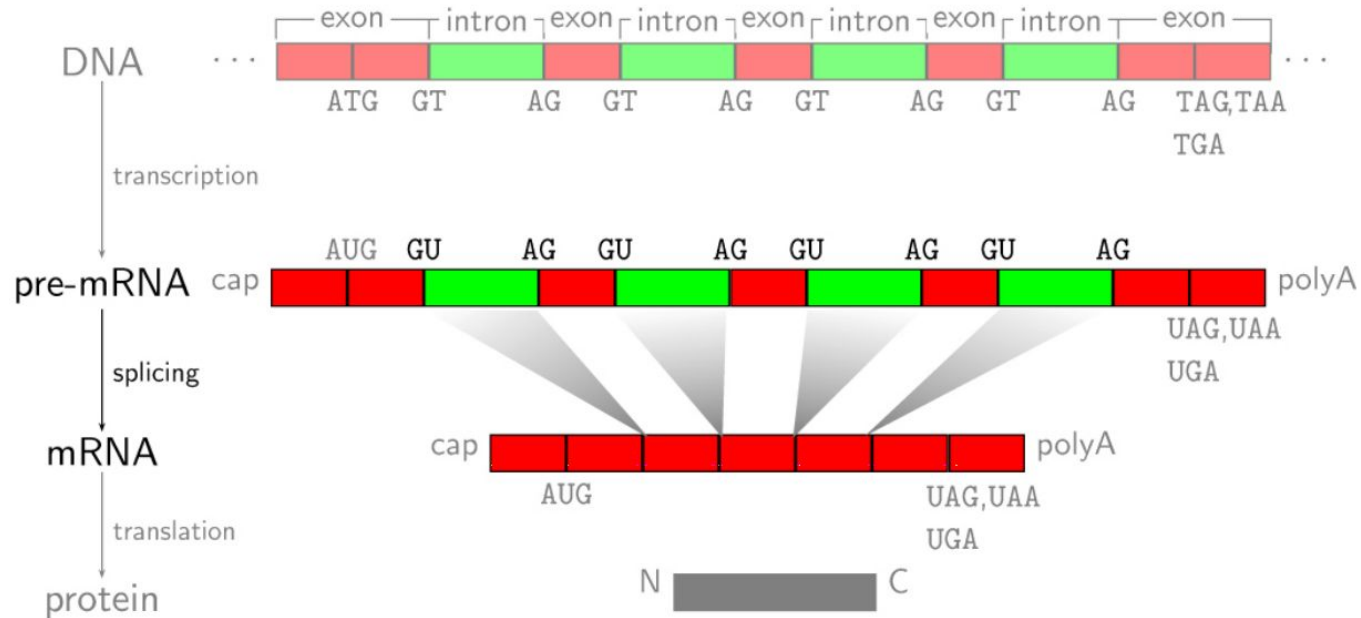


Exercise session - Project 4

ML4H - 30.04.2020

Splice Sites



- Almost all *donor splice sites* exhibit GU
- Almost all *acceptor splice site* exhibit AG
- Not all GUs and AGs are used as splice site

The project

- Two datasets:
 - C. Elegans DNA dataset.
 - Human DNA dataset.
- Both datasets contain:
 - DNA sequences.
 - Splice site annotations.
- Find the best model possible to predict splice site given the sequence.
- Groups of up to 3

C. Elegans DNA

- You get a csv file, with two columns: sequences and labels.
- 2200 samples.
- Sequences of 82 nucleotides.
- 200 true labels, 9% of the samples.
- Do your own experimental setup.
- Inside a jupyter notebook:
 - Do your own experimental setup (cross validation, random split, etc.).
 - Find best model possible (try different models, do hyperparameter search, etc).
 - ROC and PRC curves of your best model.
 - Pandas dataframe showing a comparison of the scores of the models you tried. Three columns: model name, AUROC, AUPRC, scores for the test set.

Human DNA

- You get 4 CSV files: train, validation, test and hidden test splits.
- Train CSV contains 500K samples, validation CSV contains 30K samples and test CSV contains 30K samples (90%, 5%, 5%). Hidden test CSV file also contains 30K samples.
- Sequences of 398 nucleotides.
- Use the validation set for whatever you want.
- Don't use the test set for training, or hyperparameter search, etc!
- Inside Jupyter:
 - Find best model possible (try different models, do hyperparameter search, etc).
 - ROC and PRC curves of your best model.
 - Pandas dataframe showing a comparison of the scores of the models you tried. Three columns: model name, AUROC, AUPRC, scores for the test set.
 - Predictions for the hidden test dataset saved as a 1D numpy array with `np.save` and "result.npy" as filename.

Jupyter notebook general advice

- Sequential execution without gaps.
- Don't use the test set for training or model selection!
- Do a nice organization of your code and notebook (use markdown titles, explanatory texts, etc.).

Deliverables

- Jupyter notebook for C. Elegans DNA dataset.
- Jupyter notebook for Human DNA dataset.
- results.npy predictions for hidden human DNA dataset.
- Conda yaml environment.
- Max 2 page report, including methods, results and conclusions plus the names of the group members and their main contribution.

Evaluation

- **Scores on the hidden test set.**
- Scores on the test sets.
- Quality of the experiments.
- Number of models you tried (try also simple models!).
- Project organization and quality of the documentation.

Deadline

20/05/2020

	sequences	labels
0	TTGTGTCCTACTTTGTCCATTTGGAAAAATAATTGCATGACTACA...	-1
1	CTTTCCTTTATTTCTTCGTCAACTTAATATCCTTAGCAAAACAGGA...	-1
2	TACTTAAGAGGGGTAAGAAATATATAAACTAGTGCAACATTTTTCA...	-1
3	TAGGTTTCCAAGCAGCCCATTCCTGCCTGGCACCACAGGGATCCAT...	-1
4	GCATGAGCCACTGCGCCTGGCCTGGTTCATTGCTTCTTAGTGATGC...	-1

- Only potential acceptor sites, i.e. a string with AG in the middle of the string.

Shogun

 <http://shogun-toolbox.org/>

```
conda install -c conda-forge shogun
```

Shogun

[home](#)

[mission](#)

[examples](#)

[install](#)

[showroom](#)

[dev wiki](#)

[api](#)

[contact](#)

Kernel Support Vector Machine



[CWaveKernel \(shogun\)](#)

[CWaveletKernel \(shogun\)](#)

[CWDFeatures \(shogun\)](#)

[CWeightedCommWordStringKernel \(shogun\)](#)

[CWeightedDegreePositionStringKernel \(shogun\)](#)

[CWeightedDegreeKBIKernel \(shogun\)](#)

[CWeightedDegreeStringKernel \(shogun\)](#)

[CWeightedMajorityVote \(shogun\)](#)

[CWRACCMMeasure \(shogun\)](#)

[Wrapper](#)

Detailed Description

The Weighted Degree String kernel.

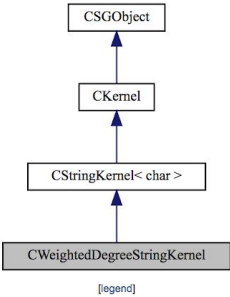
The WD kernel of order d compares two sequences \mathbf{x} and \mathbf{x}' of length L by summing all contributions of k-mer matches of lengths $k \in \{1, \dots, d\}$, weighted by coefficients β_k . It is defined as

$$k(\mathbf{x}, \mathbf{x}') = \sum_{k=1}^d \beta_k \sum_{l=1}^{L-k+1} I(\mathbf{u}_{k,l}(\mathbf{x}) = \mathbf{u}_{k,l}(\mathbf{x}')).$$

Here, $\mathbf{u}_{k,l}(\mathbf{x})$ is the string of length k starting at position l of the sequence \mathbf{x} and $I(\cdot)$ is the indicator function which evaluates to 1 when its argument is true and to 0 otherwise.

Definition at line 55 of file [WeightedDegreeStringKernel.h](#).

Inheritance diagram for CWeightedDegreeStringKernel:



Constructor & Destructor Documentation

◆ CWeightedDegreeStringKernel() [4 / 4]

```
CWeightedDegreeStringKernel ( CStringFeatures< char > * l,  
                             CStringFeatures< char > * r,  
                             int32_t                 degree  
                             )
```

constructor

Parameters

- l** features of left-hand side
- r** features of right-hand side
- degree** degree

Definition at line **86** of file **WeightedDegreeStringKernel.cpp**.

Weighted degree kernel example

```
import shogun as sg
import numpy as np

dna_train = ['TTTCCC', 'TTTCCC', 'TTTTCC', 'TTTTTC', 'TTTTTT', 'ATTTTC']
labels_train = np.array([1, 1, 1, -1, -1, -1])
dna_test = ['TTTCCC', 'TCCCC', 'TTCCCC']
labels_test = np.array([1, 1, 1])

features_train = sg.StringCharFeatures(dna_train, sg.DNA)
kernel_degree = 5
sk_train = sg.WeightedDegreeStringKernel(features_train, features_train, kernel_degree)
features_test = sg.StringCharFeatures(dna_test, sg.DNA)

# Train the Support Vector Machine
labels = sg.BinaryLabels(labels_train)
C = 1.0
svm = sg.LibSVM(C, sk_train, labels)
svm.train()

predicted_labels_train = svm.apply(features_train).get_labels()
print(predicted_labels_train)
predicted_labels_test = svm.apply(features_test).get_labels()
print(predicted_labels_test)

predicted_labels_train = svm.apply(features_train).get_values()
print(predicted_labels_train)
predicted_labels_test = svm.apply(features_test).get_values()
print(predicted_labels_test)
```

Large Scale Multiple Kernel Learning

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Quickstart

Running Shogun from the interfaces

Binary classifier

Averaged Perceptron

Kernel Support Vector Machine

Linear Discriminant Analysis

Linear Support Vector Machine

Multiclass classifier

Classification And Regression Tree

CHAID tree

Gaussian Naive Bayes

K Nearest neighbours

Large Margin Nearest Neighbours

Linear Discriminant Analysis

Multi-class Error-Correcting Output Codes

Multi-class Linear Machine

Multi-class Logistic Regression

Quadratic Discriminant Analysis

Random Forest

Relaxed Tree

Python

Octave

Java/scala

Ruby

R

Lua

C#

Native C++

Multiple Kernel Learning

Multiple kernel learning (MKL) is based on convex combinations of arbitrary kernels over potentially different domains.

$$\mathbf{k}(x_i, x_j) = \sum_{i=1}^K \beta_k \mathbf{k}_i(x_i, x_j)$$

where $\beta_k > 0$, $\sum_{k=1}^K \beta_k = 1$, K is the number of sub-kernels, \mathbf{k} is a combined kernel, \mathbf{k}_i is an individual kernel and x_{ii} are the training data.

Regression is done by using [CSVMLight](#). See [Support Vector Regression](#) for more details.

See [\[SRatschSchaferScholkopf06\]](#) for more information about MKL.

Example

Imagine we have files with training and test data. We create `CDenseFeatures` (here 64 bit floats aka `RealFeatures`) and `CRegressionLabels` as

```
features_train = RealFeatures(f_feats_train)
features_test = RealFeatures(f_feats_test)
labels_train = RegressionLabels(f_labels_train)
labels_test = RegressionLabels(f_labels_test)
```

Then we create individual kernels like [CPolyKernel](#) and [CGaussianKernel](#) which will be later combined in one [CCombinedKernel](#).

```
poly_kernel = PolyKernel(10, 2)
gauss_kernel_1 = GaussianKernel(2.0)
gauss_kernel_2 = GaussianKernel(3.0)
```

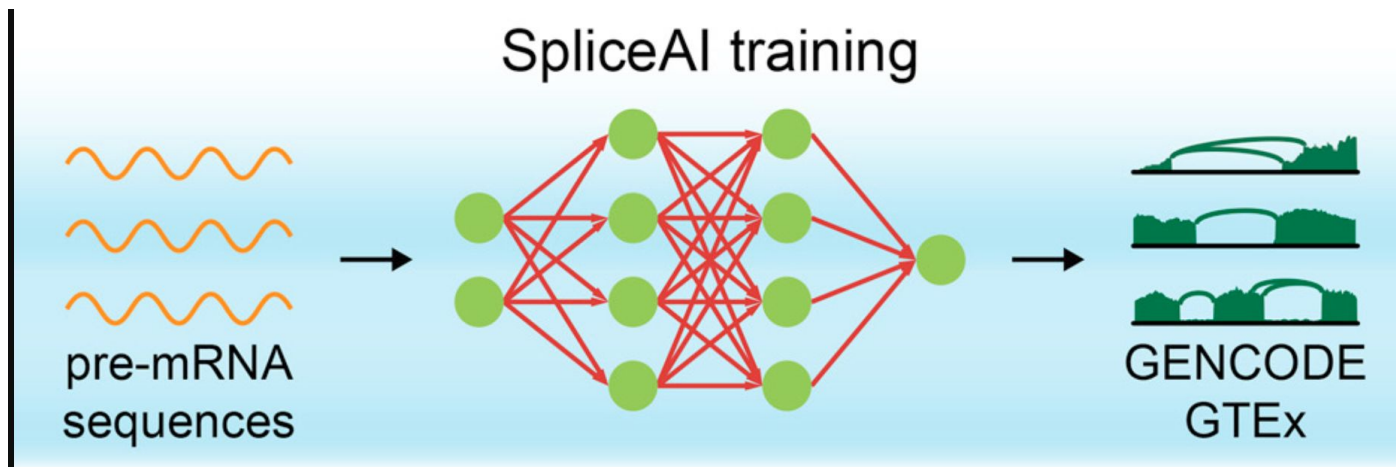
Article

Predicting Splicing from Primary Sequence with Deep Learning

Kishore Jaganathan ^{1, 6}, Sofia Kyriazopoulou Panagiotopoulou ^{1, 6}, Jeremy F. McRae ^{1, 6}, Siavash Fazel Darbandi ², David Knowles ³, Yang I. Li ³, Jack A. Kosmicki ^{1, 4}, Juan Arbelaez ², Wenwu Cui ¹, Grace B. Schwartz ², Eric D. Chow ⁵, Efstathios Kanterakis ¹, Hong Gao ¹, Amirali Kia ¹, Serafim Batzoglou ¹, Stephan J. Sanders ², Kyle Kai-How Farh ^{1, 7}



Overview

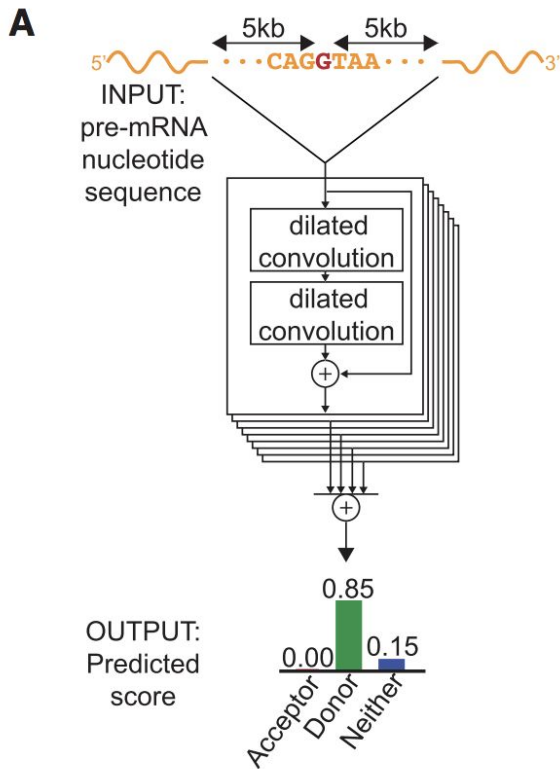


<https://www.sciencedirect.com/science/article/pii/S0092867418316295#app2>

https://en.wikipedia.org/wiki/RNA_splicing

<https://www.cell.com/action/showPdf?pii=S0168-9525%2812%2900002-9>

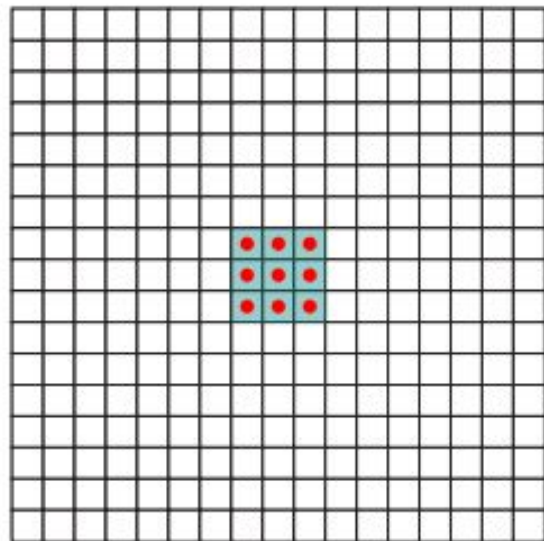
Model architecture



For each position in the pre-mRNA transcript, SpliceAI-10k uses 10,000 nucleotides of flanking sequence as input and predicts whether that position is a splice acceptor, splice donor, or neither

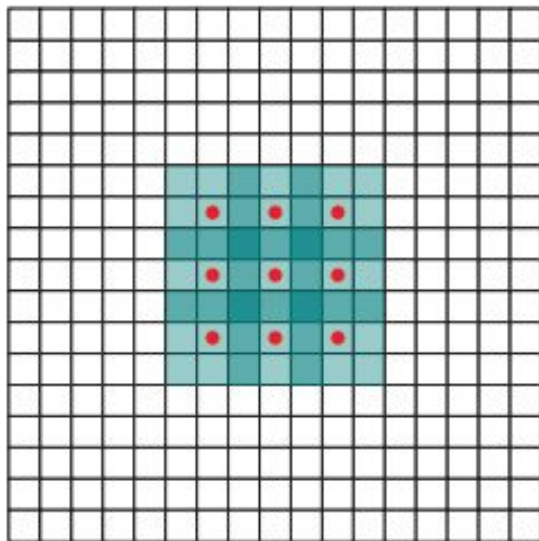
Uses GENCODE annotation as labeled data

Dilated convolution



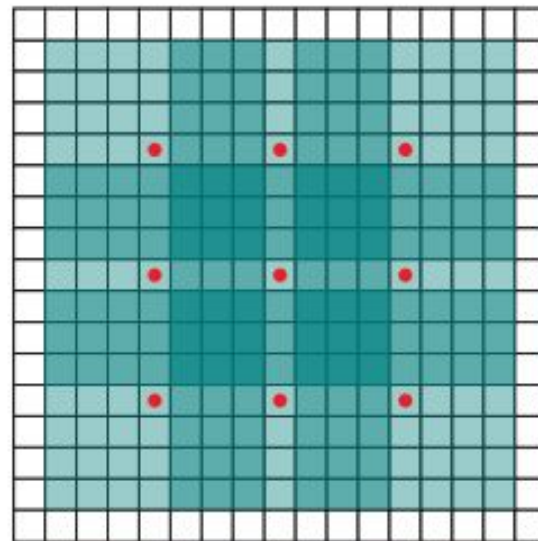
(a)

$k=1$



(b)

$k=2$

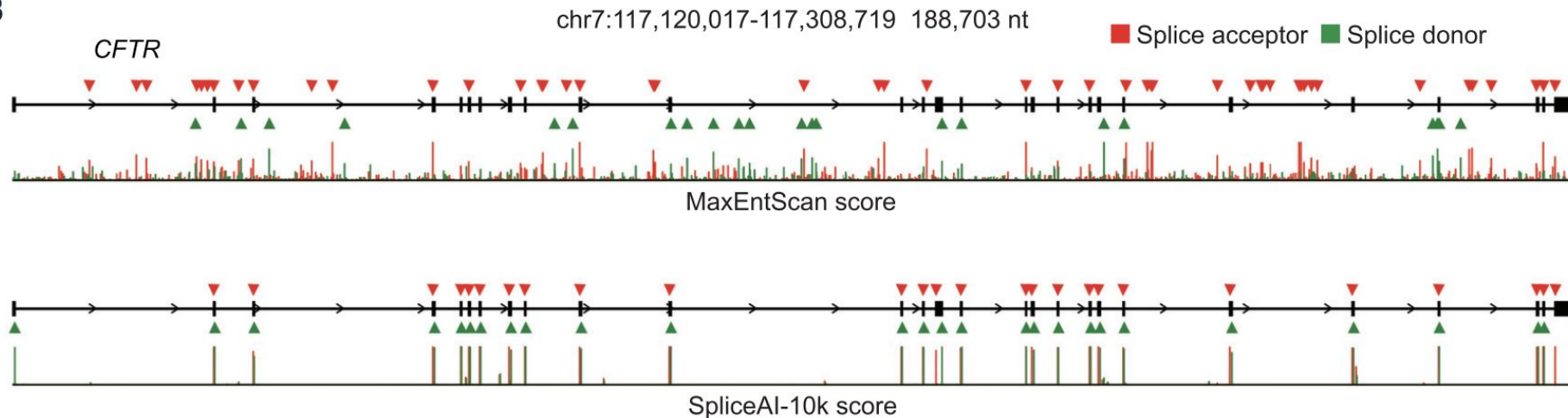


(c)

$k=2$

Example + comparison against MaxEntScan

B



The full pre-mRNA transcript for the CFTR gene scored using MaxEntScan (top) and SpliceAI-10k (bottom) is shown, along with predicted acceptor (red arrows) and donor (green arrows) sites and the actual positions of the exons (black boxes). For each method, we applied the threshold that made the number of predicted sites equal to the total number of actual sites.

To confirm that the network is not simply relying on exonic sequence biases, we also tested the network on long noncoding RNAs. Despite the incompleteness of noncoding transcript annotations, which is expected to reduce our accuracy, the network predicts known splice junctions in long noncoding RNAs (lincRNAs) with 84% top-k accuracy

E

	Top-k accuracy	PR-AUC
SpliceAI-80nt	0.57	0.60
SpliceAI-400nt	0.90	0.95
SpliceAI-2k	0.93	0.97
SpliceAI-10k	0.95	0.98
GeneSplicer	0.30	0.23
MaxEntScan	0.22	0.15
NNSplice	0.22	0.15

Effect of the size of the input sequence context on the accuracy of the network.

Top-k accuracy is the fraction of correctly predicted splice sites at the threshold where the number of predicted sites is equal to the actual number of sites present.

PR-AUC is the area under the precision-recall curve. We also show the top-k accuracy and PR-AUC for three other algorithms for splice-site detection.

A deep learning-based tool to identify splice variants

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🌿 1 branch

📦 0 releases

👤 3 contributors

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Branch: master ▾

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Jaganathan v1.2.1: clean I/O handling, improved logs

Latest commit f6e289c 6 days ago

📁 examples

v1.2.1: clean I/O handling, improved logs

6 days ago

📁 spliceai

v1.2.1: clean I/O handling, improved logs

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📁 tests

v1.2: handles gvcf, bad inputs

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📄 README.md

v1.2.1: clean I/O handling, improved logs

6 days ago

📄 setup.py

v1.2.1: clean I/O handling, improved logs

6 days ago

📖 README.md

SpliceAI: A deep learning-based tool to identify splice variants

This package annotates genetic variants with their predicted effect on splicing, as described in [Jaganathan *et al*, Cell 2019 in press](#).

Installation

The simplest way to install SpliceAI is through pip: