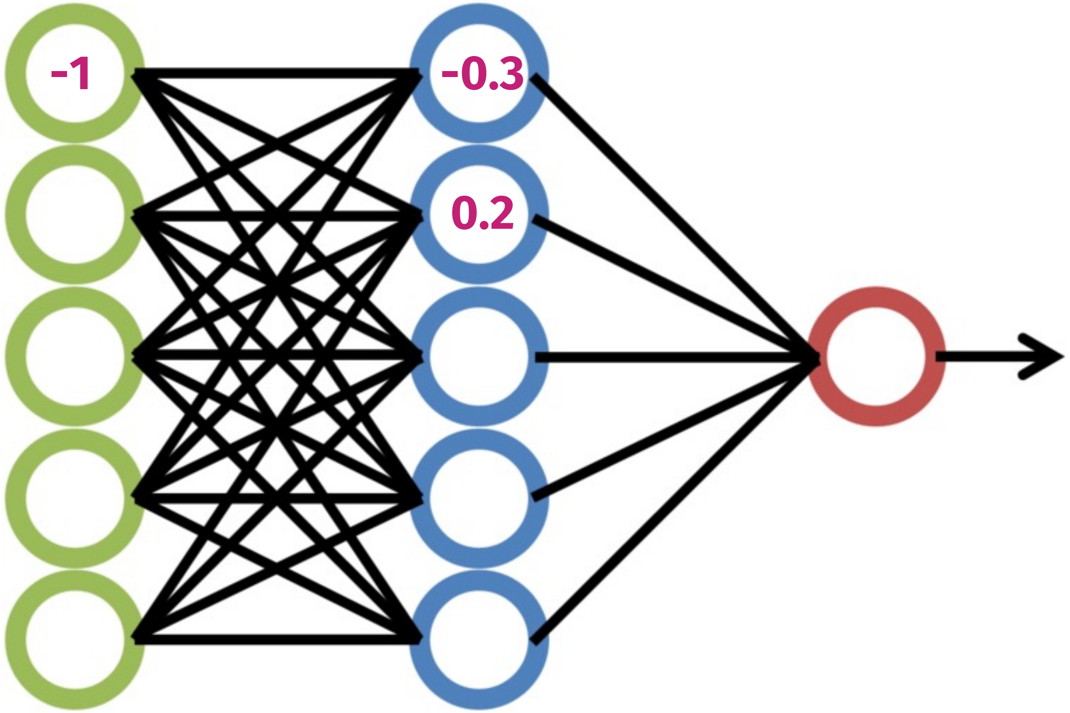
$$y = m * -1 + 0 = -m$$



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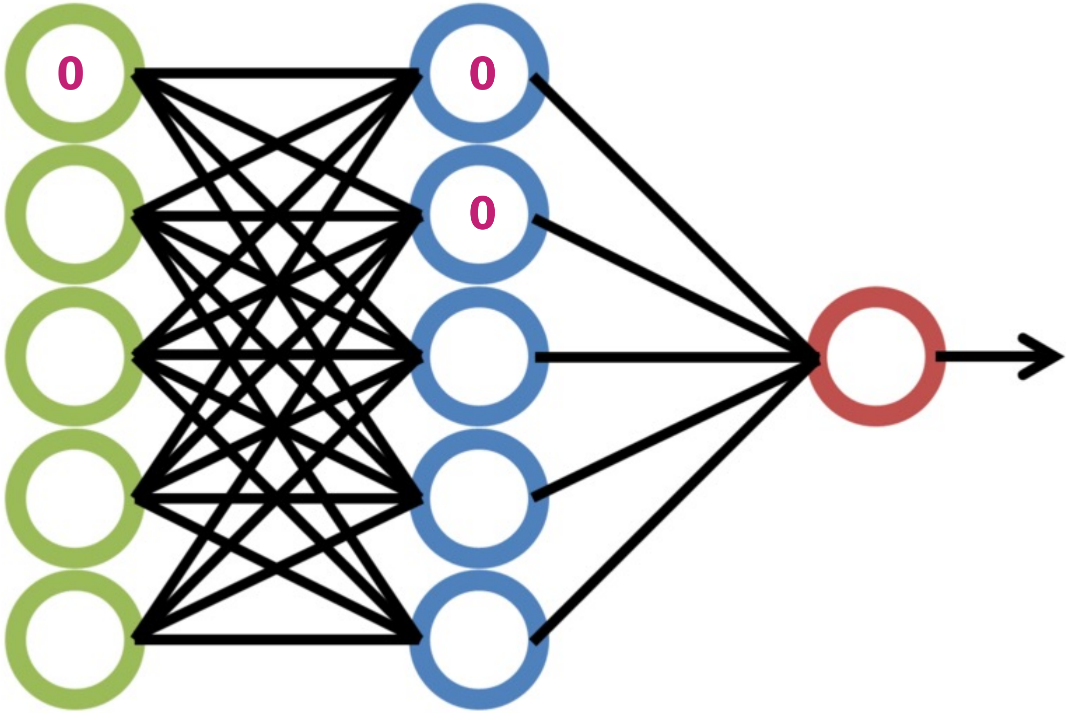

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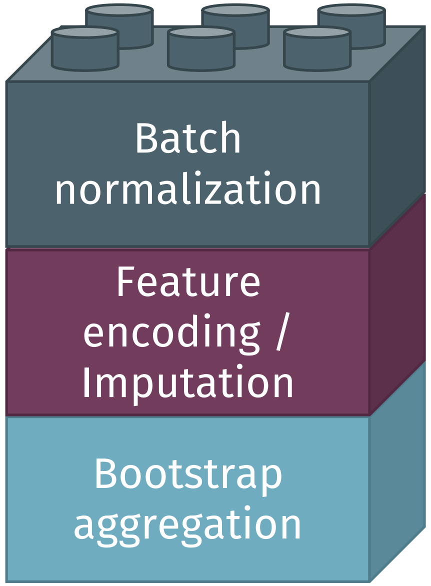
Our journey through algorithms, part III: train once



- Multilayer Perceptron
- Full training set with random feature selection each epoch
- Data encoded as: methylated(1)/unmethylated(-1)/missing(0)
- Batch normalization to harmonize weights with different predictor numbers

➔ Accuracy in tissue with >99% missing CpGs: > 80% (Top1)

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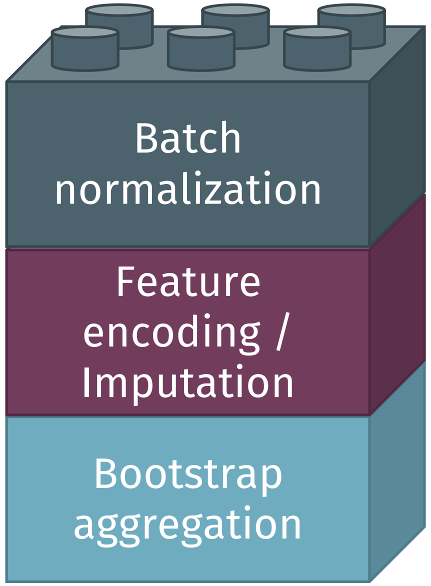
Our journey through algorithms, part IV: the KISS principle



- Once initial results are in, hyperparameters should be tuned
- In our case, the network kept suggesting fewer layers
- And fewer layers...
- And fewer layers...

➔ Our newest model: linear regression...

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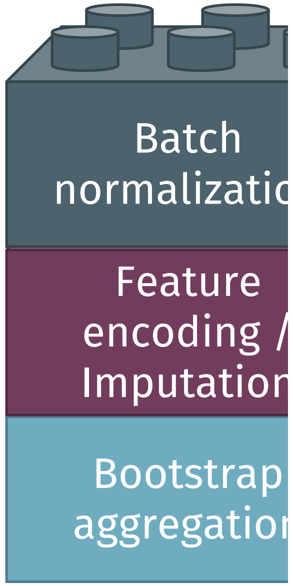
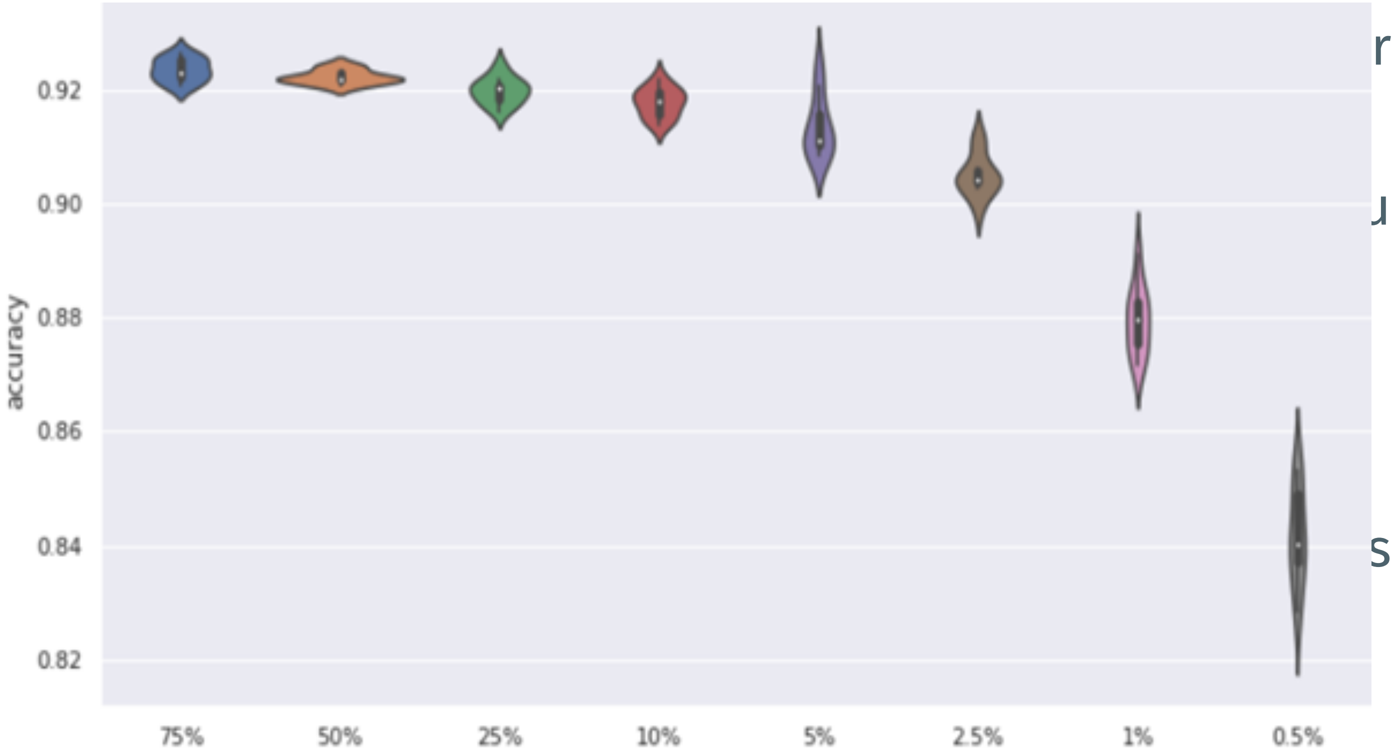
Our journey through algorithms, part IV: the KISS principle



Batch normalizatio

Feature encoding / Imputation

Bootstrap aggregatio



rparameters

uggesting fewer

ssion...

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What went wrong?

1. When we took over the project from collaborators, they were already using RFs
2. We tried to improve the solution, rather than working from the ground up
3. Either way, we probably wouldn‘t have tried linear regression – the problem looked too complicated

Beware the deep learning trap: If there‘s an easy solution, complex machine learning models will often give you reasonably good results. Starting with complex models can leave you stuck with overcomplicated pipelines.

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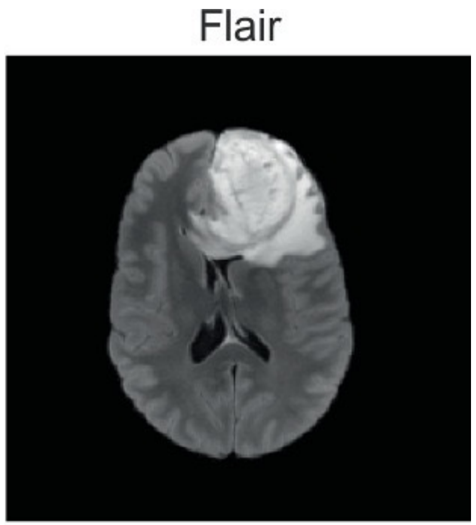
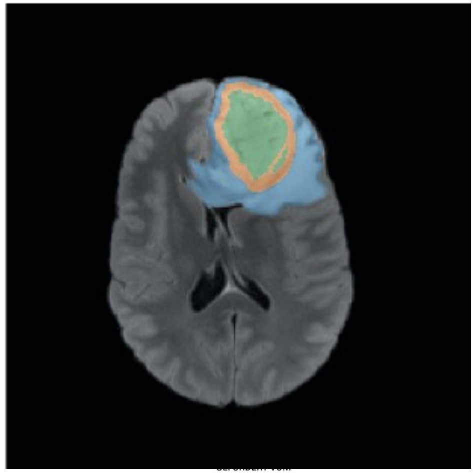
Remaining issues: liquid biopsies

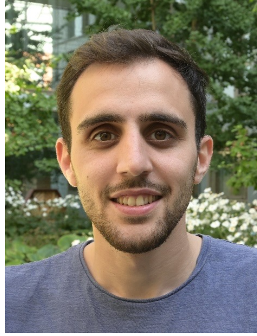
- Liquid biopsies generally contain less tumor DNA than solid tumor biopsies
- The proportion is dependent on size, proliferation, and apoptosis of the tumor

➔ Tuning the sensitivity of the tumor based on imaging

… if we manage to get access to enough samples for which we have both






Nabil Jabareen

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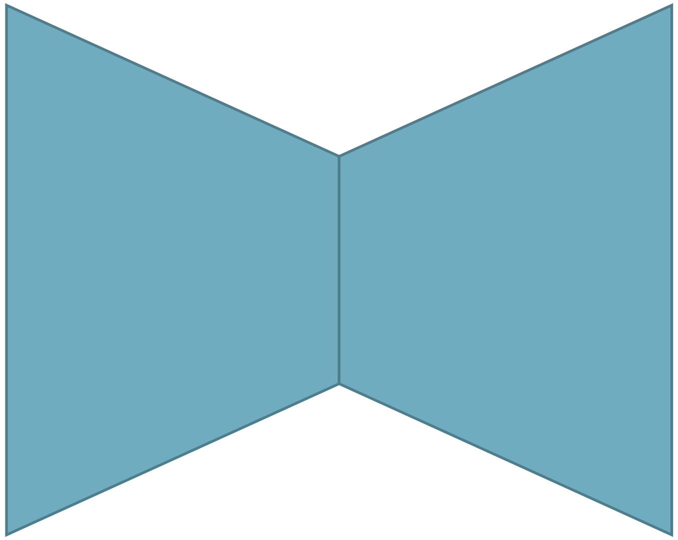
Translating multi-modal data

Foo Wei Ten

Autoencoder



encoder

decoder

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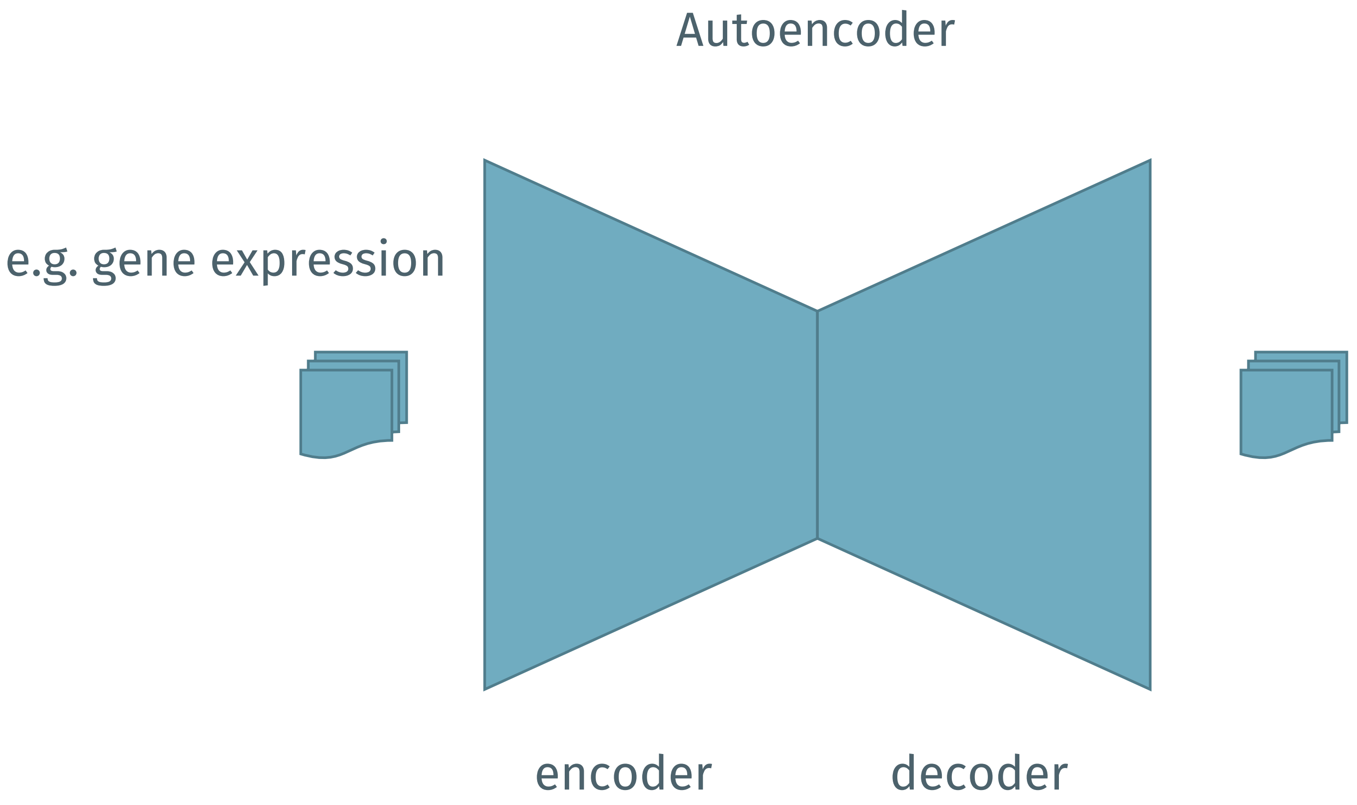

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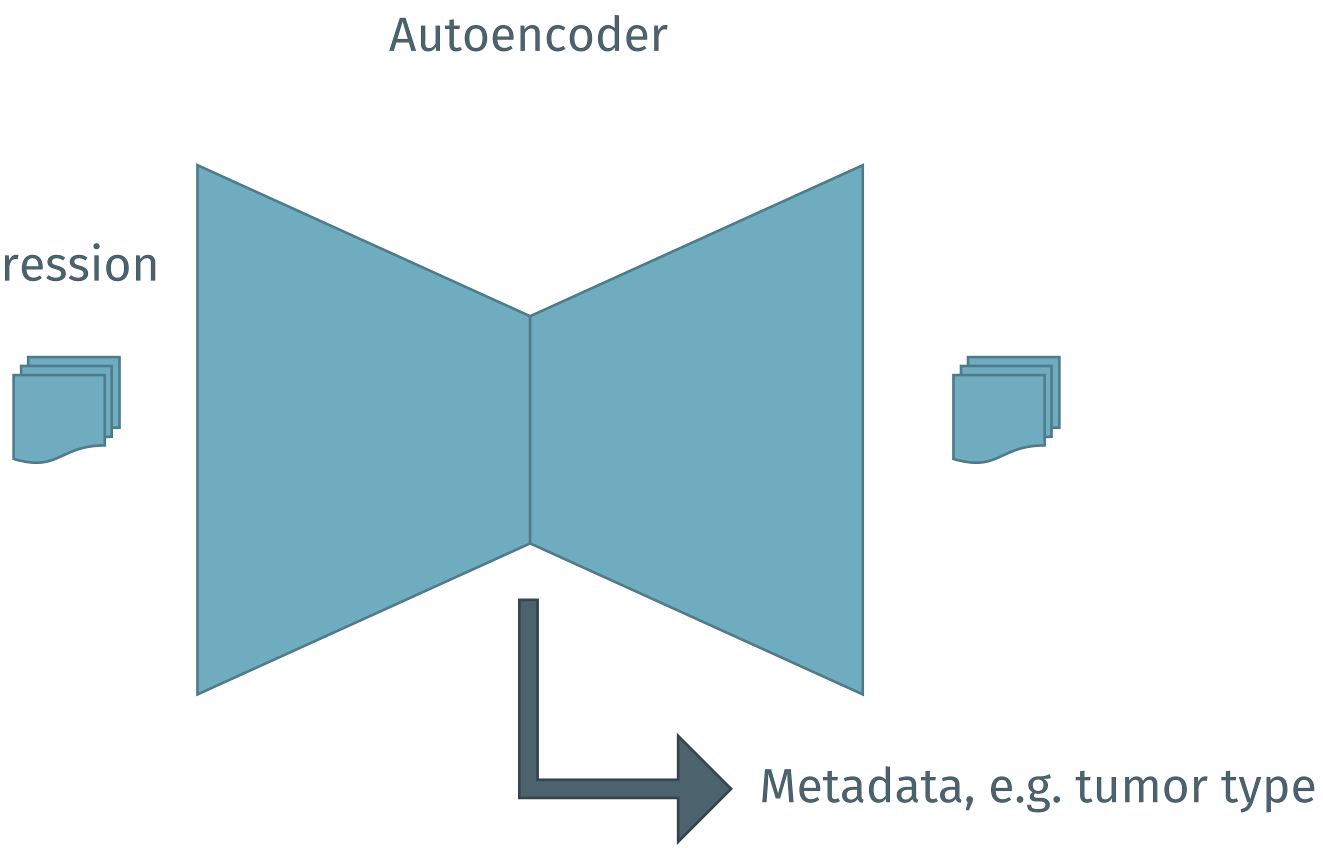

Autoencoder

e.g. gene expression

Metadata, e.g. tumor type

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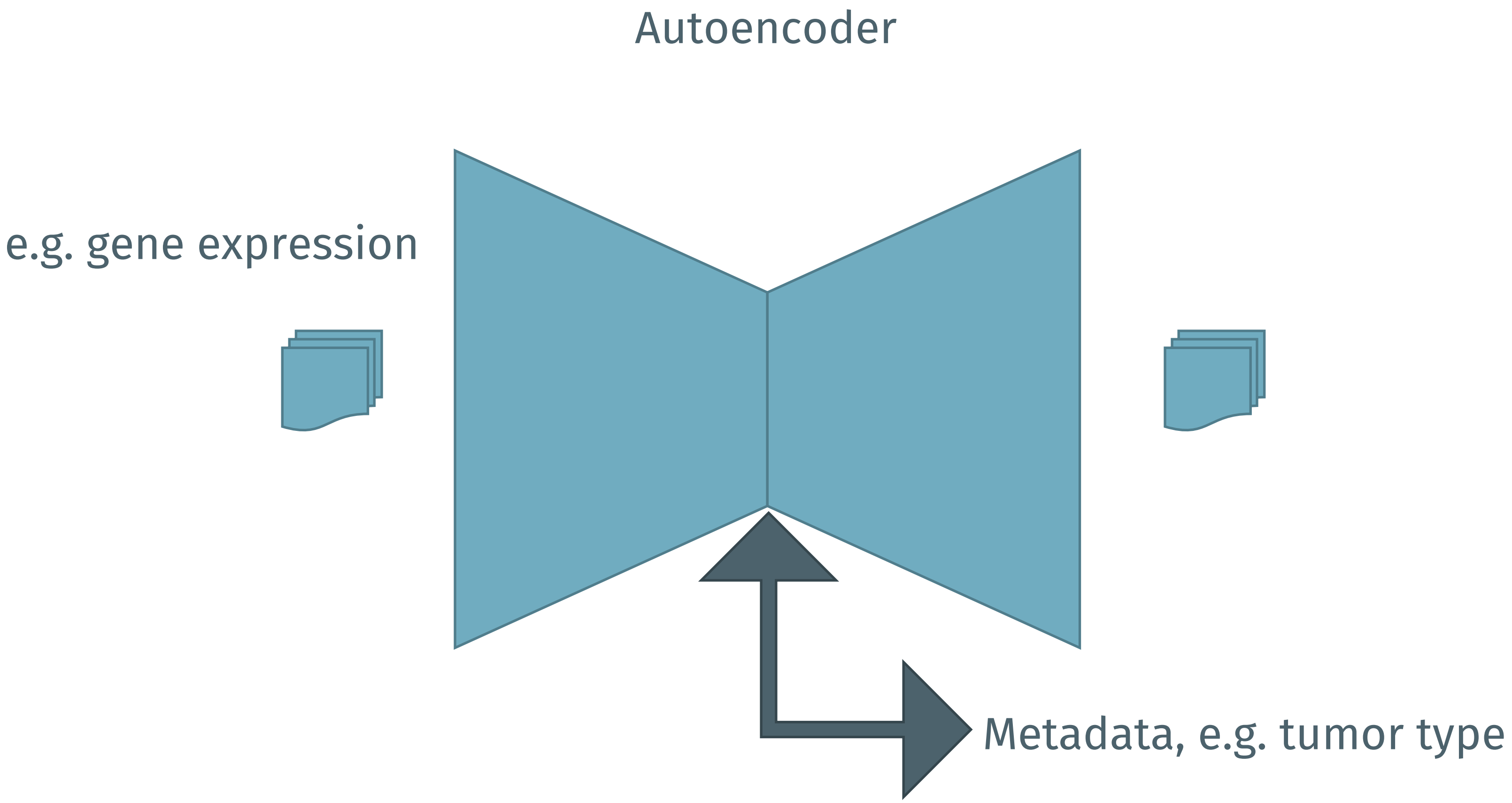

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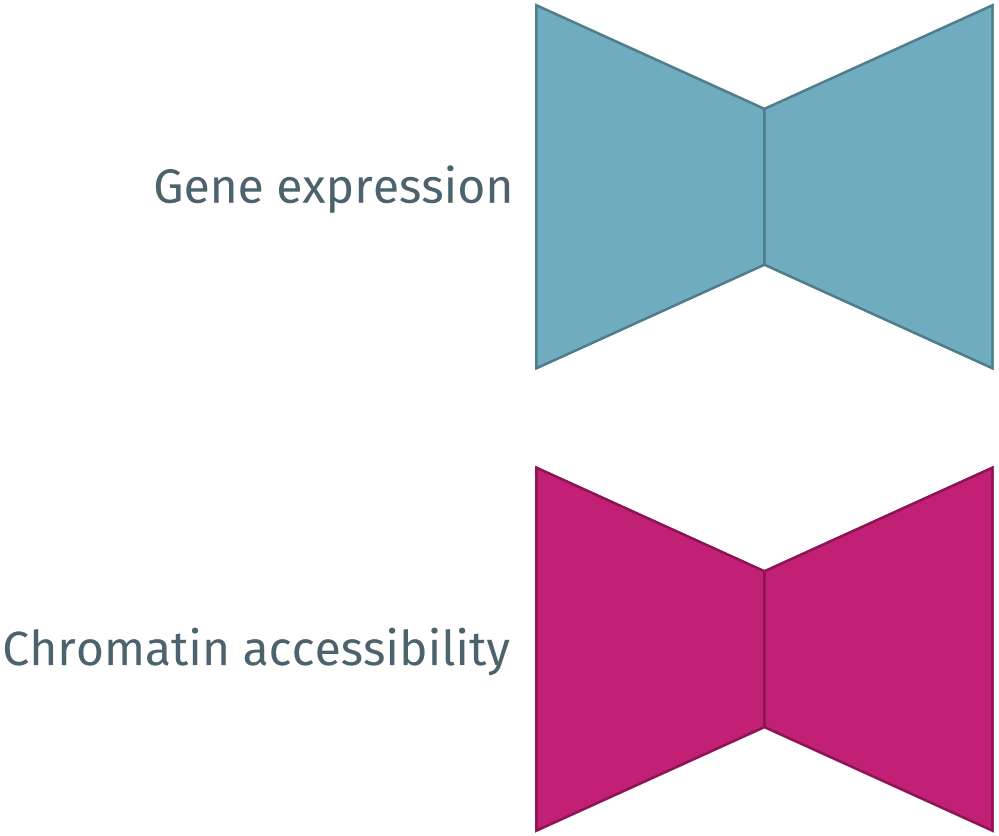
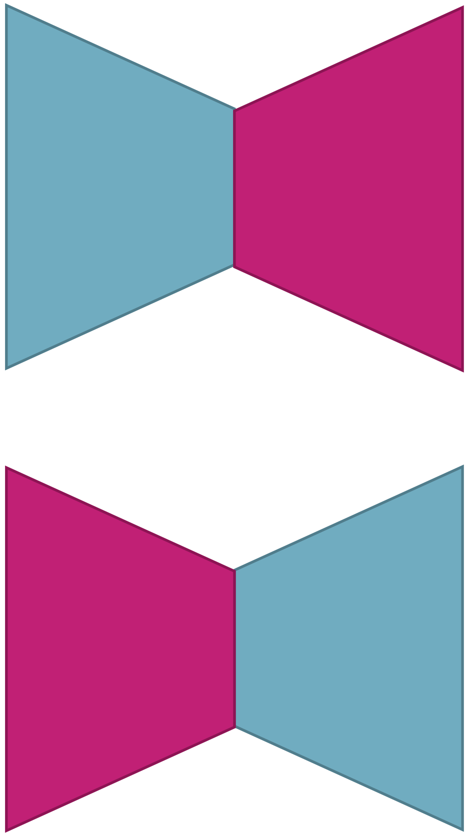


➔ Similar to a multi-layered non-linear consensus NMF

➔ Can be used similarly: decoder layers capture compentents, e.g. gene sets

Translating multi-modal data



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Summary

1. Low amounts of training data and high missingness don‘t necessarily doom a ML project
   - If redundancy is high (DNA methylation) or there is a constant structure (medical imaging)
2. Start simple*
3. Real-world data are noisy, incomplete, and hard to get → if possible, try to use methods where samples don‘t have to match
4. When planning a ML project, ~80% of the time is used for data curation even if the data exist already

* Starting complex can give you an idea whether there is something in the data

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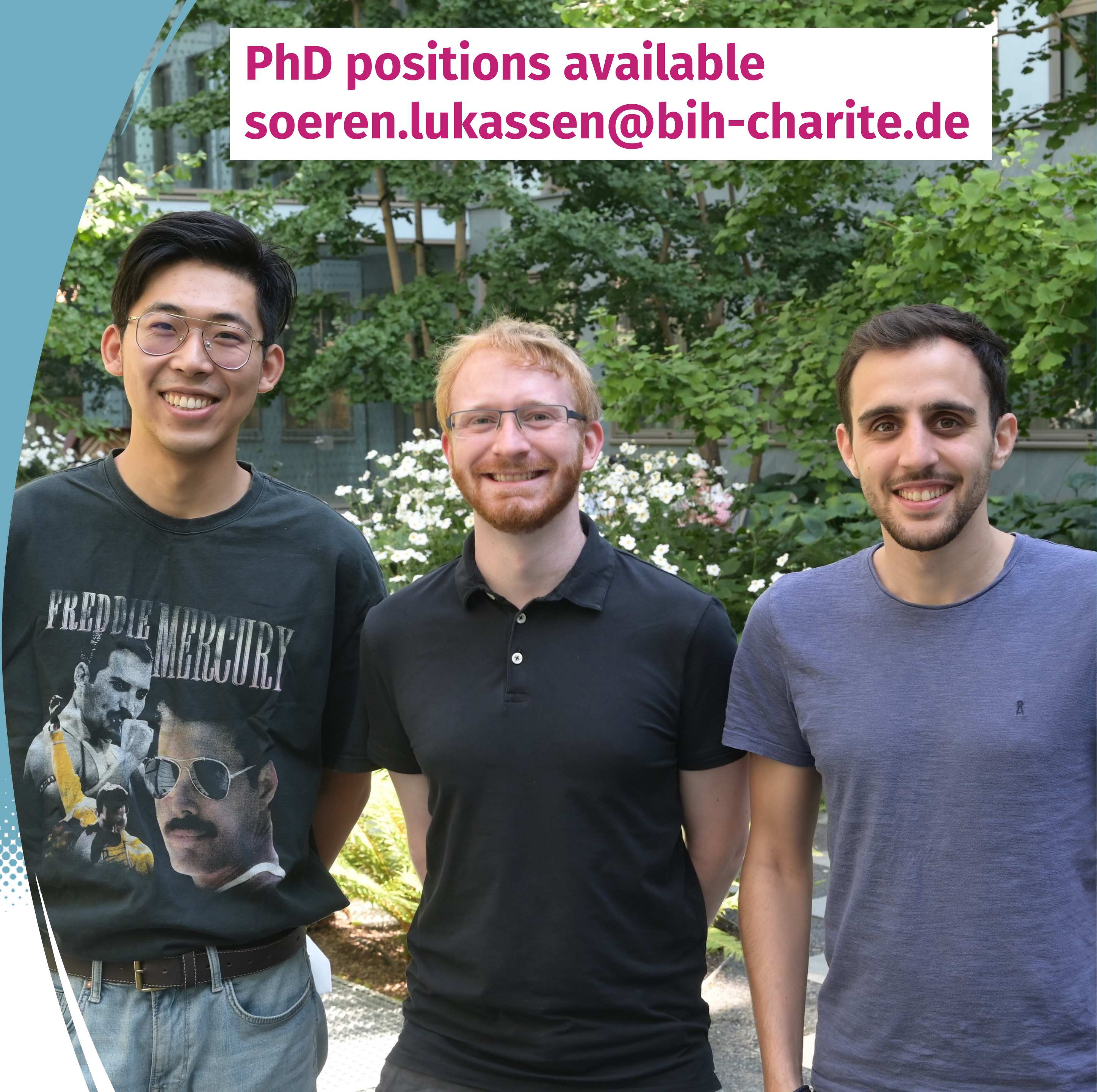

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Ismini Papageorgiou

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