A Deep Neural Network Approach to Splice Site Prediction

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Outline

Problem Description

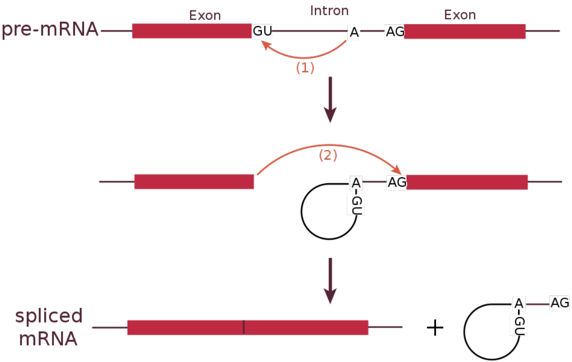

Figure: RNA splicing reaction (en.wikipedia.org)

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Splice site prediction on Arabidopsis thaliana genome

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- Donor site:
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- Acceptor site:
  ...CGTATCT AG ATG AG CA...
- Donor site:
  ...ATGATTT GT GCA GT CA...

Dataset description

Example file, e.g., acceptor site

$$\begin{bmatrix} CT \ldots 300 \text{ nt} \ldots AG \ldots 300 \text{ nt} \ldots GC \\ AG \ldots 300 \text{ nt} \ldots AG \ldots 300 \text{ nt} \ldots TT \\ GA \ldots 300 \text{ nt} \ldots AG \ldots 300 \text{ nt} \ldots AA \\ \vdots \\ 100,000 \text{ records} \\ \vdots \\ TT \ldots 300 \text{ nt} \ldots AG \ldots 300 \text{ nt} \ldots CC \end{bmatrix}$$

Simple non-convolutional NN

- Models built on one-hot-encoded data
- Dense networks with dropout

Approach	Samples	Depth	Acceptor acc.	Donor acc.
DNN	20,000	7	92.38	93.43
DNN	200,000	7	93.34	93.34

Figure: Binary classification results

Application of CNN to the DiProDB data

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- Applied PCA yielding 15 dimensions

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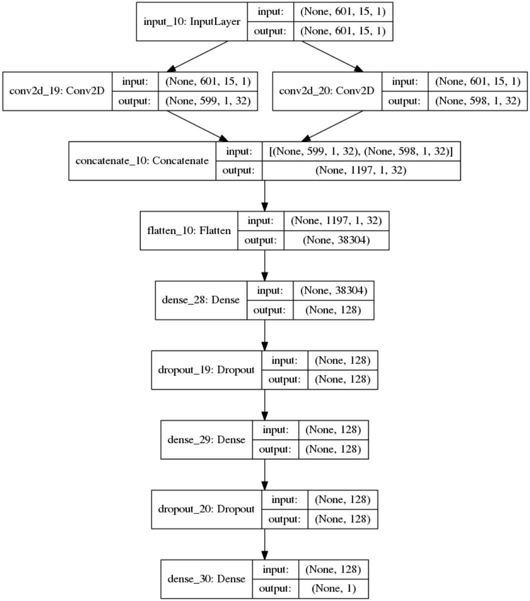
Approach	Layers		Acceptor			Donor		
	Conv.	Others	Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
CNN DPDB	4	5	94.4	95.4	94.6	94.9	94.4	94.7
CNN DPDB	4	7	93.5	93.3	94.5	94.0	94.0	93.3
CNN DPDB	6	5	94.0	93.9	94.9	94.2	95.4	91.6
CNN DPDB	6	5	94.4	97.0	93.8	95.2	96.5	93.7
SpliceRover	4	2	96.1	93.9	97.4	95.4	95.6	96.7
CNN DPDB(*)	2	4	94.3	95.6	94.3	95.3	96.9	94.4

SpliceRover[Zuallaert et al., 2018]


input_10: InputLayer
input: (None, 601, 15, 1)
output: (None, 601, 15, 1)
conv2d_19: Conv2D
input: (None, 601, 15, 1)
output: (None, 599, 1, 32)
conv2d_20: Conv2D
input: (None, 601, 15, 1)
output: (None, 598, 1, 32)
concatenate_10: Concatenate
input: [(None, 599, 1, 32), (None, 598, 1, 32)]
output: (None, 1197, 1, 32)
flatten_10: Flatten
input: (None, 1197, 1, 32)
output: (None, 38304)
dense_28: Dense
input: (None, 38304)
output: (None, 128)
dropout_19: Dropout
input: (None, 128)
output: (None, 128)
dense_29: Dense
input: (None, 128)
output: (None, 128)
dropout_20: Dropout
input: (None, 128)
output: (None, 128)
dense_30: Dense
input: (None, 128)
output: (None, 1)

Improvements on simple approach

Applying convolutional models to one hot encoding of

- single nucleotides

Approach	Samples	Acceptor			Donor		
		Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
Simple	200000	94.5	95.6	93.3	95.3	96.7	94.5

- trinucleotides

Approach	Samples	Acceptor			Donor		
		Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
Simple	40000	94.6	93.3	96.7	95.0	92.5	96.3
Simple	200000	95.6	96.6	94.6	95.8	96.7	95.0

Single nucleotides model

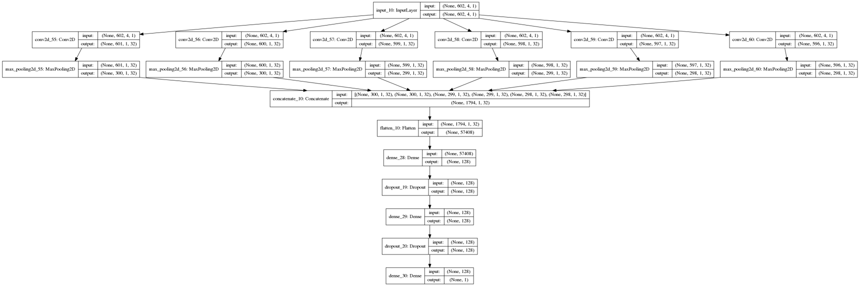


Figure: Convolutional model with filter sizes (2x4), . . . , (7x4)

Trinucleotides model

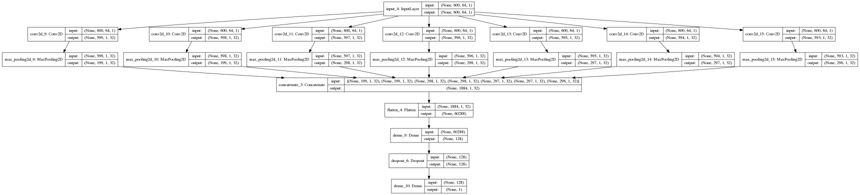


Figure: Convolutional model with filter sizes (2 x 64), . . . , (8x64)

repDNA (Liu, 2014)

A „Python package to generate various modes of feature vectors for DNA sequences“:

repDNA content

- Nucleic acid composition
  - kmer
  - Increment of diversity (ID)
- Autocorrelation
  - Dinucleotide-based auto covariance (DAC)
  - Dinucleotide-based cross covariance (DCC)
  - Dinucleotide-based auto-cross covariance (DACC)
  - Trinucleotide-based auto covariance (TAC)
  - Trinucleotide-based cross covariance (TCC)
  - Trinucleotide-based auto-cross covariance (TACC)

repDNA (Liu, 2014)

repDNA content

- Pseudo nucleotide composition
  - Pseudo dinucleotide composition (PseDNC)
  - Pseudo k-tupler nucleotide composition (PseKNC)
  - Parallel correlation pseudo dinucleotide composition (PC-PseDNC)
  - Parallel correlation pseudo trinucleotide composition (PC-PseTNC)
  - Series correlation pseudo dinucleotide composition (SC-PseDNC)
  - Series correlation pseudo trinucleotide composition (SC-PseTNC)

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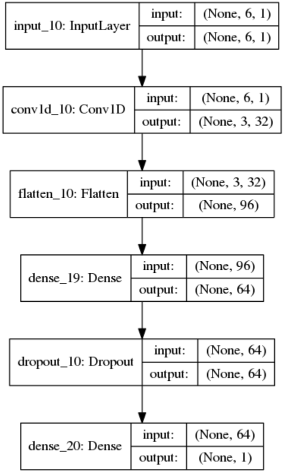
- Build model for each encoding and reuse filters for overall model

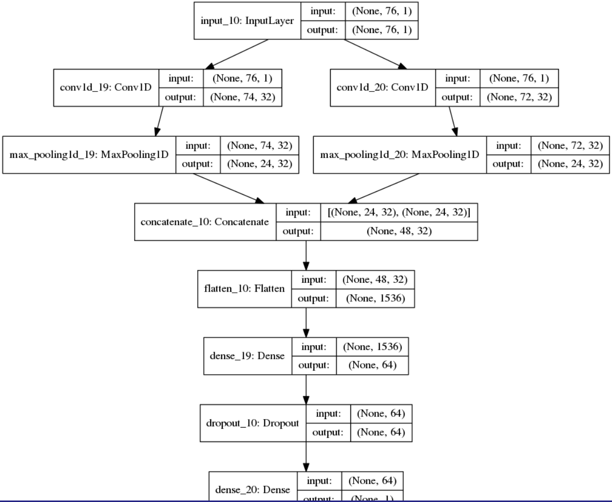
Classifier model on repDNA features: Results

Approach	Samples	Acceptor			Donor		
		Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
IDkmer	200000	75.2	72.3	76.7	72.7	77.05	75.6
DAC	200000	75.5	72.8	77.0	75.2	68.9	78.8
DCC	200000	75.1	80.0	77.7	74.5	75.2	80.0
TAC	200000	68.0	58.3	72.4	68.2	57.1	73.3
TCC	200000	73.6	75.5	72.7	75.3	65.0	82.0
PseKNC	200000	78.1	76.0	79.4	75.84	71.3	78.4
PC-PseDNC	200000	78.0	76.5	80.1	76.4	75.1	77.9
PC-PseTNC	200000	80.5	76.1	84.2	78.8	76.9	81.6
SC-PseDNC	200000	79.2	74.5	82.4	77.5	77.0	78.8
SC-PseTNC	200000	80.6	76.3	84.8	78.7	77.3	81.5

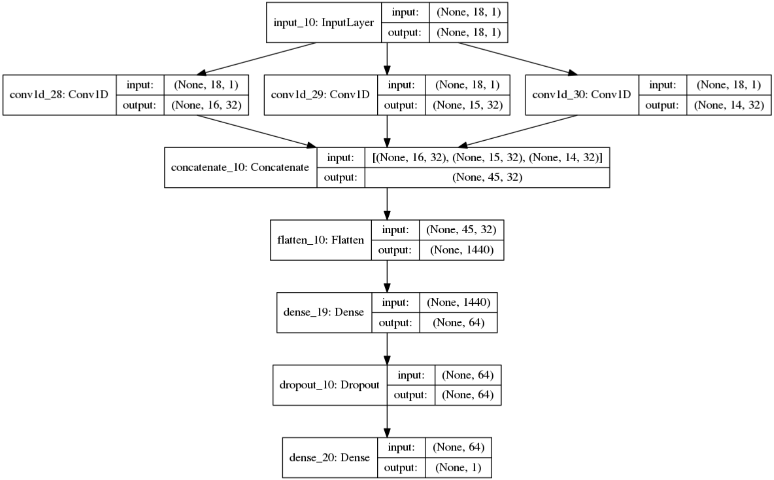
Classifier model on repDNA features: IDkmer



Classifier model on repDNA features: DAC/DCC/TAC/TCC



Classifier model on repDNA features: PseNAC



Additional models

- XGBoost: Library for gradient boosting algorithms
- Random Forest

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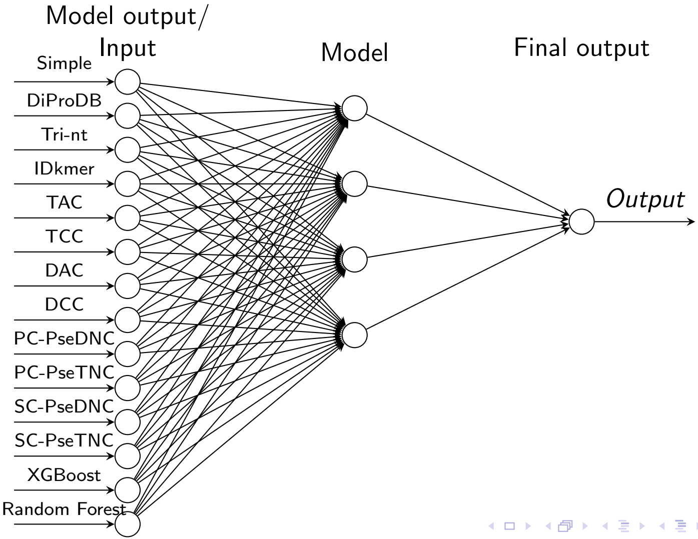
Approach	Acceptor			Donor		
	Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
XGBoost	90.8	89.5	92.0	92.0	90.6	93.3
Random Forest	83.5	83.0	83.8	86.0	86.3	85.8

Funneling method: Model



Funneling method: Soft vote results

- Random search on weighted filters

	Weights							Results					
M	S	D	T	R	X	dc	Ps	Acceptor			Donor		
								Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
S	1	0	1	0	0	0	0	95.5	96.0	95.0	96.0	96.9	95.2
H	1	0	1	0	0	0	0	95.1	97.5	93.1	95.5	97.9	93.5
S	1	1	3	1	1	0	0	95.2	95.5	95.0	95.8	96.2	95.3
H	1	1	3	1	1	0	0	95.5	96.6	94.6	95.9	97.1	94.9
S	3	2	3	2	1	0	0	95.0	95.1	94.9	95.7	96.2	95.2
H	3	2	3	2	1	0	0	95.2	95.6	94.9	95.8	96.5	95.1
S	8	5	8	2	0	0	0	95.4	95.8	95.1	95.9	96.6	95.3
H	8	5	8	2	0	0	0	95.4	96.3	94.7	95.9	97.0	94.9

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	Weights							Results					
M	S	D	T	R	X	dc	Ps	Acceptor			Donor		
								Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
S	1	1	1	1	1	1	1	92.0	90.3	92.4	94.1	93.9	94.4
H	1	1	1	1	1	1	1	85.0	80.3	88.5	85.8	80.7	89.8
S	5	2	5	4	4	1	1	94.8	94.9	94.8	95.6	95.9	95.2
H	5	2	5	4	4	1	1	95.1	95.7	94.6	95.8	96.5	95.1
S	5	5	5	4	4	1	1	95.1	95.2	95.0	95.8	96.3	95.4
H	5	5	5	4	4	1	1	95.3	95.5	95.0	95.9	96.5	95.3
S	7	7	7	5	5	1	1	95.2	95.3	95.1	95.8	96.3	95.3
H	7	7	7	5	5	1	1	95.3	95.7	95.0	96.0	96.6	95.3
S	7	7	7	5	0	0	0	95.3	95.6	95.0	95.8	96.5	95.2
H	7	7	7	5	0	0	0	95.5	96.1	95.0	96.0	96.9	95.1
S	95	95	95	90	85	80	80	93.7	92.9	94.3	94.9	95.0	94.8
H	95	95	95	90	85	80	80	86.7	82.9	89.1	84.8	80.72	90.0

Funneling method: Results

Minimization techniques:

- Nalder-Mead
- Powell

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Soft Min.	83.8	83.5	83.0	86.0	86.3	85.8
Hard Min.	83.5	83.0	84.1	86.5	86.7	86.3

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	Acc.	Prec.	Rec.	Acc.	Prec.	Rec.
Soft Min.	83.8	83.5	83.0	86.0	86.3	85.8
Hard Min.	83.5	83.0	84.1	86.5	86.7	86.3
Grad boost	83.5	83.0	83.8	86.0	86.3	85.8
Random Forest	93.7	94.2	93.3	94.1	94.9	93.4
NN	83.5	83.0	83.8	87.0	85.5	87.4
Naive Bayes	83.5	83.0	83.8	85.9	86.3	85.8

Citations

- Liu B, Liu F, Fang L, Wang X, Chou K-C.repDNA: a Python package to generate various modes of feature vectors for DNA sequences by incorporating user-defined physicochemical properties and sequence-order effects. Bioinformatics 2015;31(8):1307-1309.
- Jasper Zuallaert, Fréderic Godin, Mijung Kim, Arne Soete, Yvan Saeys, Wesley De Neve, SpliceRover: interpretable convolutional neural networks for improved splice site prediction, Bioinformatics, Volume 34, Issue 24, 15 December 2018, Pages 4180–4188, https://doi.org/10.1093/bioinformatics/bty497