Large Scale Machine Learning for Genomic Sequence Analysis

(Support Vector Machine Based Signal Detectors)

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joint work with

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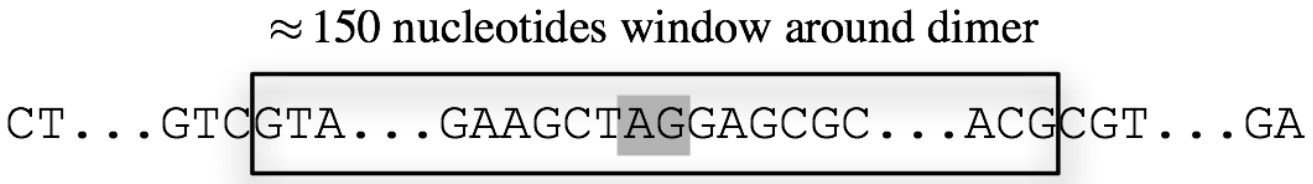
Outline

Recognizing Genomic Signals

Discriminate true signal positions against all other positions



- True sites: fixed window around a true site
- Decoy sites: all other consensus sites

```
AAACAAATAAGTAACTAATCTTTTAGGAAGAACGTTTCAACCATTTTGAG
AAGATTAAAAAAAAACAAATTTTTAGCATTACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTTTAGTTCACTAACACATCCGTCTGTGCC
TTAATTTCACTTCCACATACTTCCAGATCATCAATCTCCAAAACCAACAC
```

Examples: Transcription start site finding, splice site prediction, alternative splicing prediction, trans-splicing, polyA signal detection, translation initiation site detection

Types of Signal Detection Problems I

Vague categorization

(based on positional variability of motifs)

Position Independent

→ Motifs may occur anywhere,

```
AAACAAAAACGTAACTAATCTTTTAGAGAGAACGTTTCAACCATTTTGAG
AAGATTAACTCATCACAGATTTCATTACATACAGATATAATTCAAAAATT
CACTCCCCAAATCAACGATATTTAAAAATCACTAACACATCCGTCTGTGC
```

e.g. tissue classification using promotor region

Types of Signal Detection Problems II

Vague categorization

(based on positional variability of motifs)

Position Dependent

→ Motifs very stiff, almost always at same position,

e.g. Splice Site Classification

Types of Signal Detection Problems III

Vague categorization

(based on positional variability of motifs)

Mixture Position Dependent/Independent

→ variable but still positional information

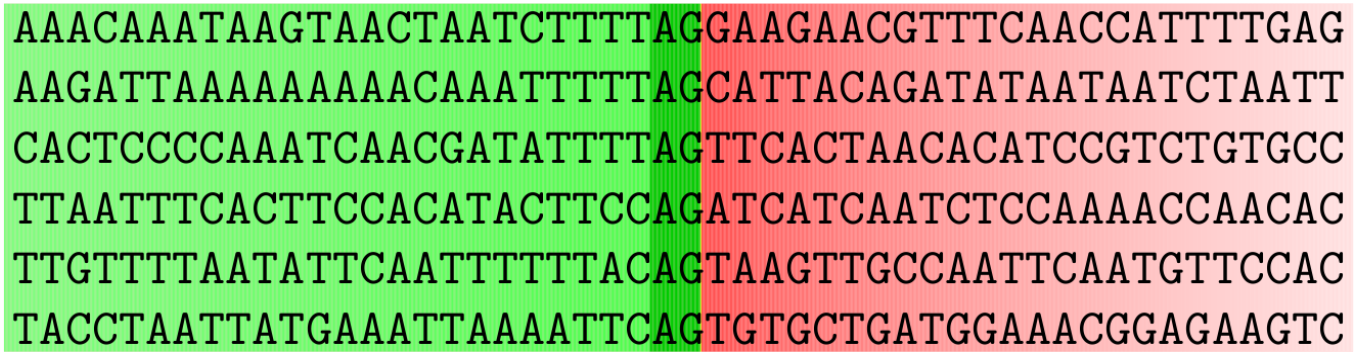
```
AAACAAATAAGTAACTAATCTTTTAAAGAGAACGTTTCAACCATTTTGAG
AAGATTAAAAAAAAACAAATTTCATTAAATACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTTAAATTTCACTAACACATCCGTCTGTGC
```

e.g. Promoter Classification

Classification - Learning based on examples

Given:

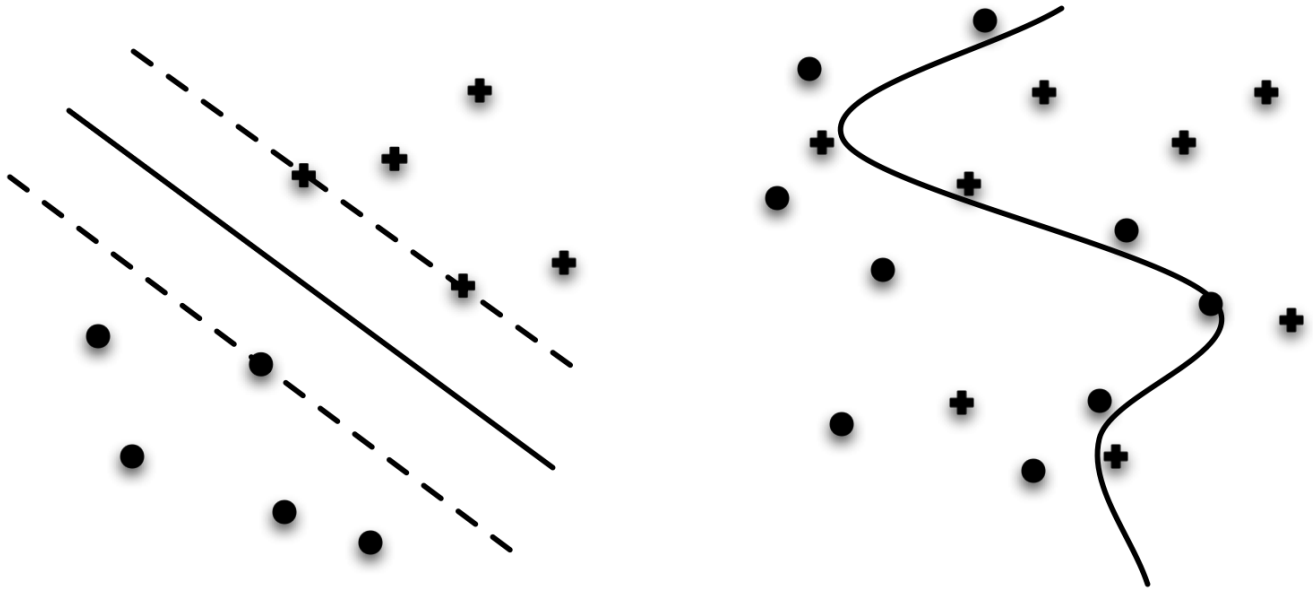
Training examples $(\mathbf{x}_i, y_i)_{i=1}^N \in (\{A, C, G, T\}^L, \{-1, +1\})^N$



Wanted:

Function (Classifier) $f(\mathbf{x}) : \{A, C, G, T\}^L \mapsto \{-1, +1\}$

Support Vector Machines (SVMs)



- **Support Vector Machines** learn weights $\alpha \in \mathbb{R}^N$ over training examples in kernel feature space $\Phi : \mathbf{x} \mapsto \mathbb{R}^D$,

$$f(\mathbf{x}) = \text{sign}\left(\sum_{i=1}^{N} y_i \alpha_i k(\mathbf{x}, \mathbf{x}_i) + b\right),$$

with kernel $k(\mathbf{x}, \mathbf{x}') = \Phi(\mathbf{x}) \cdot \Phi(\mathbf{x}')$

The Spectrum Kernel

Support Vector Machine

$$f(\mathbf{x}) = \text{sign}\left(\sum_{i=1}^{N} y_i \alpha_i \mathsf{k}(\mathbf{x}, \mathbf{x}_i) + b\right),$$

Spectrum Kernel (with mismatches, gaps)

$$K(\mathbf{x}, \mathbf{x}') = \Phi_{sp}(\mathbf{x}) \cdot \Phi_{sp}(\mathbf{x}')$$

AAACAAAAACGTAACTAATCTTTTAGAGAGAACGTTTCAACCATTTTGAG
AAGATTAACTCATCACAGATTTCATTACATACAGATATAATTCAAAAATT
CACTCCCCAAATCAACGATATTTAAAAATCACTAACACATCCGTCTGTGC

The Weighted Degree Kernel

Support Vector Machine

$$f(\mathbf{x}) = \text{sign}\left(\sum_{i=1}^{N} y_i \alpha_i \mathsf{k}(\mathbf{x}, \mathbf{x}_i) + b\right),$$

$$\mathsf{k}(\mathbf{x}, \mathbf{x}') = \sum_{k=1}^{K} \beta_k \sum_{i=1}^{L-k+1} \mathbb{I}\left\{\mathbf{x}[i]^k = \mathbf{x}'[i]^k\right\}.$$

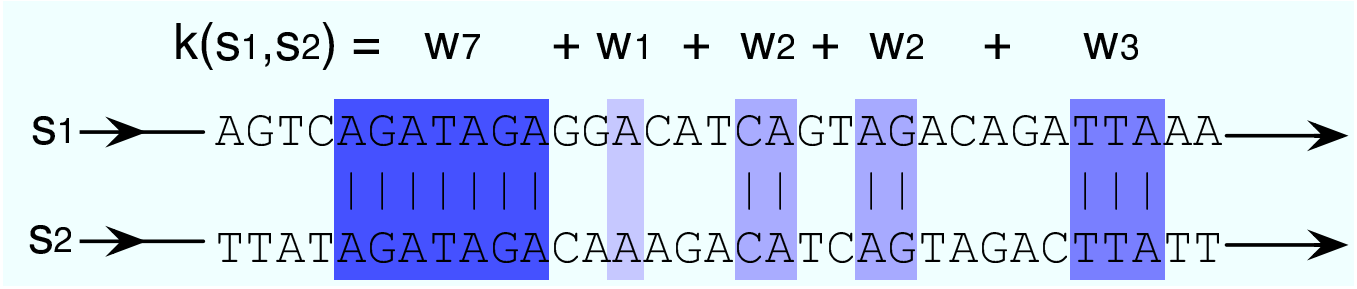
```
      x  AAACAAATAAGTAACTAATCTTTTAGGAAGAACGTTTCAACCATTTTGAG
#1-mers  .|.|.|||.|..||.|.|..|||.||...|....|...|||......|..
#2-mers  .....||.....|.......||..|............||.........
#3-mers  .....|.............|................|..........
      y  TACCTAATTATGAAATTAAATTTCAGTGTGCTGATGGAAACGGAGAAGTC
```

Example: $K = 3$: $\mathsf{k}(\mathbf{x}, \mathbf{x}') = \beta_1 \cdot 21 + \beta_2 \cdot 8 + \beta_3 \cdot 3$

The Weighted Degree Kernel with *shifts*

Support Vector Machine

$$f(\mathbf{x}) = \text{sign}\left(\sum_{i=1}^{N} y_i \alpha_i k(\mathbf{x}, \mathbf{x}_i) + b\right),$$



Accelerating String-Kernel-SVMs

1. Linear run-time of the kernel
2. Accelerating linear combinations of kernels

Idea of the `Linadd` Algorithm:

Store $\mathbf{w}$ and compute $\mathbf{w} \cdot \Phi(\mathbf{x})$ *efficiently*

$$f(\mathbf{x}_j) = \sum_{i=1}^{N} \alpha_i y_i \, \mathrm{k}(\mathbf{x}_i, \mathbf{x}_j) = \underbrace{\sum_{i=1}^{N} \alpha_i y_i \Phi(\mathbf{x}_i)}_{\mathbf{w}} \cdot \Phi(\mathbf{x}_j) = \mathbf{w} \cdot \Phi(\mathbf{x}_j)$$

Possible for low-dimensional or sparse $\mathbf{w}$

Effort: $\mathcal{O}(NL) \Rightarrow$ speedup of factor N

$\Rightarrow$ Training on millions of examples, evaluation on billions.

Accelerating String-Kernel-SVMs II

Recent work:

Further drastic speedup using advances of primal SVMs solvers

Acceleration using fast primal SVMs

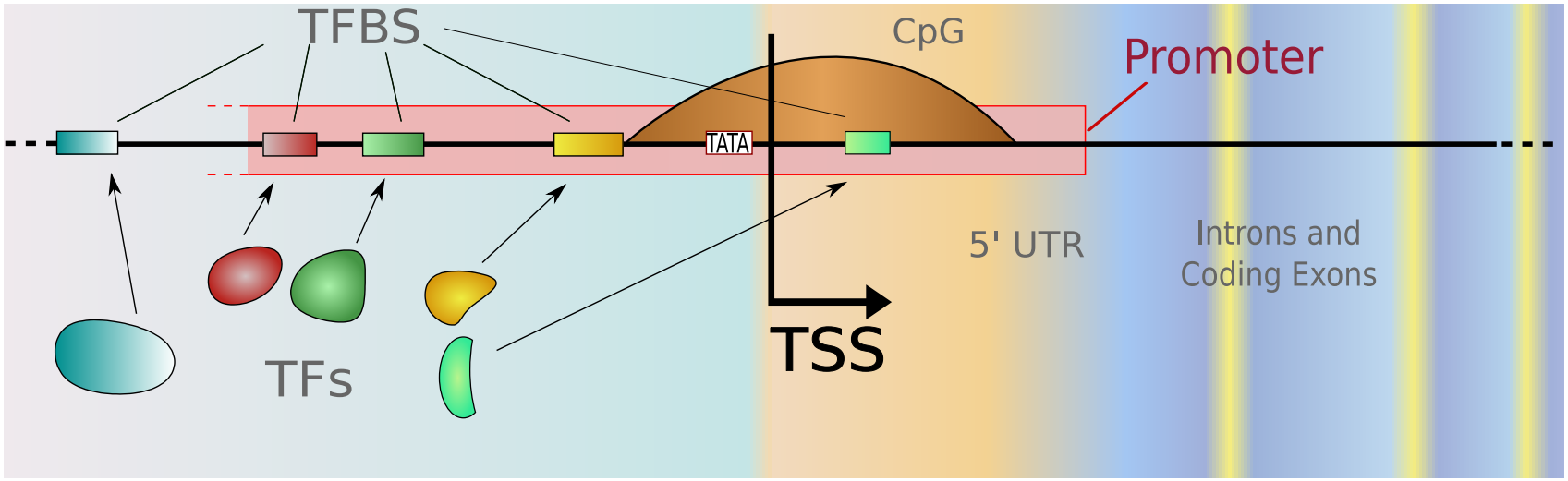
- Idea: Train SVM in primal using kernel feature space
- Problem: $>$ 12 million dims; 50 million examples
- Only $\mathbf{w} \leftarrow \mathbf{w} + \alpha\Phi(\mathbf{x})$ and $\mathbf{w} \cdot \Phi(\mathbf{x})$ required.
- Compute $\Phi(\mathbf{x})$ on-the-fly and parallelize!

Results

$\Rightarrow$ Computations are simple "table lookups" of $k-$mers weights

$\Rightarrow$ **Allows training on 50 million examples**

Detecting Transcription Start Sites



- POL II indirectly binds to a rather vague region of $\approx [-20, +20]$ bp
- Upstream of TSS: promoter containing transcription factor binding sites
- Downstream of TSS: 5' UTR, and further downstream coding regions and introns (different statistics)
- 3D structure of the promoter must allow the transcription factors to bind

Several weak features $\Rightarrow$ Promoter prediction is non-trivial

Features to describe the TSS

- TFBS in Promoter region
- condition: DNA should not be too twisted
- CpG islands (often over TSS/first exon; in most, but not all promoters)
- TSS with TATA box (≈ -30 bp upstream)
- Exon content in UTR 5" region
- Distance to first donor splice site

Idea:

Combine weak features to build strong promoter predictor

$$k(\mathbf{x}, \mathbf{x}') = k_{TSS}(\mathbf{x}, \mathbf{x}') + k_{CpG}(\mathbf{x}, \mathbf{x}') + k_{coding}(\mathbf{x}, \mathbf{x}') + k_{energy}(\mathbf{x}, \mathbf{x}') + k_{twist}(\mathbf{x}, \mathbf{x}')$$

The 5 sub-kernels

1. TSS signal (including parts of core promoter with TATA box)

   – use **Weighted Degree Shift kernel**

2. CpG Islands, distant enhancers and TFBS upstream of TSS

   – use **Spectrum kernel** (large window upstream of TSS)

3. Model coding sequence TFBS downstream of TSS

   – use another **Spectrum kernel** (small window downstream of TSS)

4. Stacking energy of DNA

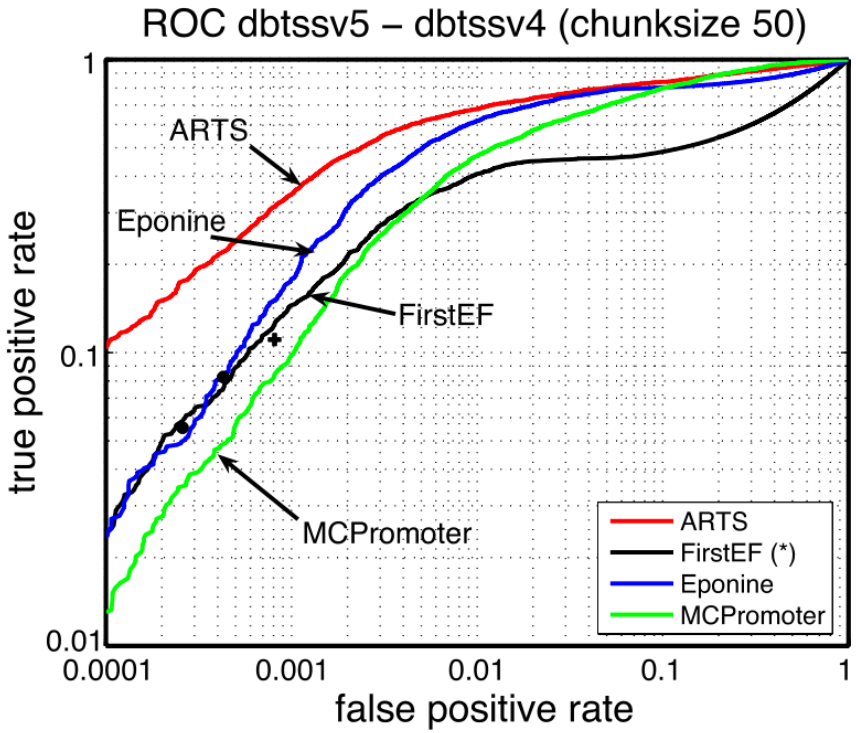
   – use *btwist* energy of dinucleotides with **Linear kernel**

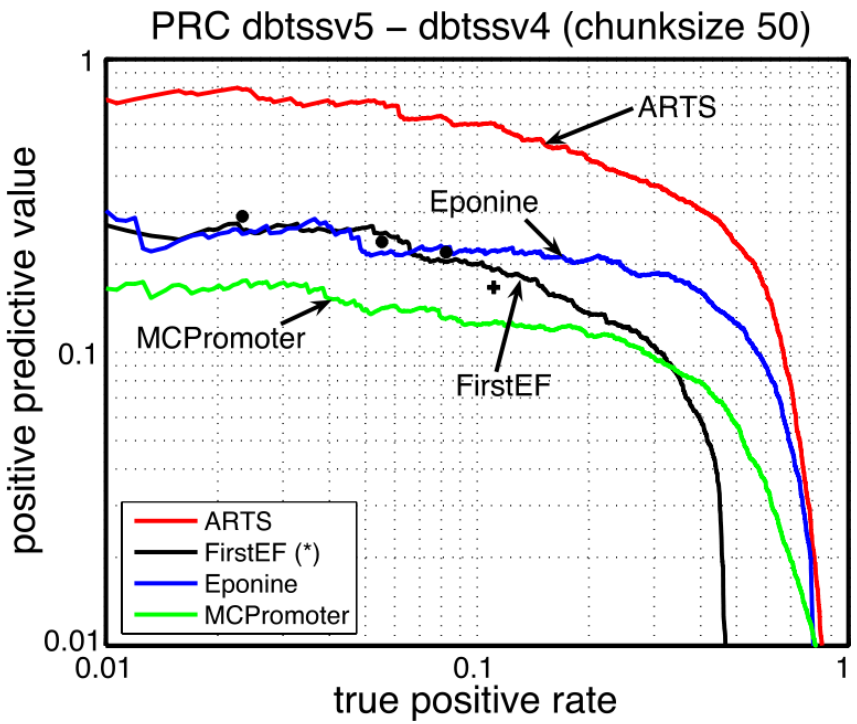
5. Twistedness of DNA

   – use *btwist* angle of dinucleotides with **Linear kernel**

State-of-the-art Performance

Receiver Operator Characteristic Curve and Precision Recall Curve





$\Rightarrow$ 35% **true positives at a false positive rate of** $1/1000$
(best other method find about a half (18%**))**

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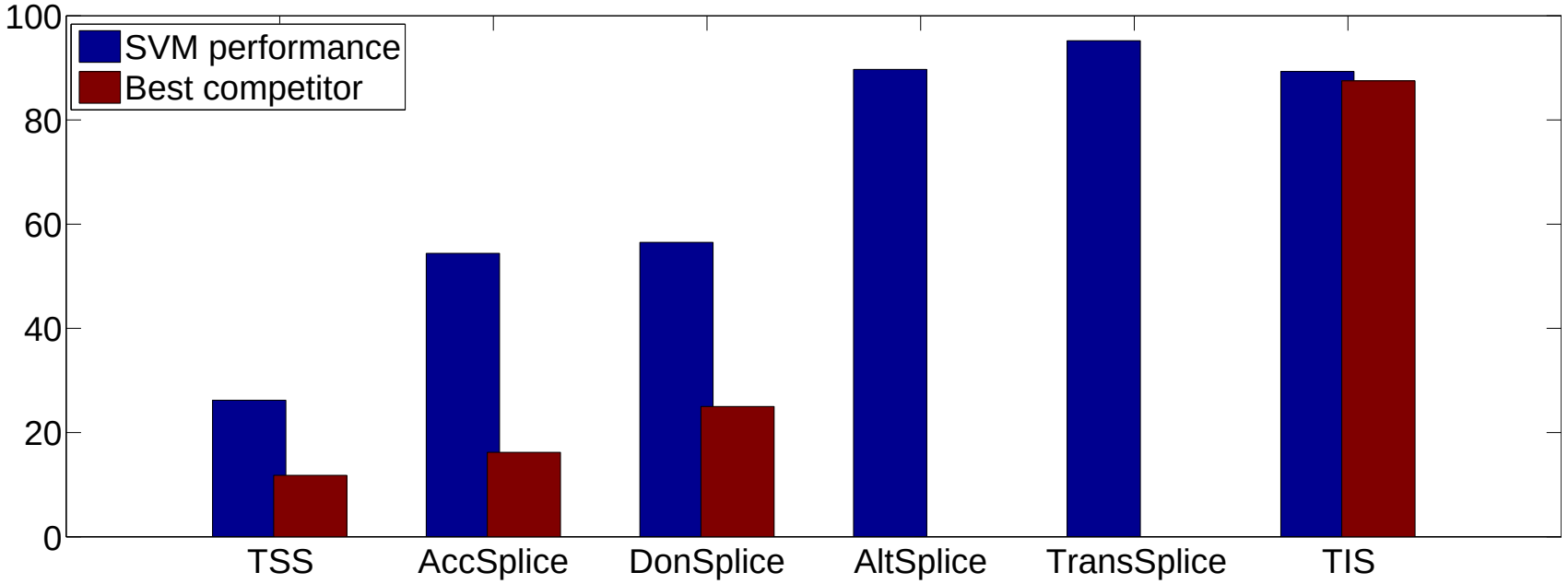
Beauty in Generality

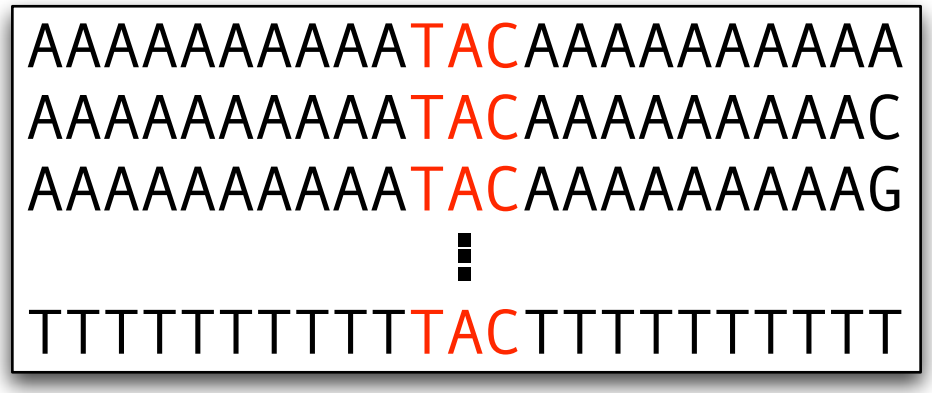


- Transcription Start (Sonnenburg et al., Eponine Down et al.)
- Acceptor Splice Site (Schweikert et al.)
- Donor Splice Site (Schweikert et al.)
- Alternative Splicing (Rätsch et al., -)
- Transsplicing (Schweikert et al., -)
- Translation Initiation (Sonnenburg et al., Saeys et al.)

Positional Oligomer Importance Matrices (POIMs)

Determine importance of $k-$mers at one glance:

- Given $k-$mer $\mathbf{z}$ at position j in the sequence, compute expected score $\mathbb{E}\left[\, s(\mathbf{x}) \mid \mathbf{x}[j] = \mathbf{z} \,\right]$ (**for small k**)



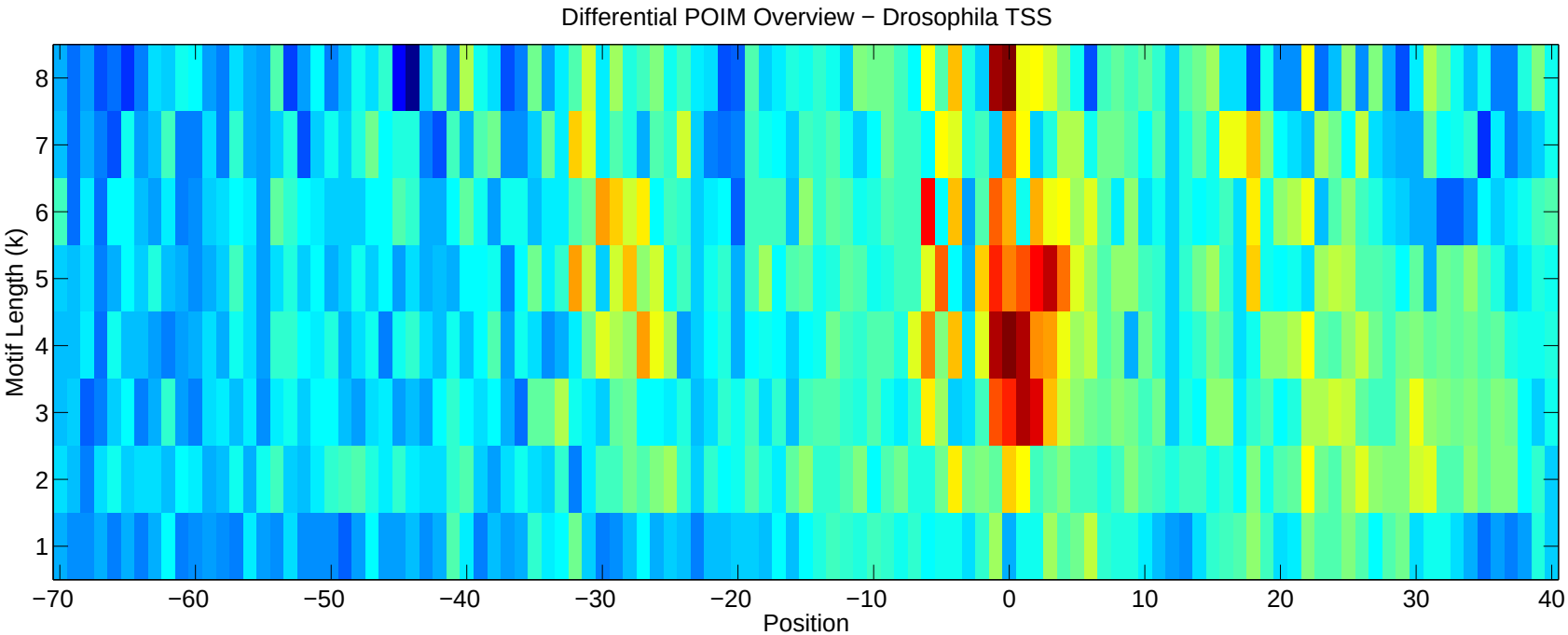
- Normalize with *expected score* over **all sequences**

POIMs

$$Q(\mathbf{z}, j) \;:=\; \mathbb{E}\left[\, s(\mathbf{x}) \mid \mathbf{x}[j] = \mathbf{z} \,\right] - \mathbb{E}\left[\, s(\mathbf{x}) \,\right]$$

Interpretable via Positional Oligomer Importance Matrices

Example: Drosophila Transcription Starts



TATAAAA	-29/++	**CAGT**CAGT	-01/++	CGTCGCG	+18/++
GTATAAA	-30/++	T**CAGT**TGT	-01/++	GCGCGCG	+23/++
ATATAAA	-28/++	CGT**CAGT**T	-03/++	CGCGCGC	+22/++
TATA-box		**Inr** **TCA**$\frac{G}{T}$**T**$\frac{T}{C}$		**CpG**	

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Conclusions

Support Vector Machines with string kernels

- General
- **Fast:** Applicable to genome-sized datasets
- Often are state-of-the art signal detectors
  - TSS
  - Acceptor and Acceptor Splice Site
  - ...
- Used in mGene gene finder `http://www.mgene.org`
- Positional Oligomer Importance Matrices help making SVMs interpretable

Galaxy web-interface `http://galaxy.fml.tuebingen.mpg.de`
Efficient implementation `http://www.shogun-toolbox.org`
More machine learning software `http://mloss.org`