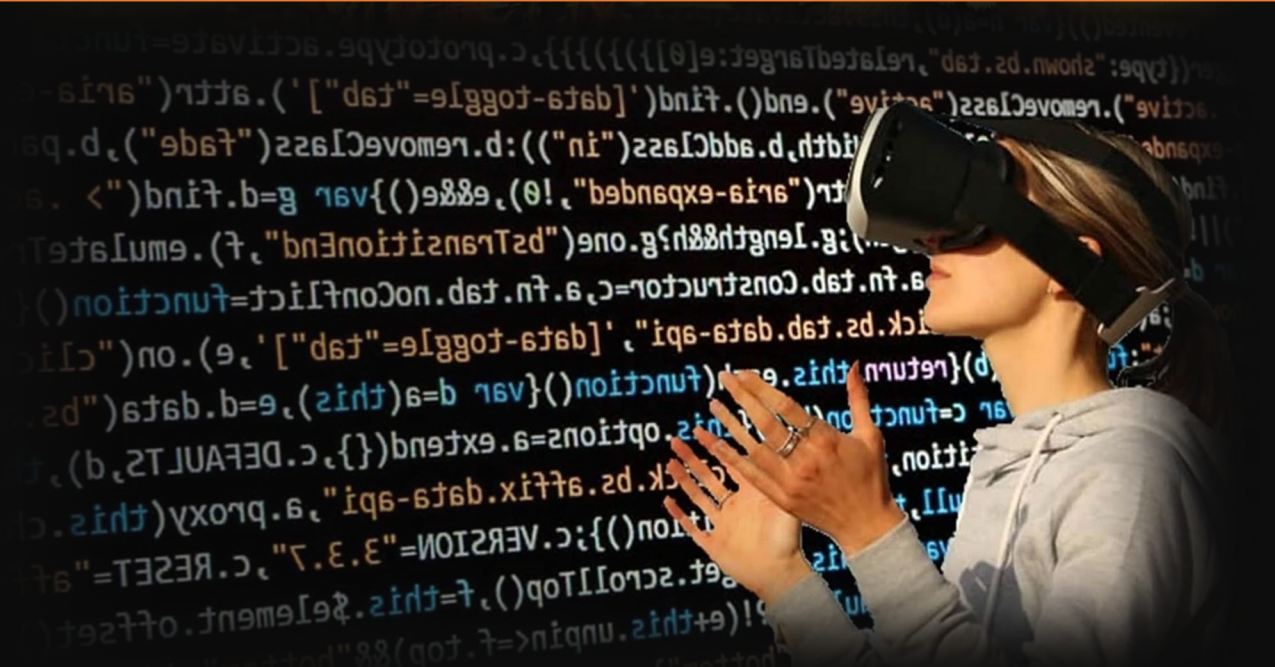
From prehistoric time to the futuristic age of AI

A human genetic perspective

Linh Tran

University of Arizona



Presenter Financial Disclosure

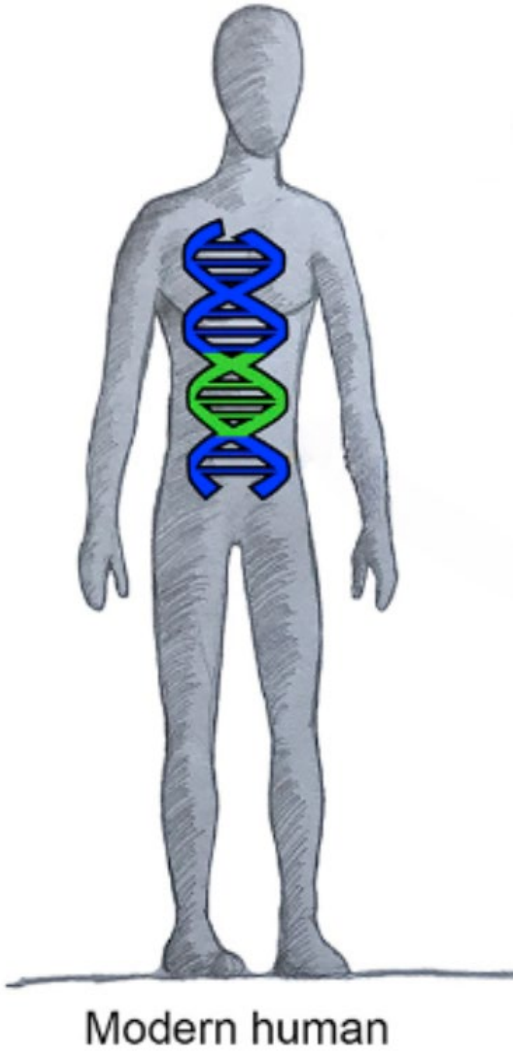
I do not have any relationships to report within the last 24 months with ACCME defined ineligible companies.

Unlabeled/Investigational Uses

I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals during this presentation.

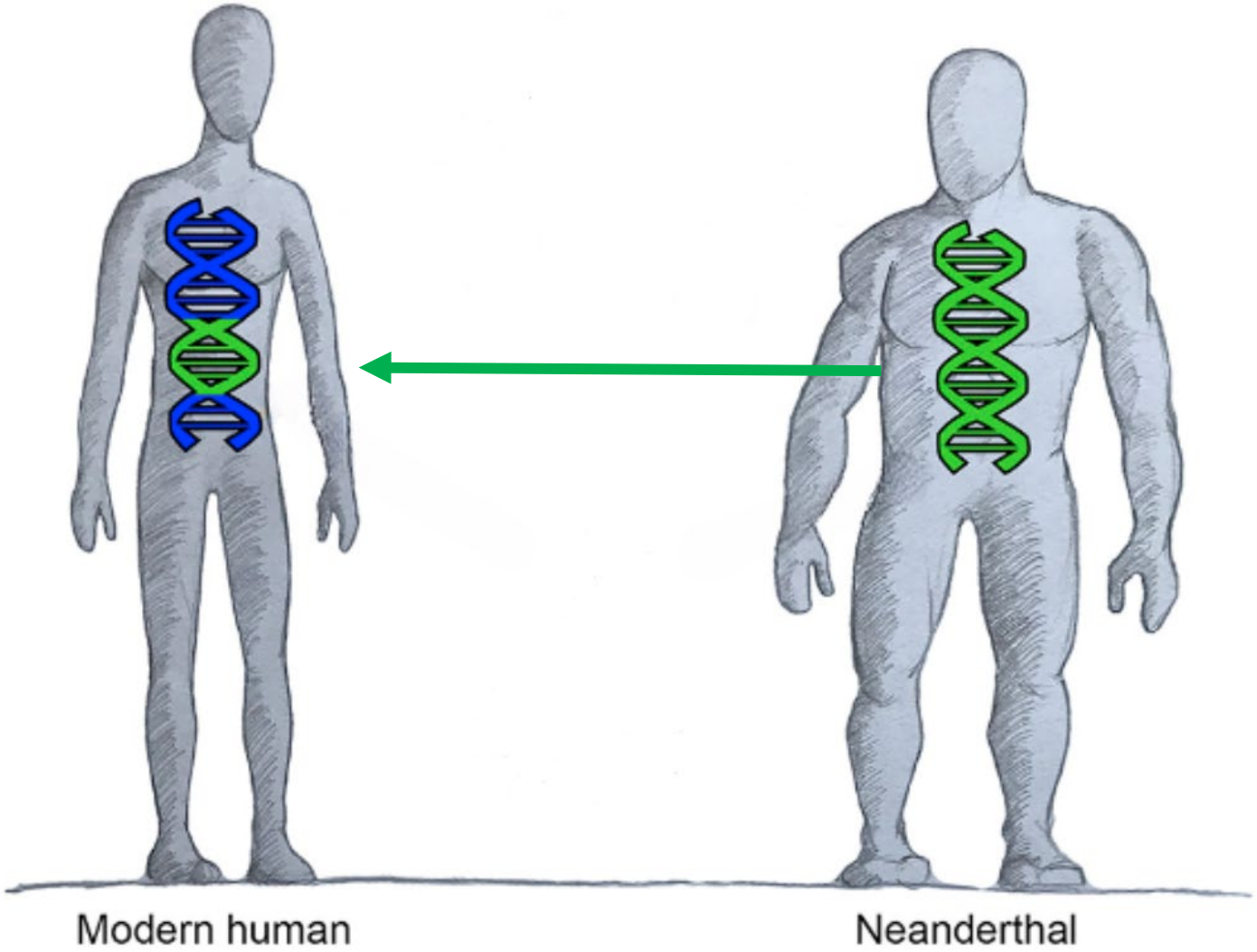
Study the past
if you would define
the future.

Confucius



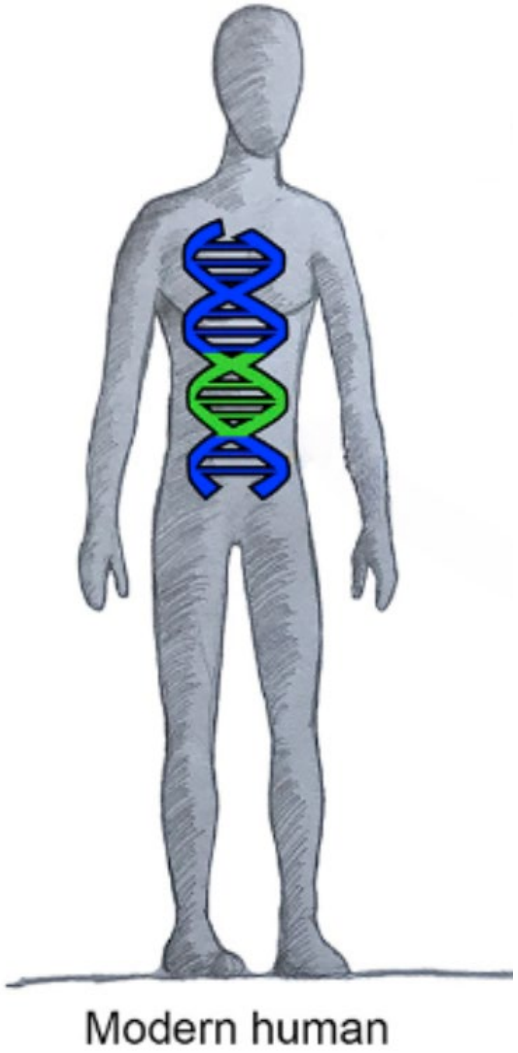
Adapted from Enard & Petrov (2018) Cell

Up to 4% of Eurasian descent genomes are of Neanderthals origin



Adapted from Enard & Petrov (2018) Cell

Some Neanderthals-originated variants are associated with disease risk



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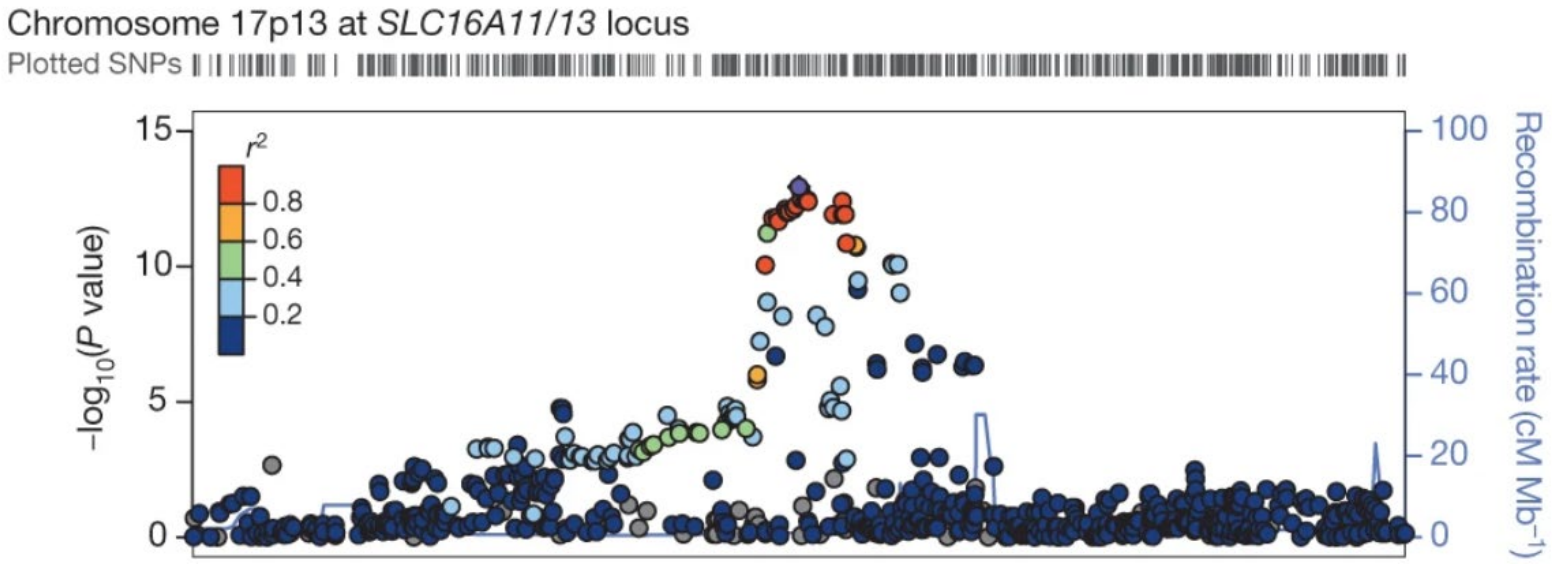
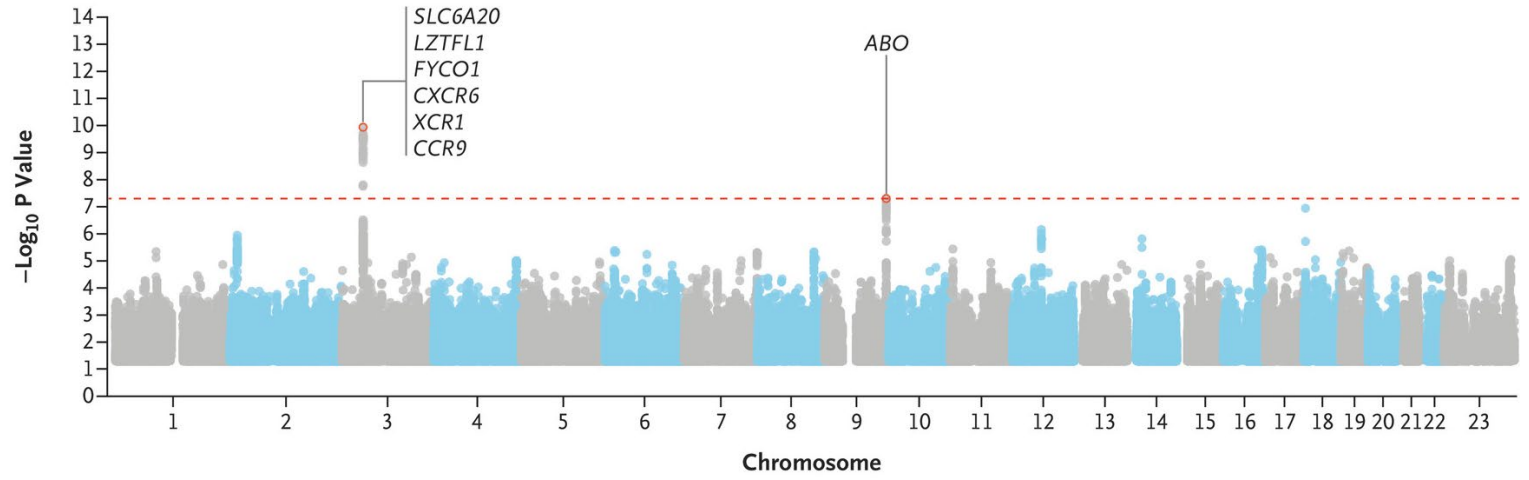
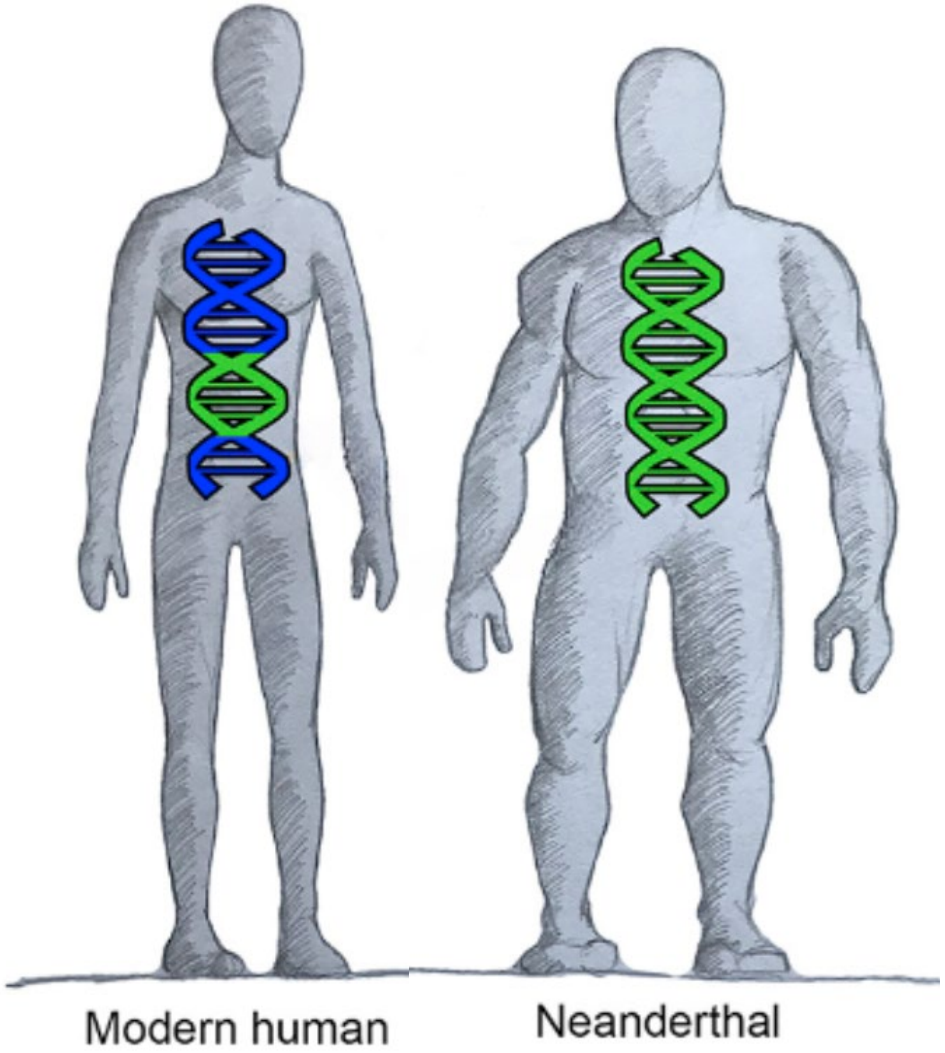


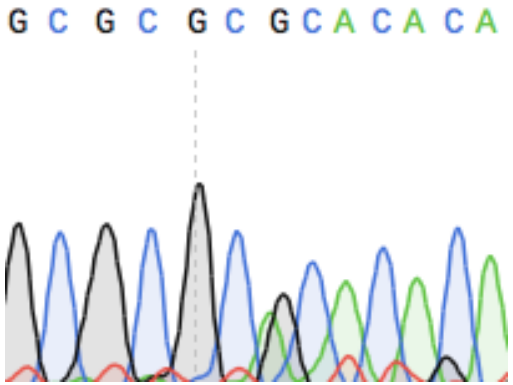
The SIGMA Type 2 Diabetes Consortium (2014) Nature



Severe Covid-19 GWAS group (2020) New England J Med

The past, present, and future within our genomes





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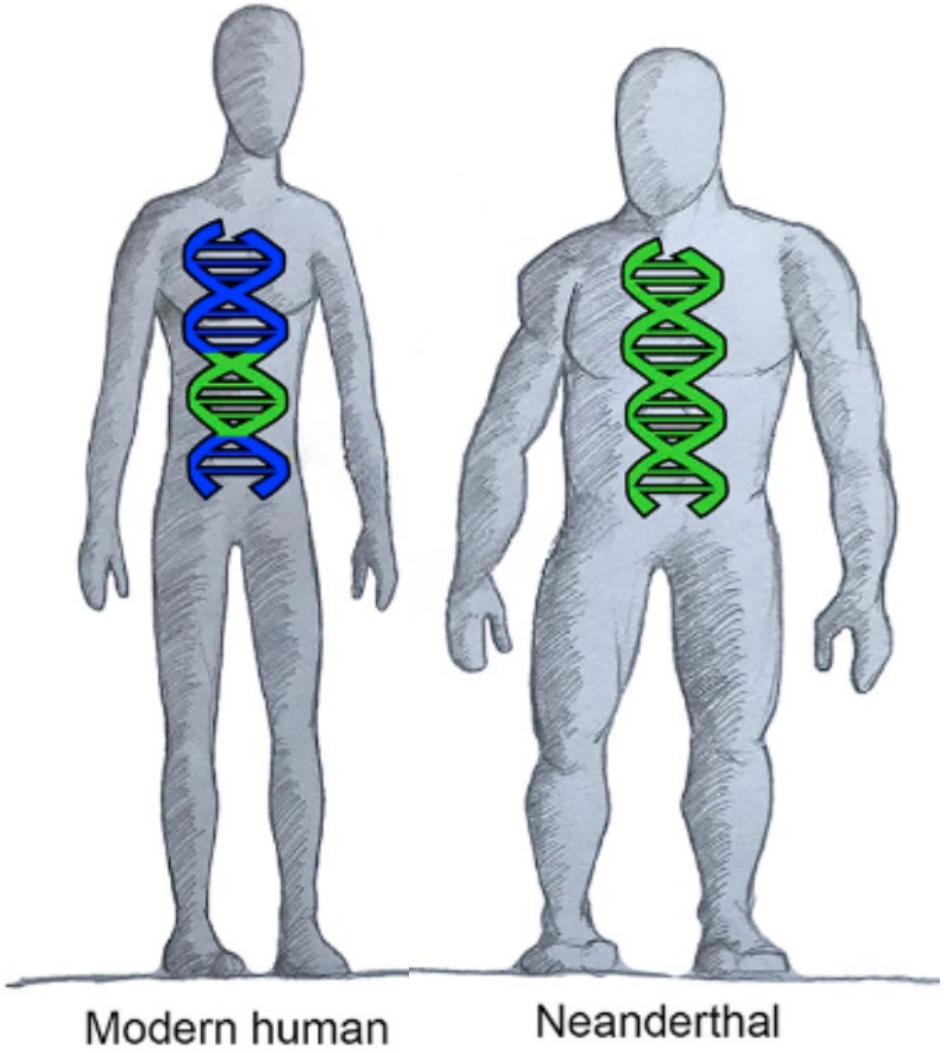

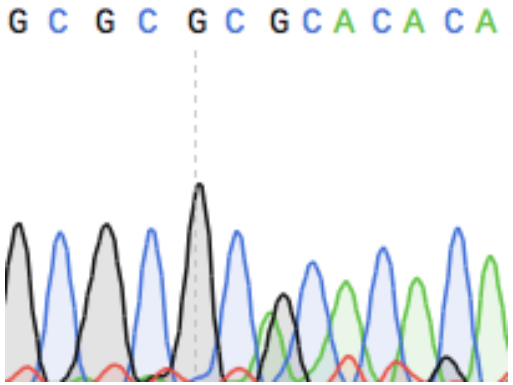

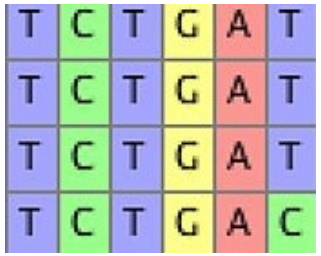

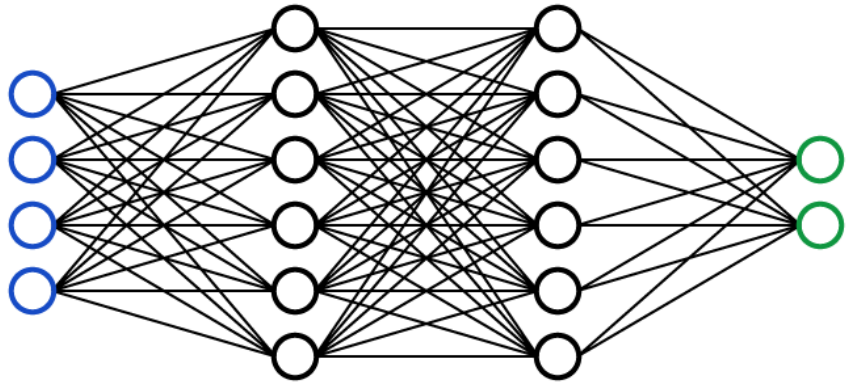

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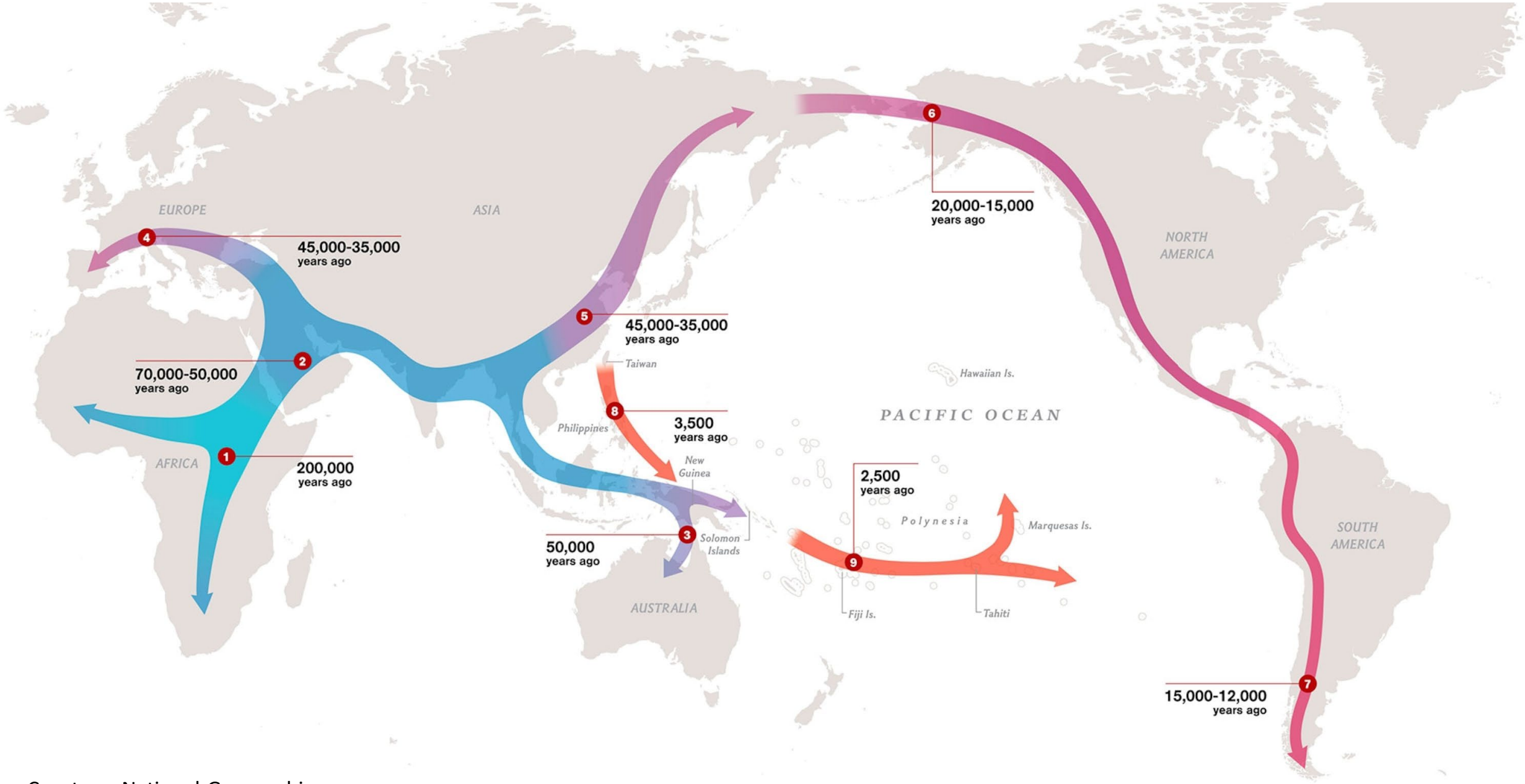


Courtesy: National Geographic

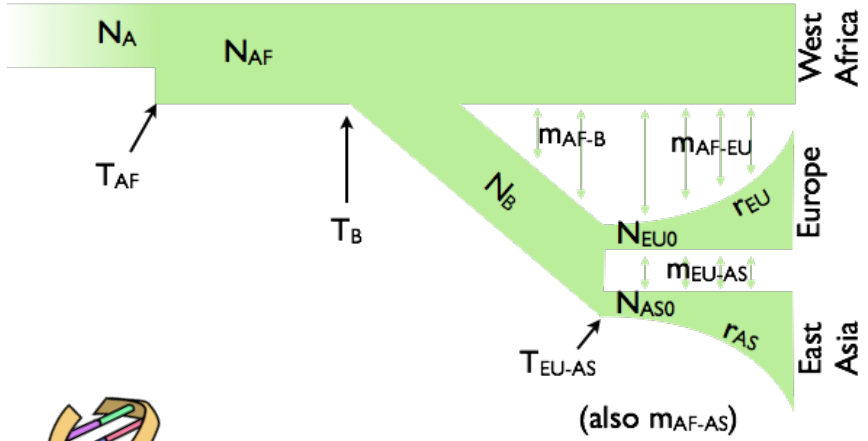
PLOS GENETICS

1,538 Citation | 59,629 View

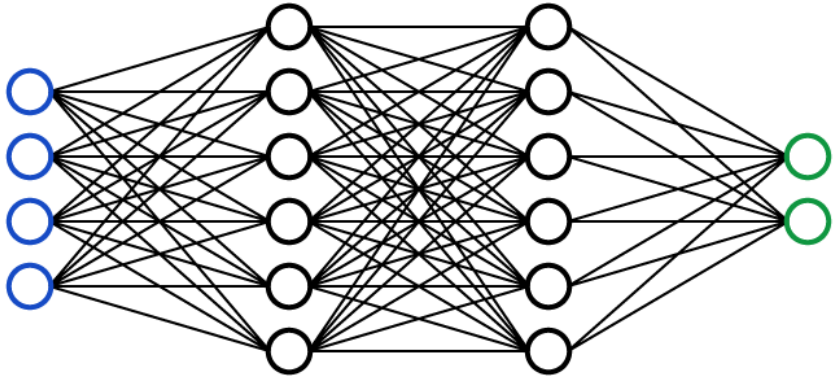
Inferring the Joint Demographic History of Multiple Populations from Multidimensional SNP Frequency Data

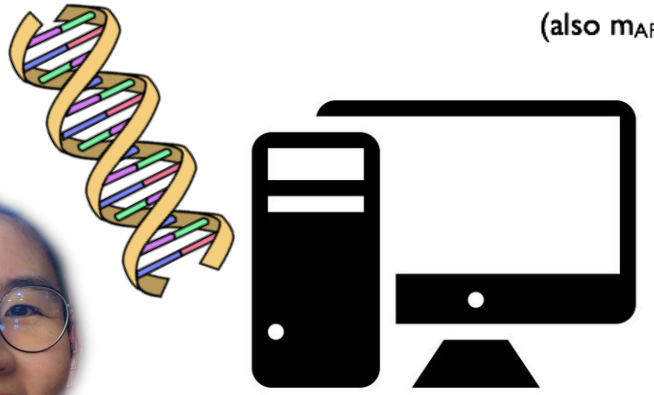
Ryan N. Gutenkunst, Ryan D. Hernandez, Scott H. Williamson, Carlos D. Bustamante

Published: October 23, 2009 • https://doi.org/10.1371/journal.pgen.1000695

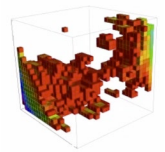


2009





2020



dadi: diffusion approximation for demographic inference

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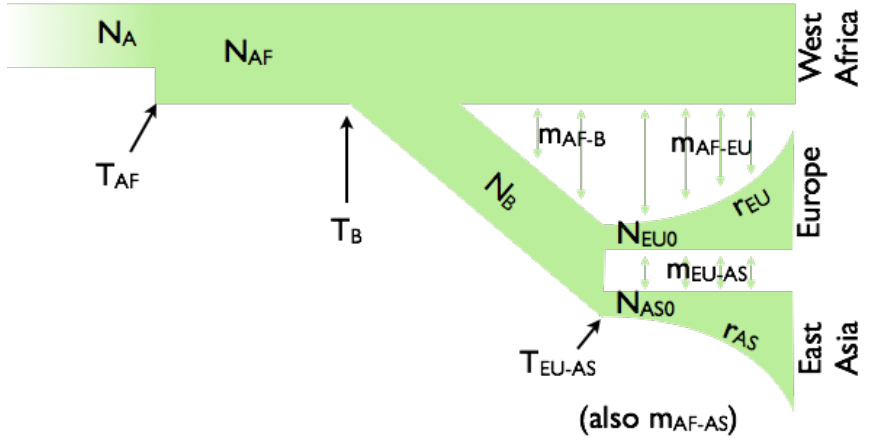

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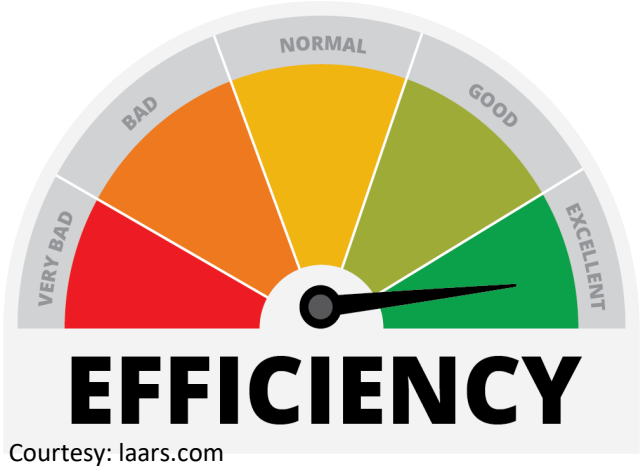
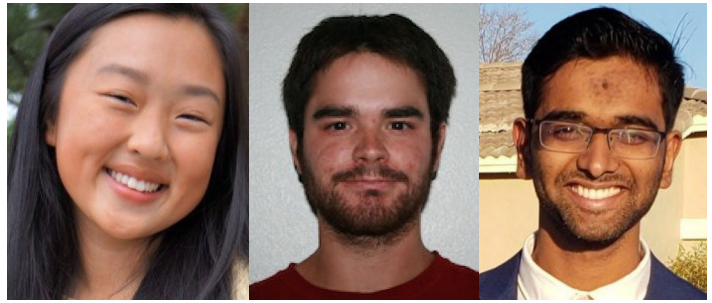


Courtesy: laars.com

Connie Sun, Travis Struck, Mathews Sajan



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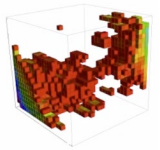

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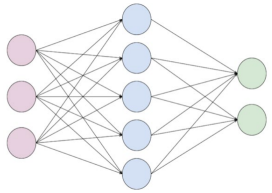


donni: demography optimization via neural network inference
Tran et al. (BioRxiv 2023)

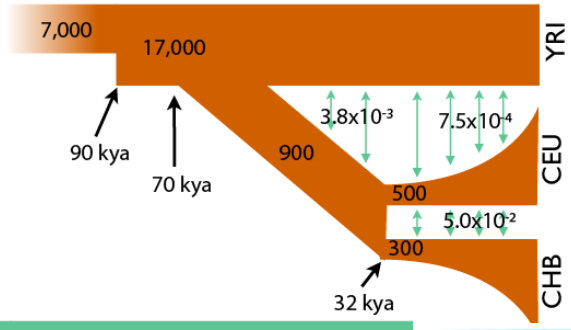
Data (SNP)

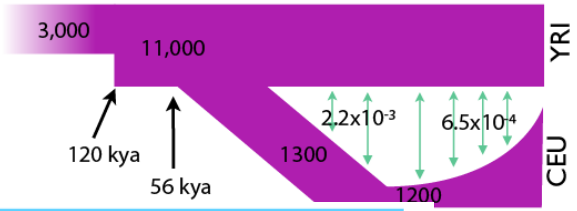


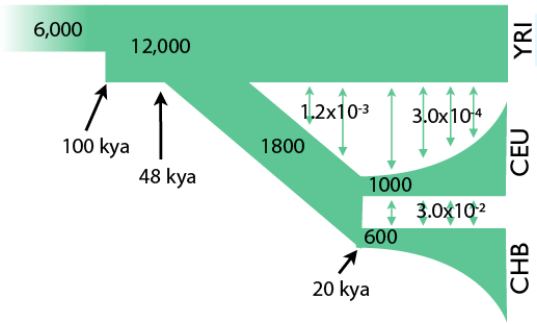
TGGTCACTCTTAT
TGGTCACTCTTAT
TGGTCACTCTTAA
TGCTCATTCTTAT
TGCTCATTCTTAT
TGCTCACTCTTAA

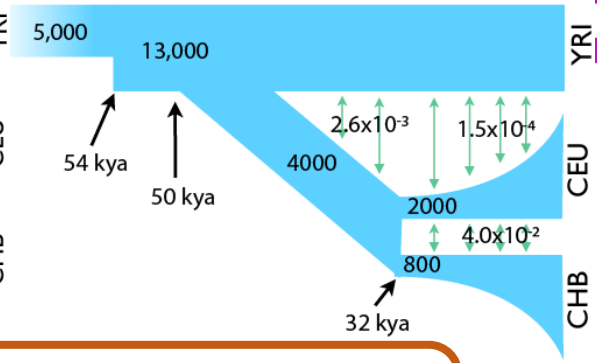
Likelihood Optimization

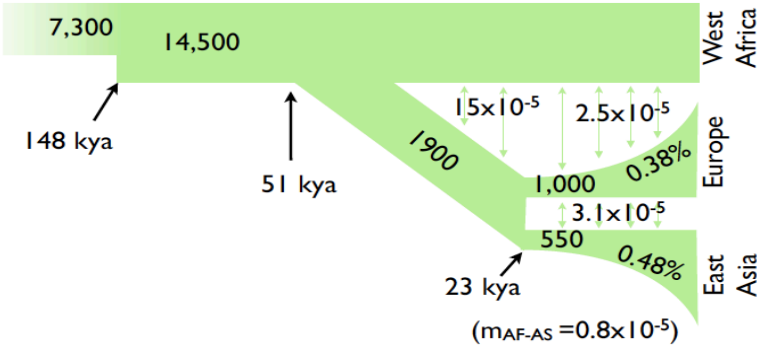
Expensive

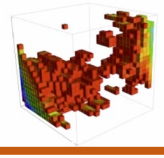




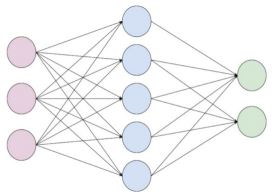








dadi: diffusion approximation for demographic inference



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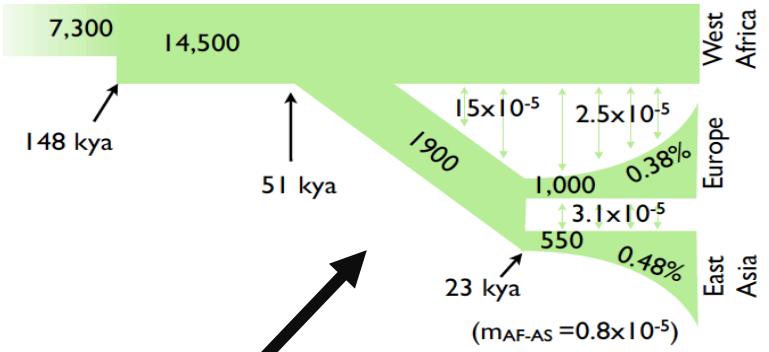
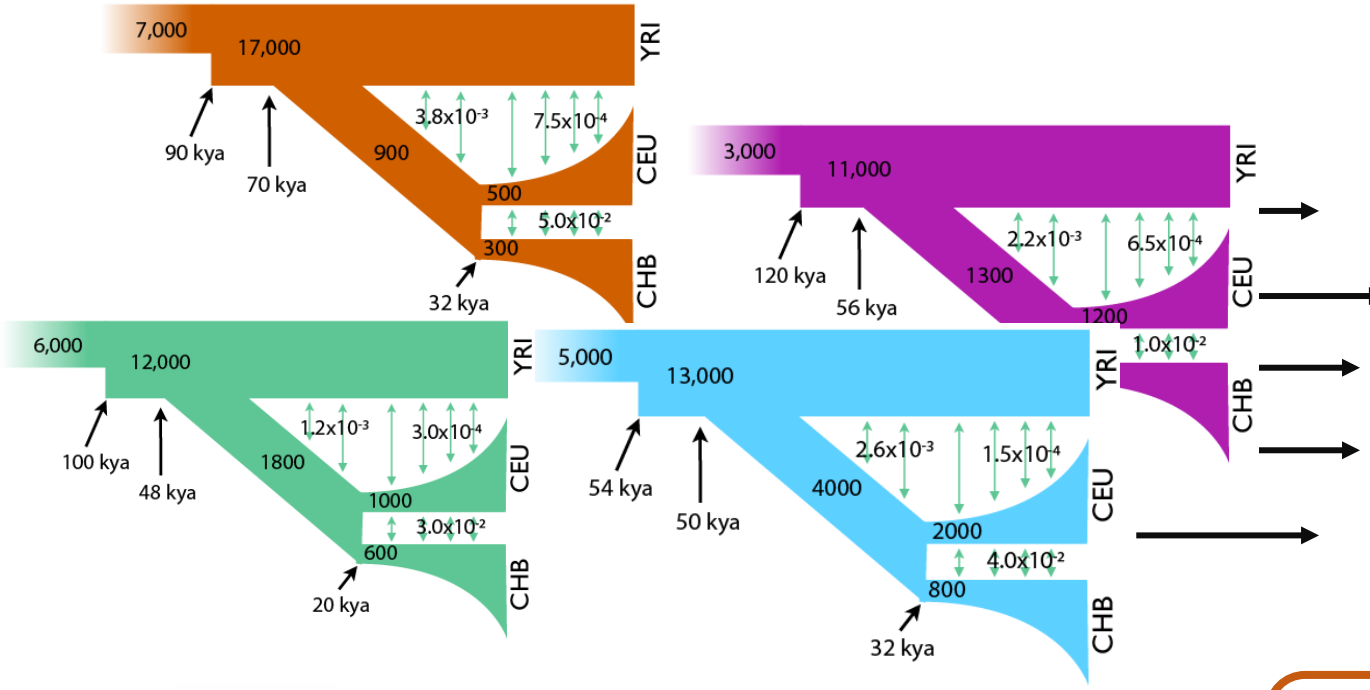
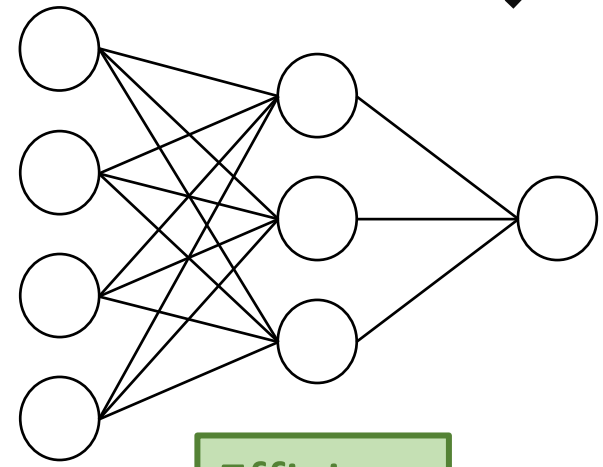
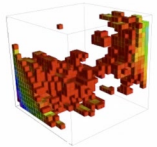






Multilayer Perceptron Regressor

Efficient



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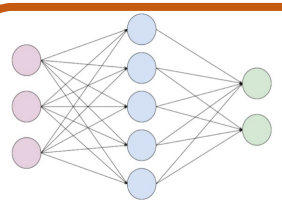

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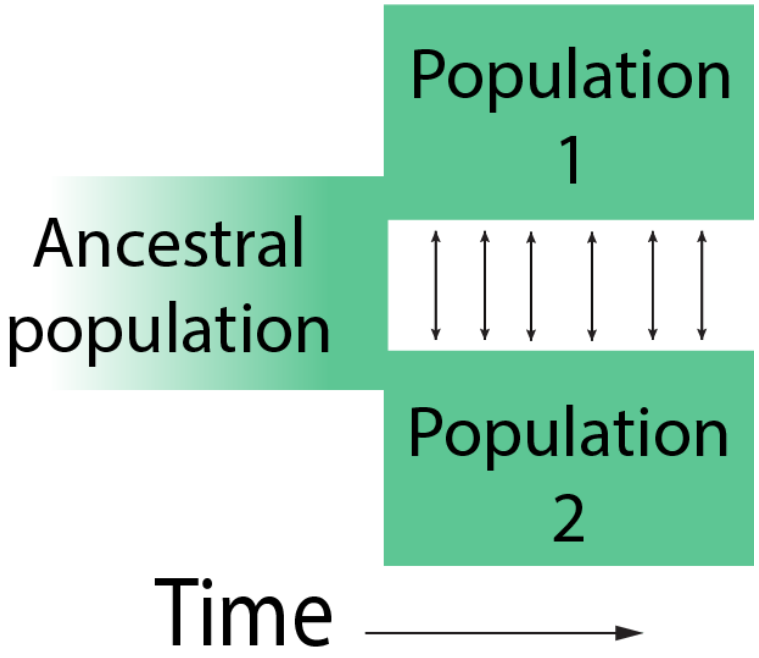
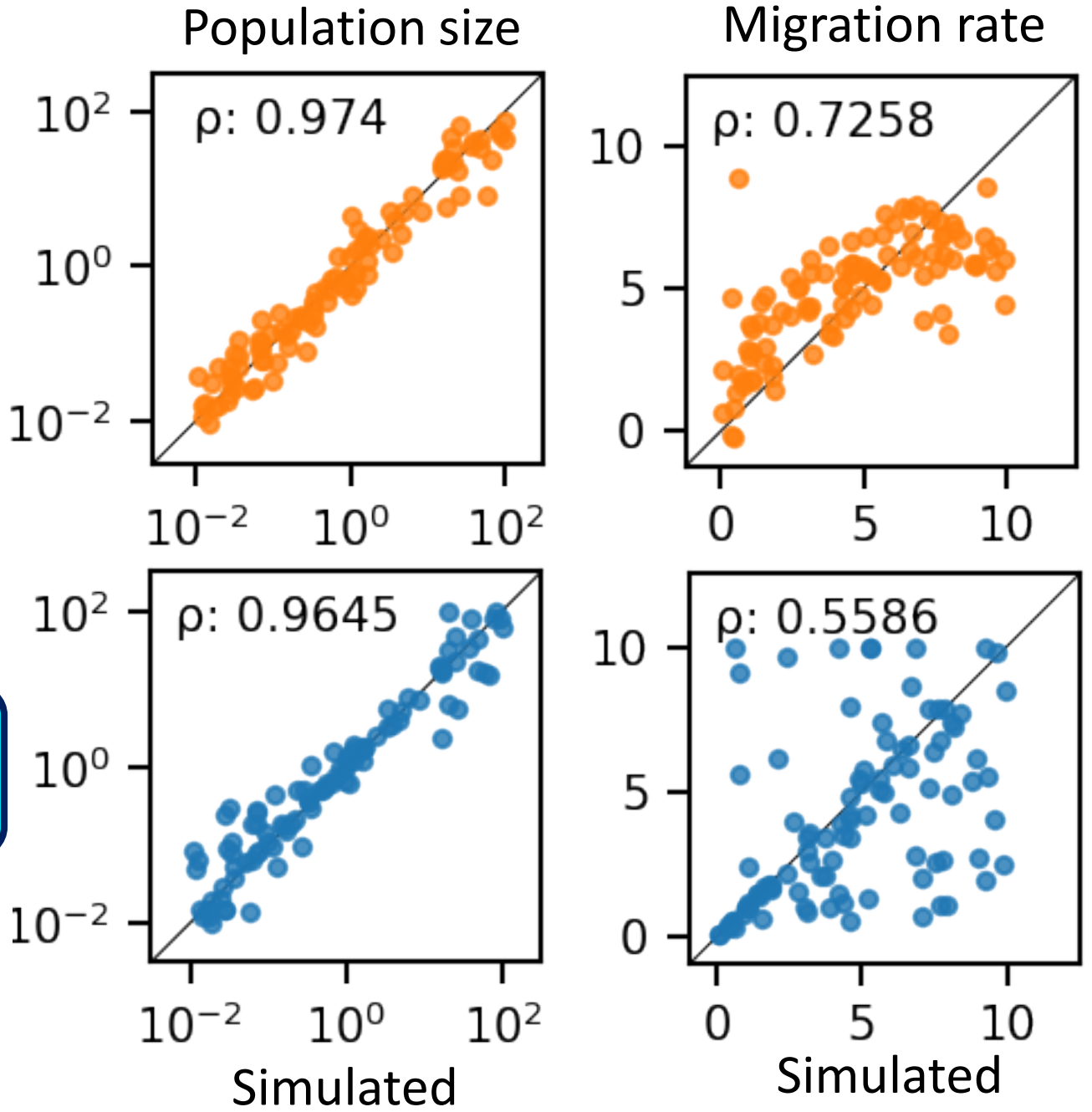


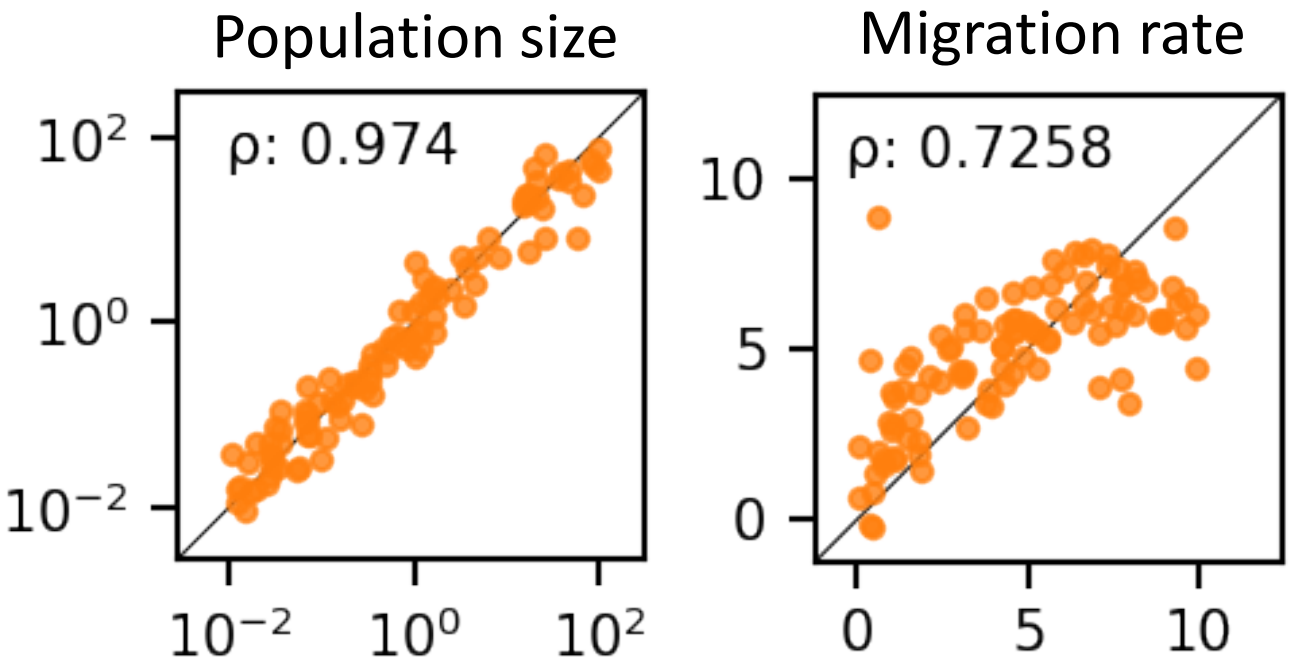
Donni inferred

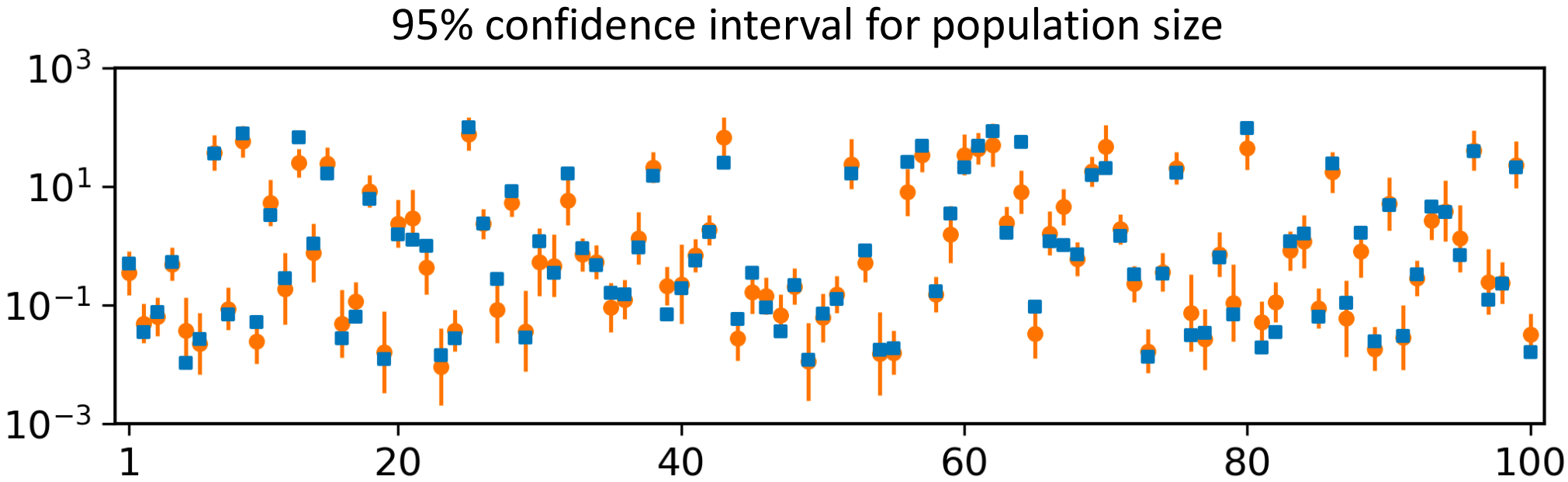
Dadi inferred



Tran et al. (2023) BioRxiv, in revision

Tensorflow Keras
Mean-Variance Estimation Net





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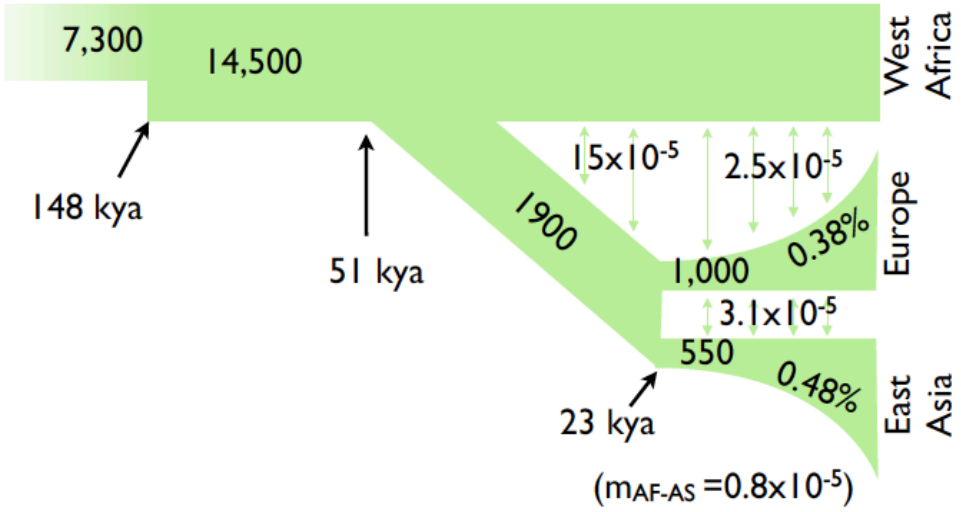
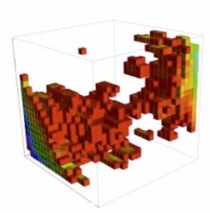


Distribution of fitness effects (DFE)

2009 2017 2020



dadi

fit-dadi
Kim et al.
(Genetics)

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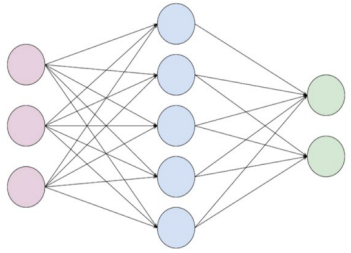

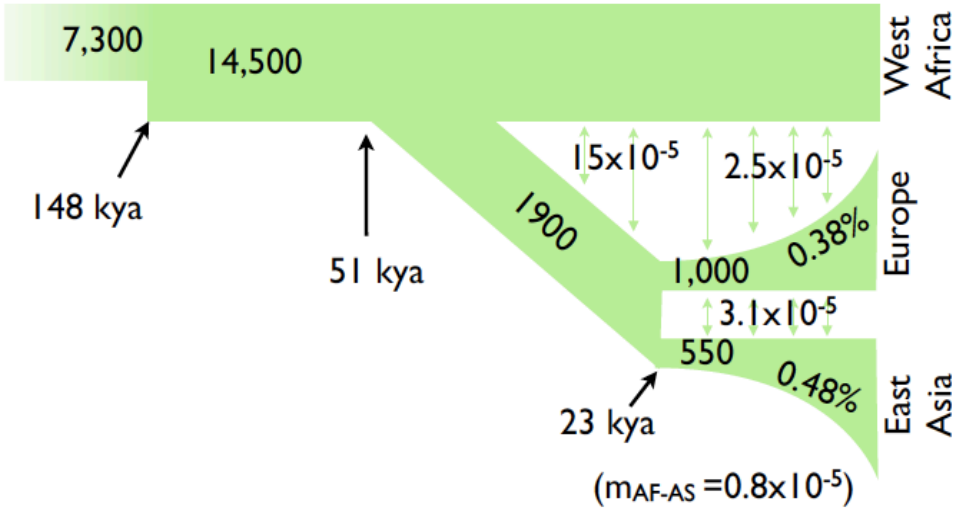

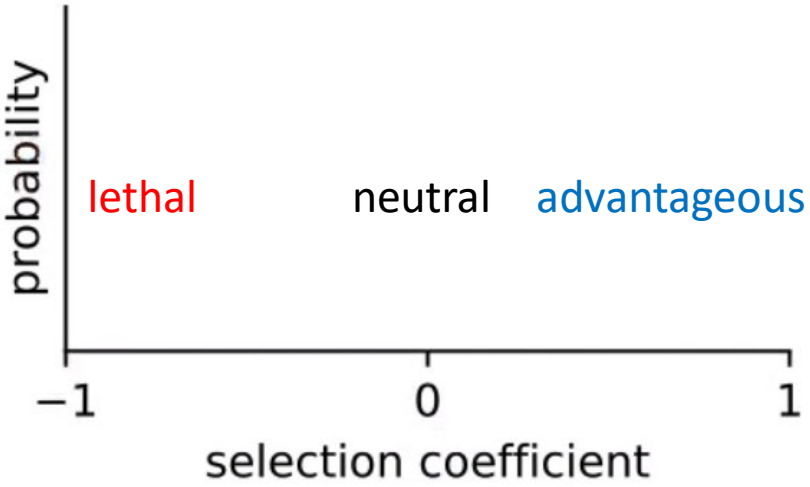

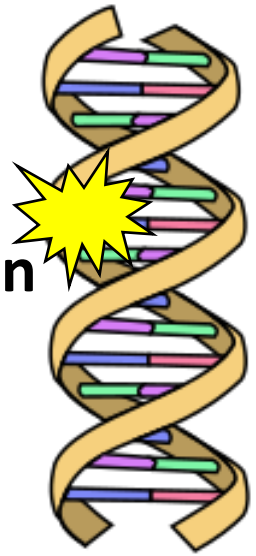

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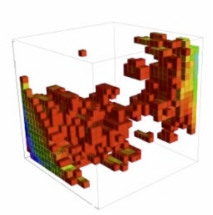

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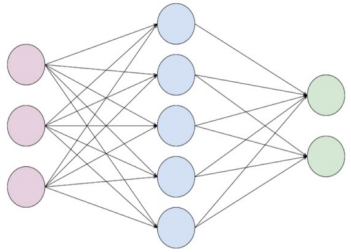

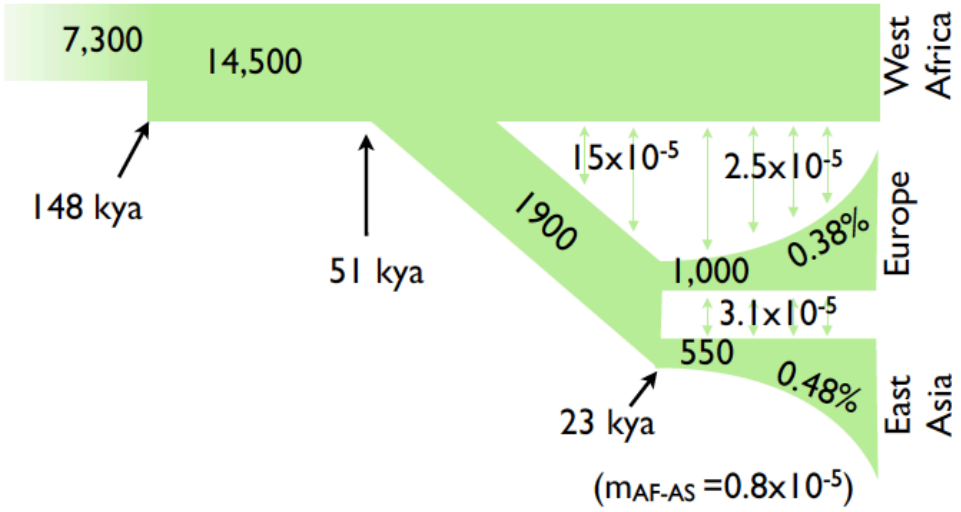

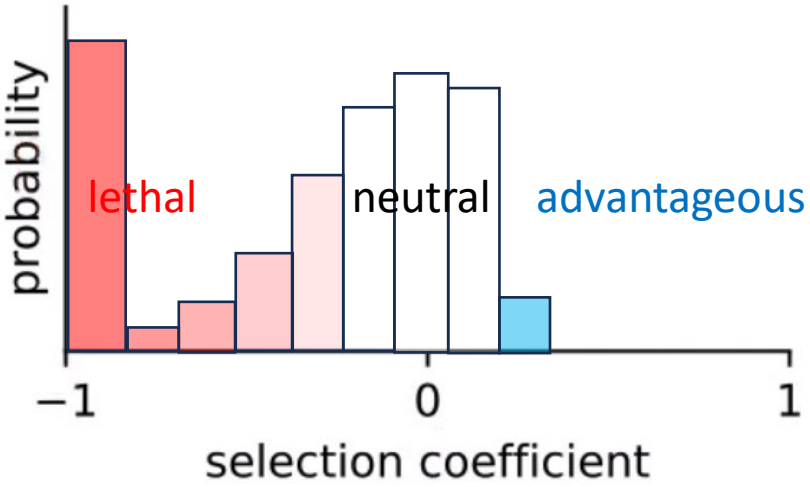

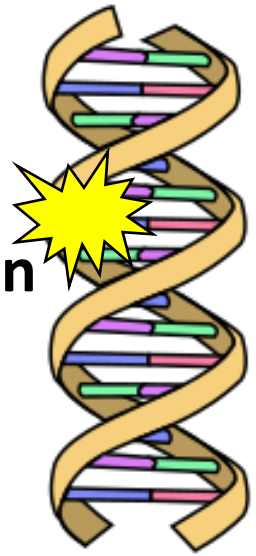

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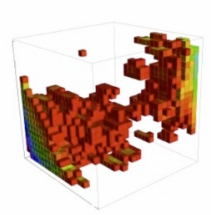

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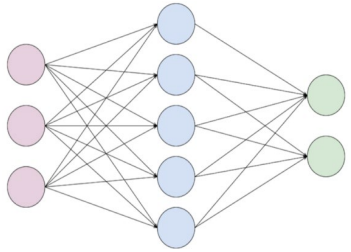
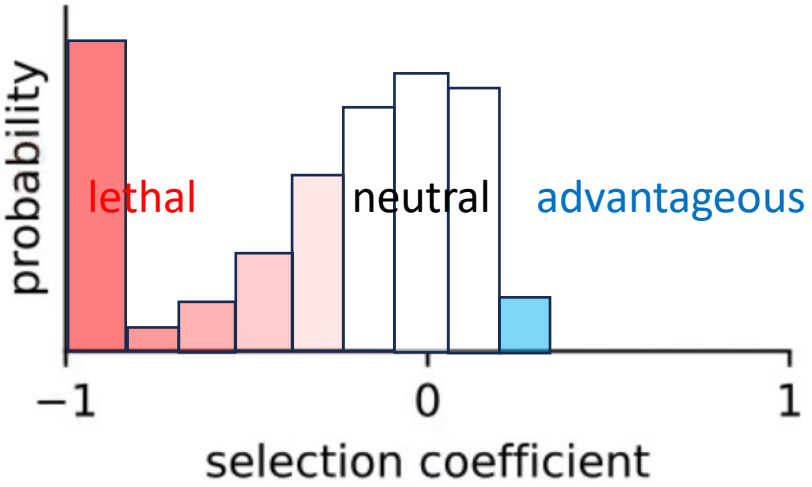
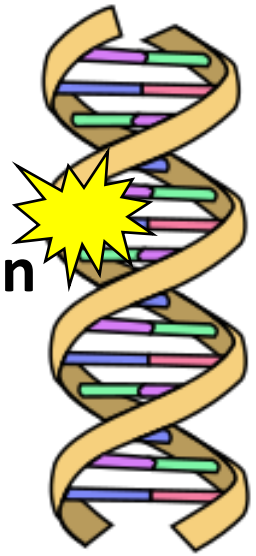
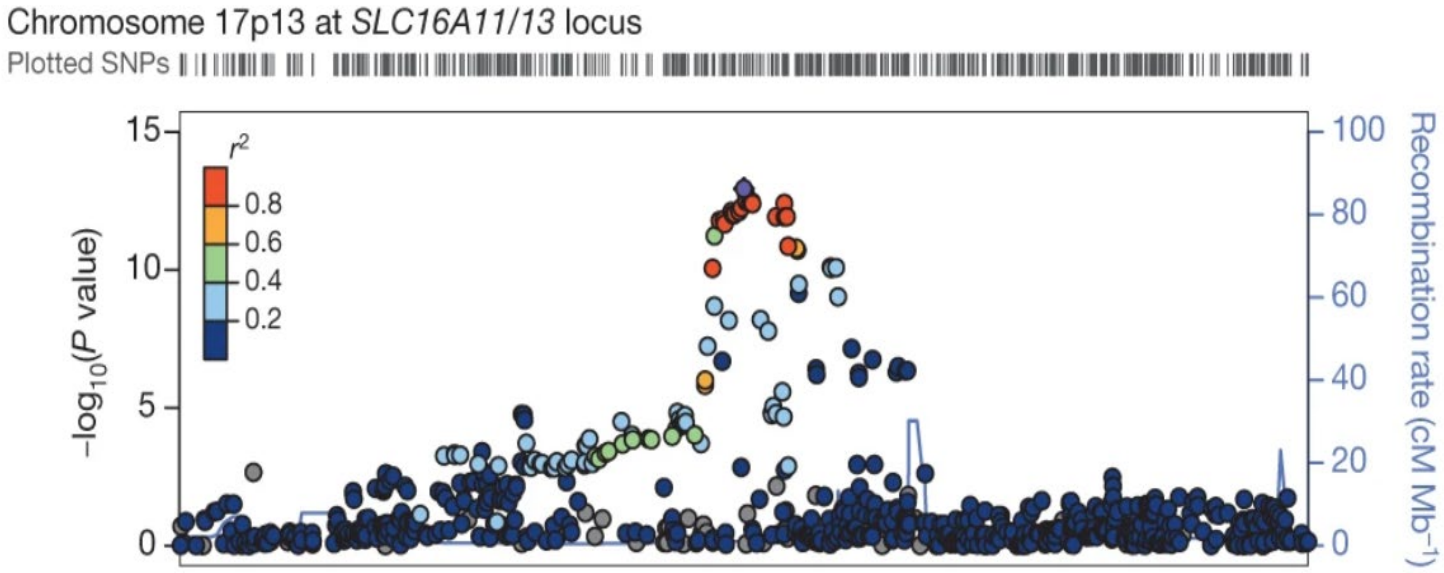


- Mutations associated with diseases are likely deleterious
- The DFE quantifies the portion of deleterious mutations along with their average affect
- Significant implications for the design and interpretation of GWAS







The SIGMA Type 2 Diabetes Consortium (2014) Nature

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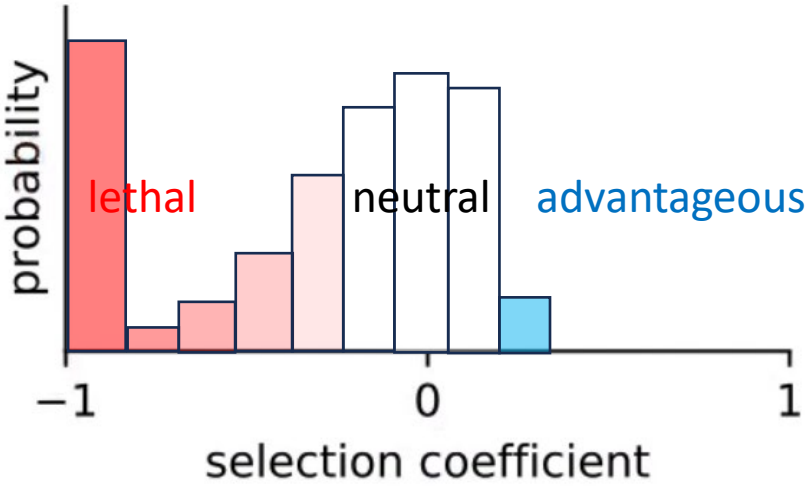
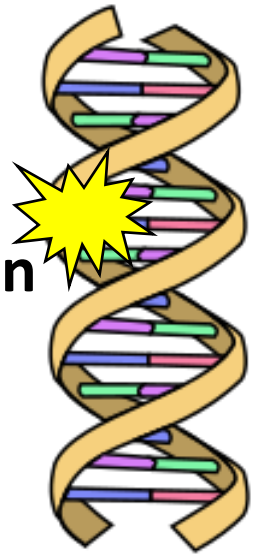


Mutation



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fitness effects (DFE)

2009 2017 2020 2023

dadi
Gutenkunst et al.
(PLOS Genetics)

fit-dadi
Kim et al.
(Genetics)

donni
Tran et al.
(BioRxiv)

DFEnn

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TGGTCACTCTTAT


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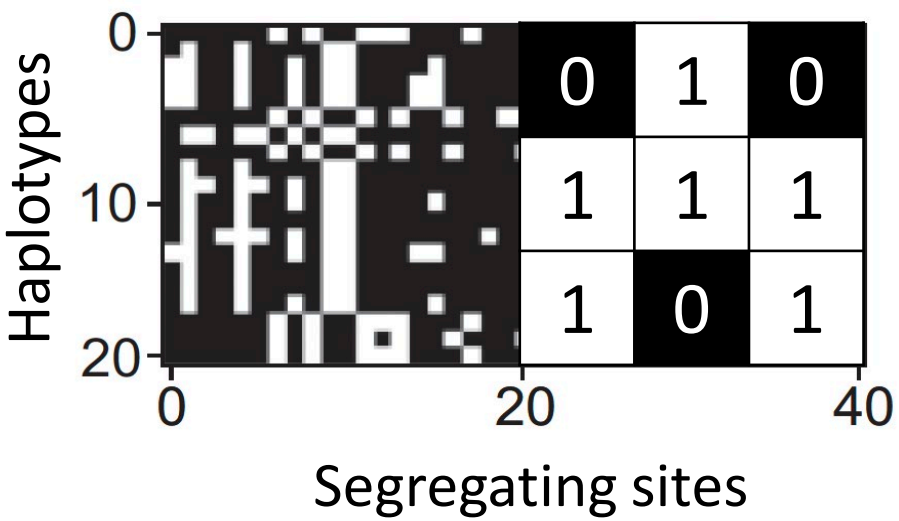
TGCTCACTCTTAA

Flagel *et al.* MBE (2018)



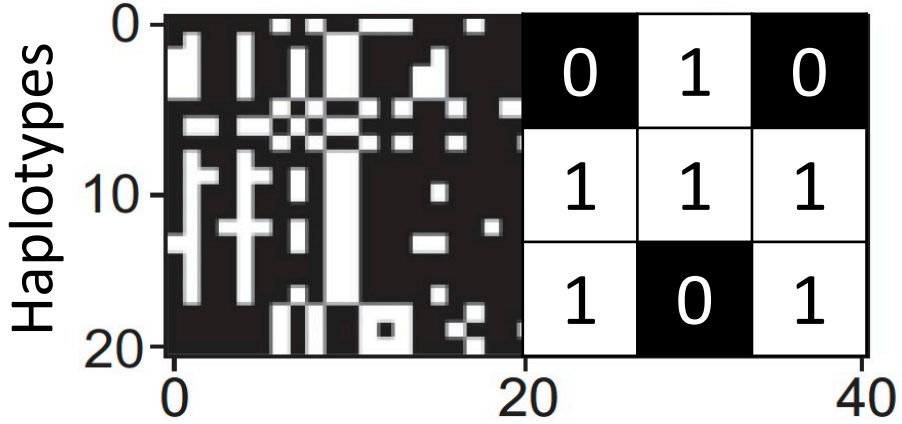
Data (SNP)

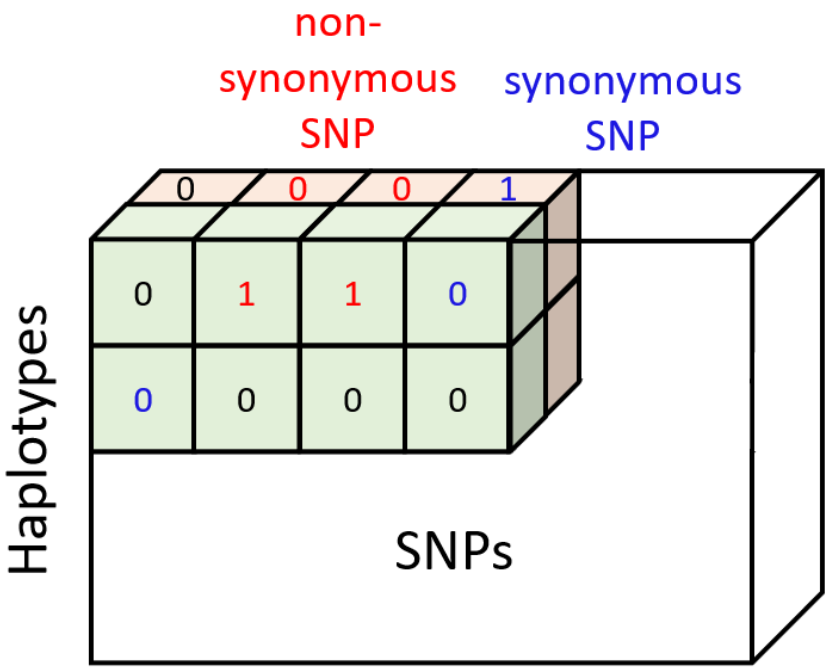

TGGTCACTCTTAT
TGGTCACTCTTAT

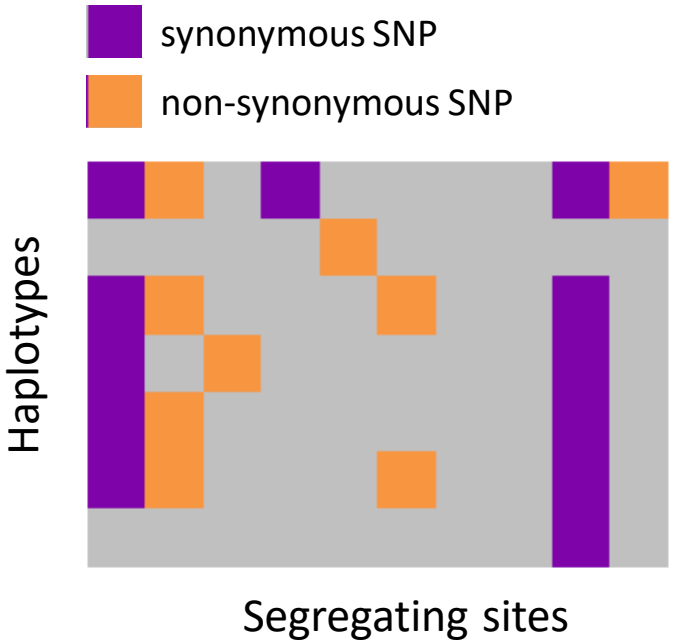

TGGTCACTCTTAA
TGCTCATTCTTAT


TGCTCATTCTTAT
TGCTCACTCTTAA

Flagel *et al.* MBE (2018)







Courtesy: The Wizard of Oz (1939)

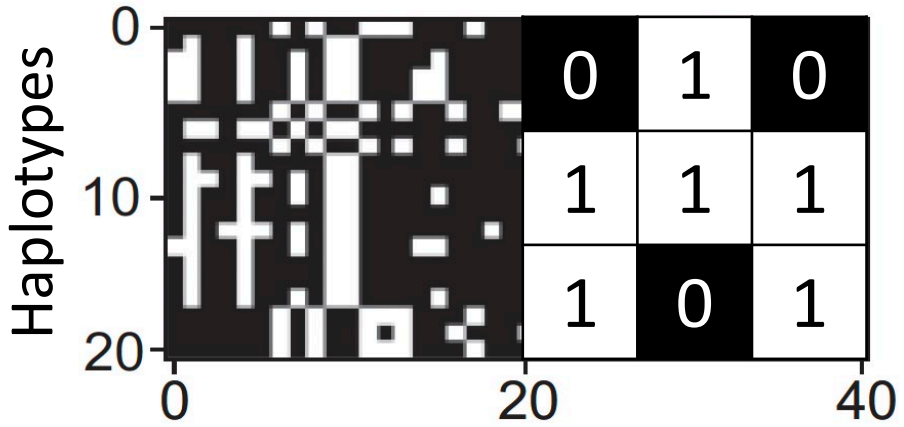
Data (SNP)

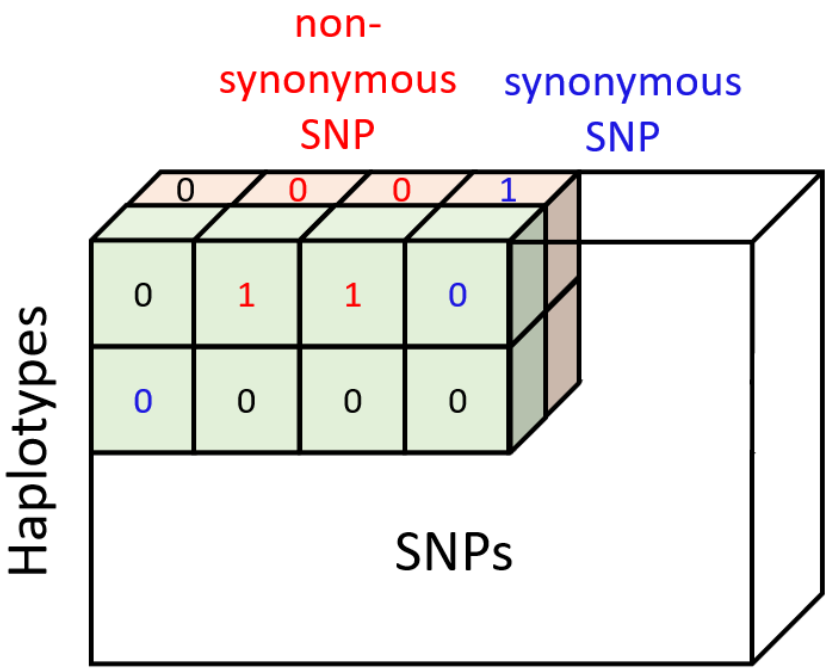

TGGTCACTCTTAT
TGGTCACTCTTAT


TGGTCACTCTTAA
TGCTCATTCTTAT


TGCTCATTCTTAT
TGCTCACTCTTAA

Flagel *et al.* MBE (2018)

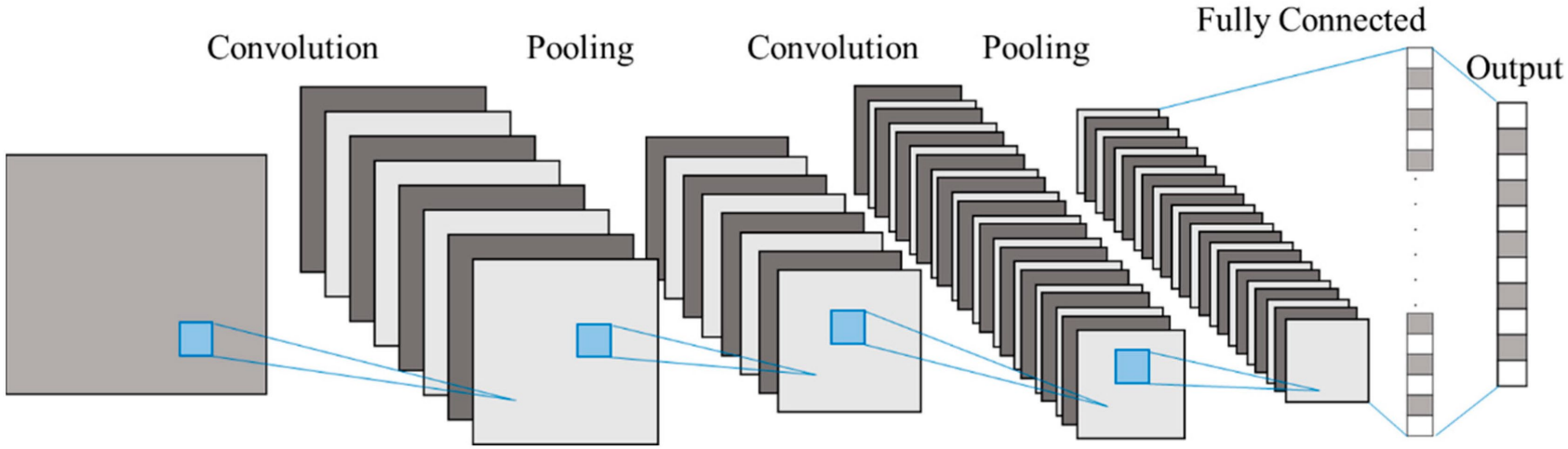




DFEnn

synonymous SNP

non-synonymous SNP



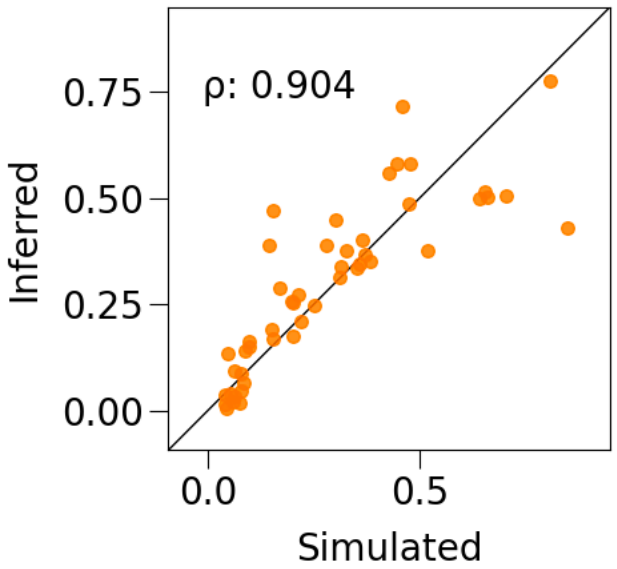
DFEnn

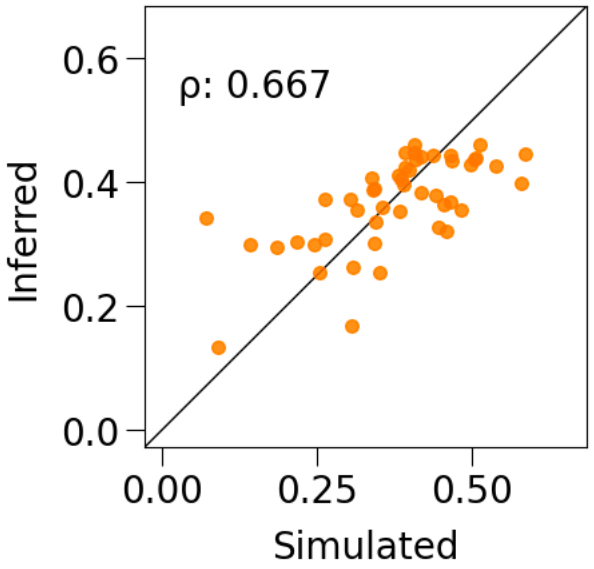
dadi

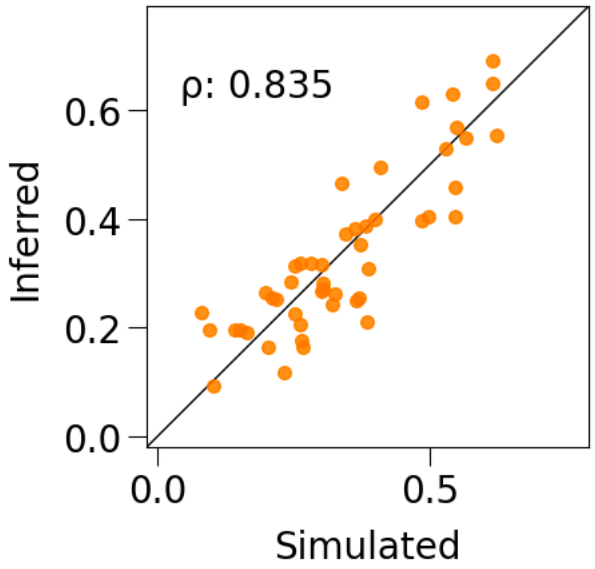
Weakly deleterious

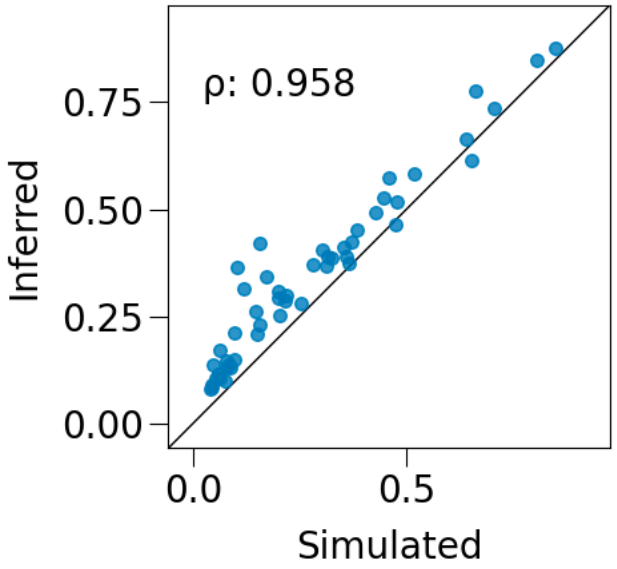
Moderately deleterious

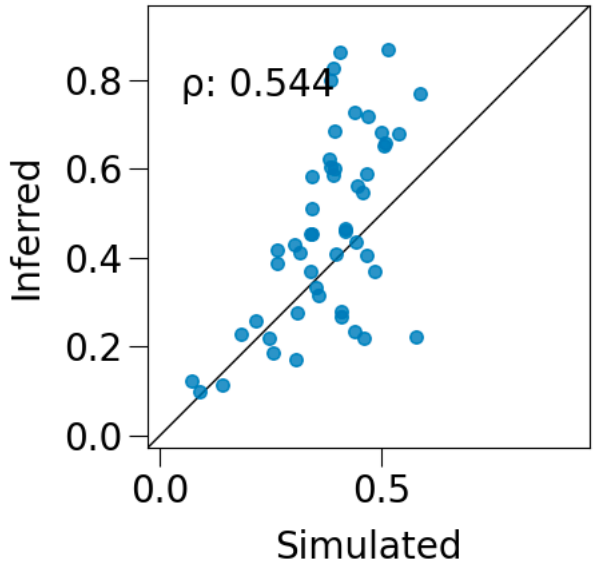
Strongly deleterious

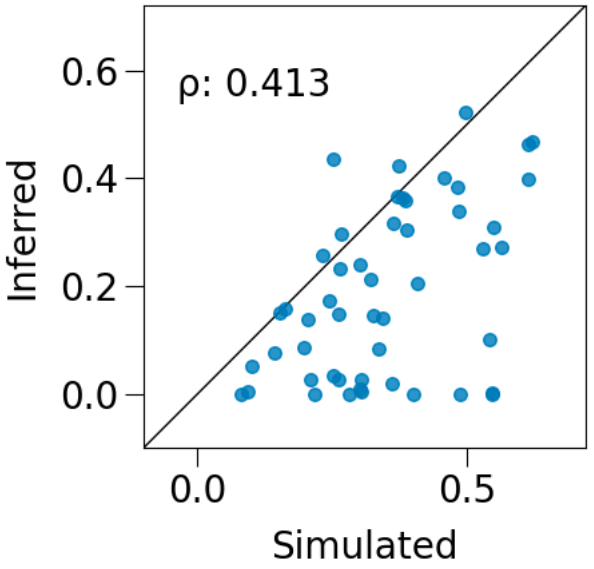






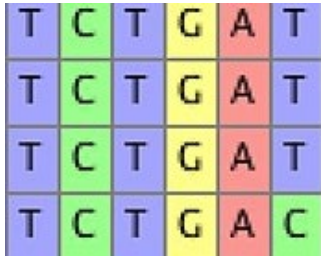


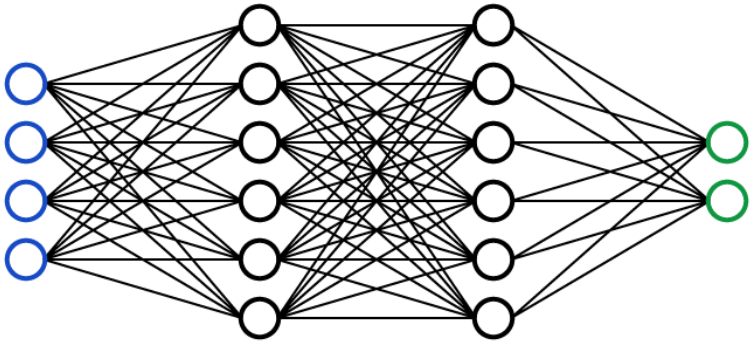




Preliminary results

Summary





- Genomic data contain a wealth of information about our genetic past and disease risk
- Deep neural networks are powerful and effective tools for extracting insights from genomic data
- donni: computationally efficient inference of population history with uncertainty quantification
- DFEnn: informative genomic data representation and processing with convolutional neural network

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