Предсказание связывания пептидов с TAP транспортером.

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Оглавление

Введение

TAP1/2 - важное звено в процессинге антигенов для MHC I. Он транспортирует пептиды из цитоплазмы в полость эндоплазматической сети. Экспериментальных данных по связыванию пептидов с этим транспортером крайне мало. Методика определения аффинности своеобразная. Определяют IC_{50} в эксперименте с микросомами относительно некоторого меченого ^{125}I пептида. Чаще всего в публикациях используется RRYNASTEL, по методике описанной в работе Ван Эндерта(Endert et al. 1994).

Материалы

Было найдено два датасета.

1. База данных MHC BN(Lata, Bhasin, and Raghava 2009)
2. Данные, использованные при обучении TAPREG(Diez-Rivero et al. 2010)
    - Два экспериментальных датасета(Daniel et al. 1998; Toseland et al. 2005)
    - Сгенерированные с помощью “Gibbs sampler with an exhaustive method and maximum blosum 62 relatedness scores of 25, 30, 35, and 37.”(Neuwald, Liu, and Lawrence 1995)

Фильтрация данных

```
library(dplyr)
library(vroom)
library(stringr)
library(readxl)
library(caret)
library(ggplot2)
#MHC BN
mhcbn = vroom("data/source/TAP/MHCBN_2023-02-16.tsv", delim = "\t") %>%
  select(-1) %>%
  filter(`MHC Allele` == "TAP") %>%
  filter(`Host Organism` == "HUMAN") %>%
  filter(!is.na(Comment)) %>%
  mutate(dup_check = paste(`Peptide Sequence`, Comment)) %>%
```

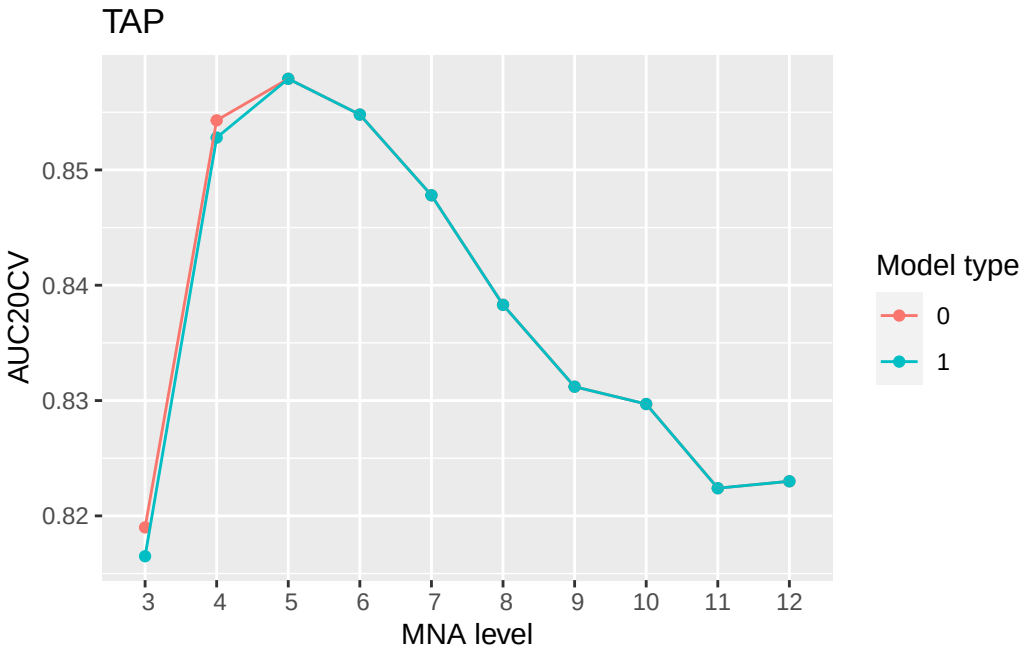
```
  filter(!duplicated(dup_check)) %>%
  filter(grepl("Relative", Comment)) %>%
  filter(!grepl("approx", Comment)) %>%
  filter(grepl("nM|uM",Comment,ignore.case = T)) %>%
  mutate(unit = str_extract(Comment,"\\(([^)]+)\\)",group = T),
         value = if_else(grepl("u",unit),
                         sapply(str_split(Comment,"="),function(x){as.double(x[2])}) * 1000,
                         sapply(str_split(Comment,"="),function(x){as.double(x[2])}))) %>%
  filter(!is.na(value)) %>%
  mutate(log_IC50_rel = log10(value)) %>%
  select(all_of(c("Peptide Sequence", "log_IC50_rel"))) %>%
  rename("PEPTIDE" = "Peptide Sequence")
#activity = if_else(pIC50 < (9 - log10(800)), 0, 1)
table(mhcbn$activity)
#TAPREG supplementary
# 1 - 10.4049/jimmunol.161.2.617 + 10.1186/1745-7580-1-4
# 2 - 5 613-peptide dataset using the purge utility of the Gibbs Sampler (10.1002/pro.556004082)
# with an exhaustive method and maximum blosum 62 relatedness scores of 25, 30, 35, and 37.
# 6 - 723 unique 9-mer CD8 T cell epitopes obtained from the IMMUNEEPITOPE and EPIMHC databa
# 7- tapreg parameters

#let tapreg log(IC50_relative) as is pIC50_relative in mhc bn
first = read_excel("data/source/TAP/TAPREG/prot_22535_sm_supptable1.xls") %>%
  rename("log_IC50_rel" = "log(IC50_relative)")

second = read_excel("data/source/TAP/TAPREG/prot_22535_sm_supptable2.xls") %>%
  rename("log_IC50_rel" = "log(IC50_relative)")

third = read_excel("data/source/TAP/TAPREG/prot_22535_sm_supptable3.xls") %>%
  rename("log_IC50_rel" = "log(IC50_relative)")
```

```
fourth = read_excel("data/source/TAP/TAPREG/prot_22535_sm_supptable4.xls") %>%
  rename("log_IC50_rel" = "log(IC50_relative)")

fifth = read_excel("data/source/TAP/TAPREG/prot_22535_sm_supptable5.xls") %>%
  rename("log_IC50_rel" = "log(IC50_relative)")

total = bind_rows(mhcbn, first,second,third,fourth,fifth) %>%
  group_by(PEPTIDE) %>%
  summarise(median_log10_IC50_rel = median(log_IC50_rel)) %>%
  mutate(activity = if_else(median_log10_IC50_rel <= (log10(800)), 0, 1))
```

Порог в 800 нМ был взять по данным из аналогичных сервисов: там прогнозируют результат по ранговой шкале, где 0 баллов для IC50>1000 нМ, 10 баллов IC50<0,03 нМ(Daniel et al., n.d.). Пептиды с баллами 0-2 считаются неактивными(Zhang et al. 2006). В итоге обучающая выборка состояла из 683 пептидов: 388 неактивных и 295 активных. Модель строилась с помощью программы PASS на MNA дескрипторах.

Результаты

Оптимальный уровень для моделирования - 5.



Была проведена 5-кратная кросс-валидация.

```
import pandas as pd
import os
from sklearn import metrics
from glob import glob
import numpy as np
folds = glob(os.path.join("/media/stotoshka/STotoshka/cross_val", "*.CSV"))
#print(folds)
```

```
union = pd.DataFrame()
#print("Parse results")
for f in folds:
    tbl = pd.read_csv(f, sep=";", header=4, decimal=",")
    union = pd.concat([union, tbl])
#print(f"Folds union {union.shape}")

union = union.drop(columns=["Substructure Descriptors", "New Descriptors", "Possible Activities at Pa
union = union.rename(columns={union.columns[0]: "activity"})
activities = union.columns[1:]
prediction = union.copy(deep = True)
result = pd.DataFrame(columns=["AUROC", "Average precision", "Precision", "Accuracy", "BA", "Recal
#print("a\troc_auc\tpr_auc\tprecision\taccuracy\tba\trecall\tf1\tsensitivity\tspecifity")
#print("a\ttp\ttn\tfp\tfn")
pred = np.where(prediction.loc[prediction["1"].notnull(), "1"] <= 0, 0, 1)
true = prediction.loc[prediction["1"].notnull(), "activity"]
try:
    roc_auc = round(metrics.roc_auc_score(true, pred),4)
    pr_auc = round(metrics.average_precision_score(true, pred),4)
    precision = round(metrics.precision_score(true,pred),4)
    accuracy = round(metrics.accuracy_score(true, pred),4)
    ba = round(metrics.balanced_accuracy_score(true, pred),4)
    recall = round(metrics.recall_score(true, pred),4)
    f1 = round(metrics.f1_score(true, pred),4)
    tn, fp, fn, tp = metrics.confusion_matrix(true, pred).ravel()
    sensitivity = round(tp / (tp + fn),4)
    specifity = round(tn / (tn + fp),4)
        #print(f"{a}\t{roc_auc}\t{pr_auc}\t{precision}\t{accuracy}\t{ba}\t{recall}\t{f1}\t{sensitivity}\t{specifity}"
        #print(f"{a}\t{tp}\t{tn}\t{fp}\t{fn}")
    result.loc[0] = [roc_auc, pr_auc,precision,accuracy,ba,recall,f1,sensitivity,specifity]
```

```
except ValueError as ve:
    print(f"{a} {ve}")
```

```
library(knitr)
library(reticulate)
kable(py$result)
```

	AUROC	Average precision	Precision	Accuracy	BA	Recall	F1	Sens	Spec
0	0.7689	0.6548	0.7294	0.7716	0.7689	0.7492	0.7391	0.7492	0.7887

Без жесткого порога AUROC и AUC-PR будут несколько выше.

```
pred = np.where(prediction.loc[prediction["1"].notnull(), "1"] <= 0, 0, prediction.loc[prediction["1"].notnull
true = prediction.loc[prediction["1"].notnull(), "activity"]
curve = metrics.roc_curve(true,pred)
#plt.plot(curve)
print(f"AUC ROC = {metrics.roc_auc_score(true,pred)}")
```

AUC ROC = 0.7916477372007689

```
print(f"AUC PRC = {metrics.average_precision_score(true,pred)}")
```

AUC PRC = 0.7194385123388266

Выводы

Модели получились удолетворительного качества. Необходимо сравнить с аналогами. Существует недостаток экспериментальных данных. В дальнейшем возможно необходимо задавать малый вес выходу модели для принятия решения

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