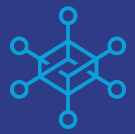
Fighting Antibiotic Resistance with Deep Learning

ML in PL | Maciej Wiatrak | 27.10.2023



Cambridge Centre for AI in Medicine

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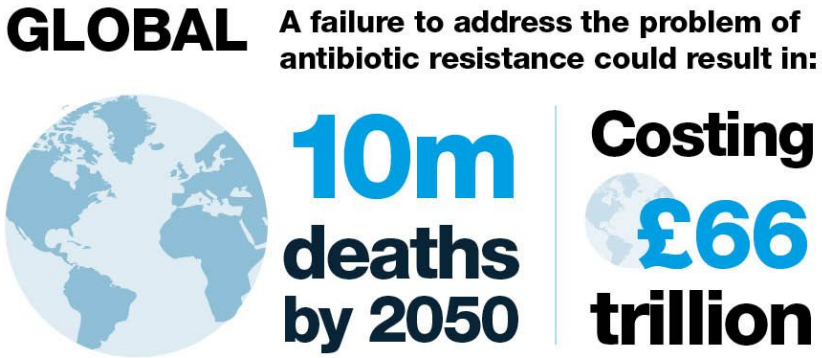
Motivation

The burden and state of Antibiotic Resistance drug pipeline



Source: gov.uk

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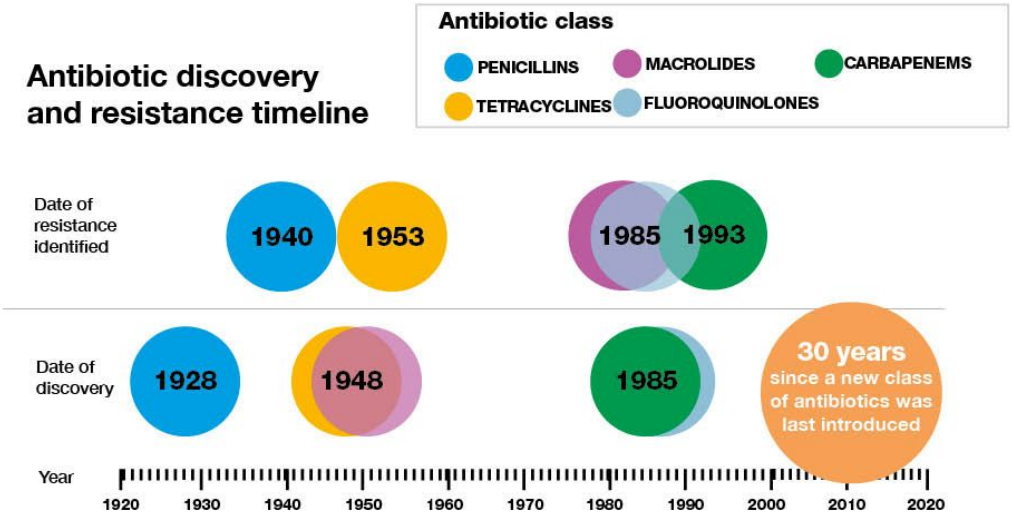

Source: gov.uk

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Can we develop machine learning method which could help us diagnose and understand the molecular mechanisms leading to antibiotic resistance?

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DNA defines antibiotic resistance levels

Bacterial strain

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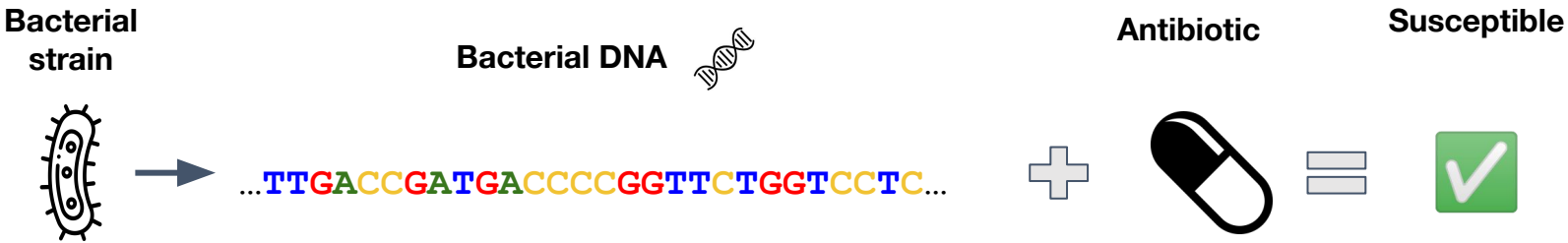
DNA defines antibiotic resistance levels

Bacterial strain

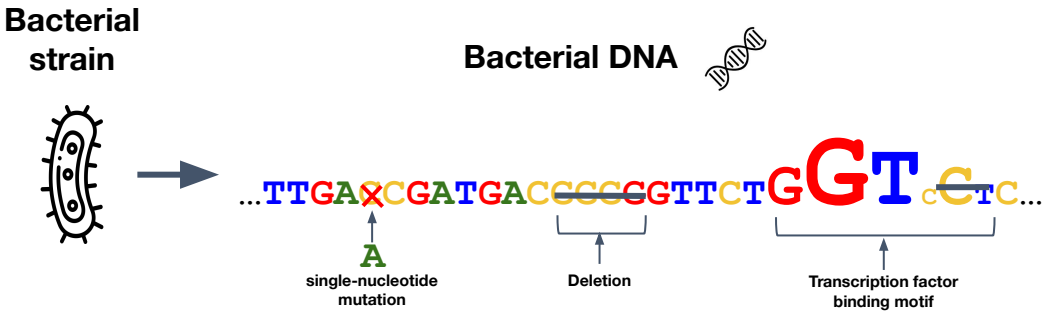
Bacterial DNA

...TTGACCGATGACCCCGGTTCTGGTCCTC...

DNA defines antibiotic resistance levels



DNA defines antibiotic resistance levels



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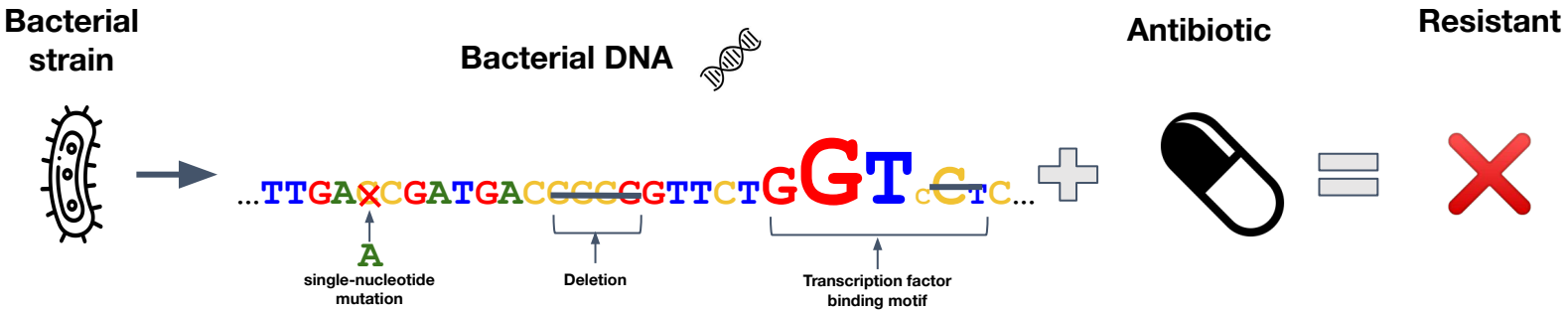

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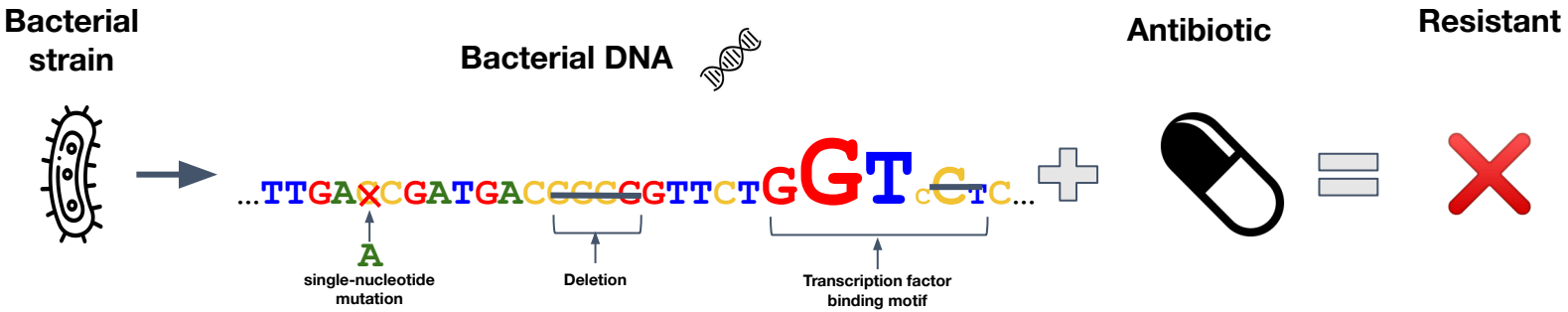

DNA is a full of patterns!

GeneBac

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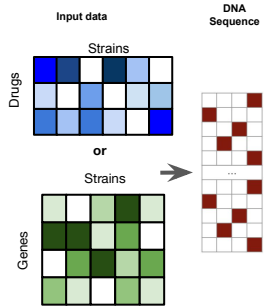
GeneBac



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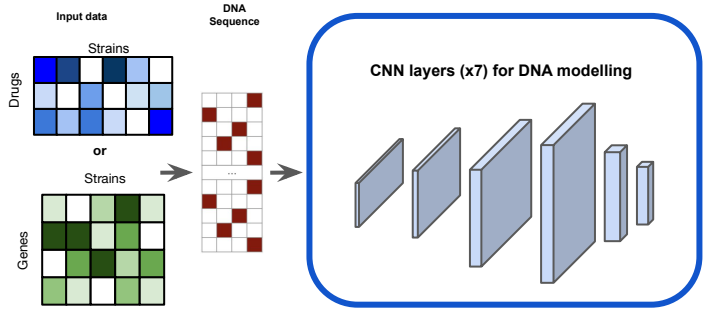
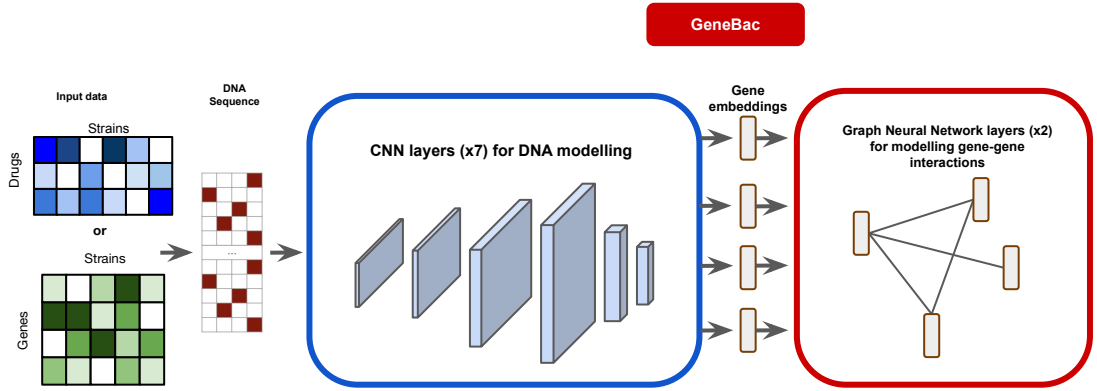

Input data
DNA Sequence
Strains
Drugs
or
Strains
Genes
CNN layers (x7) for DNA modelling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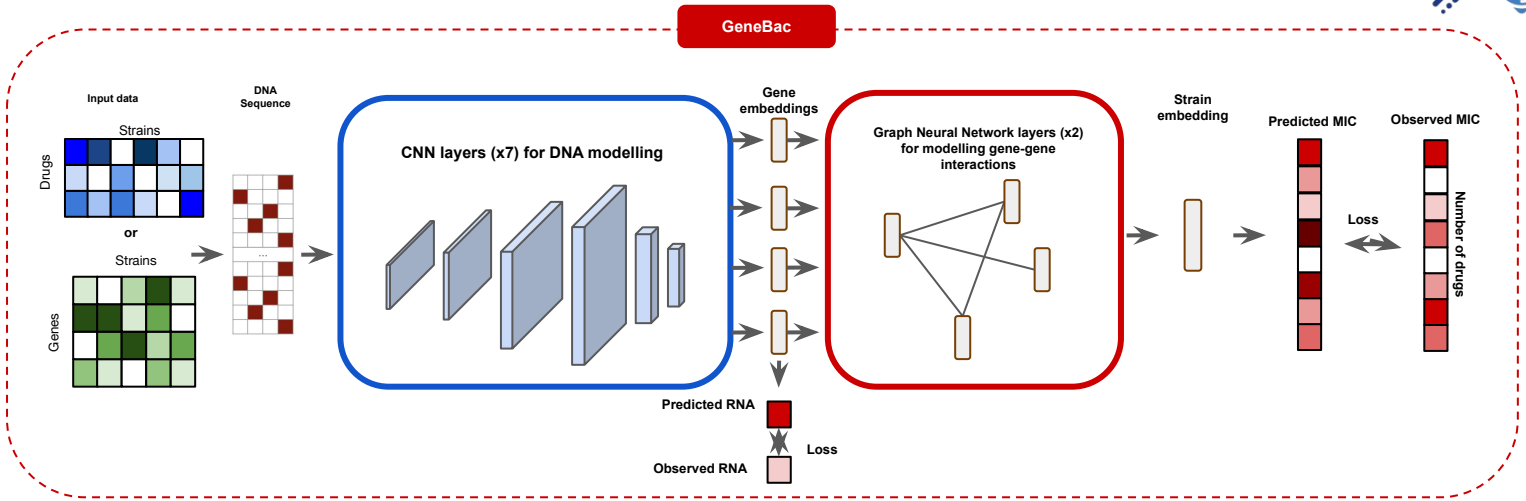
CNN layers (x7) for DNA modelling
Gene embeddings
Graph Neural Network layers (x2) for modelling gene-gene interactions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Strain embedding
Predicted MIC
Observed MIC
Loss
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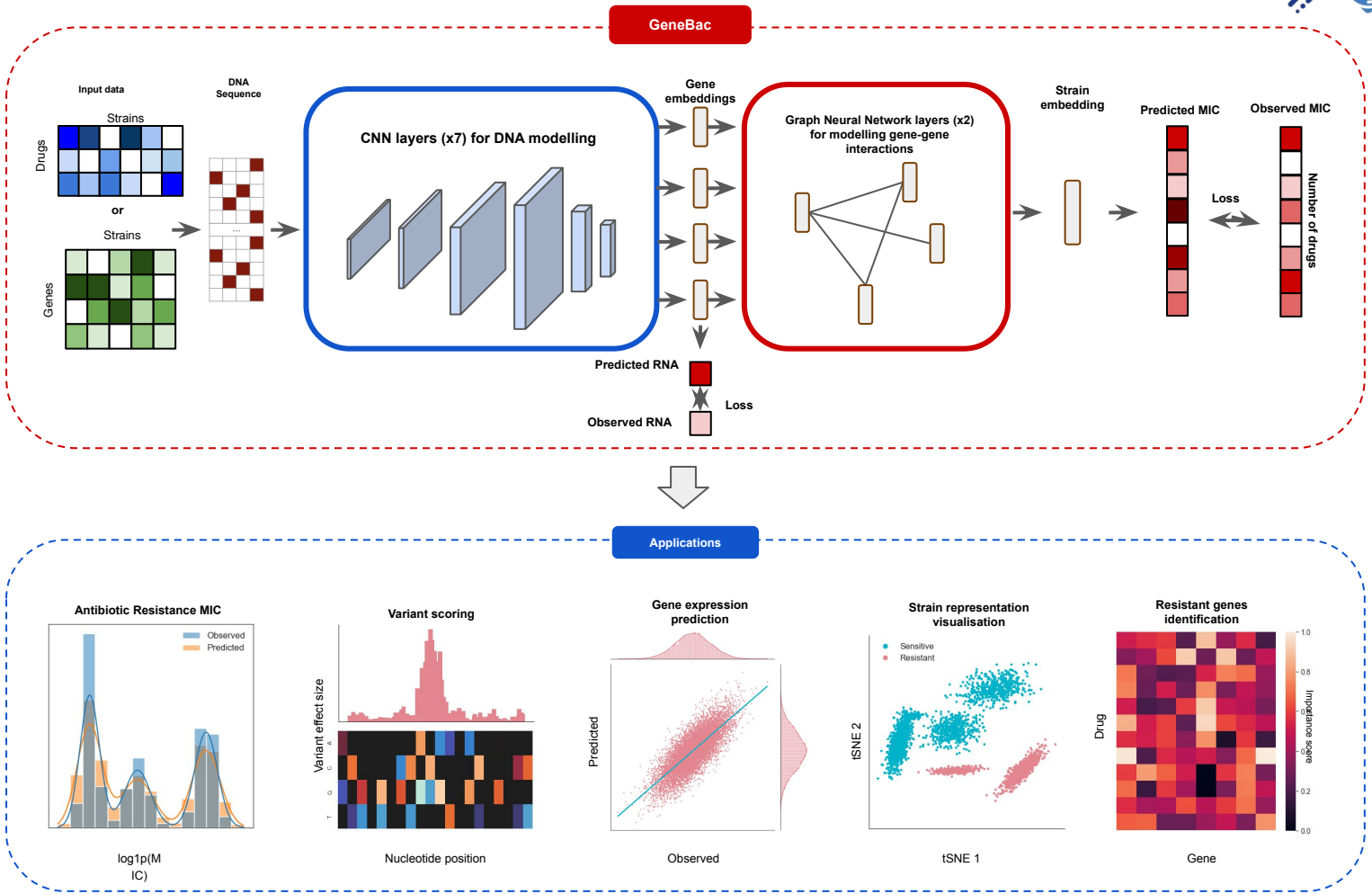
Predicted RNA
Observed RNA
Loss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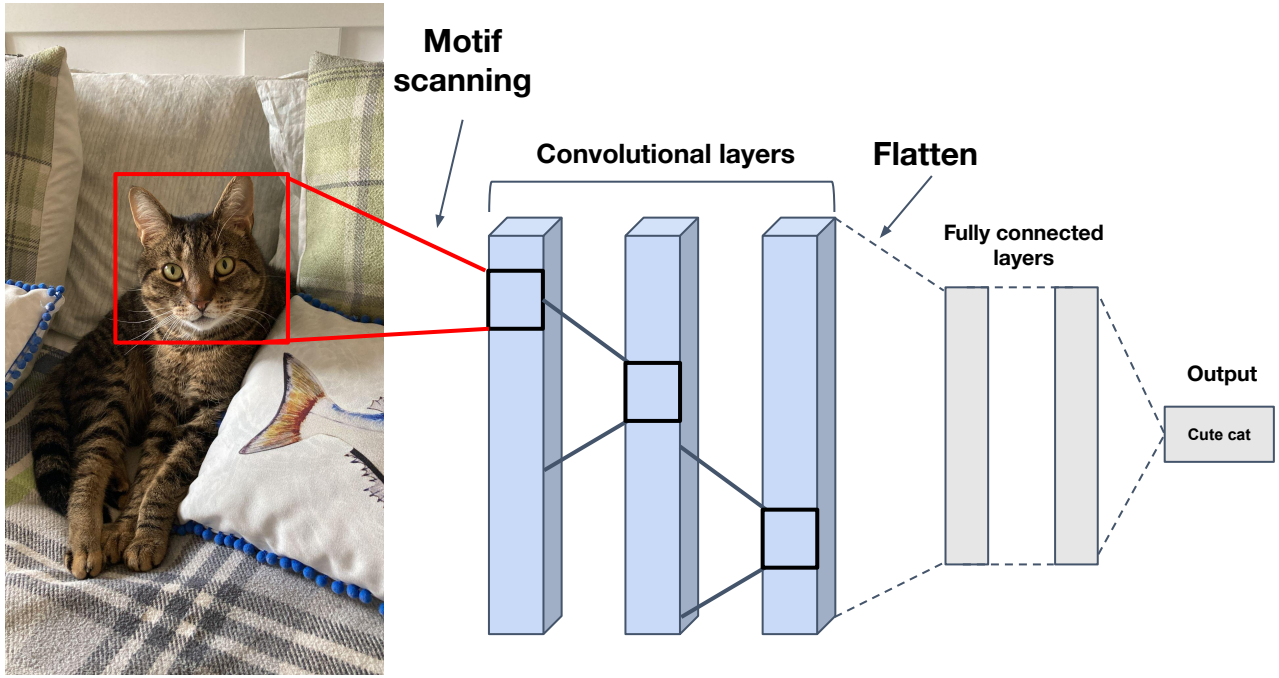
Applications
Antibiotic Resistance MIC
Observed
Predicted
log1p(MIC)
Variant scoring
Variant effect size
Nucleotide position
Gene expression prediction
Predicted
Observed
Strain representation visualisation
Sensitive
Resistant
tSNE 2
tSNE 1
Resistant genes identification
Drug
Importance score
Gene

Convolutional Neural Networks



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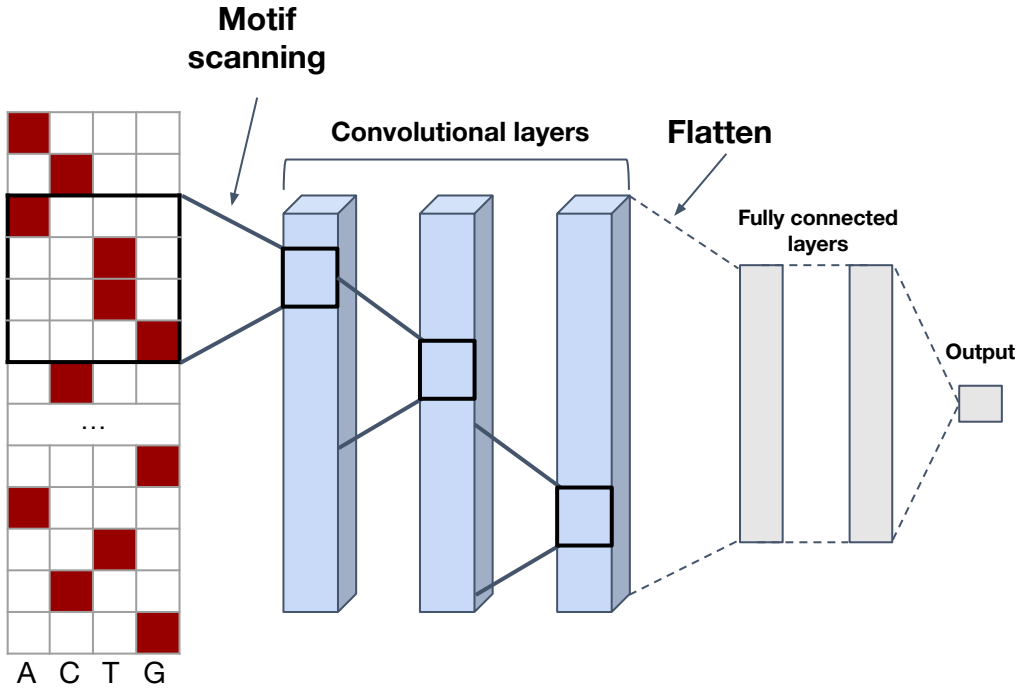
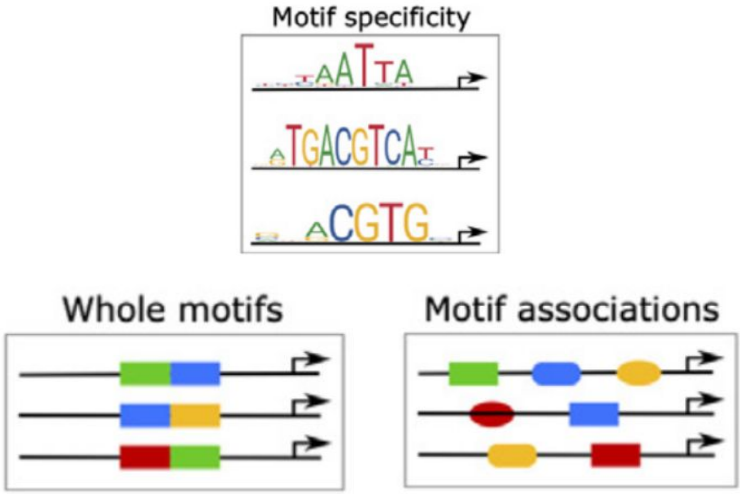
Convolutional Neural Networks for DNA Sequence learning



DNA sequence models learn DNA grammar

What do DNA sequence models learn?



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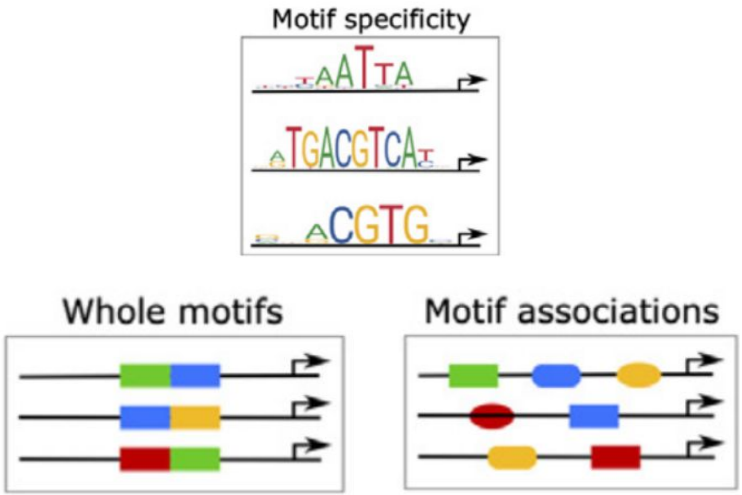

Some DNA sequence models applications:

- **TF-DNA binding discovery and prediction**
  - BPNet
- **Gene expression prediction**
  - Enformer
- **Chromatin accessibility prediction**
  - scBasset

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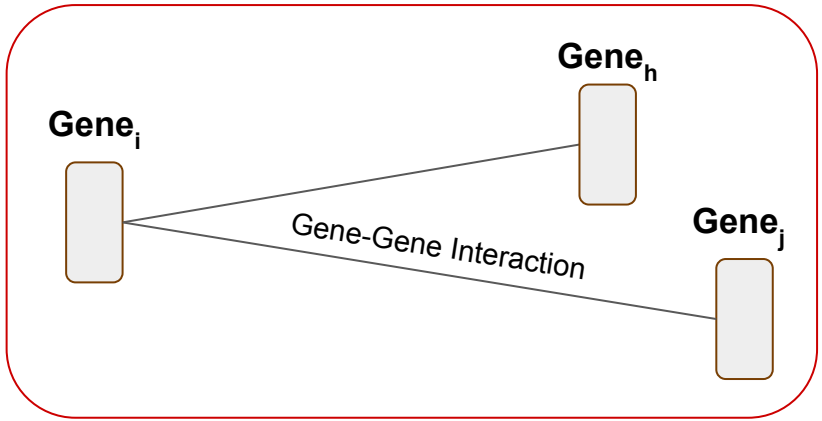
Graph Neural Network



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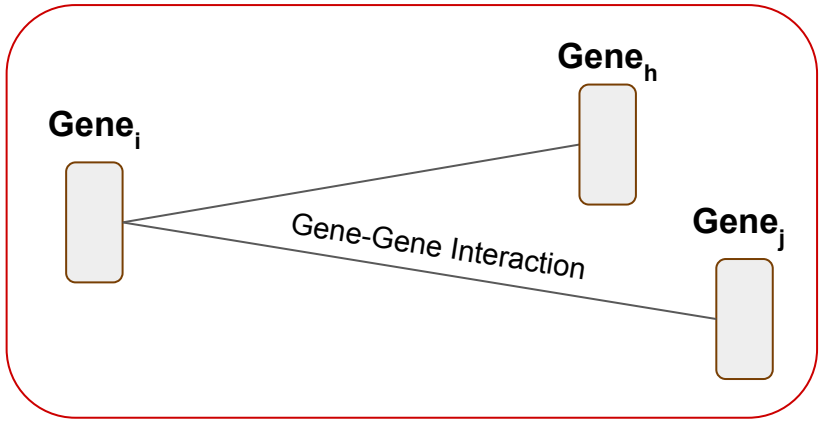

- Accounts for interactions between genes
- Incorporates prior knowledge on protein-protein interactions
- Learns to weight the interactions between genes depending on the gene-gene relationship and the DNA sequence

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Can we predict antibiotic resistance based on the DNA sequence?

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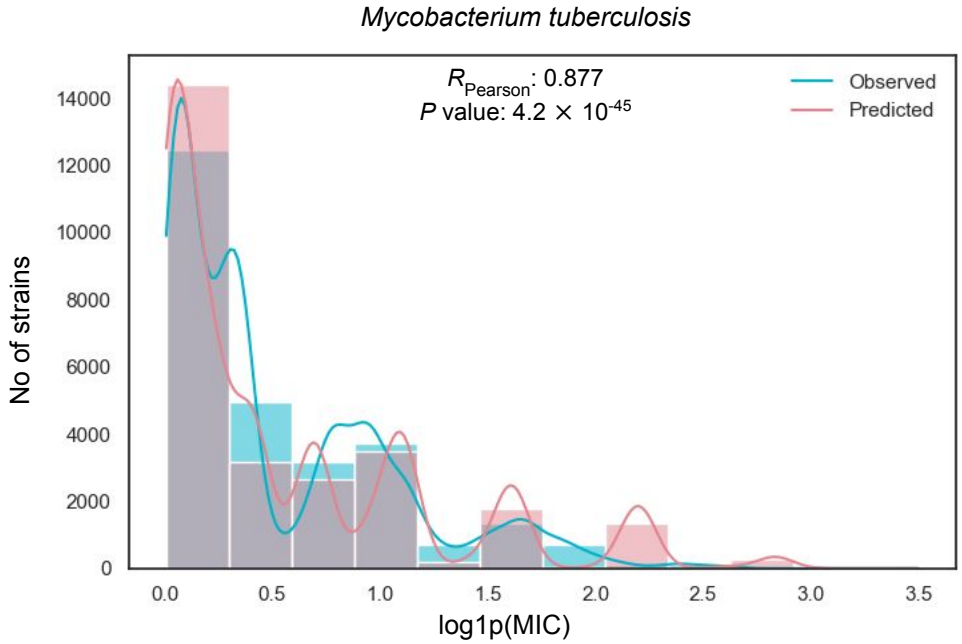
GeneBac predicts antibiotic resistance



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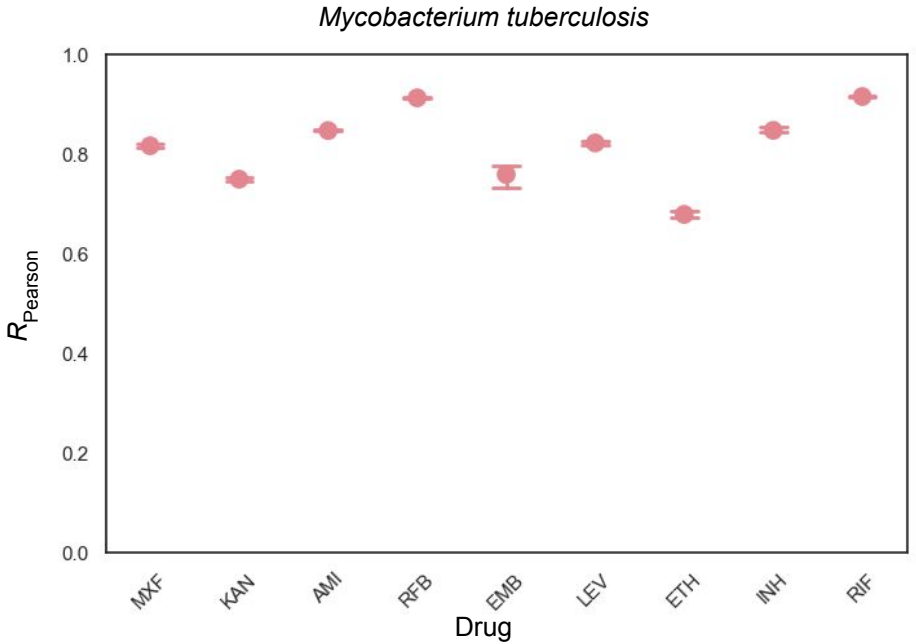
GeneBac predicts antibiotic resistance across distinct drugs



Can we uncover genetic variants driving the change in antibiotic resistance level?

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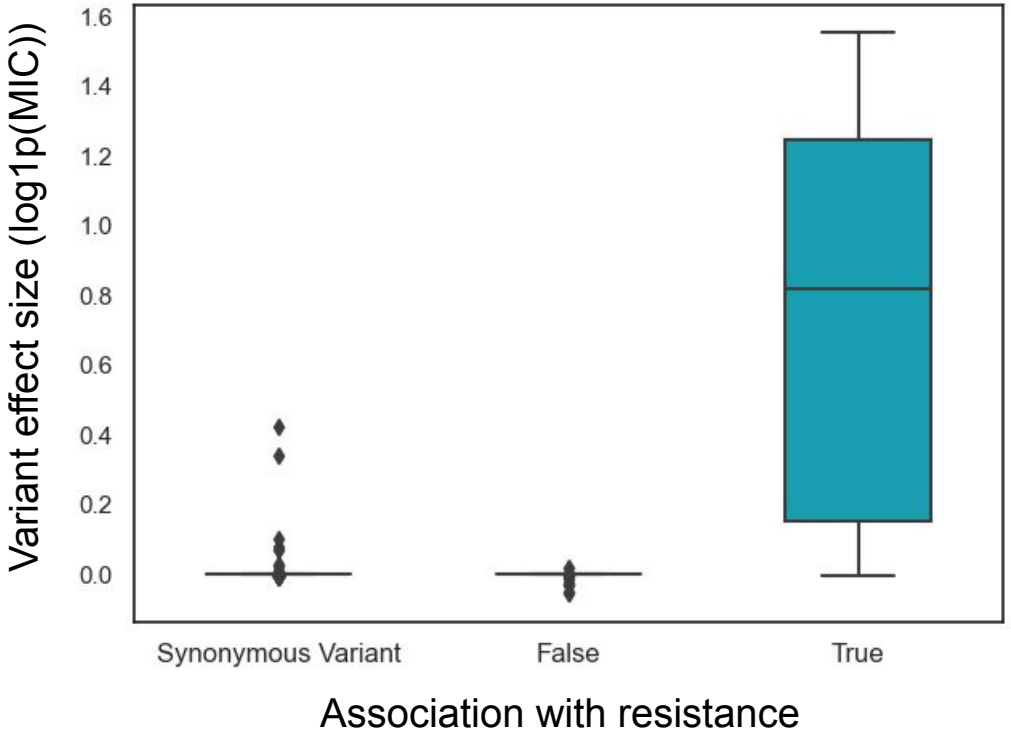
GeneBac predicts variant effect



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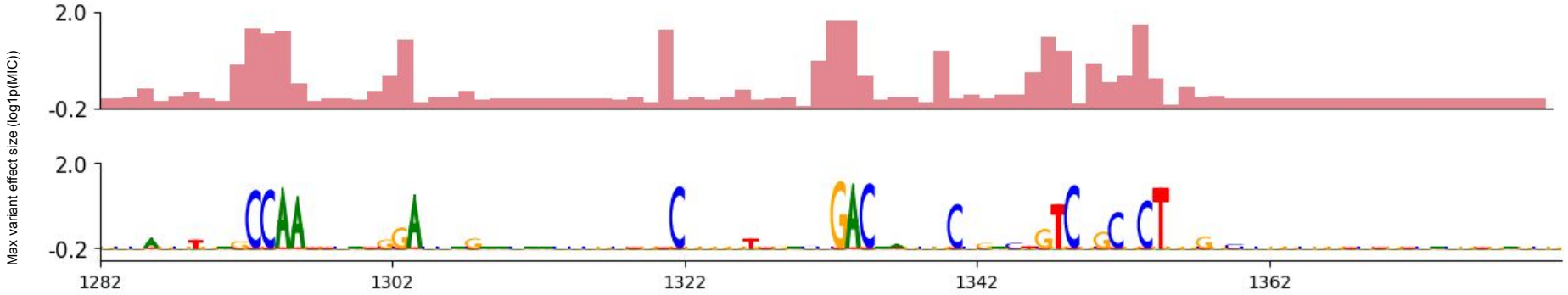

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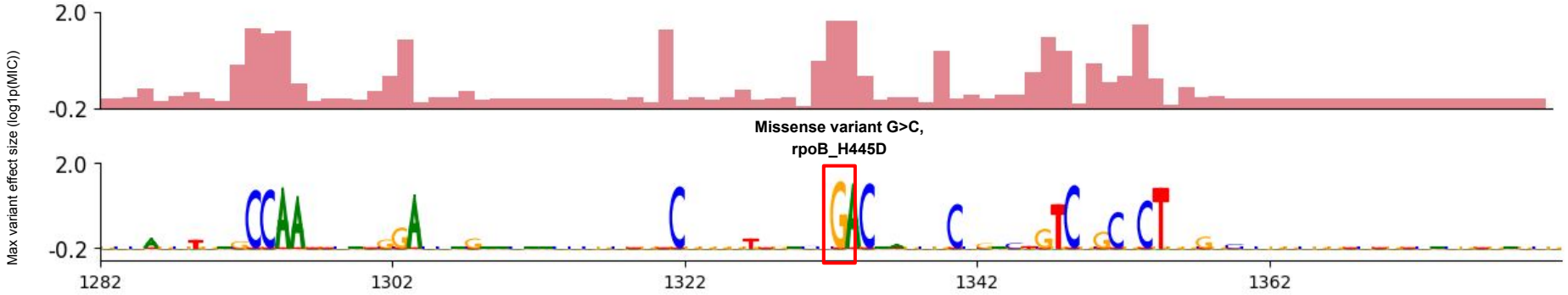
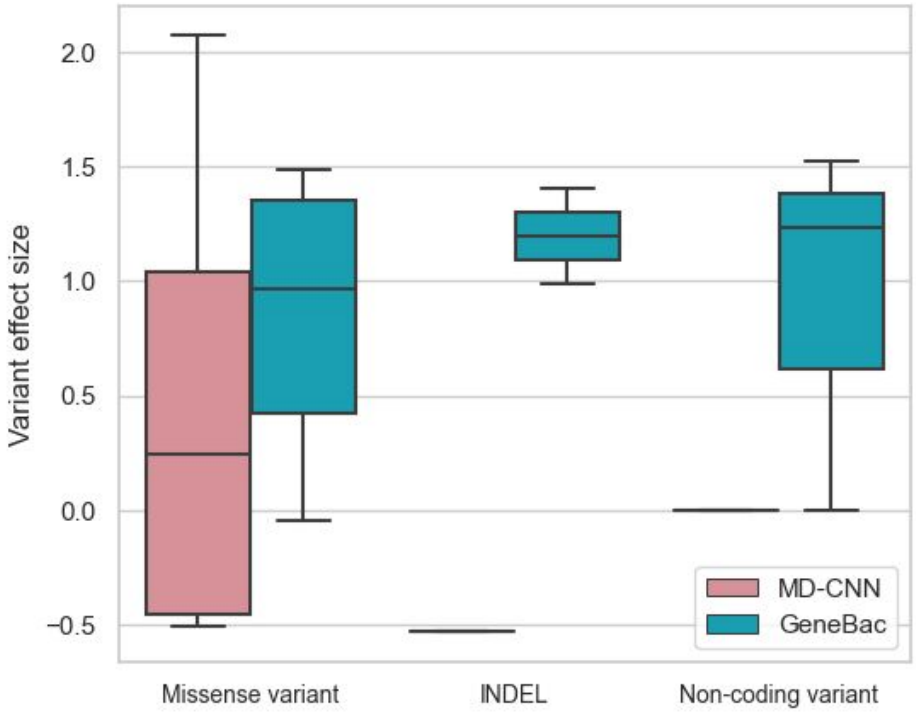


GeneBac improves variant effect scoring



Can we identify drug resistant genes?

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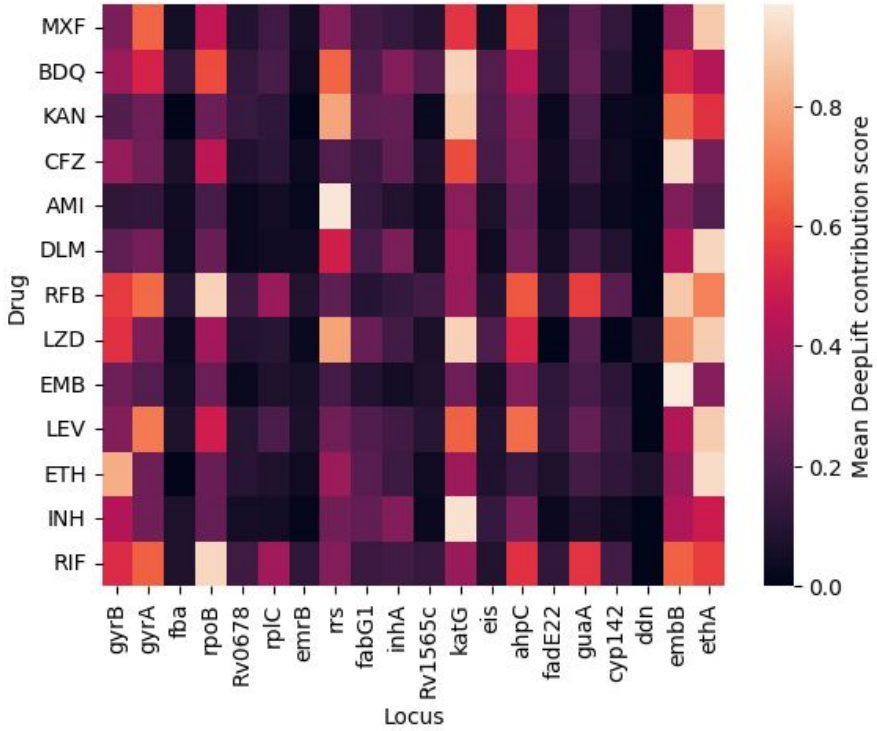
GeneBac recovers genomic loci associated with drug resistance



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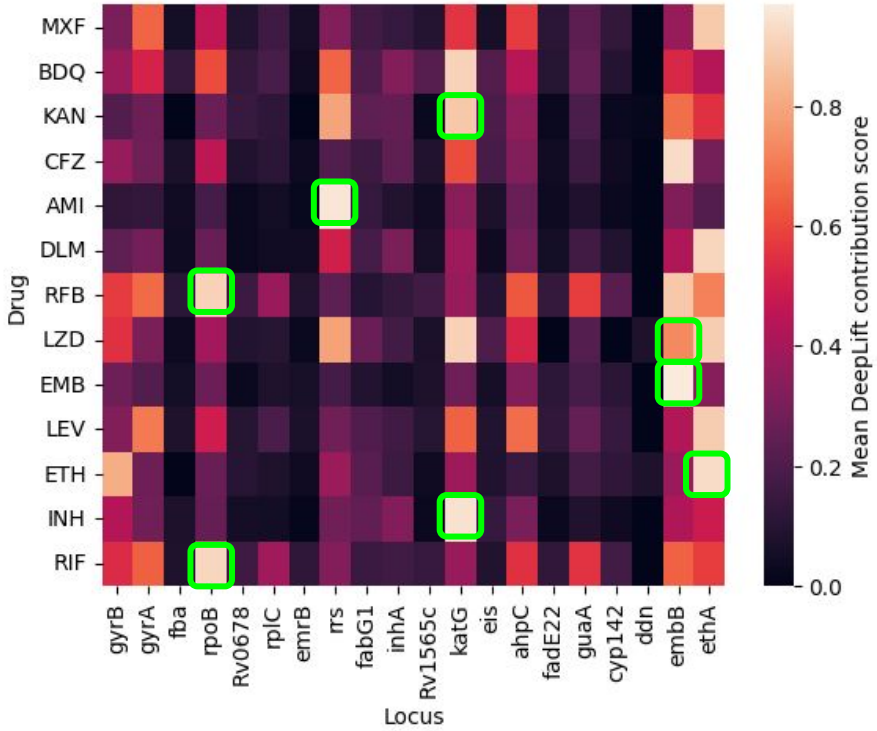

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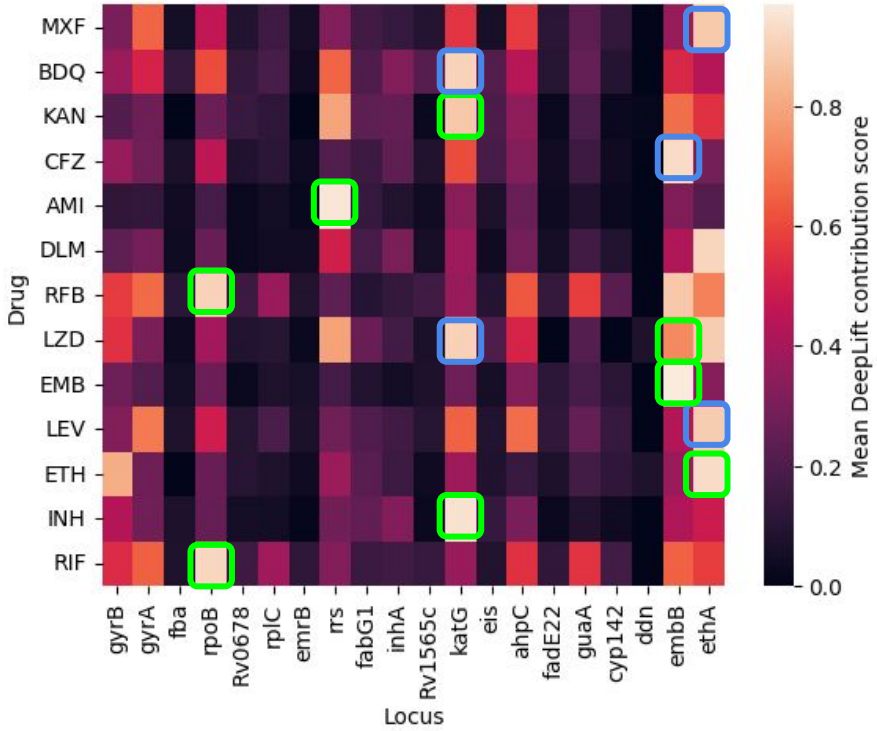

Can we leverage modular architecture of GeneBac to transfer learn across data modalities?

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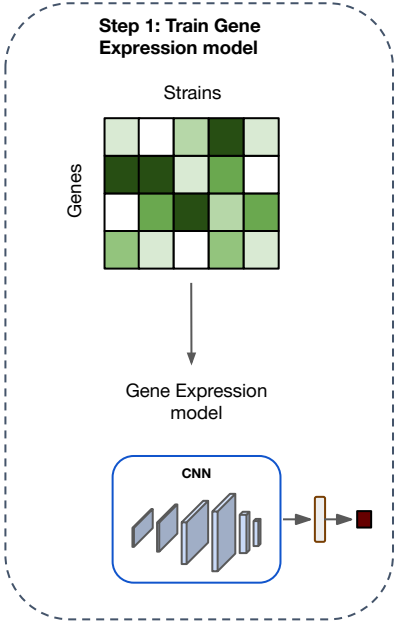
GeneBac transfer learns across modalities



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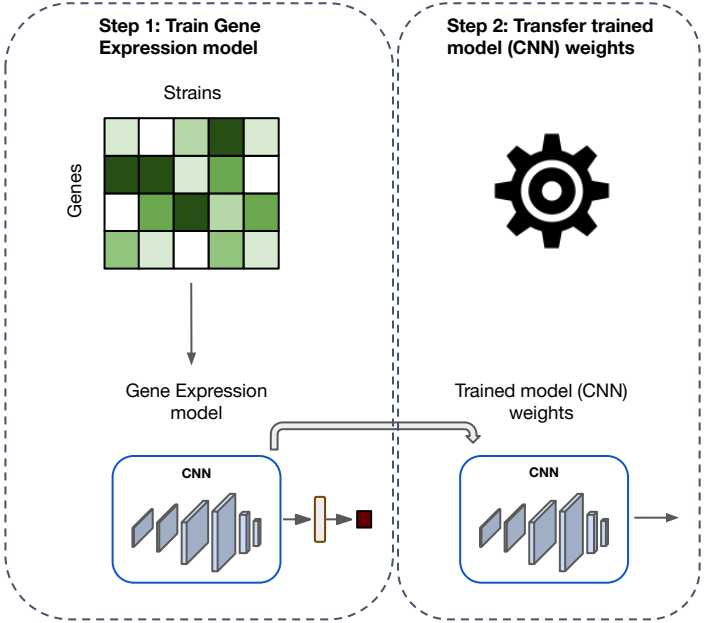

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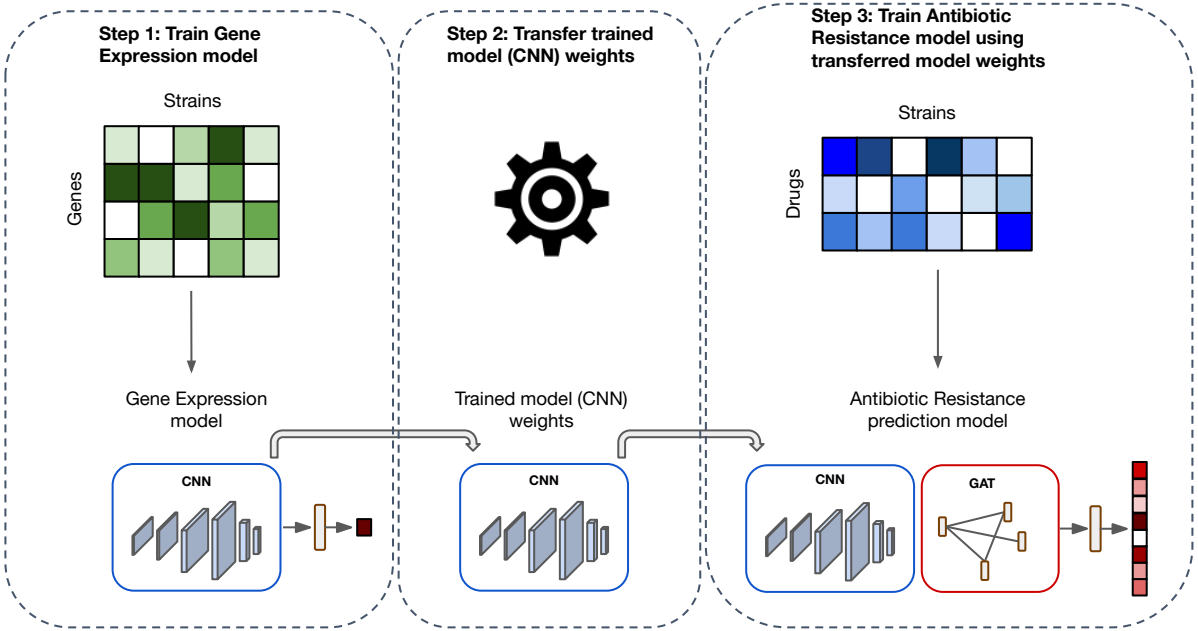
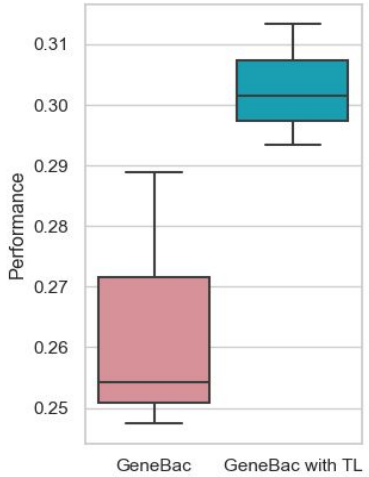
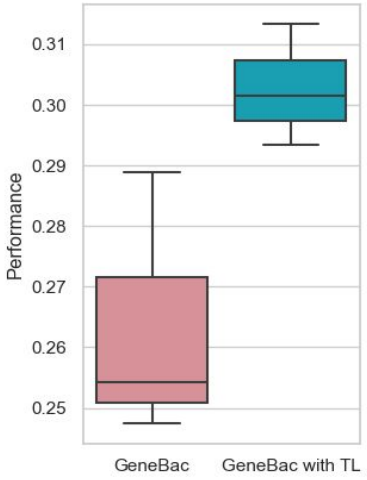
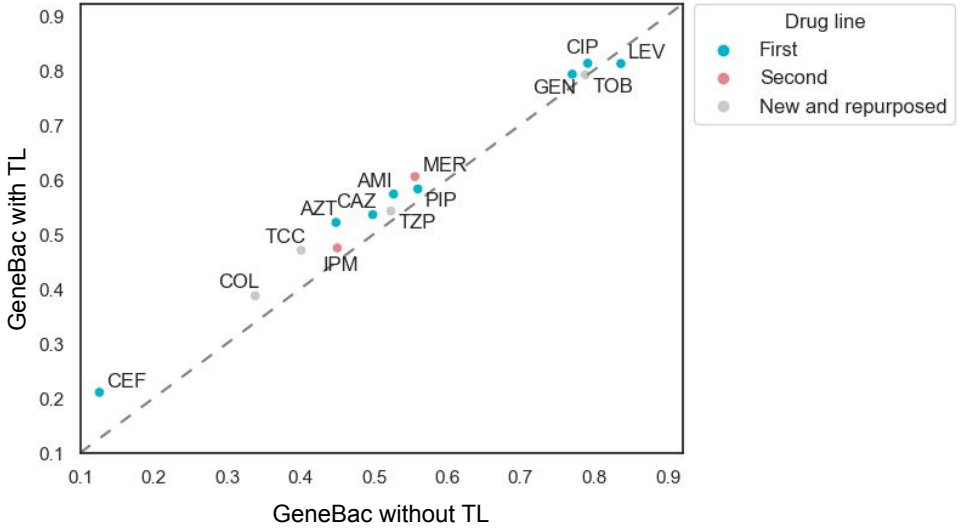


GeneBac transfer learns across modalities



GeneBac transfer learns across modalities





Conclusions

- GeneBac predicts antibiotic resistance
- GeneBac predicts variant effect
- GeneBac recovers genes associated with drug resistance
- GeneBac transfer learns across modalities

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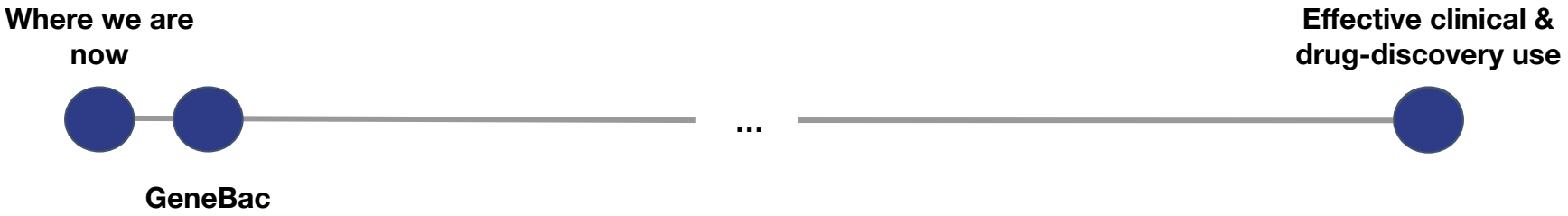
The Path Ahead for ML for AMR



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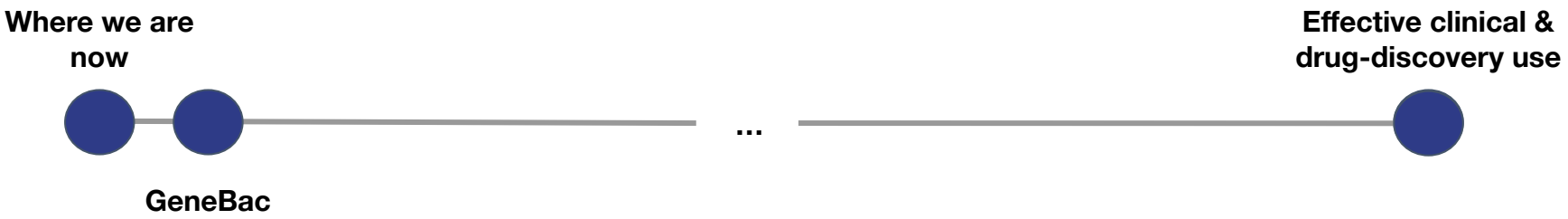

We need more high quality and diverse data!

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Thank you!

Floto Lab

Andres Floto
Aaron Weimann
Adam Dinan

Wellcome Sanger Institute

Sarah Teichmann
Vitalii Kleschevnikov
Jacob Hepkema
Alexander Predeus
Mohammad Loftollahi
Lorenz Kretschmer

EPFL

Maria Brbic