Identification of drug combinations for the treatment of Chagas disease

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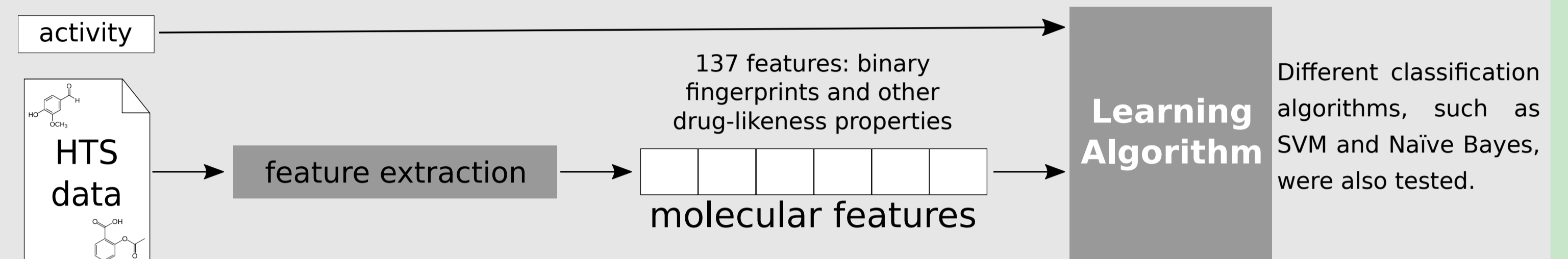ROYAL HOLLOWAY UNIVERSITY OF LONDON

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Background

○ Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi*.

○ Around 6 to 7 million people are infected worldwide, and over 40 million are at risk of infection.

○ There is **no treatment** for the disease at its chronic stage.

○ A number of parasitic diseases, such as malaria, have shown to have effective treatments using drug combinations.

■ Endemic countries
□ Non-endemic countries but present

https://www.dndi.org/diseases-projects/chagas/

Machine Learning Approach

Training the predictive model

activity

HTS data → feature extraction → 137 features: binary fingerprints and other drug-likeness properties → molecular features → **Learning Algorithm** → Different classification algorithms, such as SVM and Naïve Bayes, were also tested.

Predicting biological activity of FDA approved drugs

FDA drugs → feature extraction → molecular features → **Predictive Model** → label

unlabelled input

Random Forest

Accuracy
75%

ROC AUC
0.81
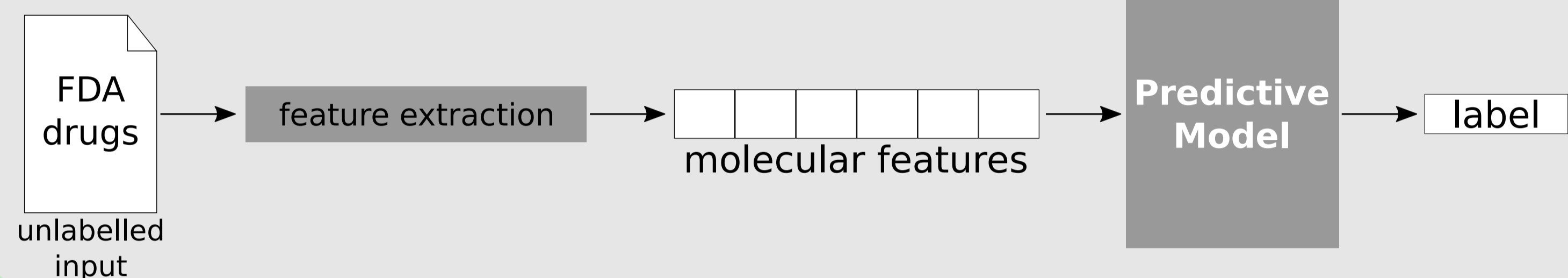
Metabolic Pathways Approach

2. Extract the FDA approved drugs and their drug-targets (enzymes) from DrugBank.

3. Identify the similar proteins between the drug targets and the *T. cruzi* enzymes. We use BLAST to calculate the sequence-sequence similarity.

1. Retrieve the metabolic pathways from *Trypanosoma cruzi* from the KeGG database.

T. cruzi metabolic pathways

enzyme

metabolite

■ **Drug A** ■ **Drug B** ■ **Drug C**
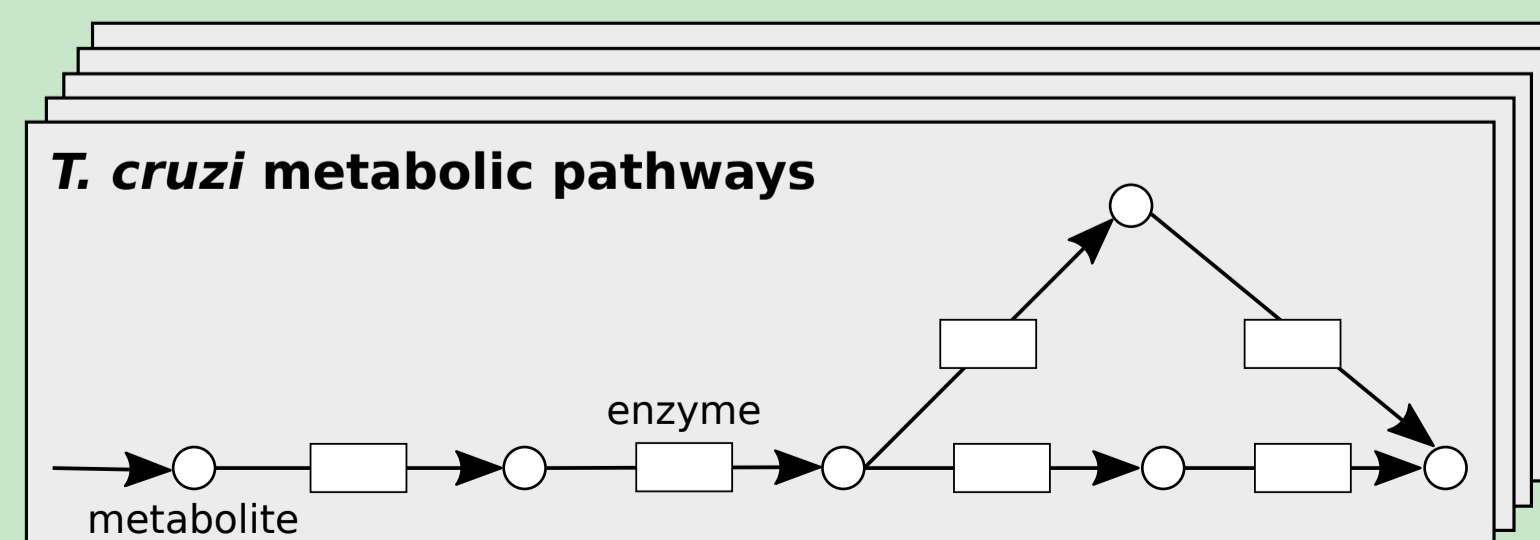
Pathway A
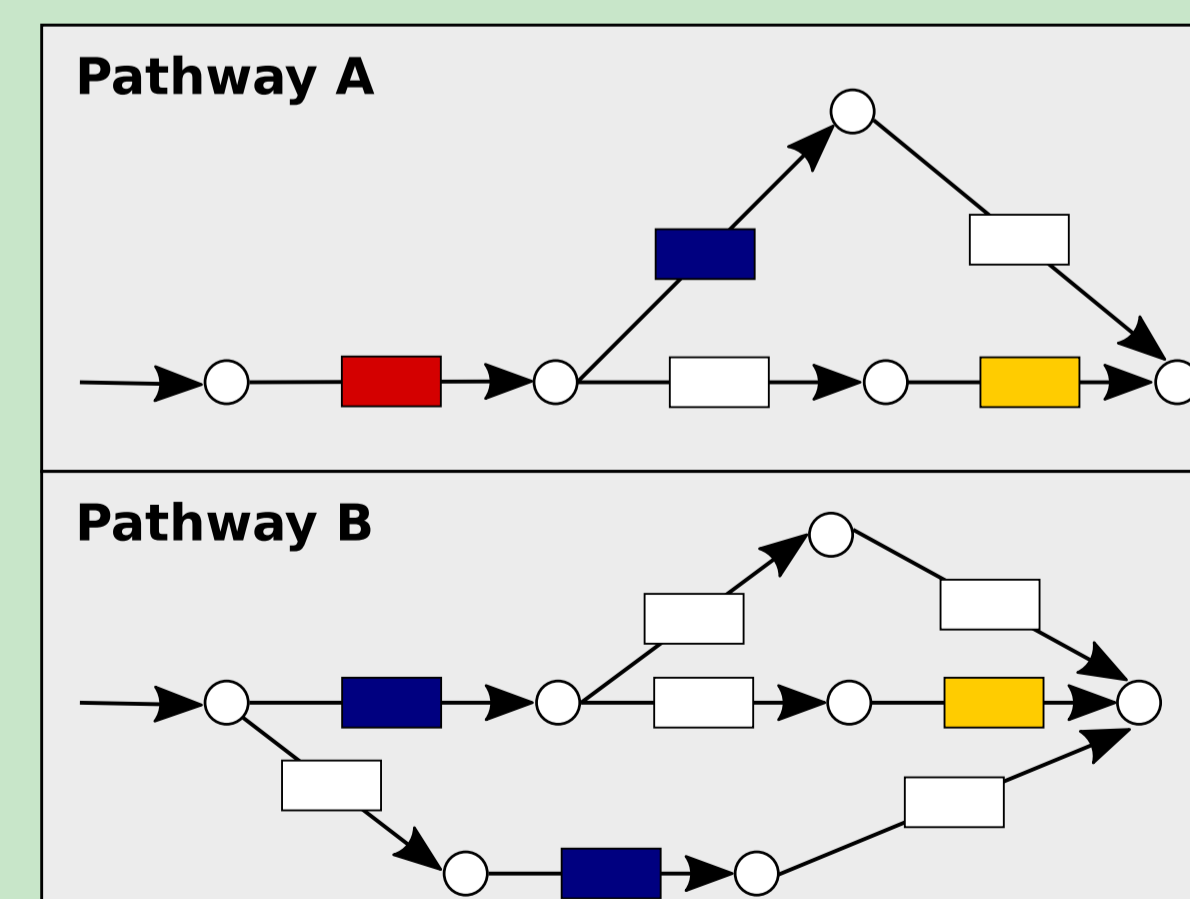
Pathway B

4. Map the drugs that have targets identified in step 3 to the metabolic pathways. These drugs could potentially disrupt the pathways by binding to the enzymes.

Results

Drugs mapped to *T. cruzi* pathways

Drugs classified as biologically active

384   8   63

In both sets we were able to identify drugs that were clinically trialled against *T. cruzi* in the past. The intersection includes *Itraconazole*, a drug that has been extensively tested as a treatment for Chagas disease. This is encouraging evidence that our approaches are able to produce reasonable treatment candidates.