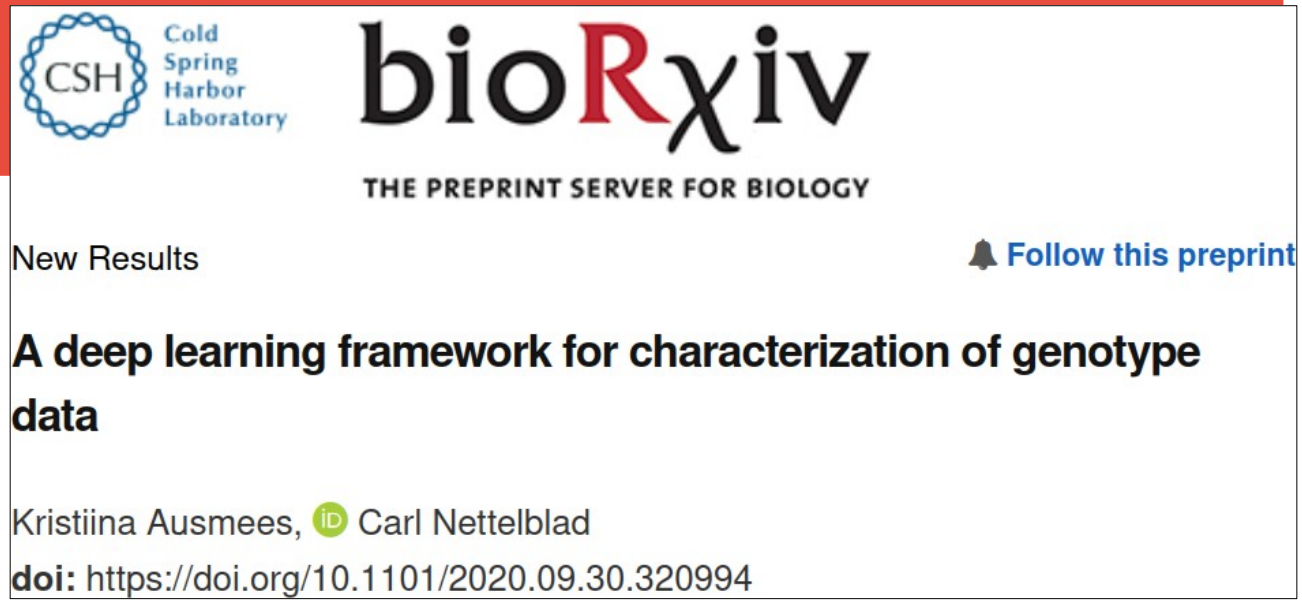
Journal Club



https://github.com/richelbilderbeek/journal_club_20220120

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Why this article

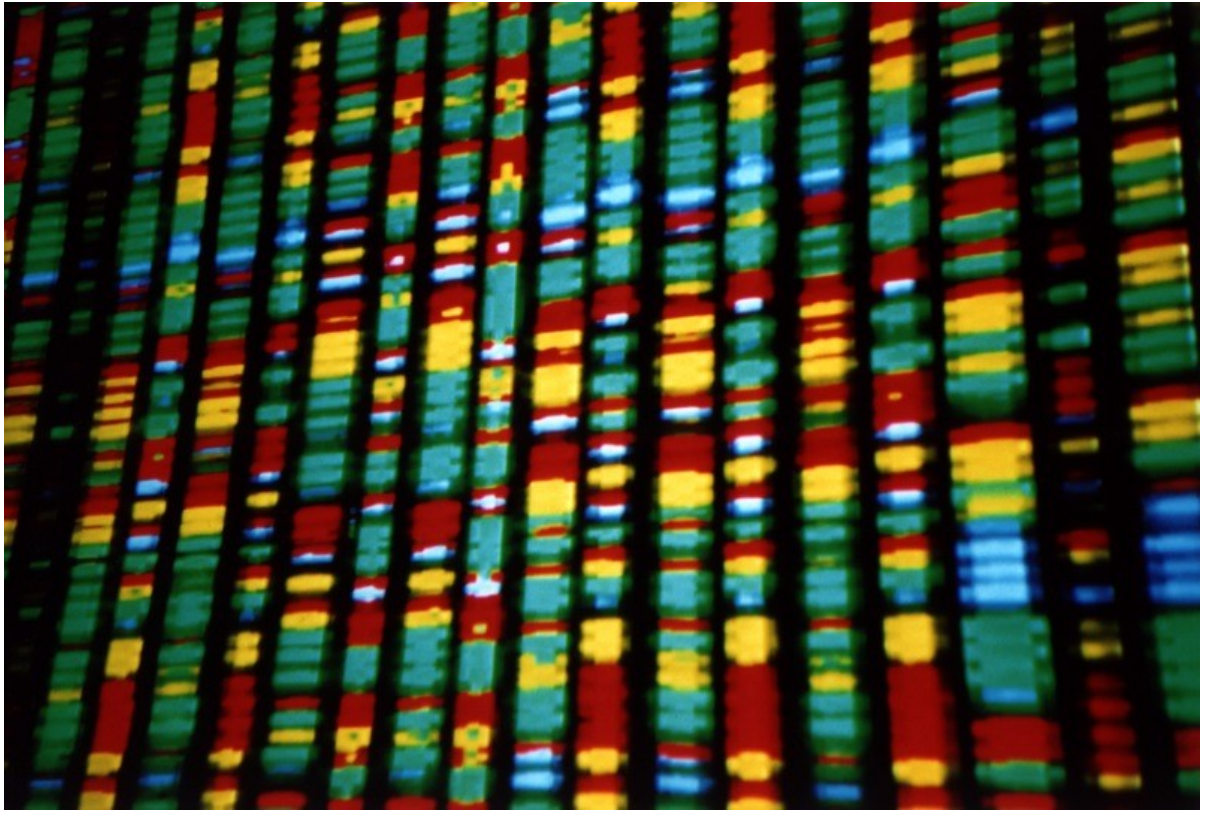
Google ‘GWAS + “machine learning”’ for 2021

Start of collaboration

Carl Nettelblad

Kristiina Ausmees

Background



Can we order genomes?

- Similar genomes close

Because then we can …

- See amount of genetic variation
- Identify population structure
- Do ancestry mapping
- Simulate genotypes

https://upload.wikimedia.org/wikipedia/commons/b/bc/DNA_representation.jpg

It is easy to order genomes

A A A A

(1, 1, 1, 1, ...)

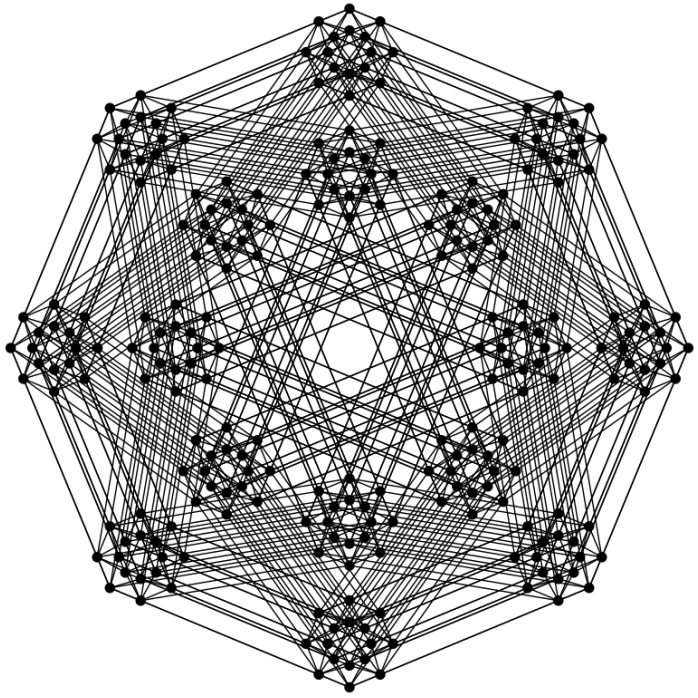
A A A T

(1, 1, 1, 4, ...)

A C G T

(1, 2, 3, 4, ...)

3 billion base pairs



$$d(p,q) = \sqrt{(p_1 - q_1)^2 + (p_2 - q_2)^2 + \cdots + (p_i - q_i)^2 + \cdots + (p_n - q_n)^2}.$$

https://commons.wikimedia.org/wiki/File:Octeract_graph.svg

Background

https://upload.wikimedia.org/wikipedia/commons/b/bc/DNA_representation.jpg

Can we order genomes in a smart way?

Similar genomes close

Because then we can …

See amount of genetic variation

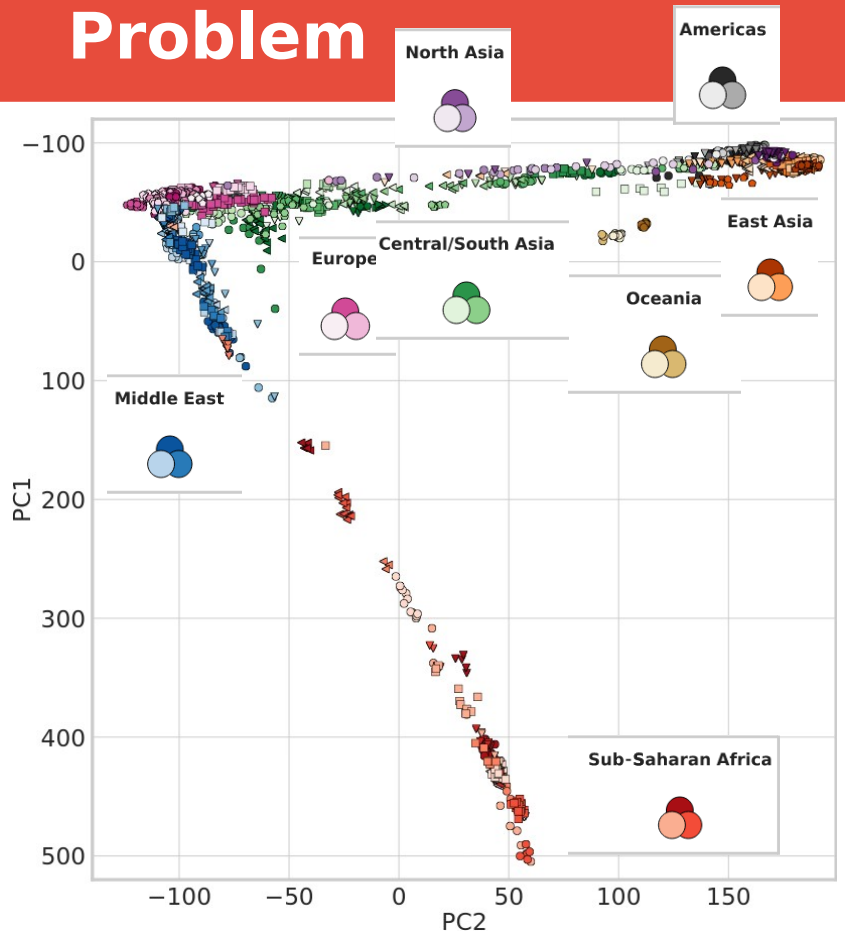
Identify population structure

Do ancestry mapping

Simulate genotypes

Dimensionality reduction

Problem



PCA reduces dimensionality linearily

Typical V shape

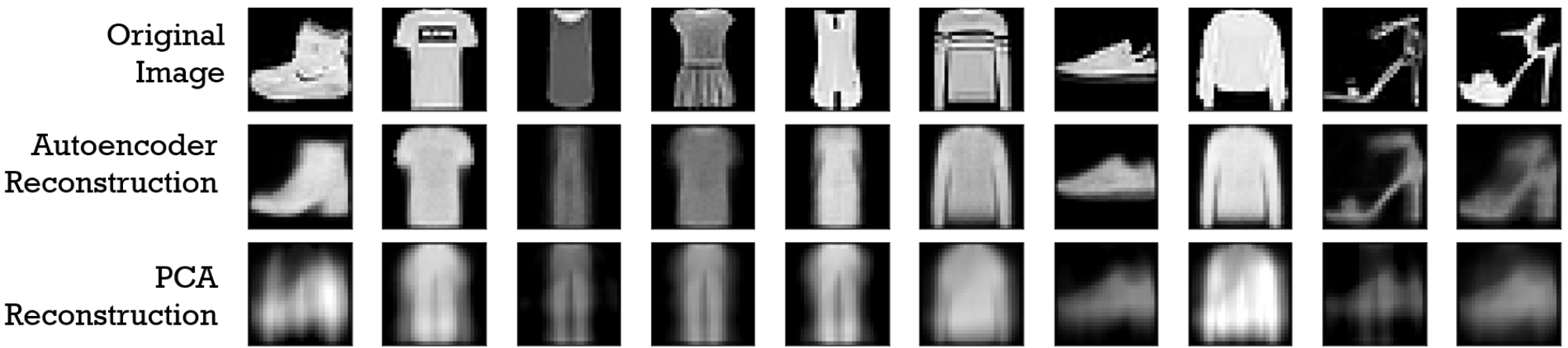
Overlap in first 2 dimensions

Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

Hypothesis

Convolutional autoencoders seem promising

Can work with noisy data as well



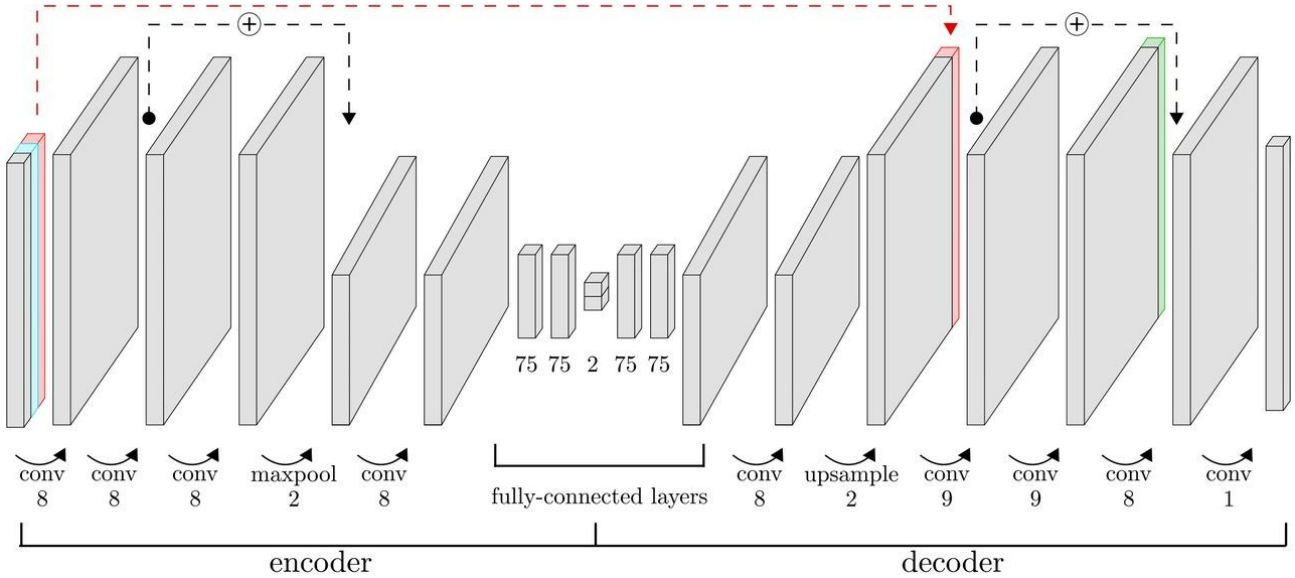
https://commons.wikimedia.org/wiki/File:Reconstruction_autoencoders_vs_PCA.png

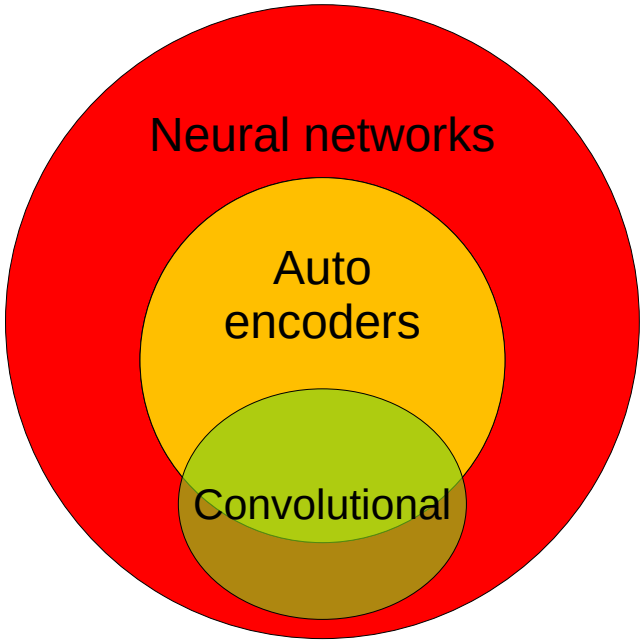
Method

Set up a convolutional autoencoder

NEW

See how well it performs



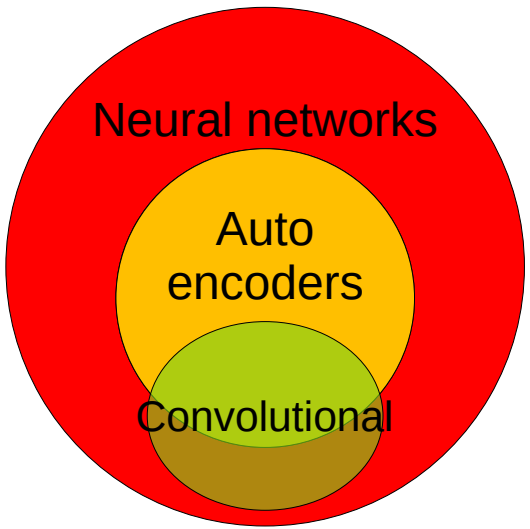


Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

What is a convolutional autoencoder?

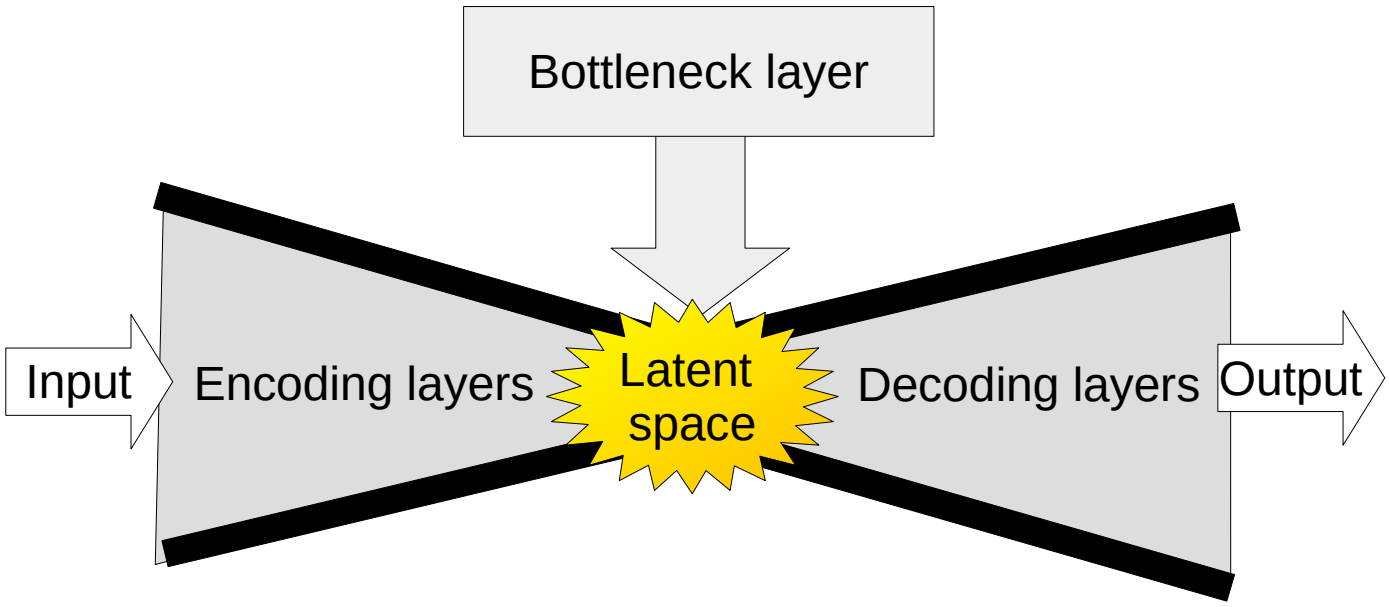
Convolutional: preprocess the data, i.e. do not only use the raw data

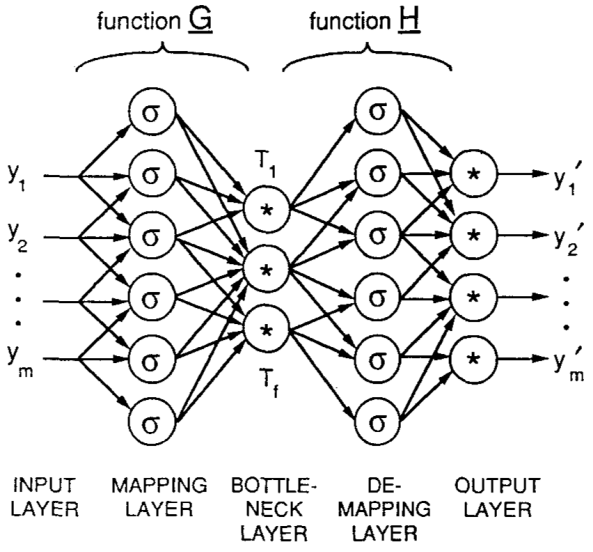
Autoencoder: type of neural network that learns how to encode data



https://github.com/richelbilderbeek/the_bochum_project

What is an autoencoder?





Goal: *learn* to represent/label data, nonlinearily

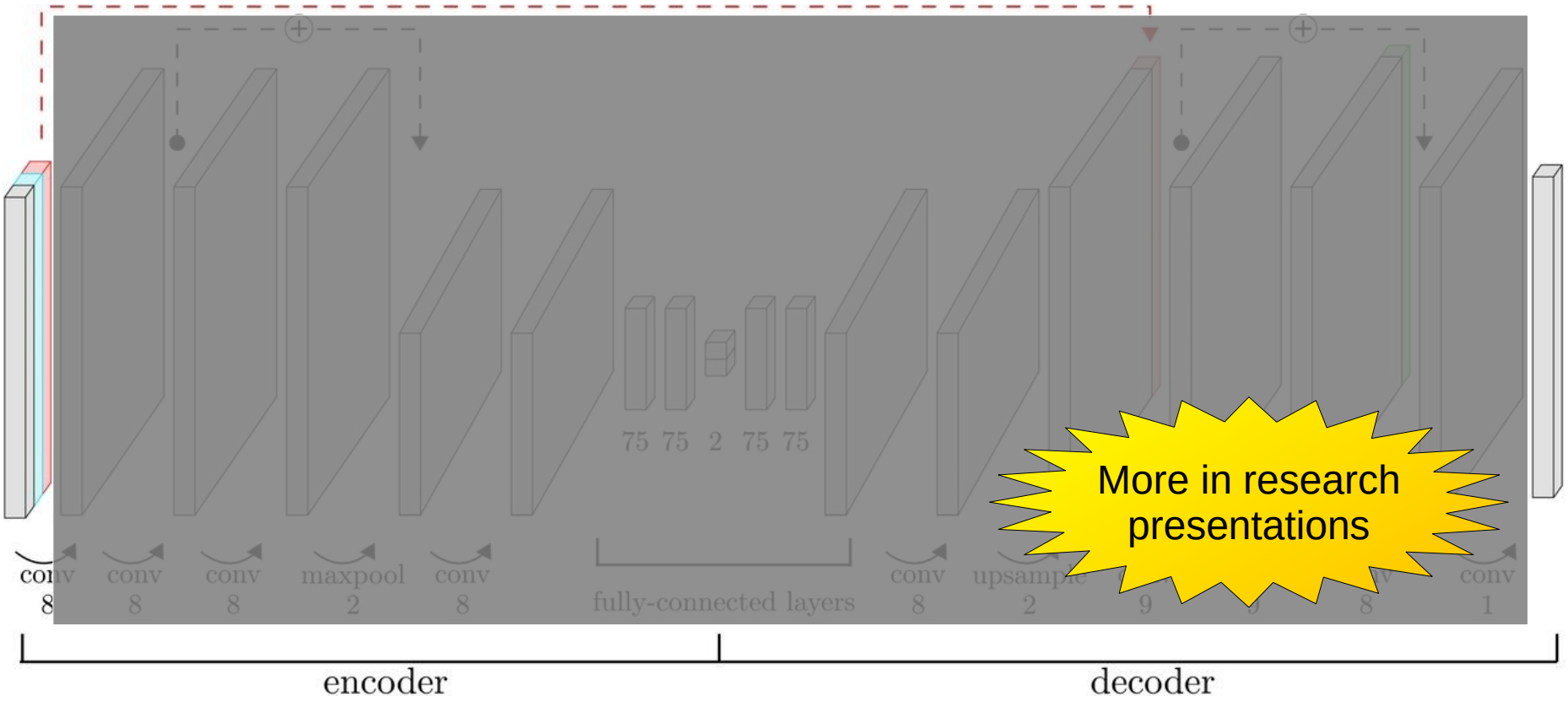
$Y = \{ y_1, y_2, \ldots \}$

$Y' = \{ y'_1, y'_2, \ldots \}$

Loss function = $E = Y - Y'$

Kramer, Mark A. "Nonlinear principal component analysis using autoassociative neural networks." AIChE journal 37.2 (1991): 233-243.

GCAE



More in research presentations

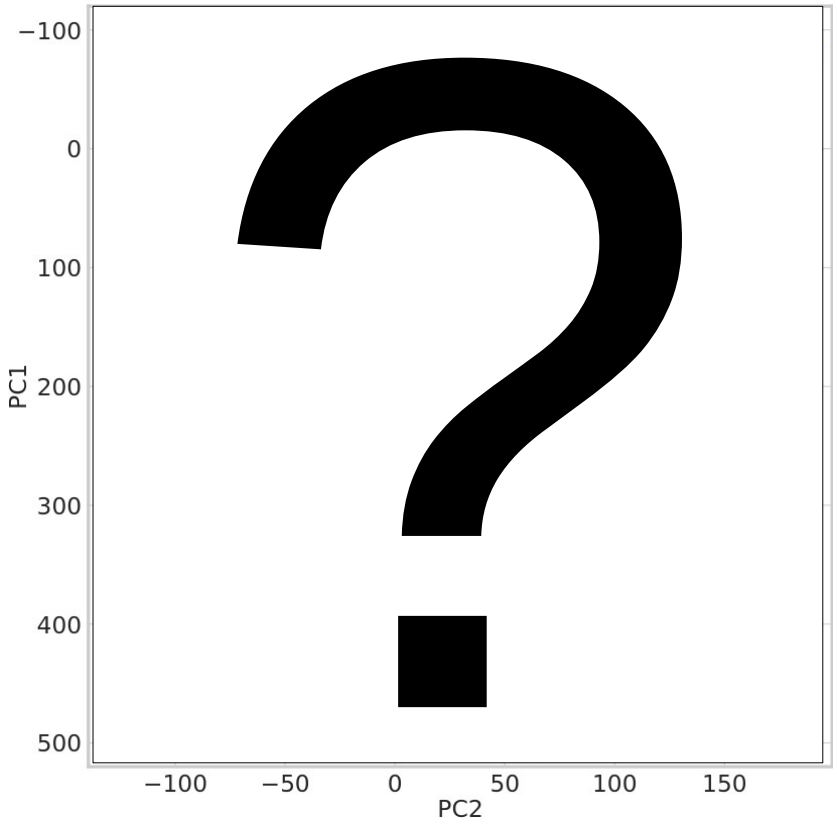
Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

Article

How well does GCAE perform?

- genotype separation
- deduce genotype origin
- rare and common alleles
- LD

Separating genotypes



Affymetrix Human Origins SNP array

2,067 unrelated humans from 166 populations

No sex chromosomes

Remove MAF < 1%

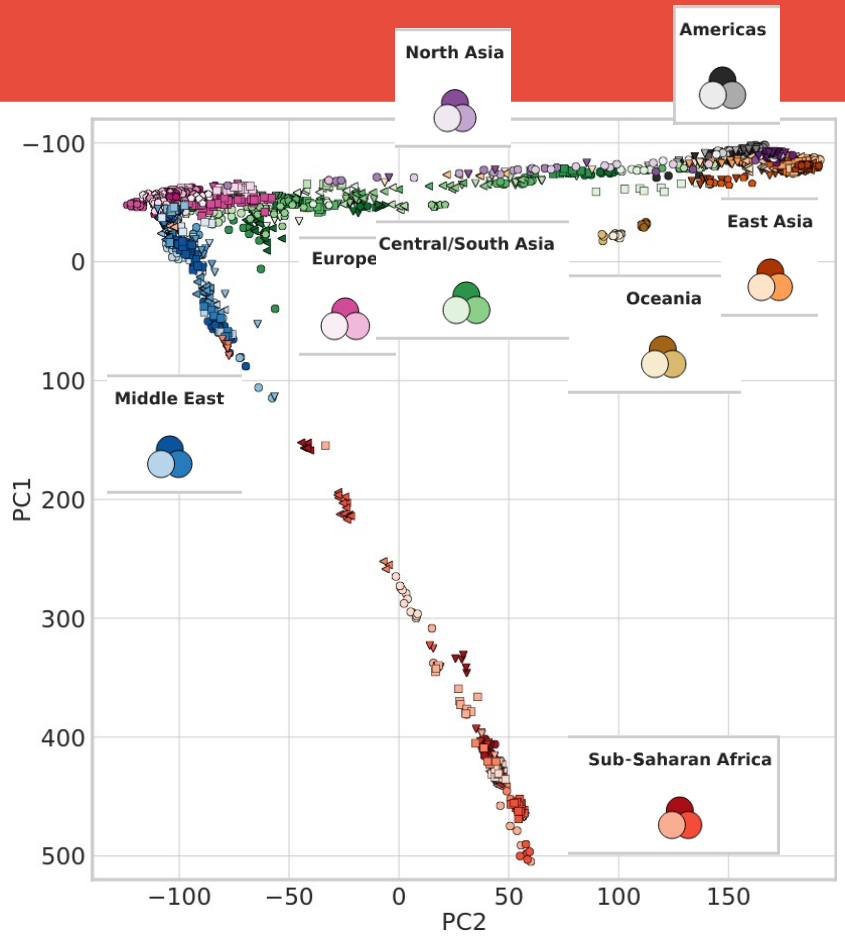
LD pruning, remove $R^2 > 0.2$

160,858 biallelic sites

Show genotypes in first 2 PCs

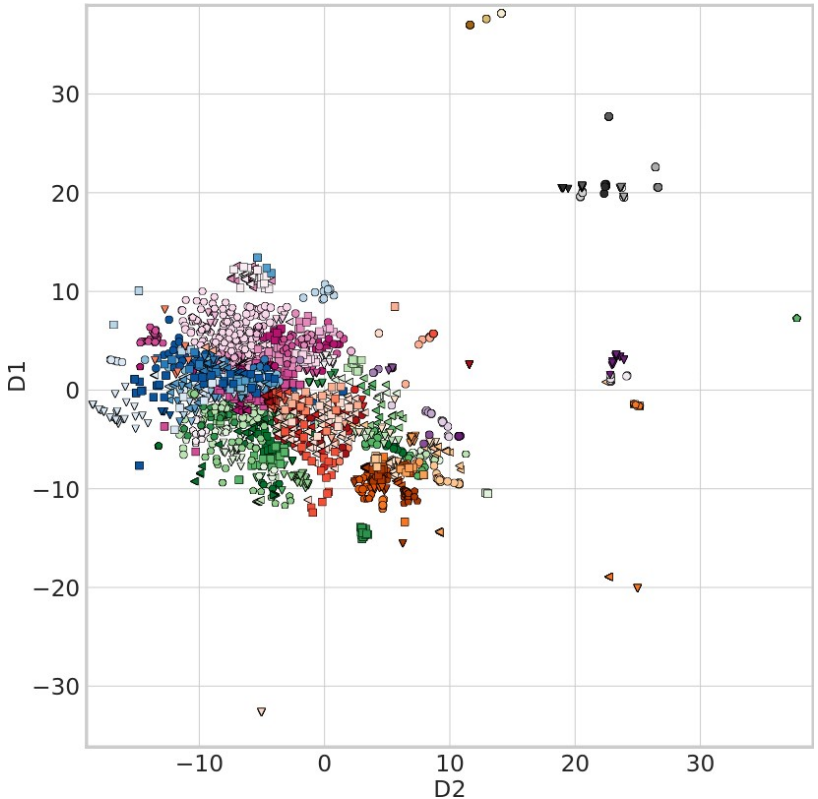
Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

PCA dimensionality reduction



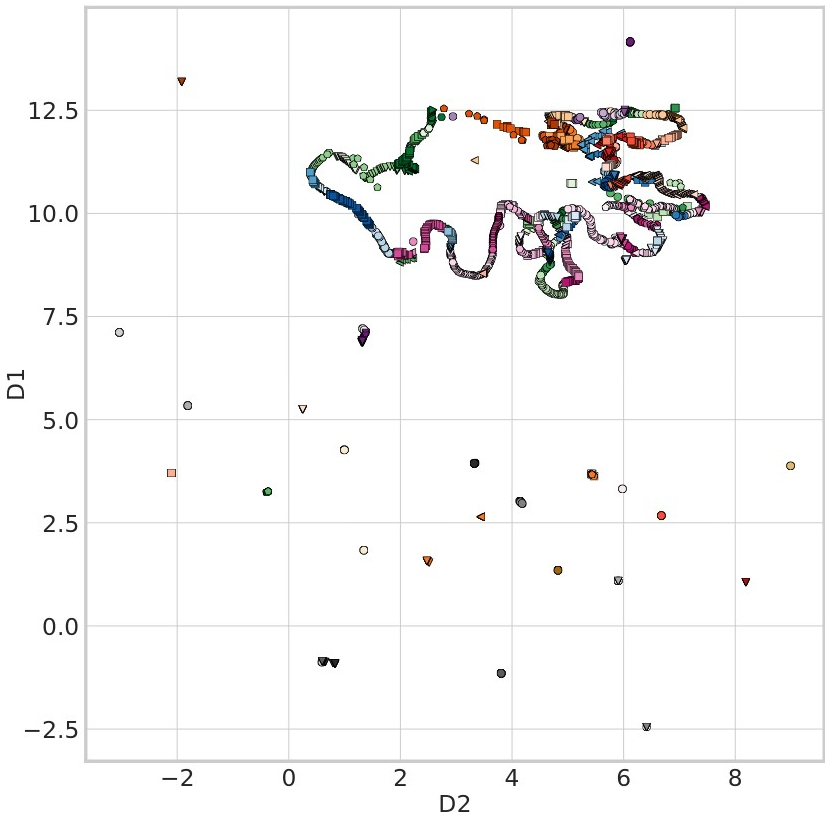
Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

t-SNE dimensionality reduction



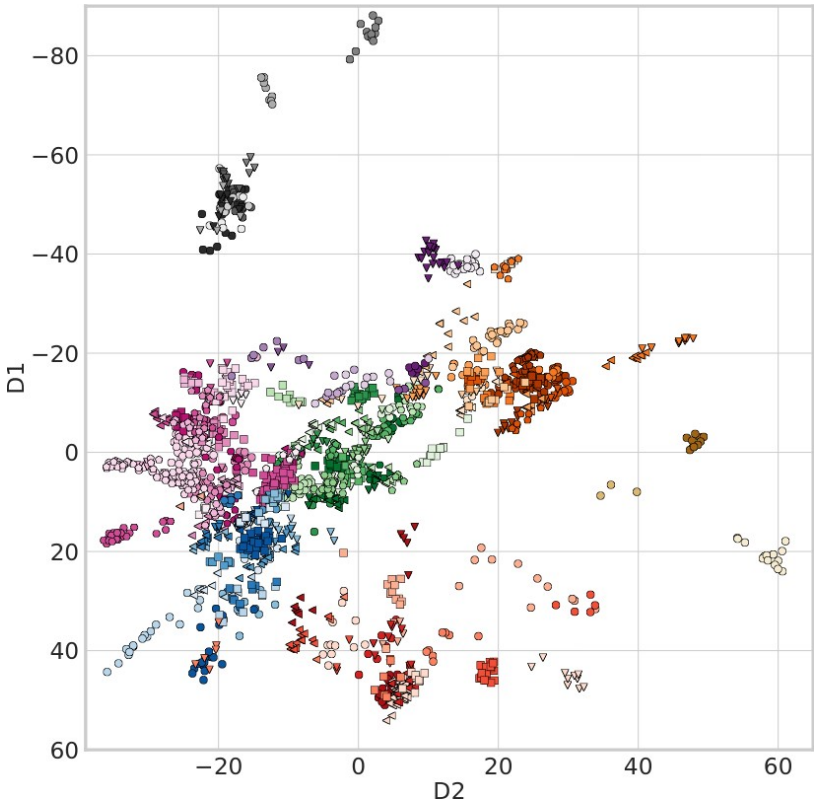
Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

UMAP dimensionality reduction



Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

GCAE dimensionality reduction



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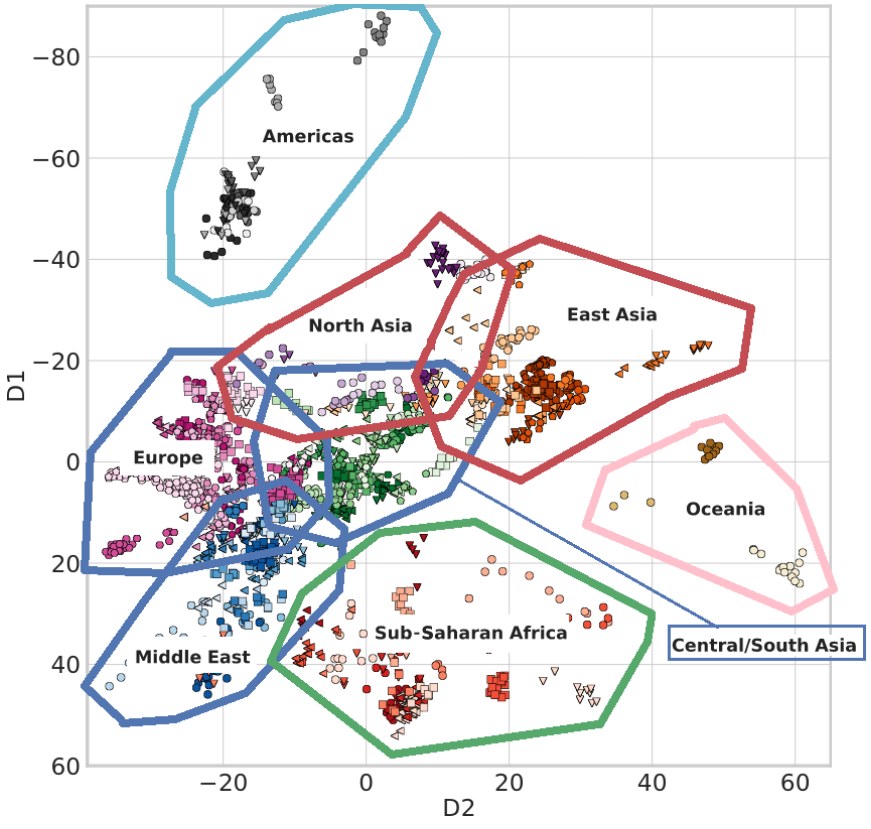
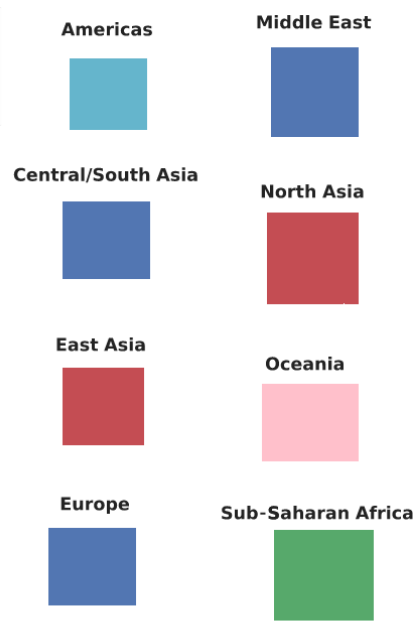
GCAE dimensionality reduction





Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020). Adapted by Richel Bilderbeek

Questions

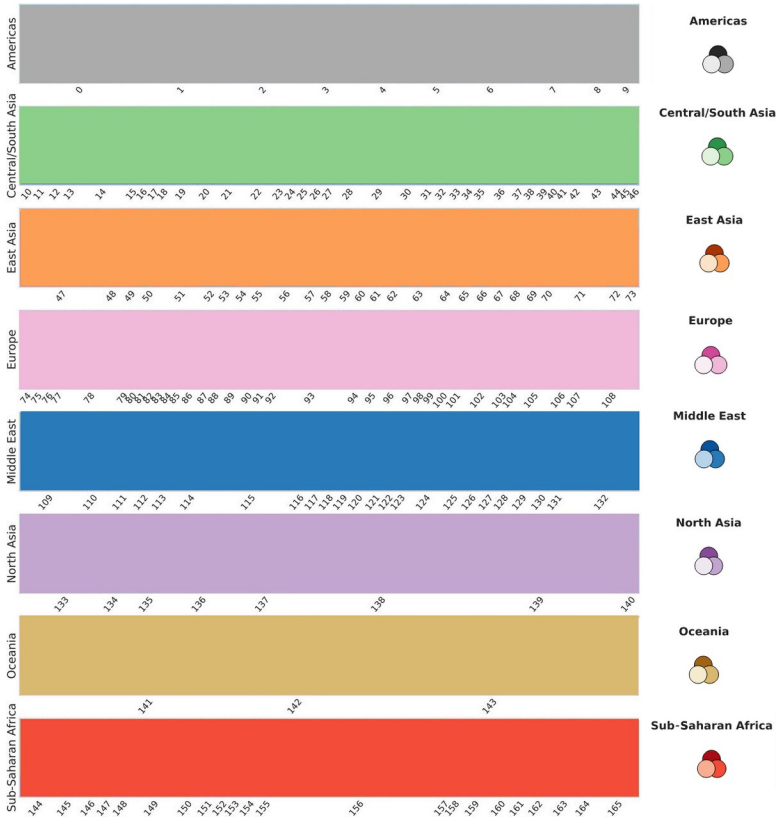
How well can genotypes be separated by eye?

How well can we deduce the origin of a genotype?

- Clustering similar to ADMIXTURE
- F1 scrore

Other measurements

How well can we deduce the origin of a genotype?

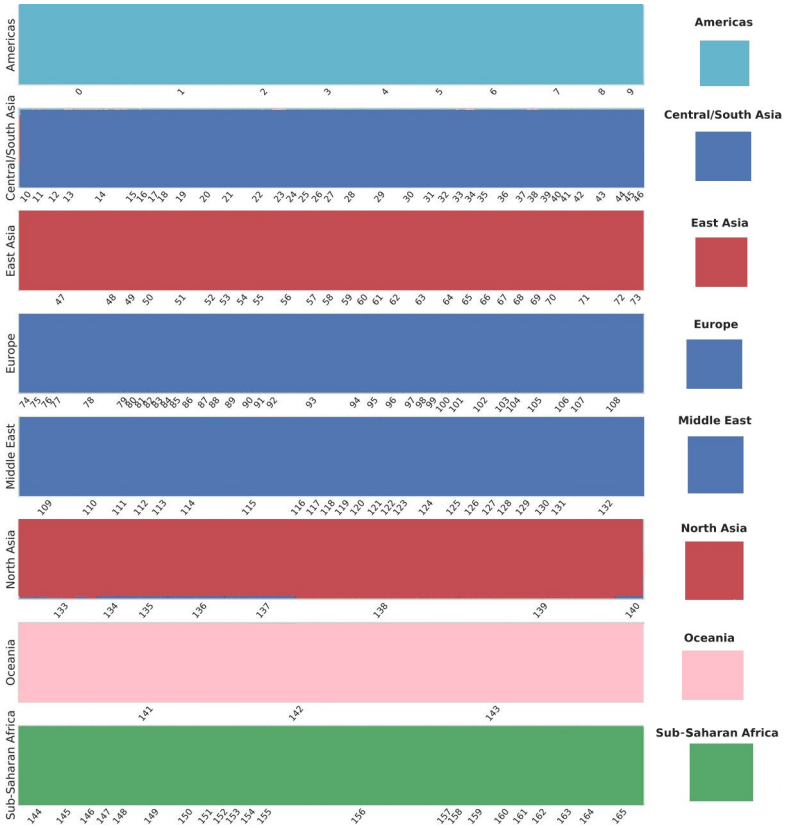


Go through all individuals (x axis)

Assign the likelihood it belong to a subcontinent (the rows)

Ideally, all individuals are assigned their correct subcontinent

How well can we deduce the origin of a genotype?



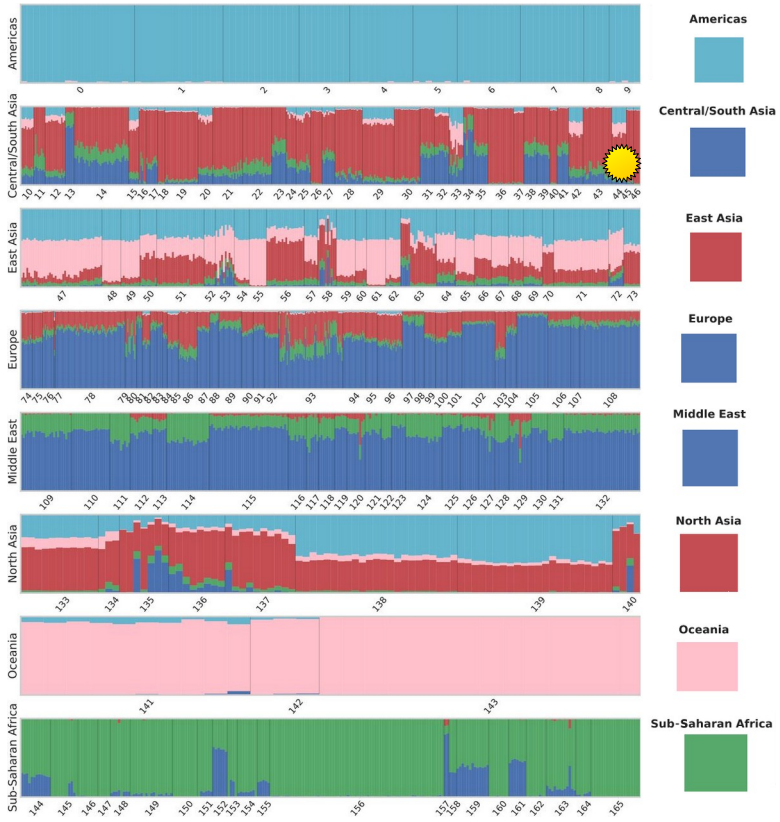
Go through all individuals (x axis)

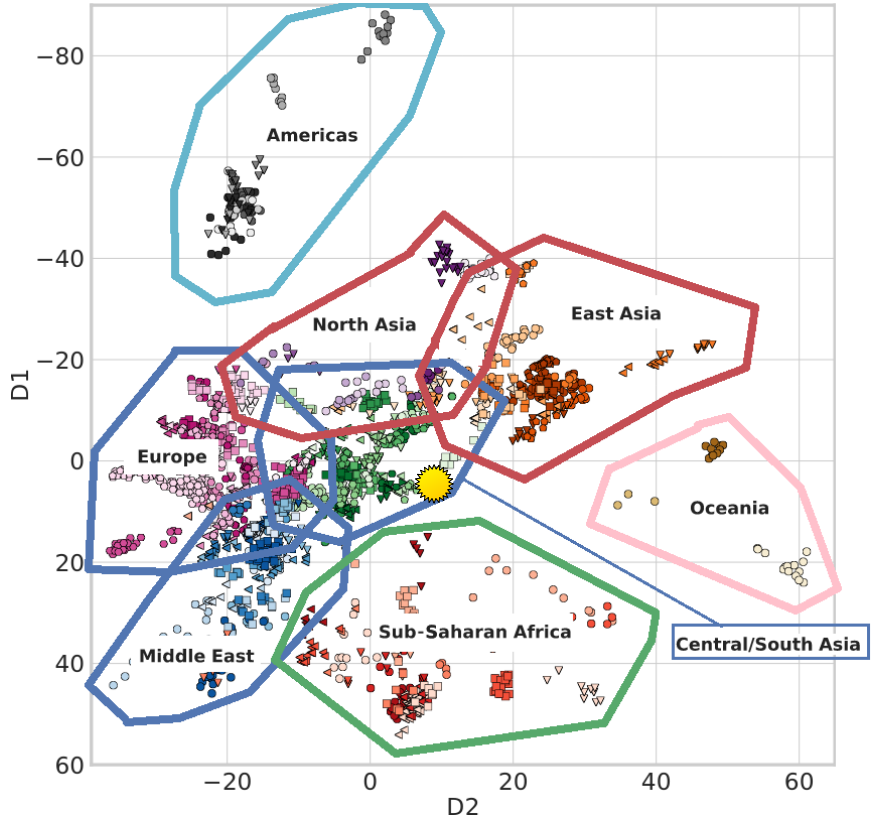
Assign the likelihood it belong to a subcontinent (the rows)

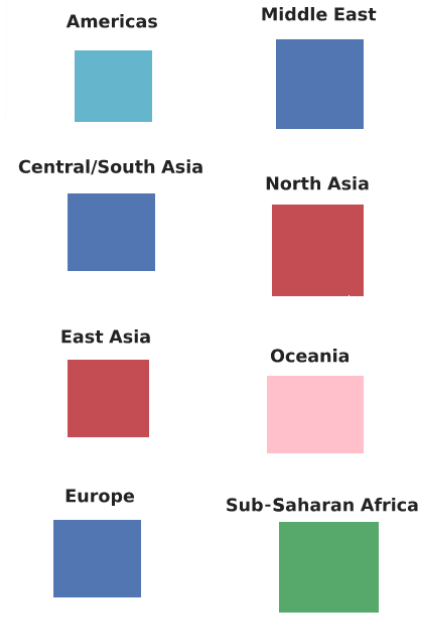
Ideally, all individuals are assigned their correct subcontinent

Use five clusters

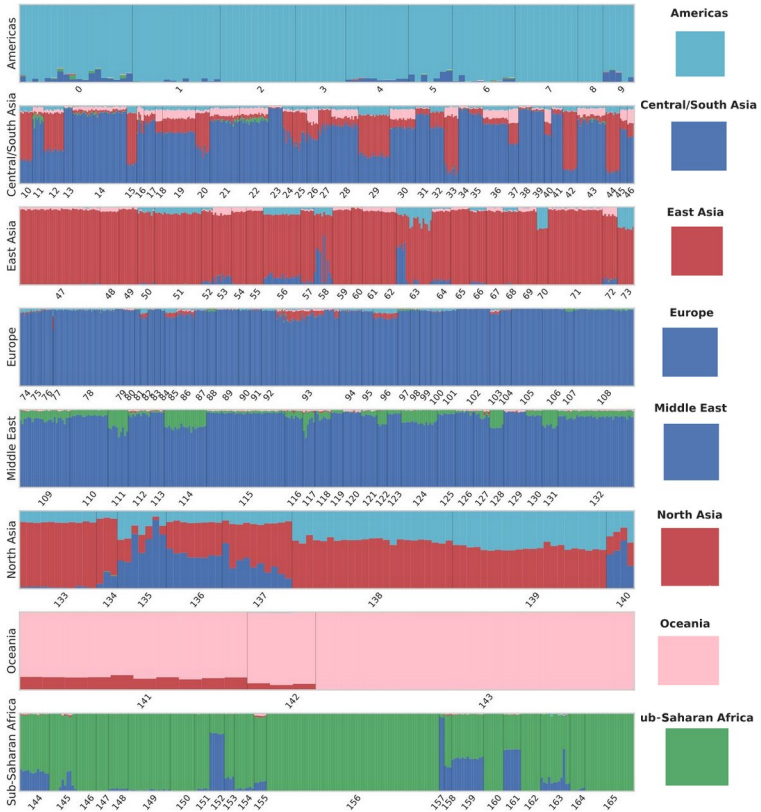
GCAE: ADMIXTURE ↔ plot







PCA: ADMIXTURE



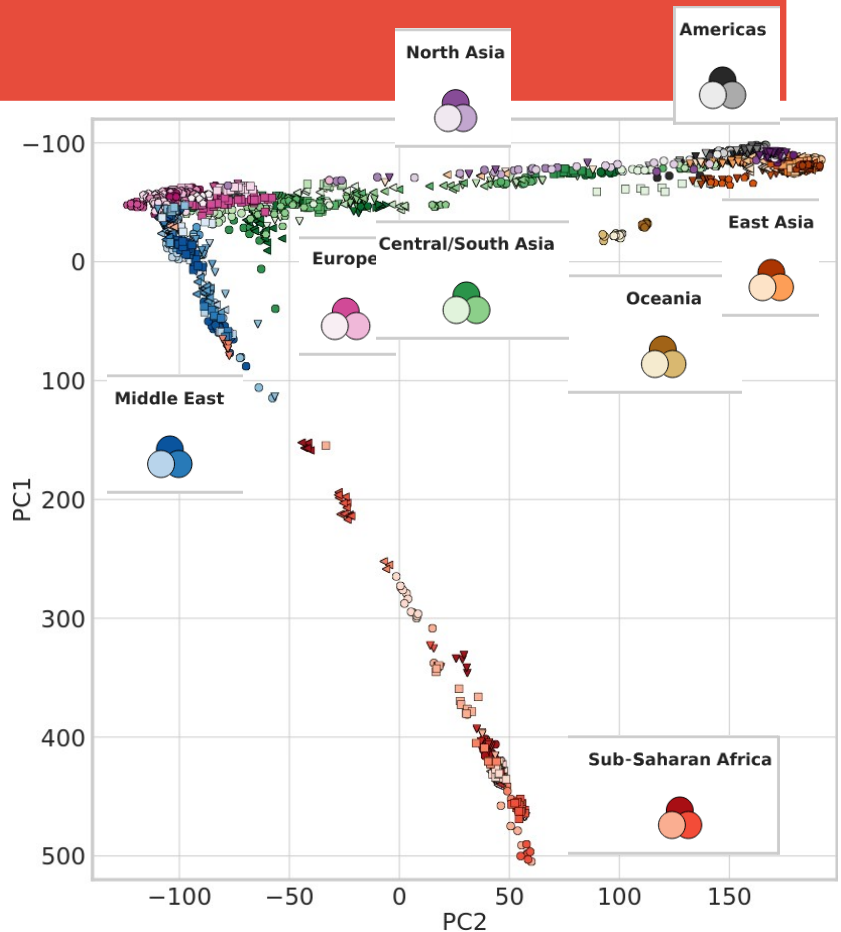
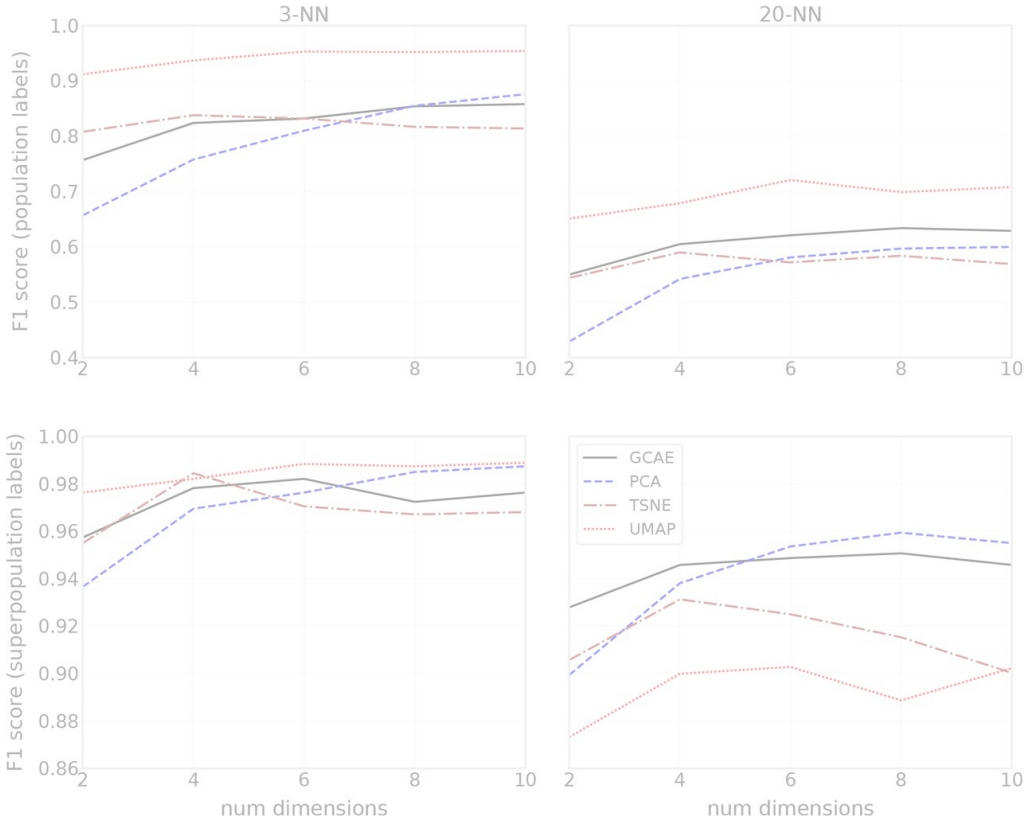
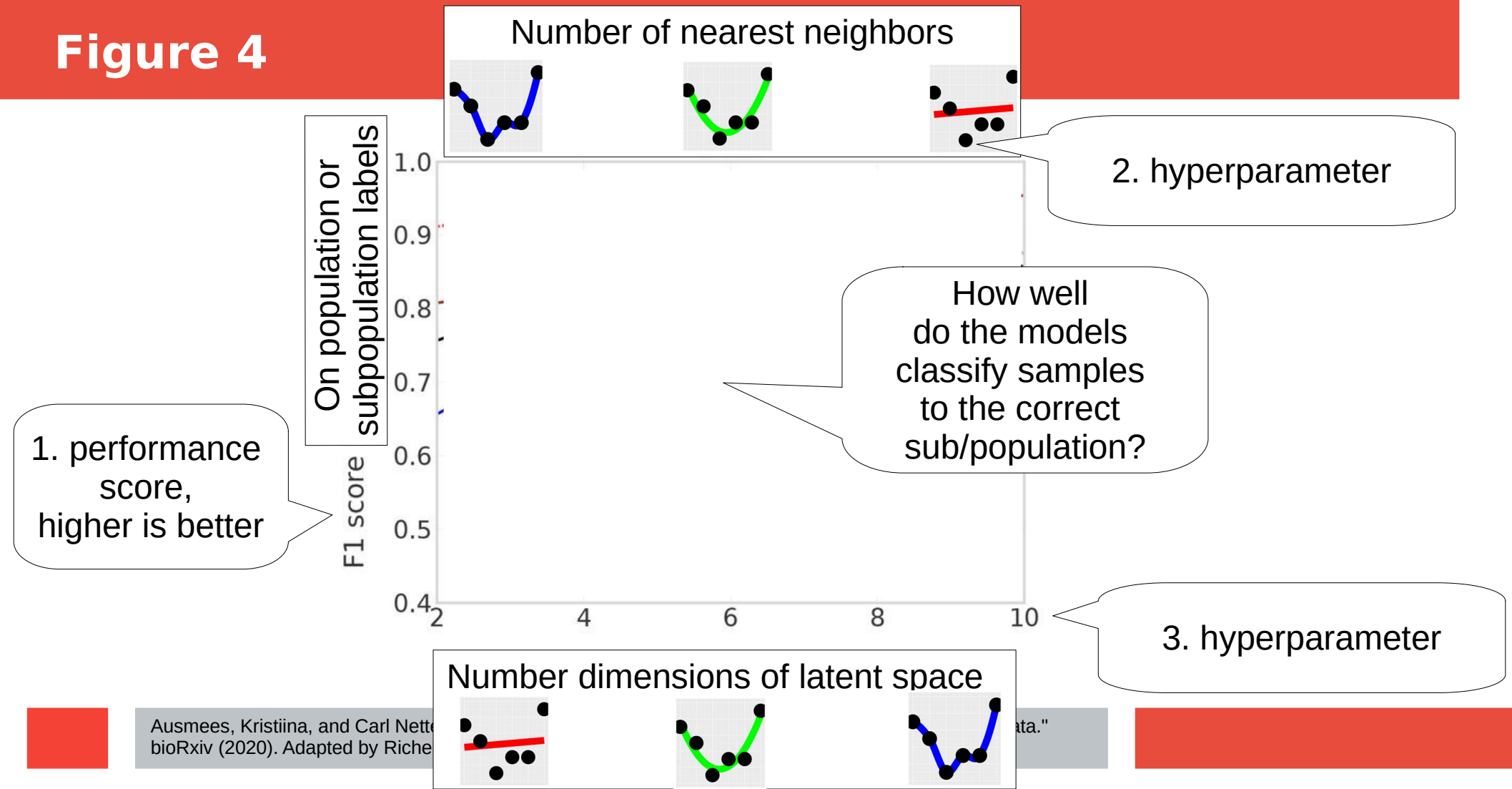


Figure 4



Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

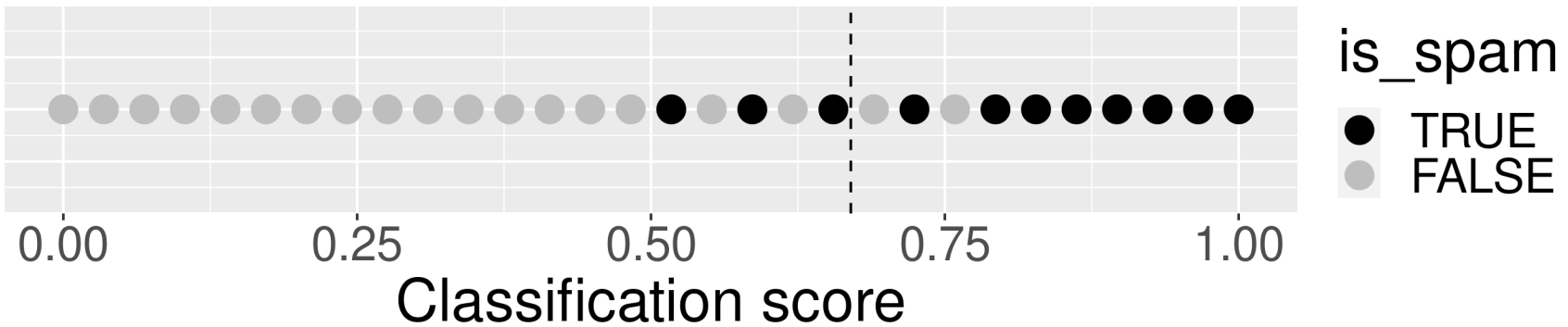
Figure 4



Ausmees, Kristiina, and Carl Nett ata."
bioRxiv (2020). Adapted by Riche

What is the F1 score?

A metric for the trade-off between precision and recall →



https://developers.google.com/machine-learning/crash-course/classification/precision-and-recall
https://github.com/richelbilderbeek/journal_club_20211216/f1_score.R

What is precision?

Precision:

how often is the classifier right?

the number of true positives of all ***estimated*** positives

precision

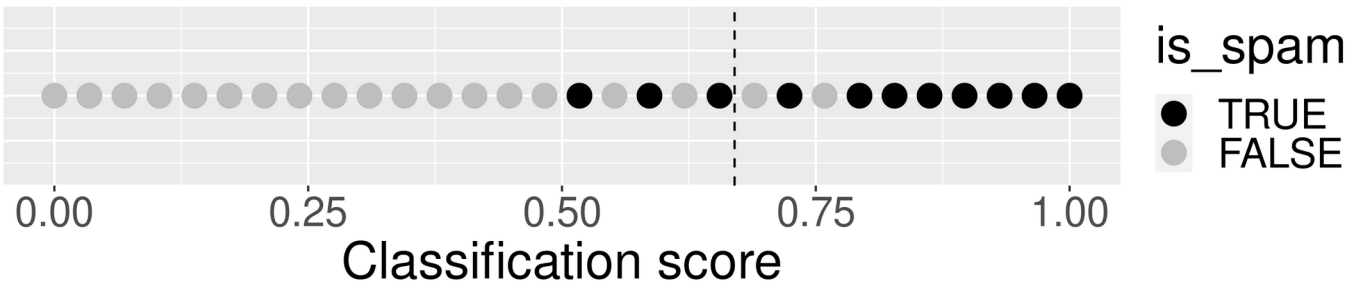
$= n_{tp} / (n_{tp} + n_{fp})$

$= 8 / (8 + 2) = 8/10$

where

n_{tp} = # of true positives

n_{fp} = # of false positives



https://github.com/richelbilderbeek/journal_club_20211216/f1_score.R

What is recall?

Recall:

how often are the positive cases recognized as such?

the number of true positives of all ***known*** positives

recall

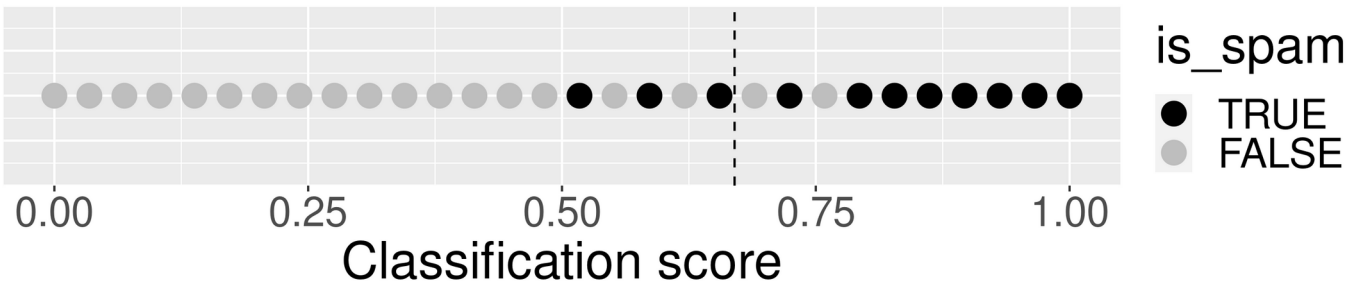
$= n_{tp} / (n_{tp} + n_{fn})$

$= 8 / (8 + 3) = 8/11$

where

n_{tp} = # of true positives

n_{fn} = # of false negatives



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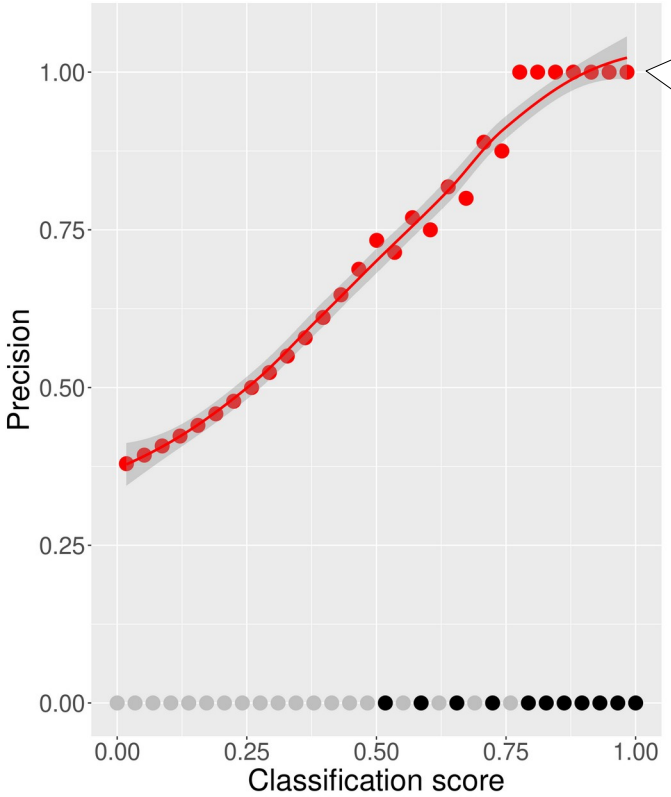
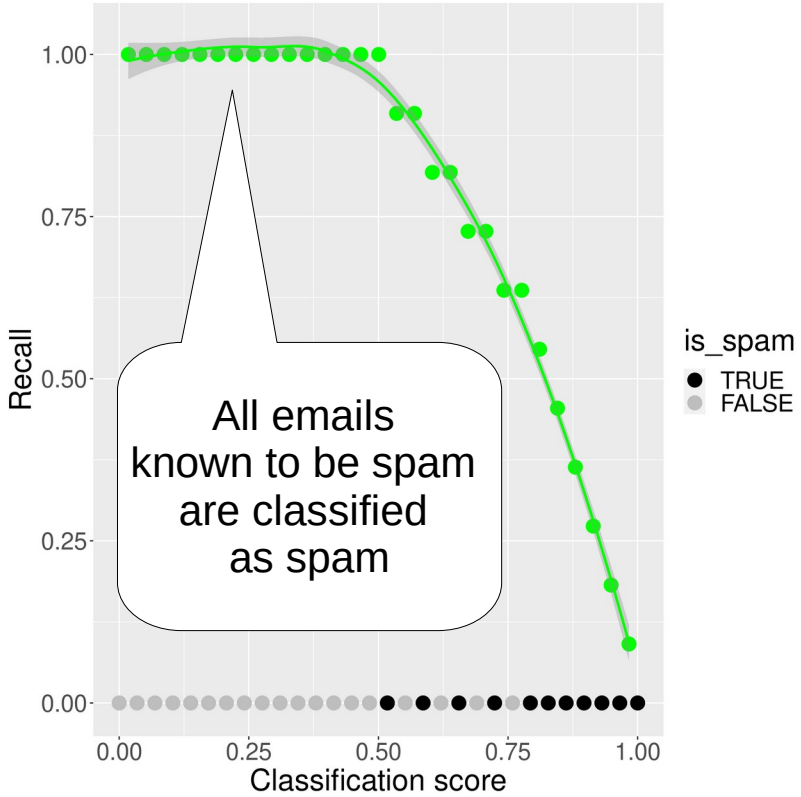
Trade-off between precision and recall



All emails classified as spam are spam



All emails known to be spam are classified as spam

https://github.com/richelbilderbeek/journal_club_20211216/f1_score.R

F1 Score

A metric for the trade-off between precision and recall:

The harmonic mean of precision and recall

F_1

$= 2 / (\text{precision}^{-1} + \text{recall}^{-1})$

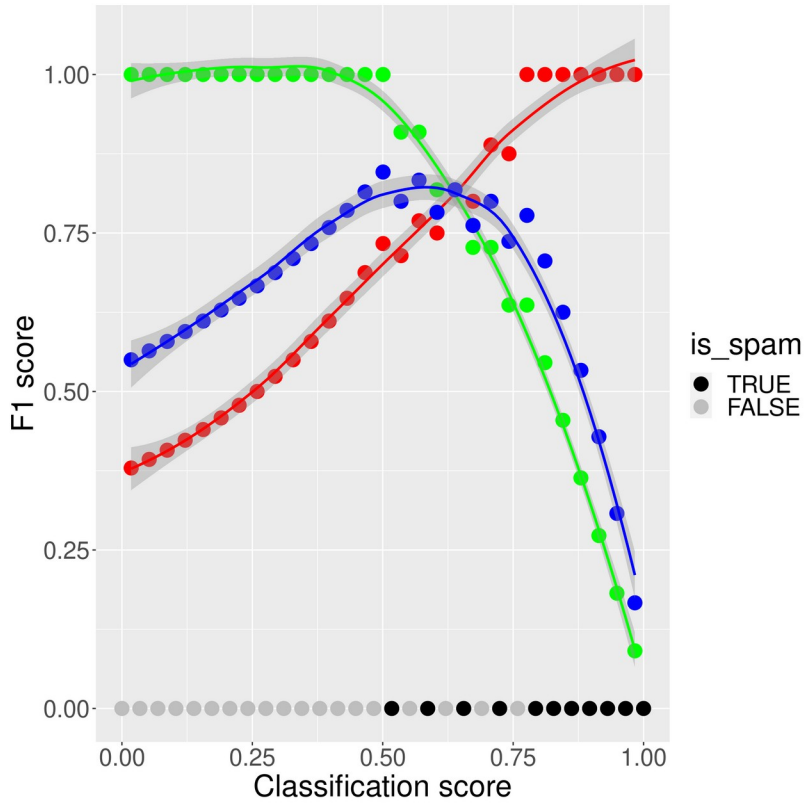
$= n_{tp} / (n_{tp} + ½(n_{fp} + n_{fn}))$

where

n_{tp} = # of true positives

n_{fp} = # of false positives

n_{fn} = # of false negatives



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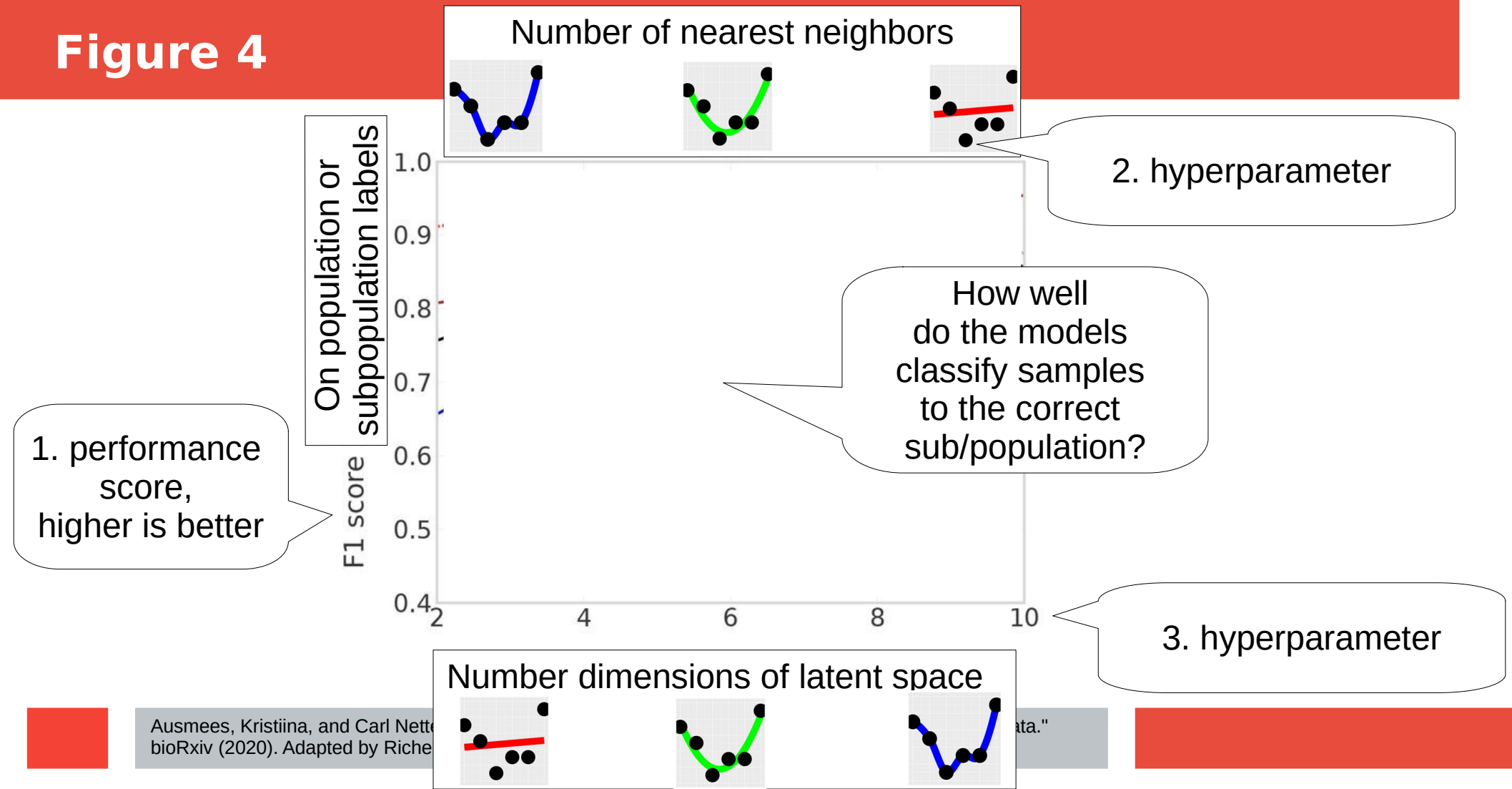
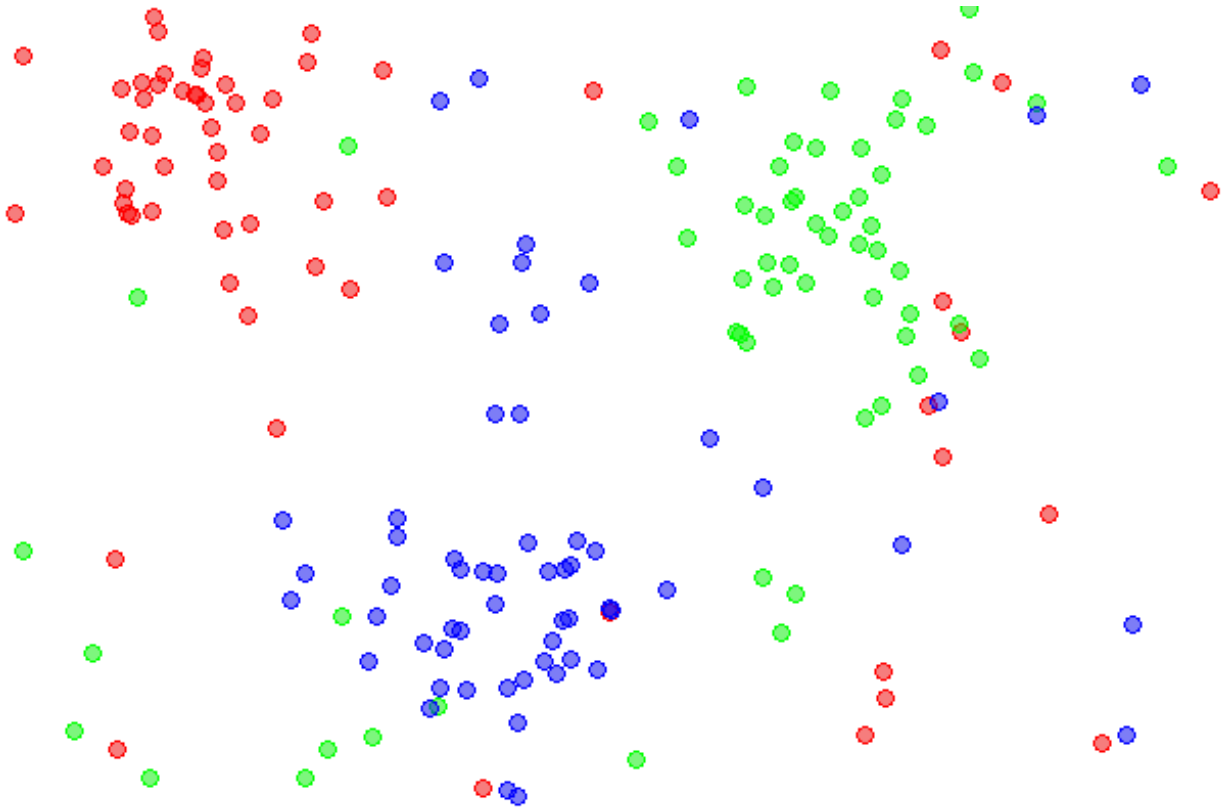


Ausmees, Kristiina, and Carl Nett ata."
bioRxiv (2020). Adapted by Riche

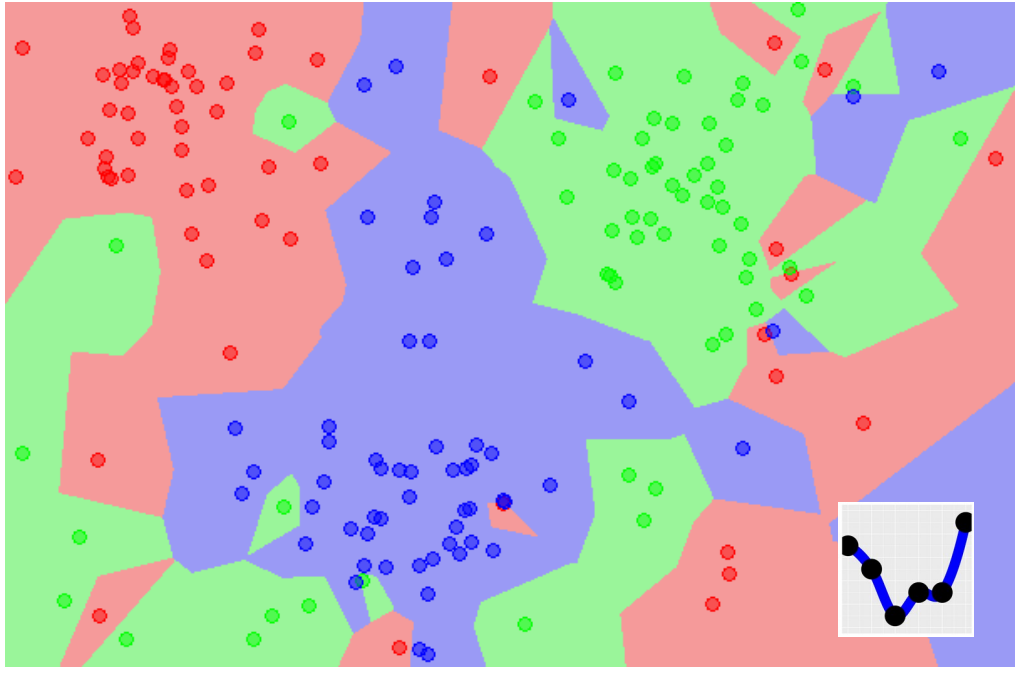
Number of nearest neighbors



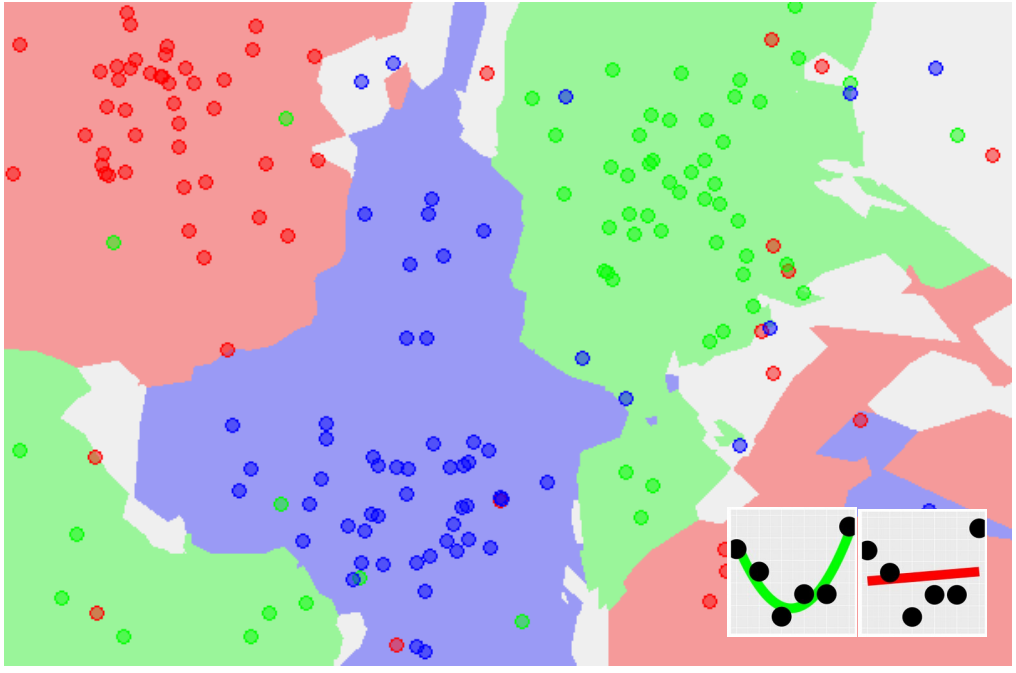
https://en.wikipedia.org/wiki/File:Data3classes.png

Number of neighbors

1



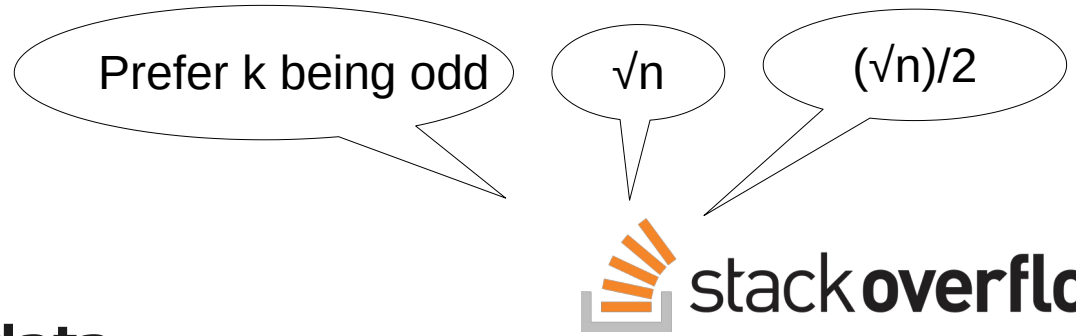
5



https://en.wikipedia.org/wiki/File:Map1NN.png
https://en.wikipedia.org/wiki/File:Map5NN.png

Optimal number for k?

Nontrivial to determine a priori



Possible to determine from data

e.g. calculate the k with the lowest error

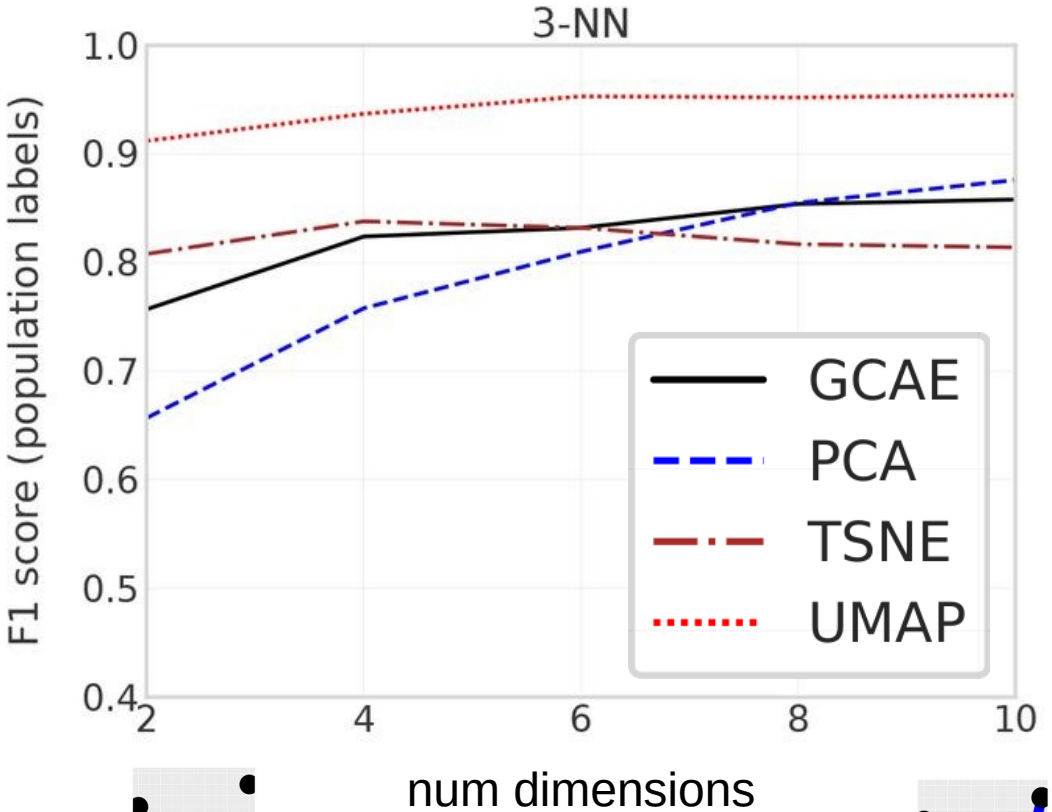
problem: these may differ between different methods (i.e. PCA, GCAE)

166 populations → $\sqrt{n} \approx 13$, $(\sqrt{n})/2 \approx 6$

8 superpopulations → $\sqrt{n} \approx 3$, $(\sqrt{n})/2 \approx 1$

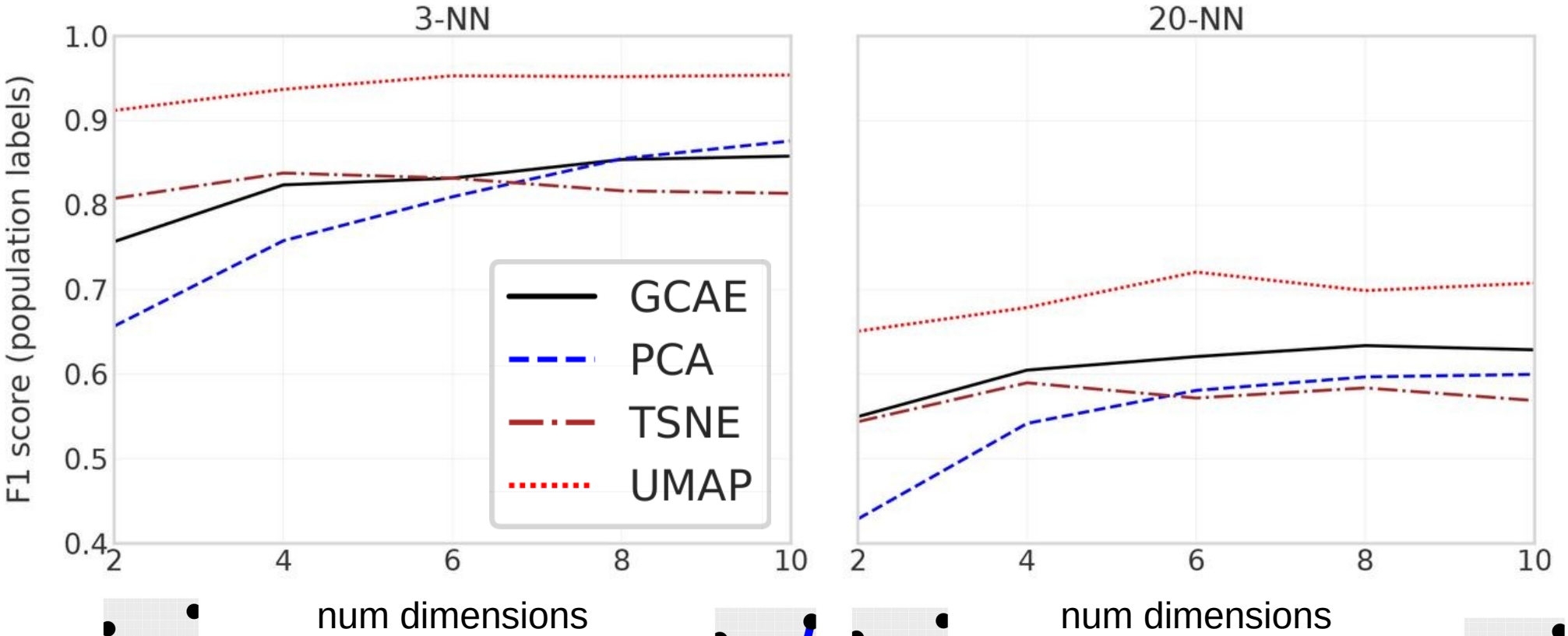
k = number of neighbors
n = the number of categories

Figure 4a



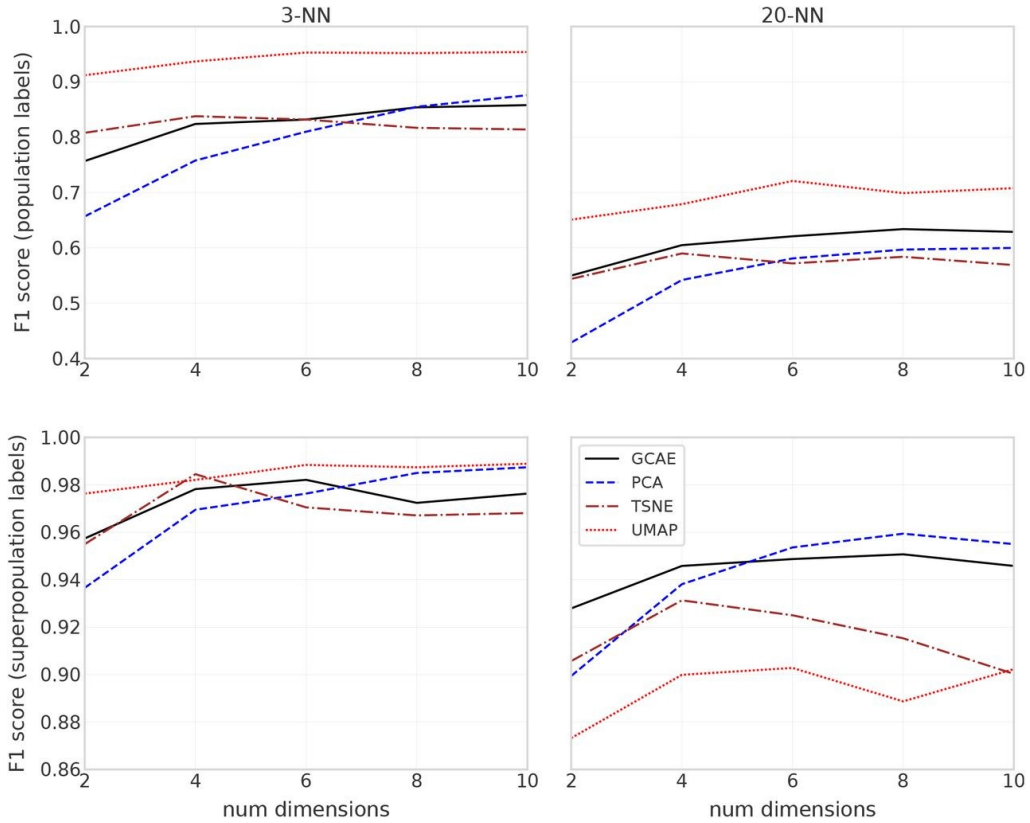
es, Kristiina, and Carl Nettelblad. "A deep learning framew aracterization of genotype data." bioRxiv (2020).

Figure 4ab



es, Kristiina, and Carl Nettelblad. "A deep learning framev arac f genotype data." bioRxiv (2020).

Figure 4 revisited



Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

Questions

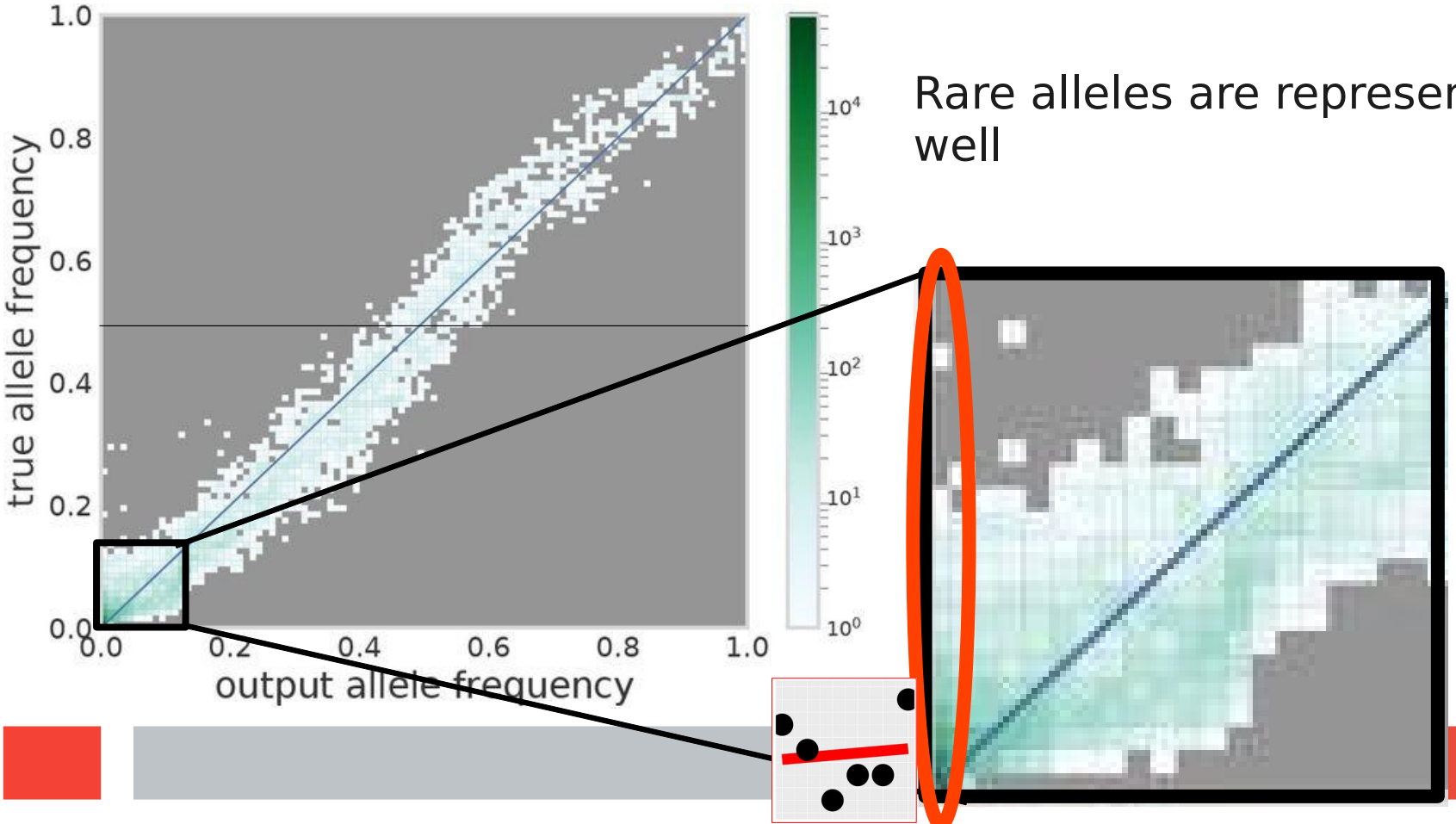
How well can genotypes be separated by eye?

How well can we deduce the origin of a genotype?

Other measurements

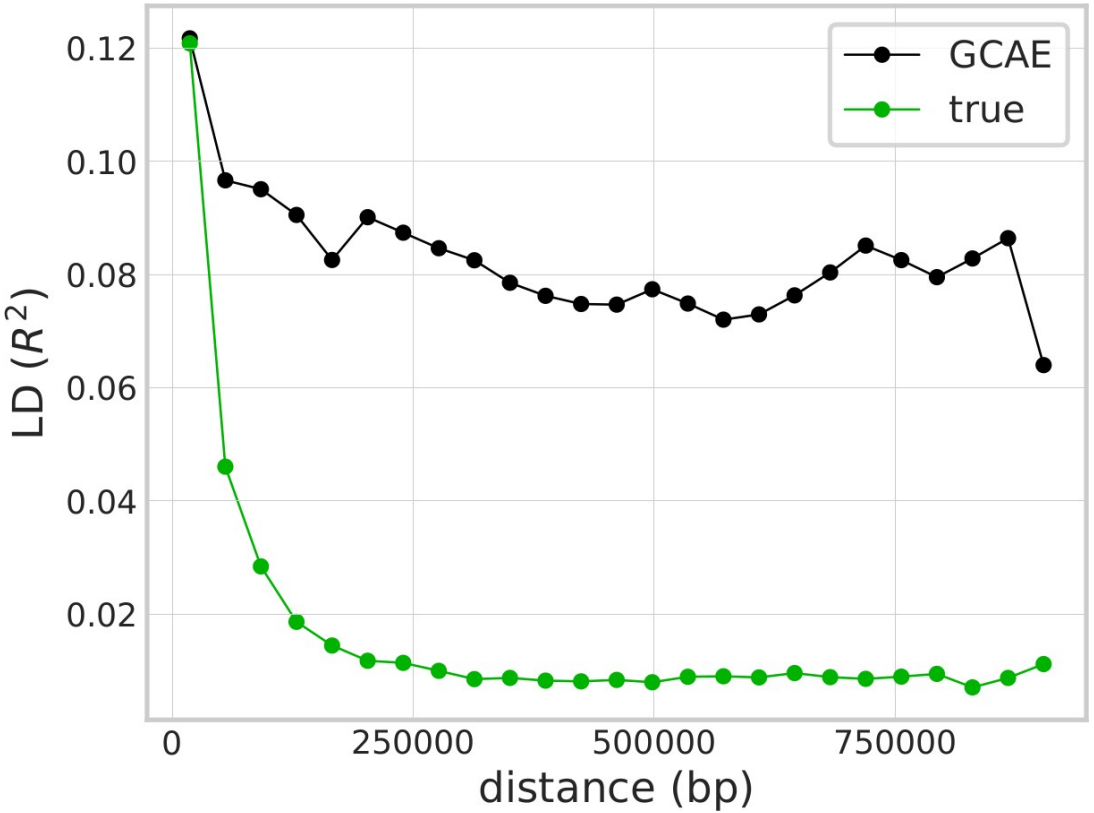
- Representing rare alleles
- Representing linkage disequilibrium

Representing of rare alleles



Rare alleles are represented less well

Representing LD



GCAE ‘feels’ all alleles are in LD

Proof it takes local structure into account

Pruned on LD < 0.2 ?

Allele independent

Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020). Adapted by Richel Bilderbeek

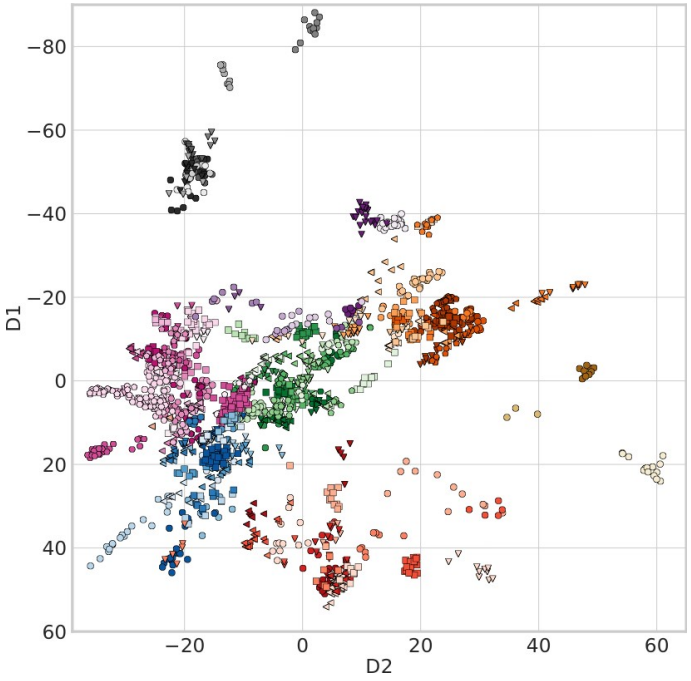
Discussion

Dimensionality reduction

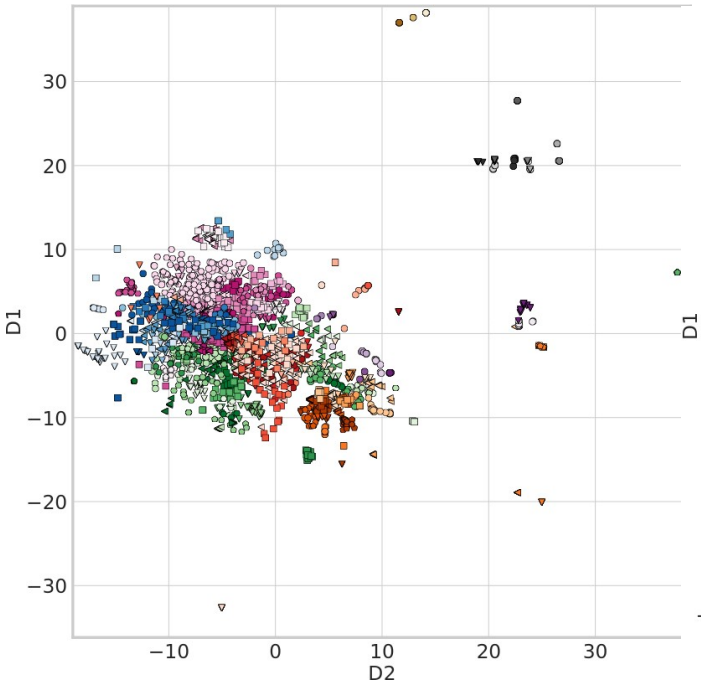
ADMIXTURE

F1 scores

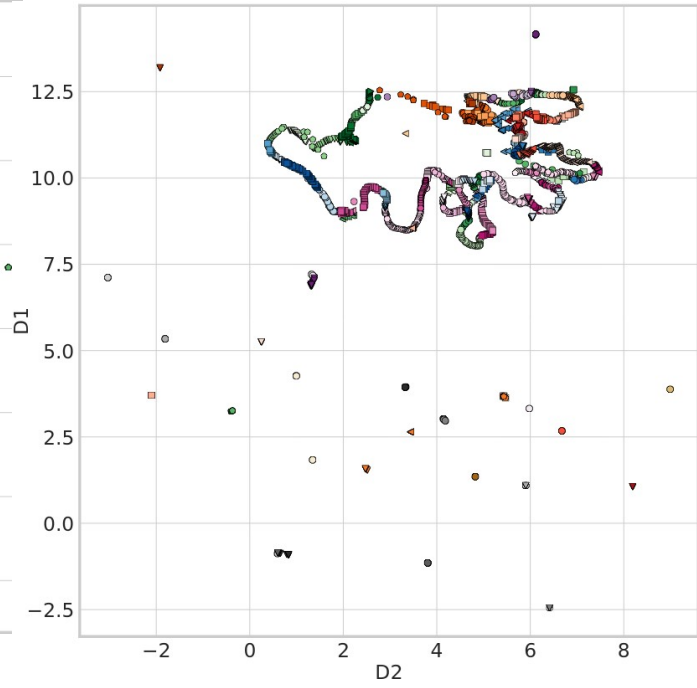
GCAE versus t-SNE and UMAP again



GCAE



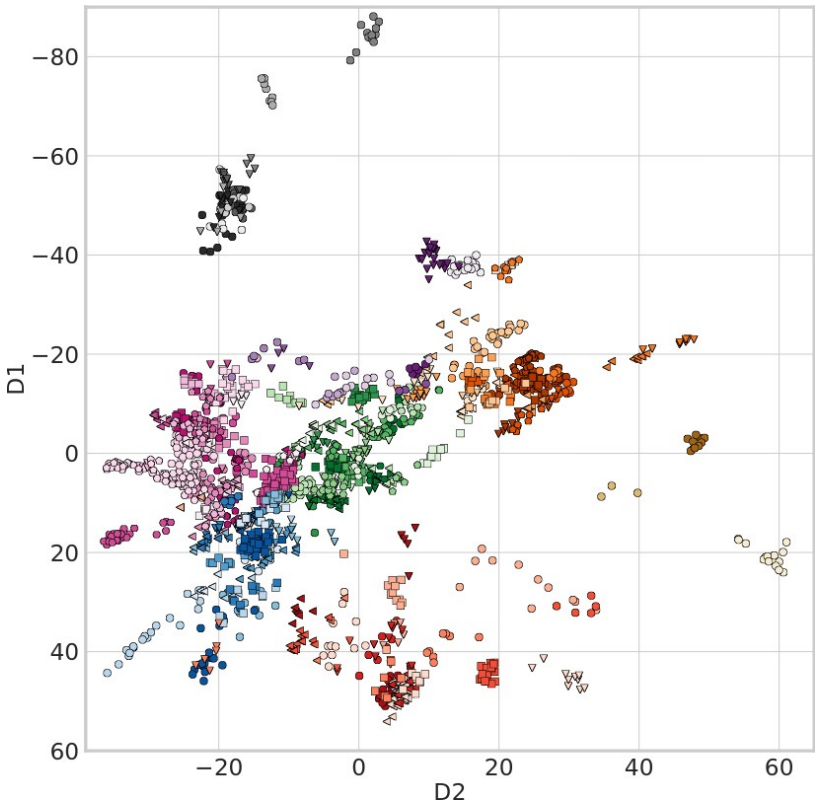
t-SNE

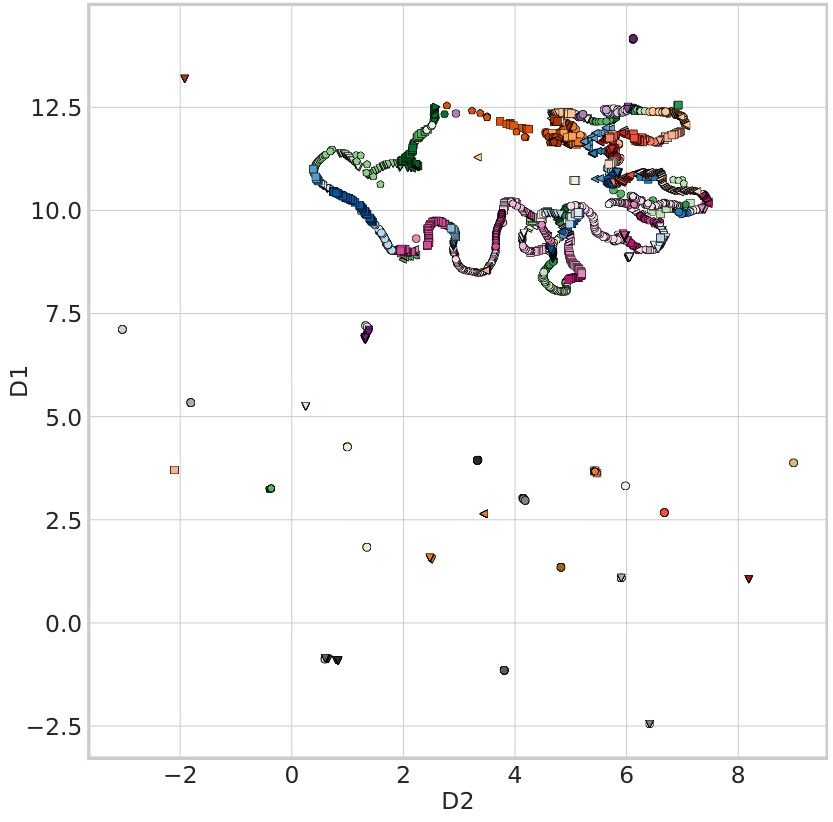


UMAP

Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

GCAE versus UMAP

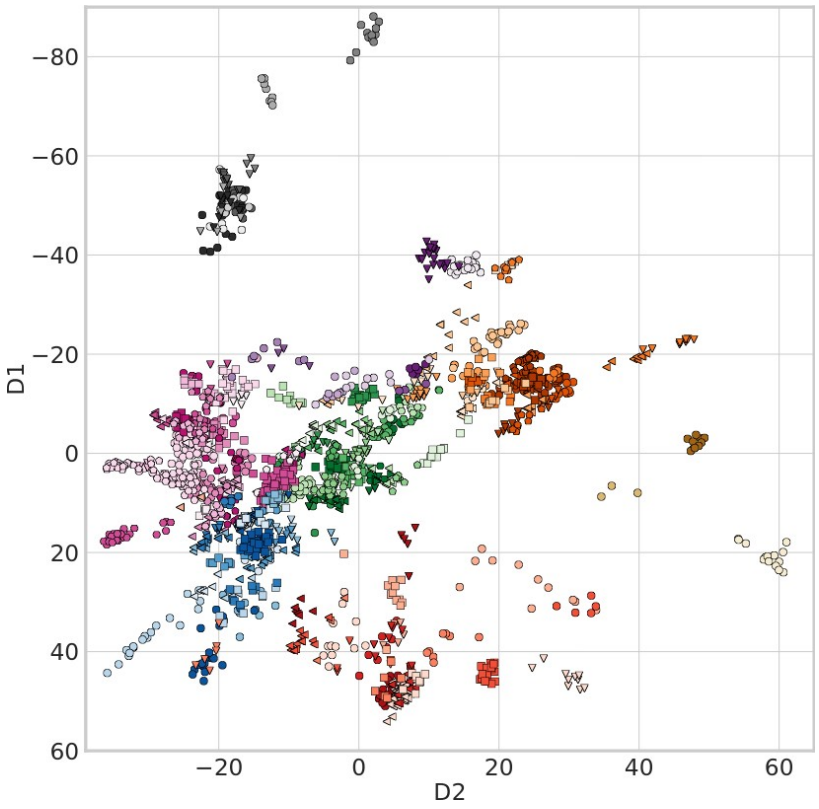


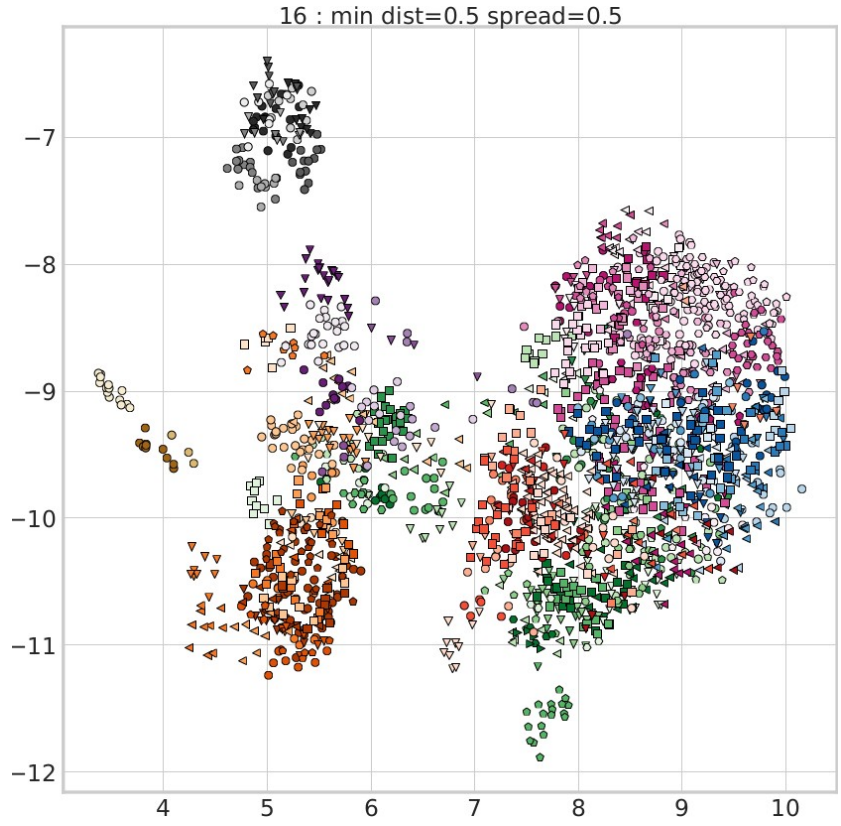


Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

GCAE versus UMAP

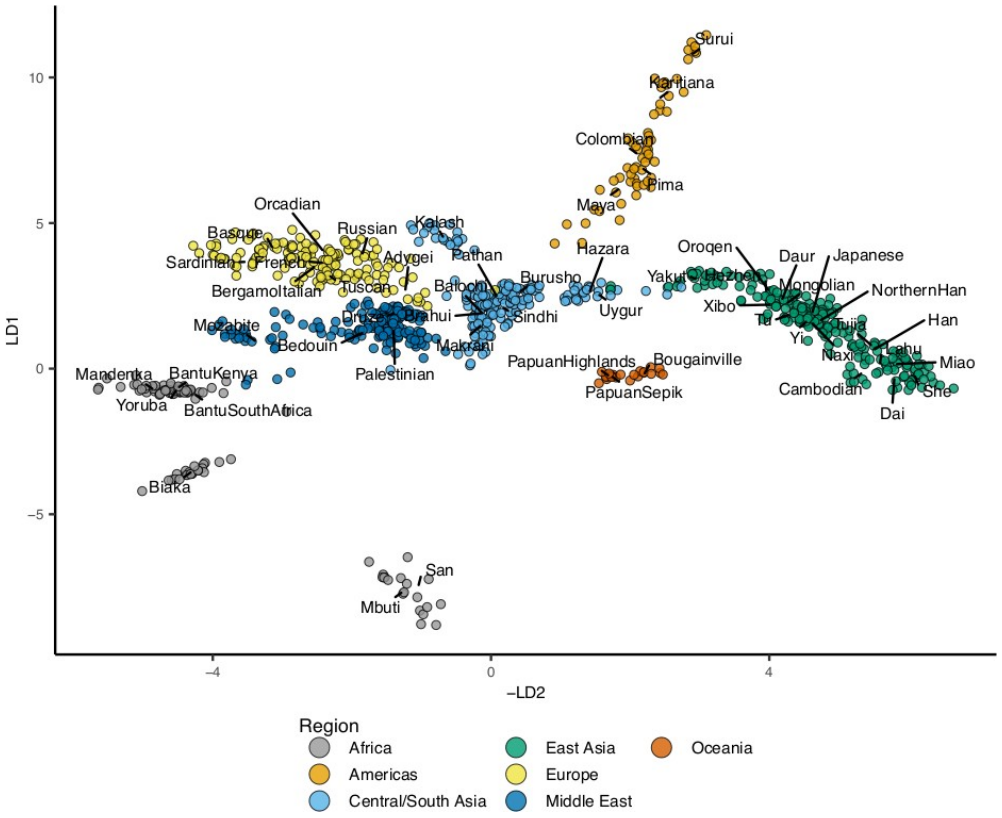
While in the Supplementary Materials ...

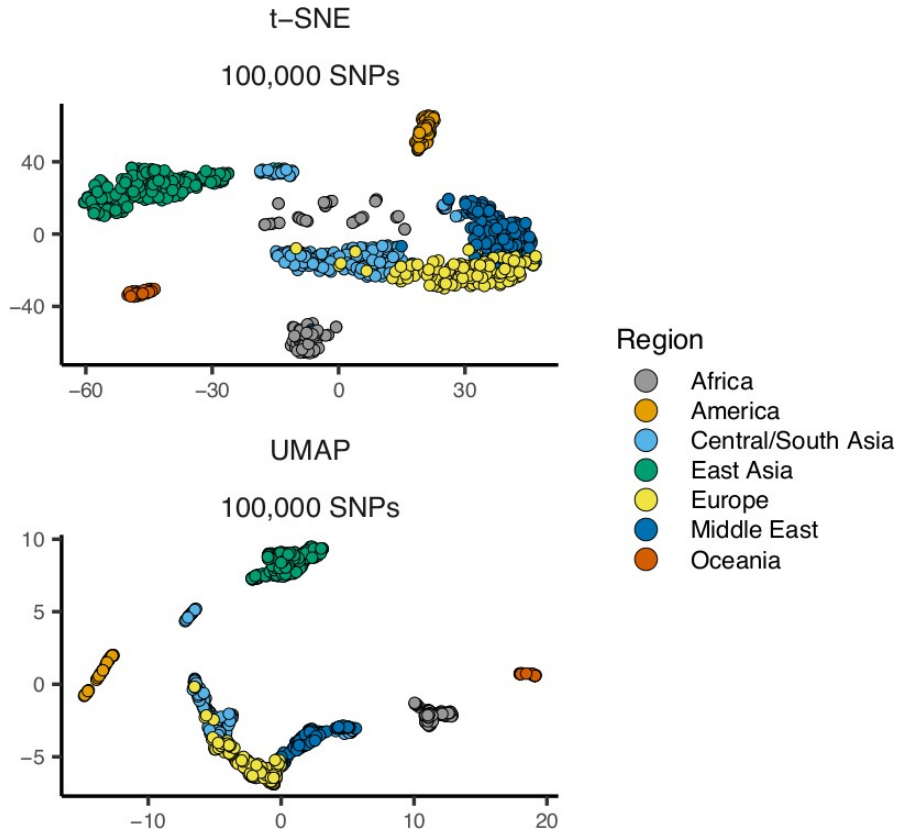




Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

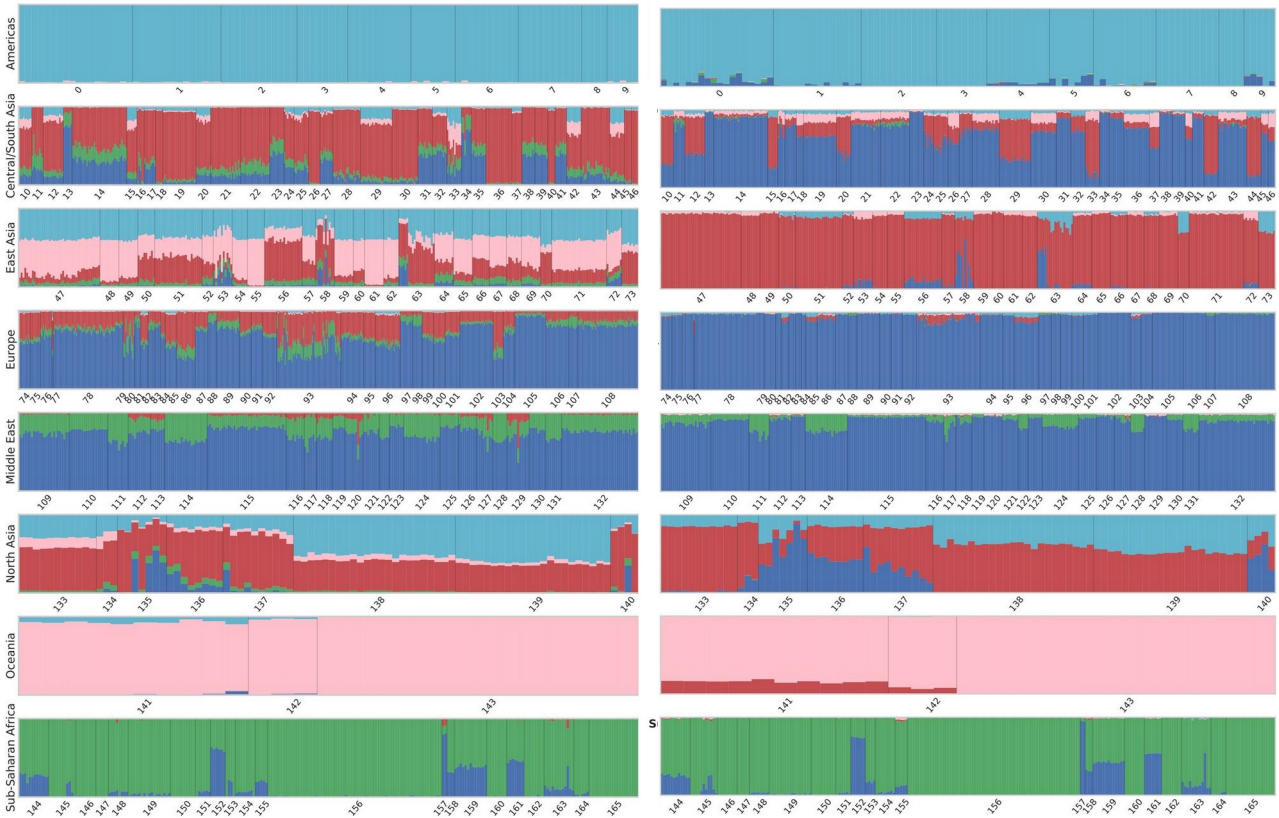
Comparisons by other study





Battey, C. J., Gabrielle C. Coffing, and Andrew D. Kern. "Visualizing population structure with variational autoencoders." G3 11.1 (2021): 1-11.

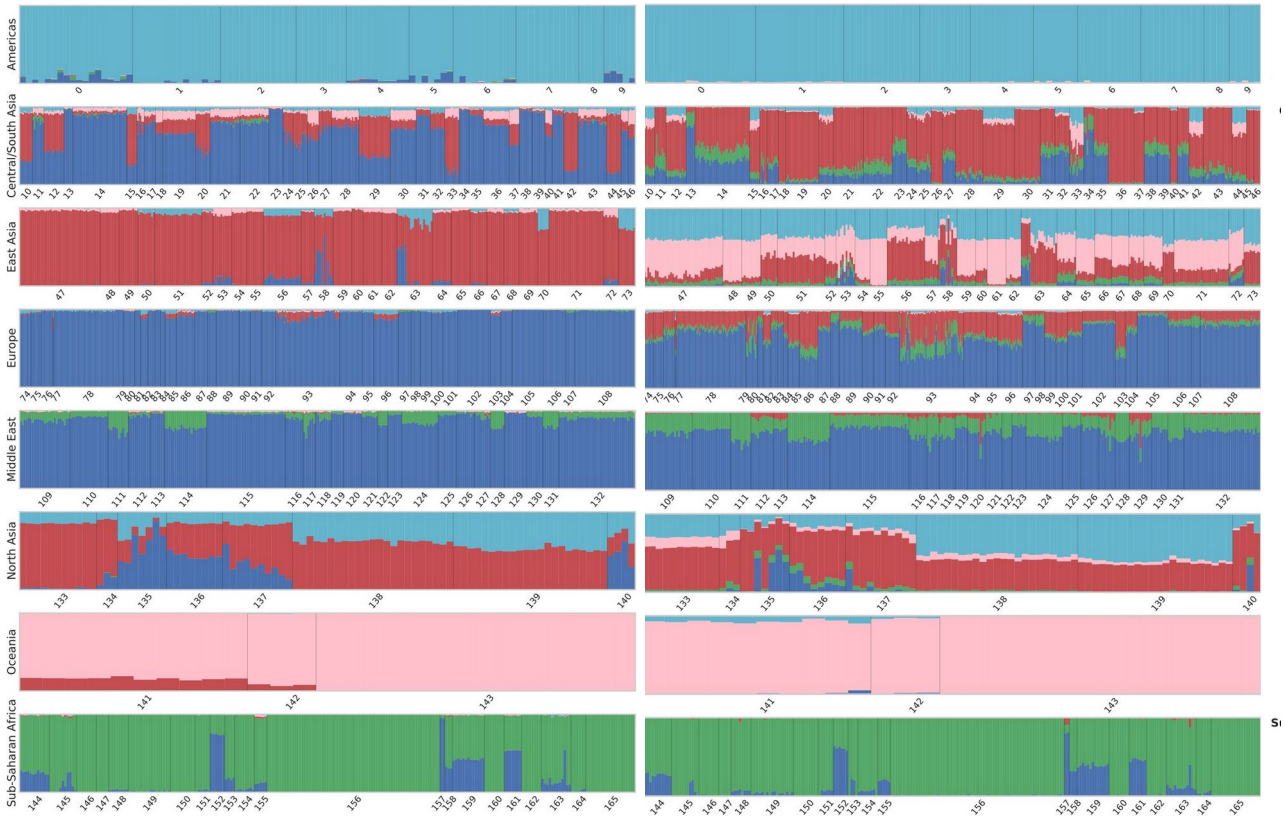
ADMIXTURE



So, which one is better?

No figure legend on purpose :-)

ADMIXTURE



So, which one is better?

No figure legend on purpose :-)

Method

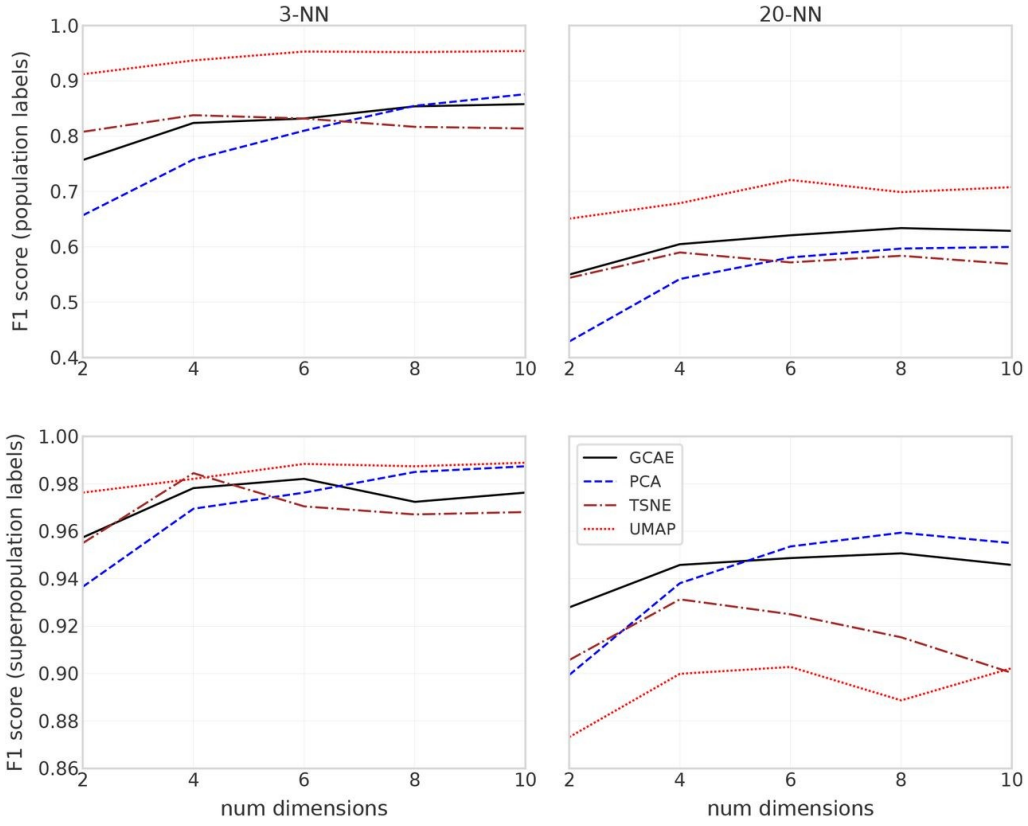
How is the ADMIXTURE-like plot generated?

Reproducible from text only?

No code

> […] what you see is not
> ADMIXTURE w/PCA vs ADMIXTURE w/GenoCAE,
> but rather ADMIXTURE vs. k-pop softmaxed GenoCAE

F1 Scores



So, which one is better?

"The F1 score of a classification model based on the dimensionality reduction is not a simple metric for which the method with the highest score is the most correct"

Ausmees, Kristiina, and Carl Nettelblad. "A deep learning framework for characterization of genotype data." bioRxiv (2020).

Discussion

Novel approach

… but there are others (non-convolutional) autoencoders

… best for non-linear effects on common SNPs

Dimensionality reduction looks impressive

… how well do other autoencoders do?

Performance is measured

… but how conclusively?

Performance is compared

… but how much care/tuning for these comparisons?

The end

https://github.com/richelbilderbeek/journal_club_20220220

Data removal procedure

Human Origins data set

[…]

The data was filtered to exclude sex chromosomes and non-informative sites, and *one sample* **(NA13619) was removed due to relation to another (HGDP01382).**

Because of ADMIXTURE assumption

Equations

$$E(y, \hat{y}) = \sum_{i}^{3} y_i log(\hat{y}_i) + \alpha \sum_{j}^{d} e_j^2$$

E(y, y^{hat}): error

i: one of the three variants, i.e. AA, AC, CC

y_i: the actual value of a variant, i.e.

AA = 0.0, AC = 0.5, CC = 1.0

y^{hat}_i: the decoded value of a variant

```
"loss": {
    "module": "tf.keras.losses",
    "class": "CategoricalCrossentropy",
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},
```

Equations

$$E(y,\hat{y}) = \sum_{i}^{3} y_i log(\hat{y}_i) + \alpha \sum_{j}^{d} e_j^2$$

Lower = better

G	y_i	y^{hat}_i	E
AA	0	0.5	0
AC	1	0.1	-2.3
CC	0	0.3	0

One-hot encoding

Zero = best

Lower = better

Equations

$$E(y, \hat{y}) = \sum_{i}^{3} y_i log(\hat{y}_i) + \alpha \sum_{j}^{d} e_j^2$$

i: one of the three variants, i.e. AA, AC, CC

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