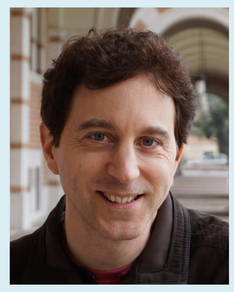

Didier Devaurs
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Interpreting the health impact of genetic variation via deep mutational scanning and machine learning

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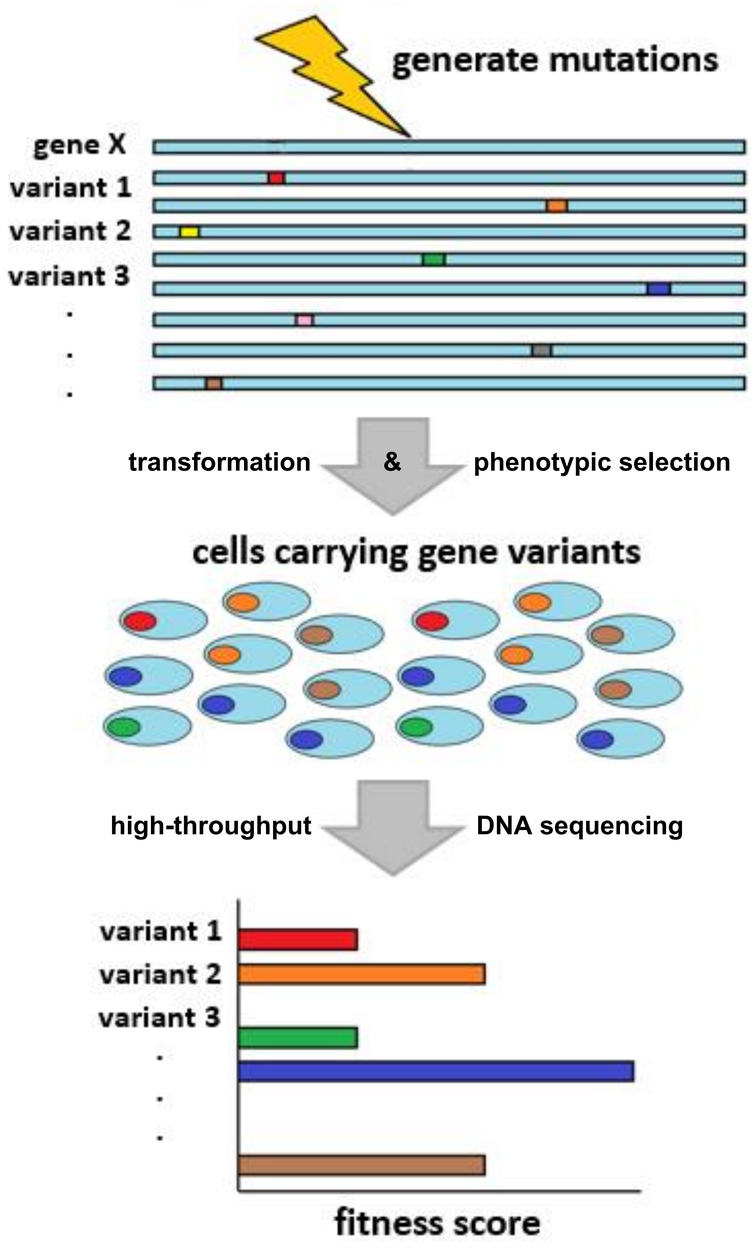
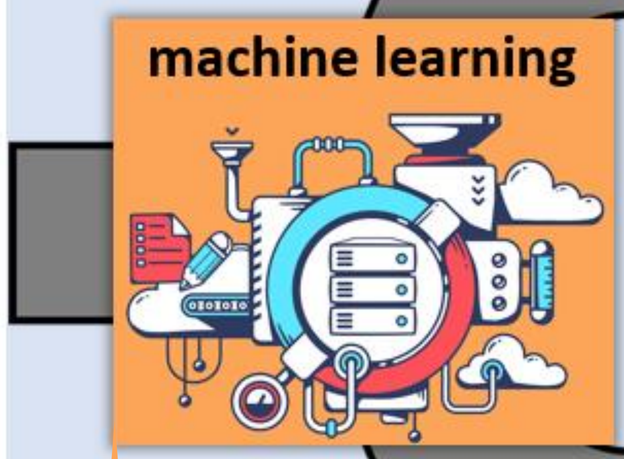
Institute of Genetics and Cancer, The University of Edinburgh

deep mutational scanning (DMS) experiment



problem:
genetic variants of uncertain significance

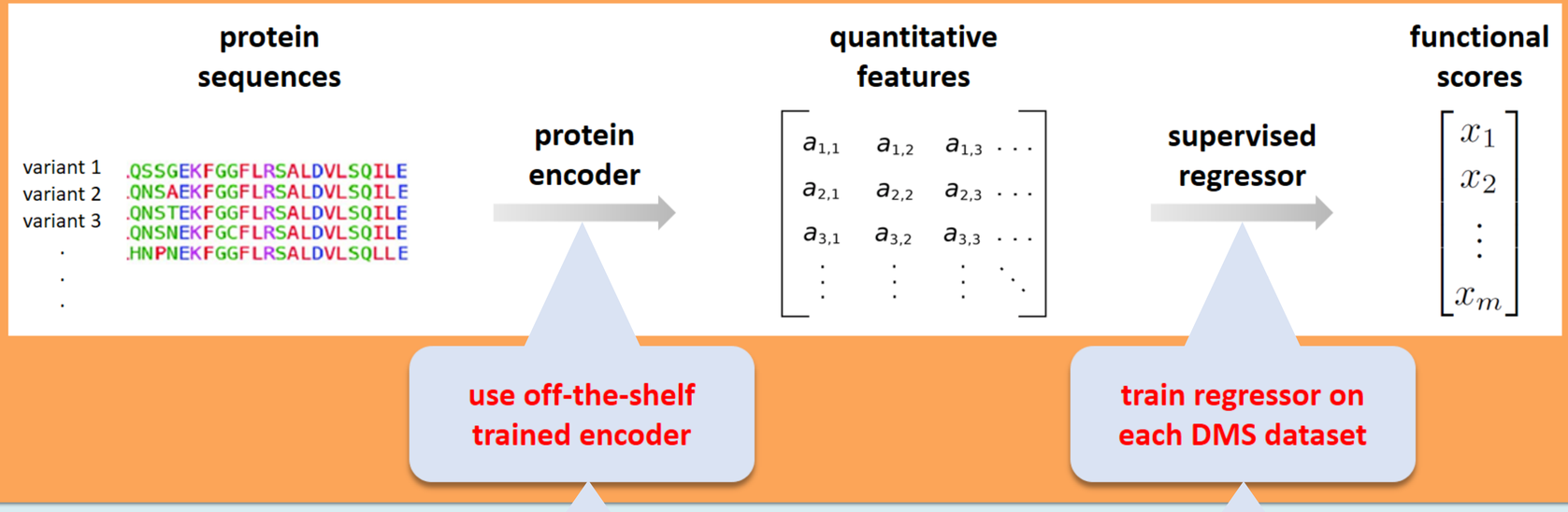


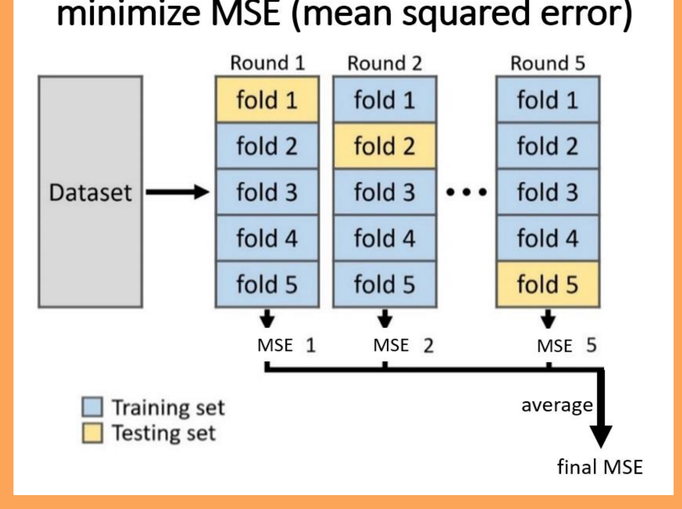
solution:
decipher the relationship between fitness scores and the health impact of genetic variants

good mutations

bad mutations

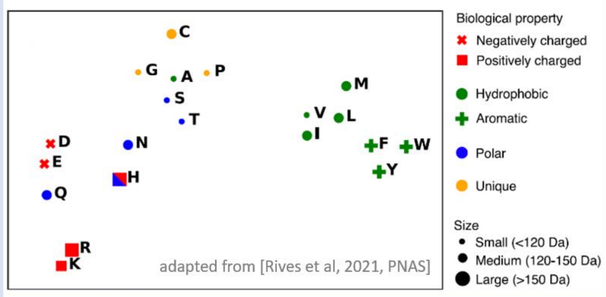
bilayer machine learning architecture



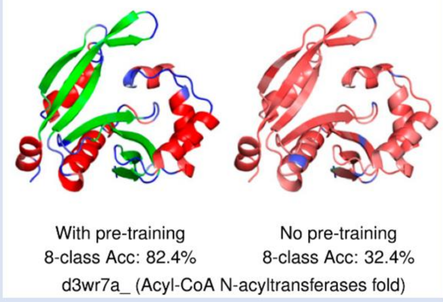


protein encoder: Evolutionary Scale Modelling (ESM) developed by Facebook AI research

recapitulate amino acid properties



predict protein secondary structure



17 encoders: deep neural networks (Transformer) trained on UniProt protein sequences

20 regressors:
linear regression
lasso
partial least squares regression
Gaussian process regression
elastic-net
kernel ridge regression
support vector machines
k-nearest neighbours
stochastic gradient descent
multi-layer Perceptron
decision tree
random forest
extremely randomized trees
AdaBoost
gradient boosted decision trees
XGBoost
4 voting regressors

short-term impact: addressing quality issues in DMS datasets, e.g., by reducing noise, imputing missing scores, and improving overall interpretability

long-term impact: interpreting genetic variant effects in people directly from experimental DMS data (i.e., DMS fitness scores)