Accurate and Interpretable Large Scale Genomic Signal Detection

(Support Vector Machine Based Signal Detectors)

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joint work with
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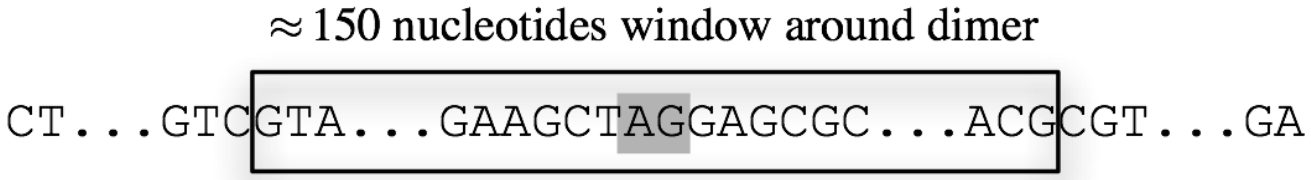
Outline

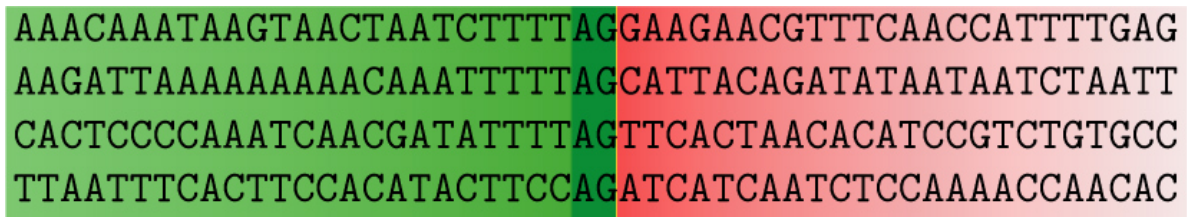
Outline

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



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,

```
AAACAAATAAGTAACTAATCTTTTAAGAAGAACGTTTCAACCATTTTGAG
AAGATTAAAAAAAAACAAATTTTTAACATTACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTTTAATTCACTAACACATCCGTCTGTGCC
```

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:

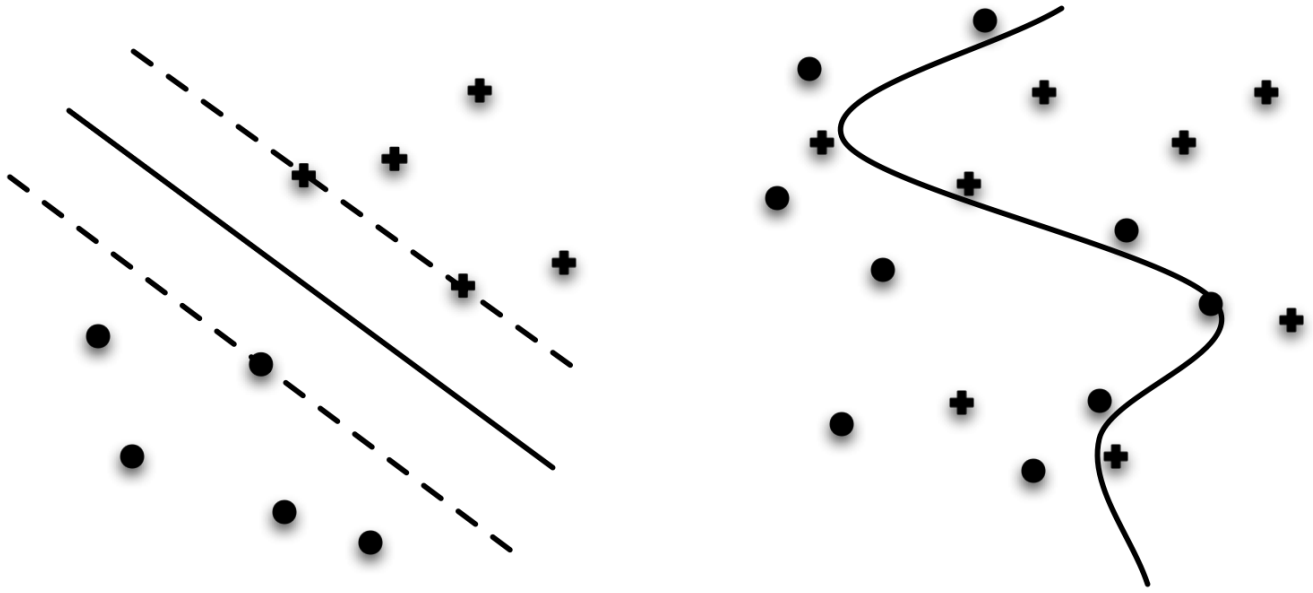
Training examples $(\mathbf{x}_i, y_i)_{i=1}^{N} \in (\{A, C, G, T\}^L, \{-1, +1\})^N$

```
AAACAAATAAGTAACTAATCTTTTAGGAAGAACGTTTCAACCATTTTGAG
AAGATTAAAAAAAAACAAATTTTTAGCATTACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTTTAGTTCACTAACACATCCGTCTGTGCC
TTAATTTCACTTCCACATACTTCCAGATCATCAATCTCCAAAACCAACAC
TTGTTTTAATATTCAATTTTTTACAGTAAGTTGCCAATTCAATGTTCCAC
TACCTAATTATGAAATTAAAATTCAGTGTGCTGATGGAAACGGAGAAGTC
```

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 $\Phi : \mathbf{x} \mapsto \mathbb{R}^D$,

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

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

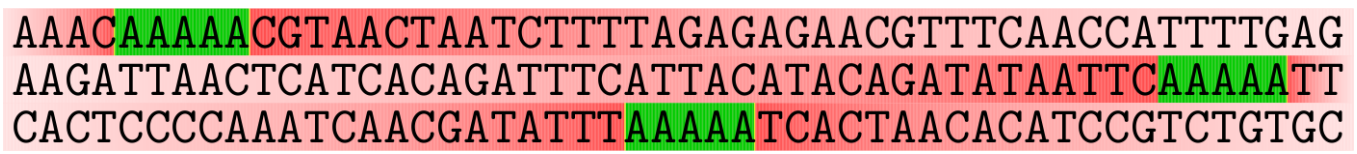
The Spectrum Kernel

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)

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

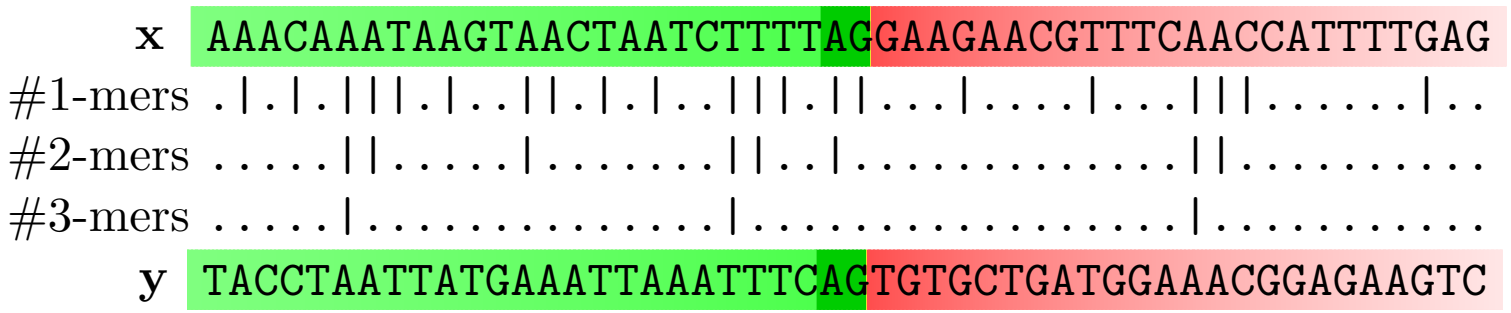


The Weighted Degree Kernel

Support Vector Machine

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

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

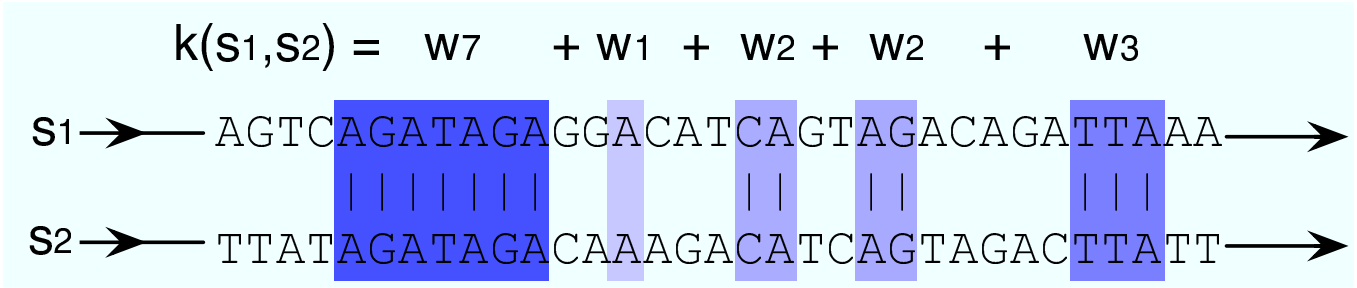


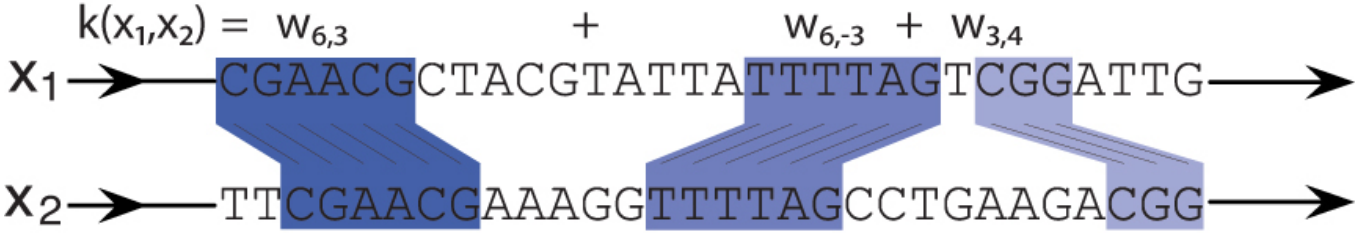
Example: $K = 3$: $\mathrm{k}(\mathbf{x}, \mathbf{x}') = \beta_1 \cdot 21 + \beta_2 \cdot 8 + \beta_3 \cdot 3$

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:

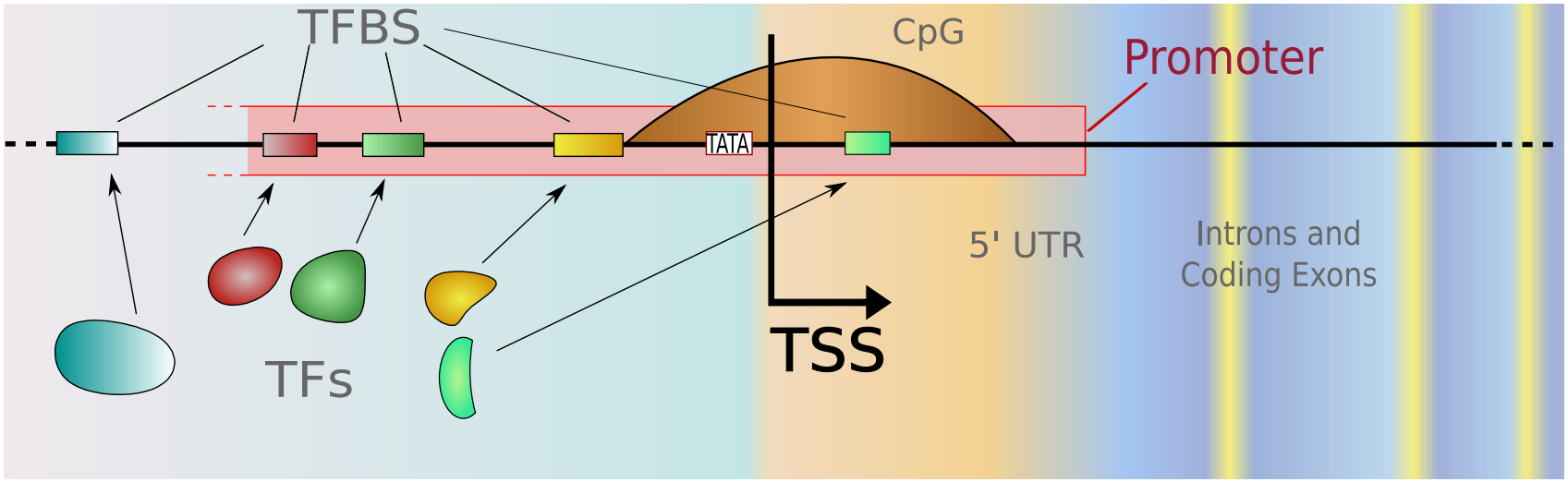
Store $\mathbf{w}$ and compute $\mathbf{w} \cdot \Phi(\mathbf{x})$ *efficiently*

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

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

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

Detecting Transcription Start Sites



- POL II 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

$\Rightarrow$ **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

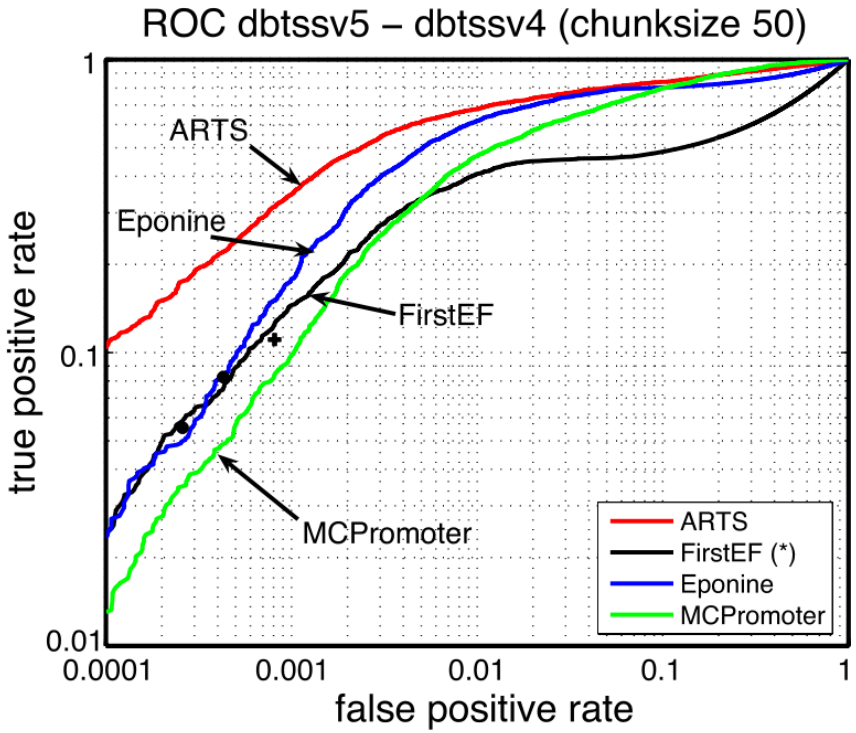
$$k(\mathbf{x}, \mathbf{x}') = k_{TSS}(\mathbf{x}, \mathbf{x}') + k_{CpG}(\mathbf{x}, \mathbf{x}') + k_{coding}(\mathbf{x}, \mathbf{x}') + k_{energy}(\mathbf{x}, \mathbf{x}') + k_{twist}(\mathbf{x}, \mathbf{x}')$$

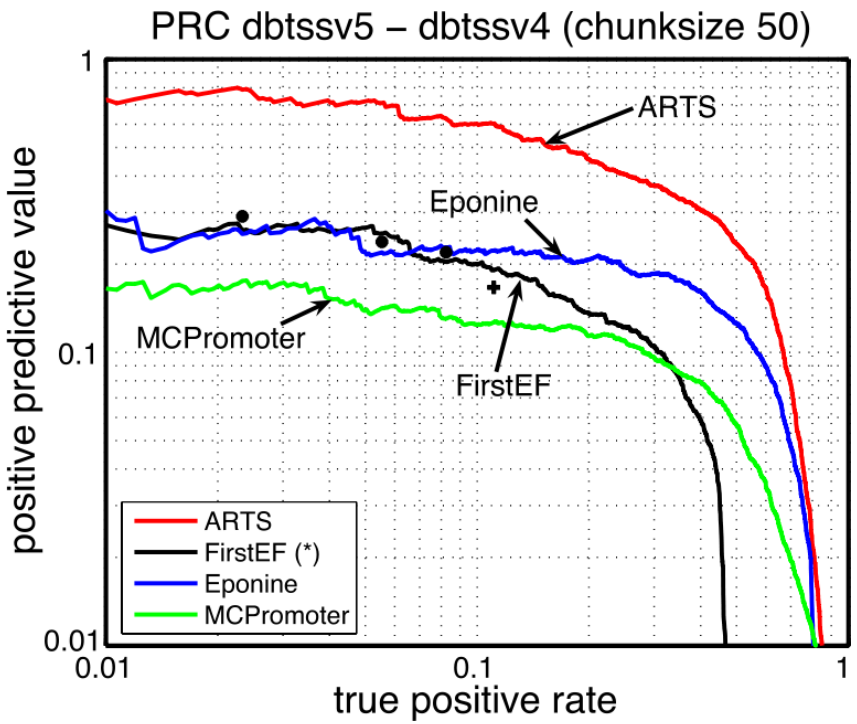
The 5 sub-kernels

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

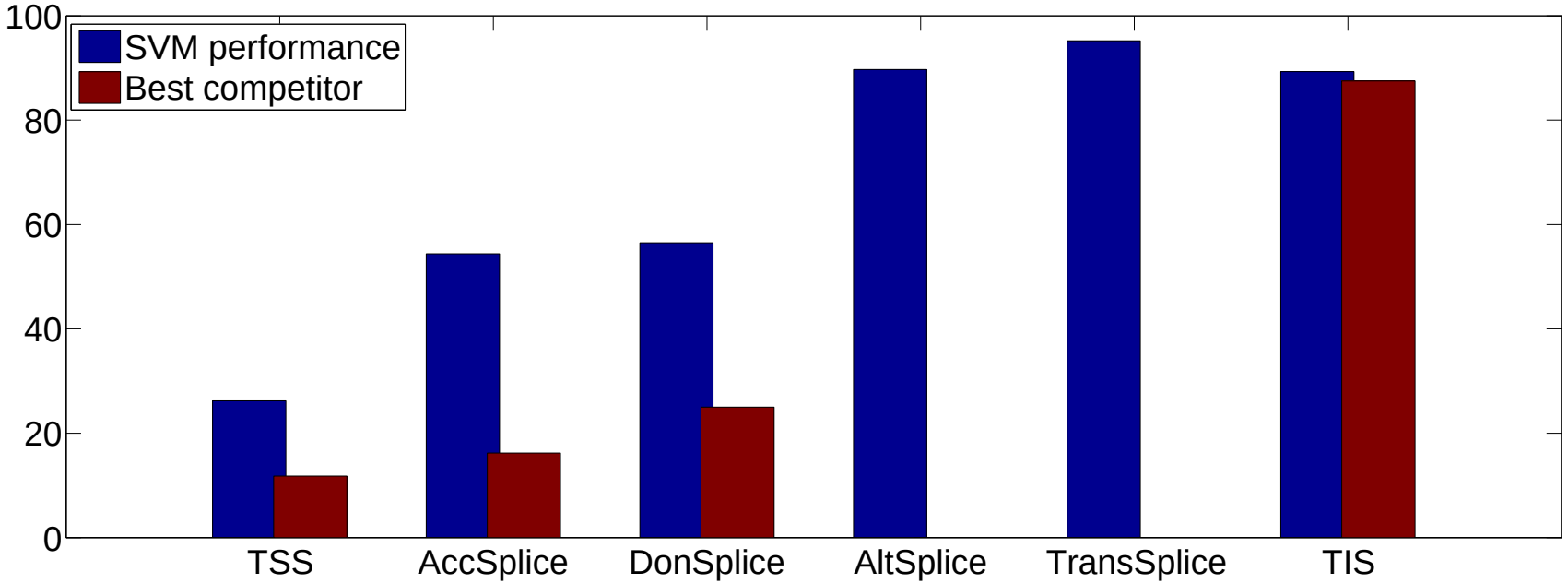
Receiver Operator Characteristic Curve and Precision Recall Curve





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

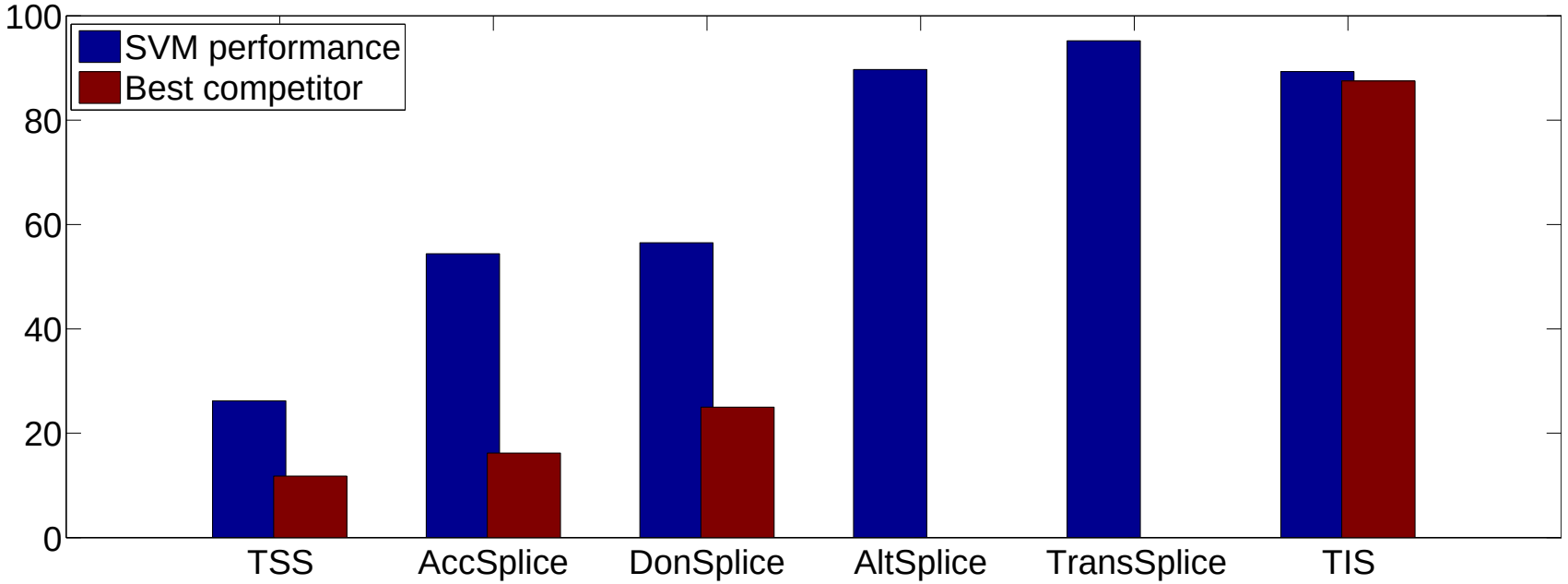
Beauty in Generality



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

Drawback: SVM solution is hard to interpret!!

Beauty in Generality



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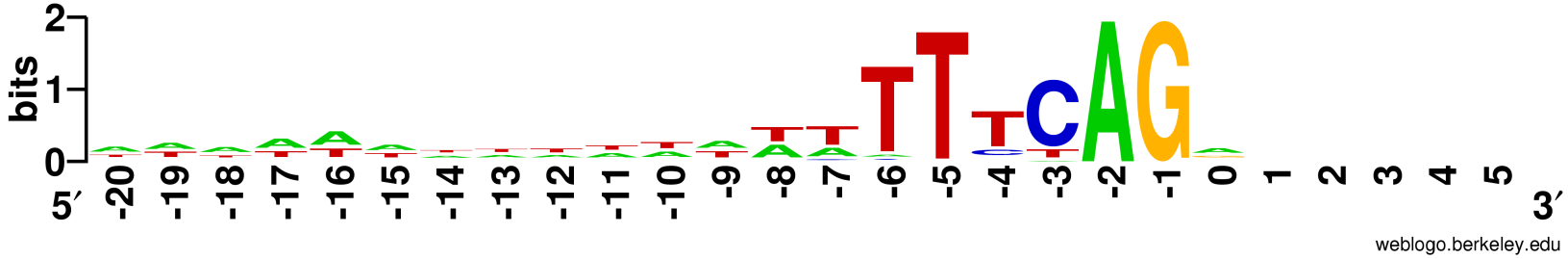
Drawback: SVM solution is hard to interpret!!

Outline

Understanding Support Vector Machines

Goal

For PWMs we have sequence logos:

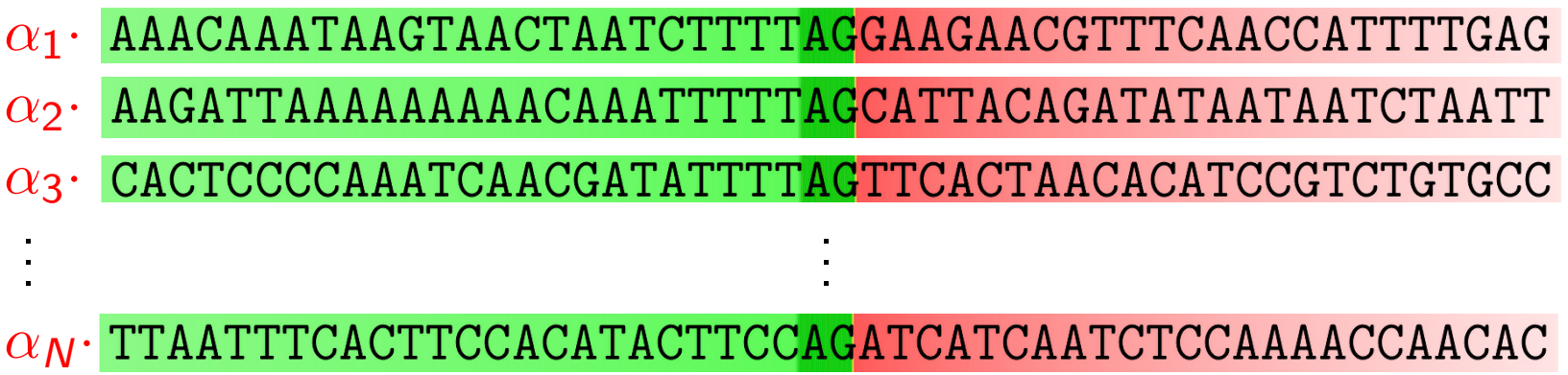


We would like to have **similar means to understand Support Vector Machines.**

Why Are SVM's Hard to Interpret?

SVM decision function is α weighting of training points

$$s(\mathbf{x}) = \sum_{i=1}^{N} \alpha_i y_i \, \mathrm{k}(\mathbf{x}_i, \mathbf{x}) + b$$



But we are interested in weights over features.

SVM Scoring Function

$$\mathbf{w} = \sum_{i=1}^{N} \alpha_i y_i \Phi(\mathbf{x}_i)$$

$$s(\mathbf{x}) := \sum_{k=1}^{K} \sum_{i=1}^{L-k+1} w\left(\mathbf{x}[i]^k, i\right) + b$$

k-mer	pos. 1	pos. 2	pos. 3	pos. 4	⋯
A	+0.1	-0.3	-0.2	+0.2	⋯
C	0.0	-0.1	+2.4	-0.2	⋯
G	+0.1	-0.7	0.0	-0.5	⋯
T	-0.2	-0.2	0.1	+0.5	⋯
AA	+0.1	-0.3	+0.1	0.0	⋯
AC	+0.2	0.0	-0.2	+0.2	⋯
⋮	⋮	⋮	⋮	⋮	⋱
TT	0.0	-0.1	+1.7	-0.2	⋯
AAA	+0.1	0.0	0.0	+0.1	⋯
AAC	0.0	-0.1	+1.2	-0.2	⋯
⋮	⋮	⋮	⋮	⋮	⋱
TTT	+0.2	-0.7	0.0	0.0	⋯

The Scoring System - Examples

$$s(\mathbf{x}) := \sum_{k=1}^{K} \sum_{i=1}^{L-k+1} w\left(\mathbf{x}[i]^k, i\right) + b$$

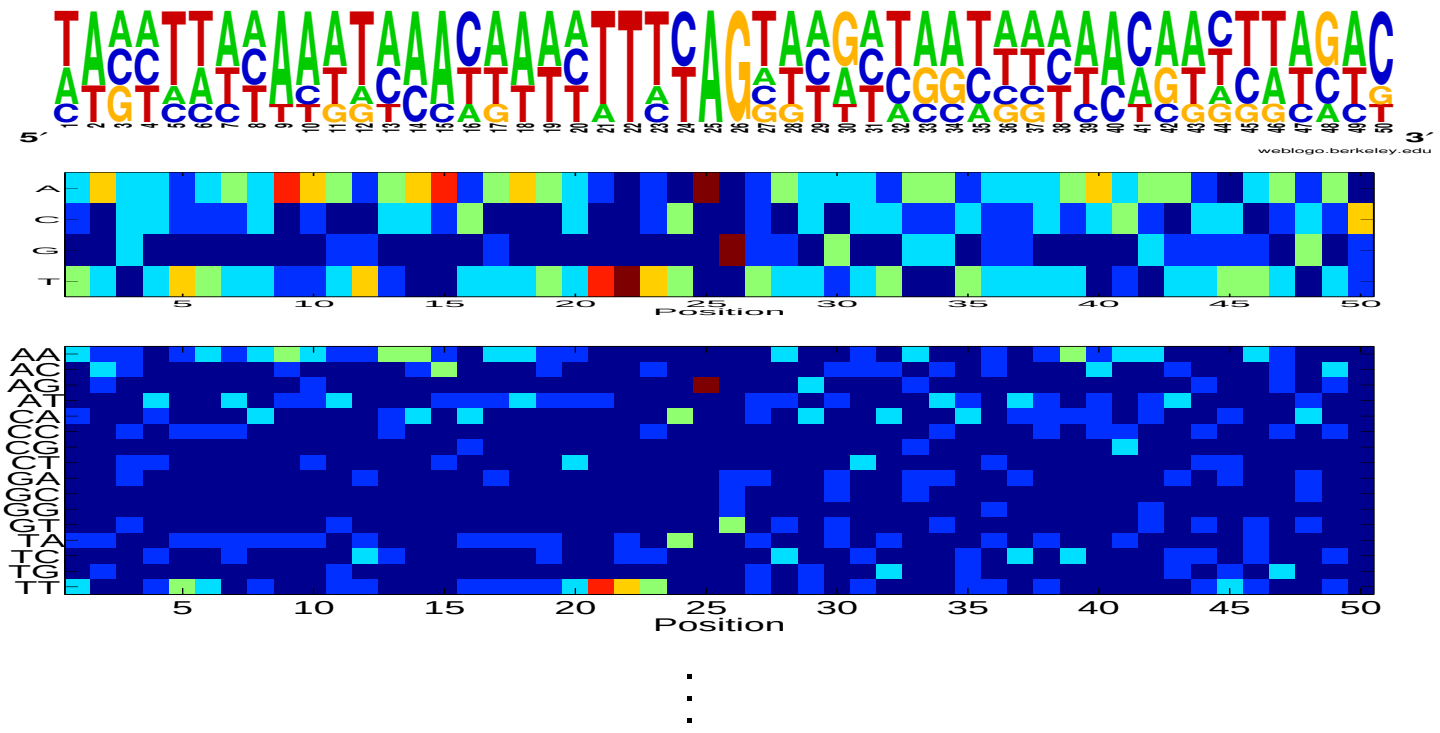
Examples:

- WD-kernel (Rätsch, Sonnenburg, 2005)
- WD-kernel with shifts (Rätsch, Sonnenburg, 2005)
- Spectrum kernel (Leslie, Eskin, Noble, 2002)
- Oligo Kernel (Meinicke et al., 2004)

Not limited to SVM's:

- Markov Chains (higher order/inhomogeneous/mixed order)

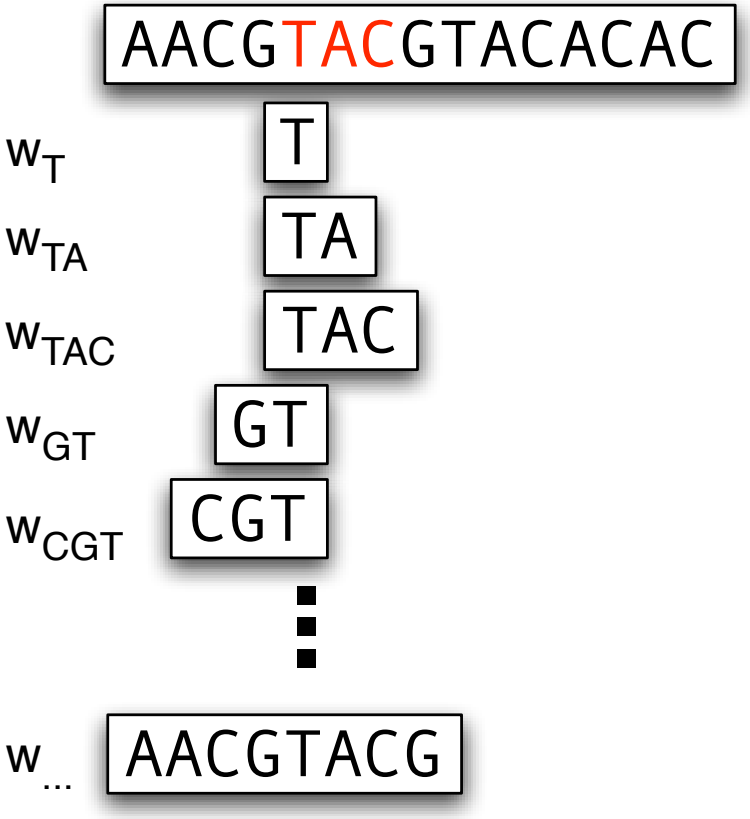
The SVM Weight Vector **w**



- Explicit representation of **w** allows for (some) interpretation!
- String kernel SVMs capable of efficiently dealing with large k-mers $k > 10$

But: Weights for substrings not independent

Interdependence of $k-$mer Weights



What is the score for TAC?

- Take w_{TAC}?
- But substrings and overlapping strings contribute too!

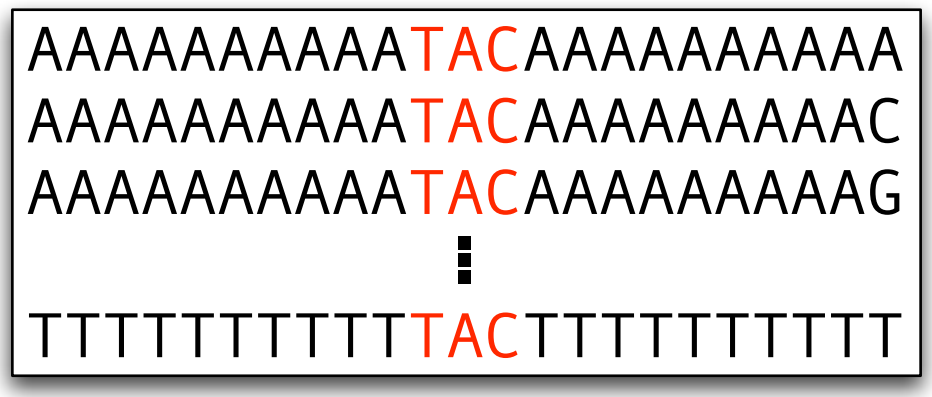
Problem

The SVM-w does NOT reflect the score for a motif

Positional Oligomer Importance Matrices (POIMs)

Idea:

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



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

POIMs

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

$\Rightarrow$ **Needs efficient algorithm for computation**

Efficient Computation

Effort of naive approach exponential $\mathcal{O}(|\Sigma|^L + L|\Sigma|^k)$
(e.g. Splice Sites 10^{120})

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

- Number of k-mers grows linearly with size of input
- Only features which are dependent on $(\mathbf{z}, j)$ matter
- Computation can be split in contributions from 4 cases

Efficient Recursive Algorithm:

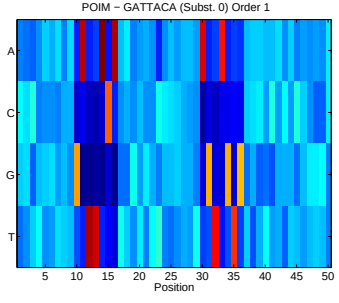
Effort linear in length of input: $\mathcal{O}(LN + L|\Sigma|^k)$

Ranking Features and Condensing Information

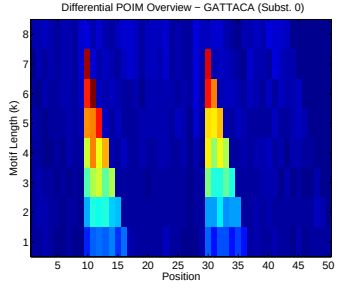
- Obtain highest scoring $\mathbf{z}$ from $Q(\mathbf{z}, i)$ (Enhancer or Silencer)

$\mathbf{z}$	i	$Q(\mathbf{z}, i)$
GATTACA	10	+30
AGTAGTG	30	+20
AAAAAAA	10	-10
...	...	...

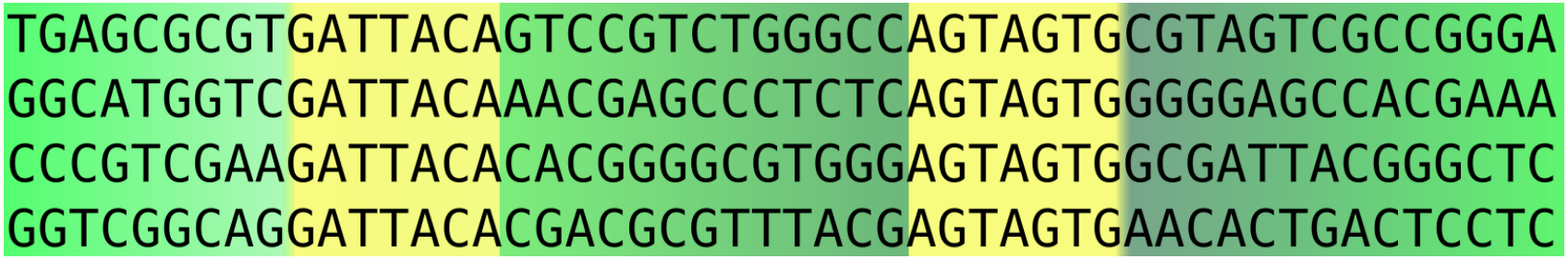
- Visualize POIM as heat map;
  x-axis: position
  y-axis: k-mer
  color: importance



- For large k: Differential POIMs;
  x-axis: position
  y-axis: k-mer length
  color: importance



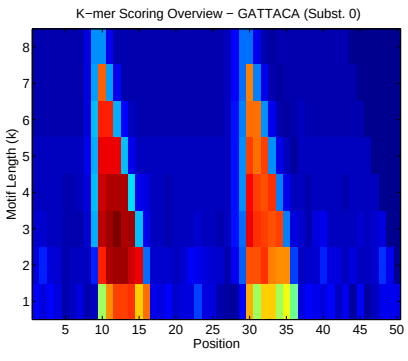
GATTACA and AGTAGTG at Fixed Positions 10 and 30



GATTACA and AGTAGTG at fixed positions 10 and 30

TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
GGTCGGCAGGATTACACGACGCGTTTACGAGTAGTGAACACTGACTCCTC

w



GATTACA and AGTAGTG at fixed positions 10 and 30

TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
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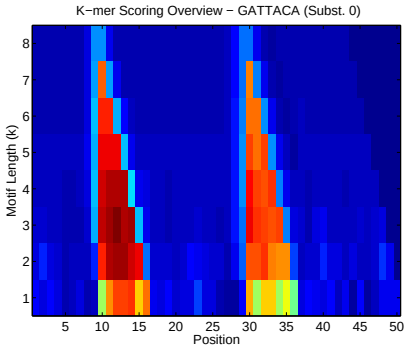
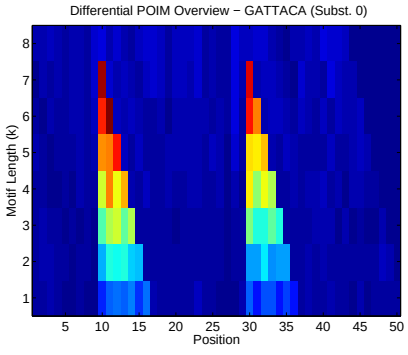
w



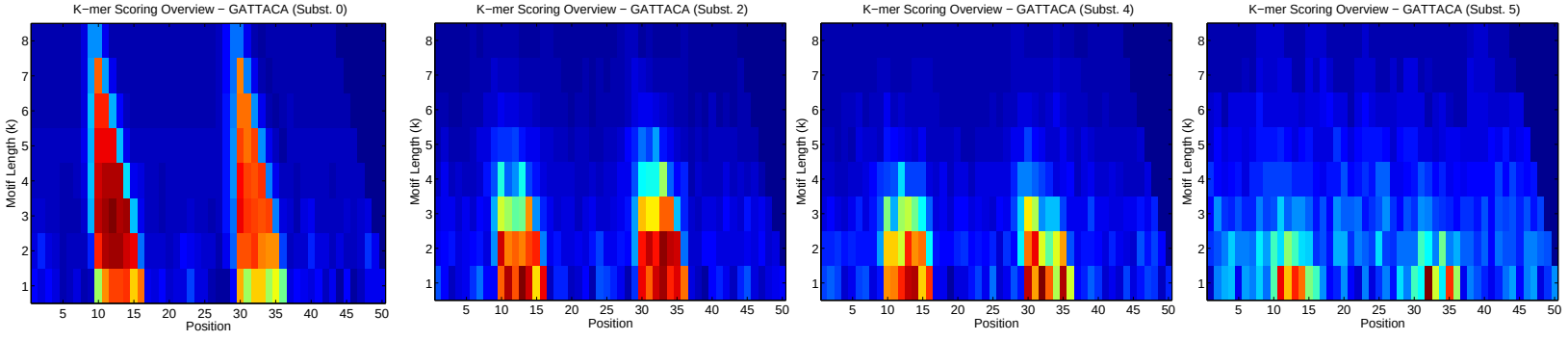
Q



GATTACA and AGTAGTG at fixed positions 10 and 30

TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
GGTCGGCAGGATTACACGACGCGTTTACGAGTAGTGAACACTGACTCCTC

w



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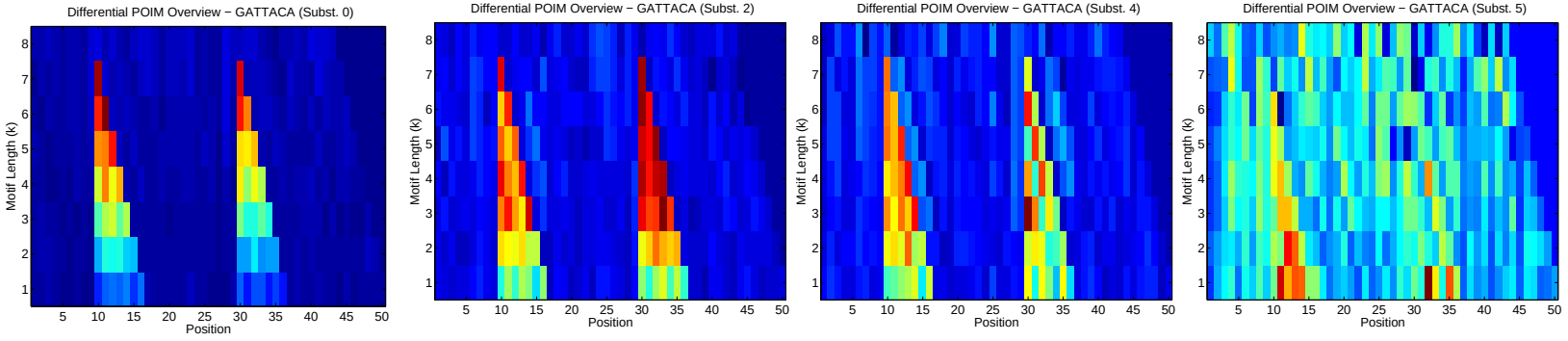
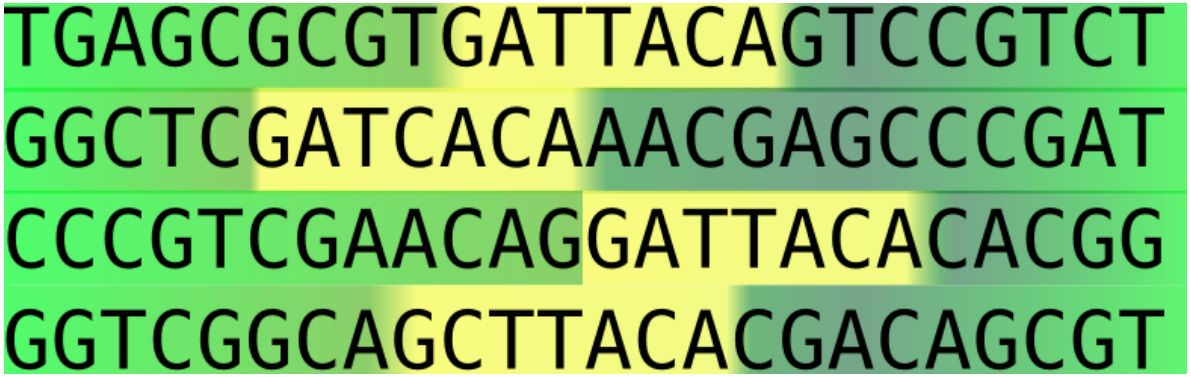
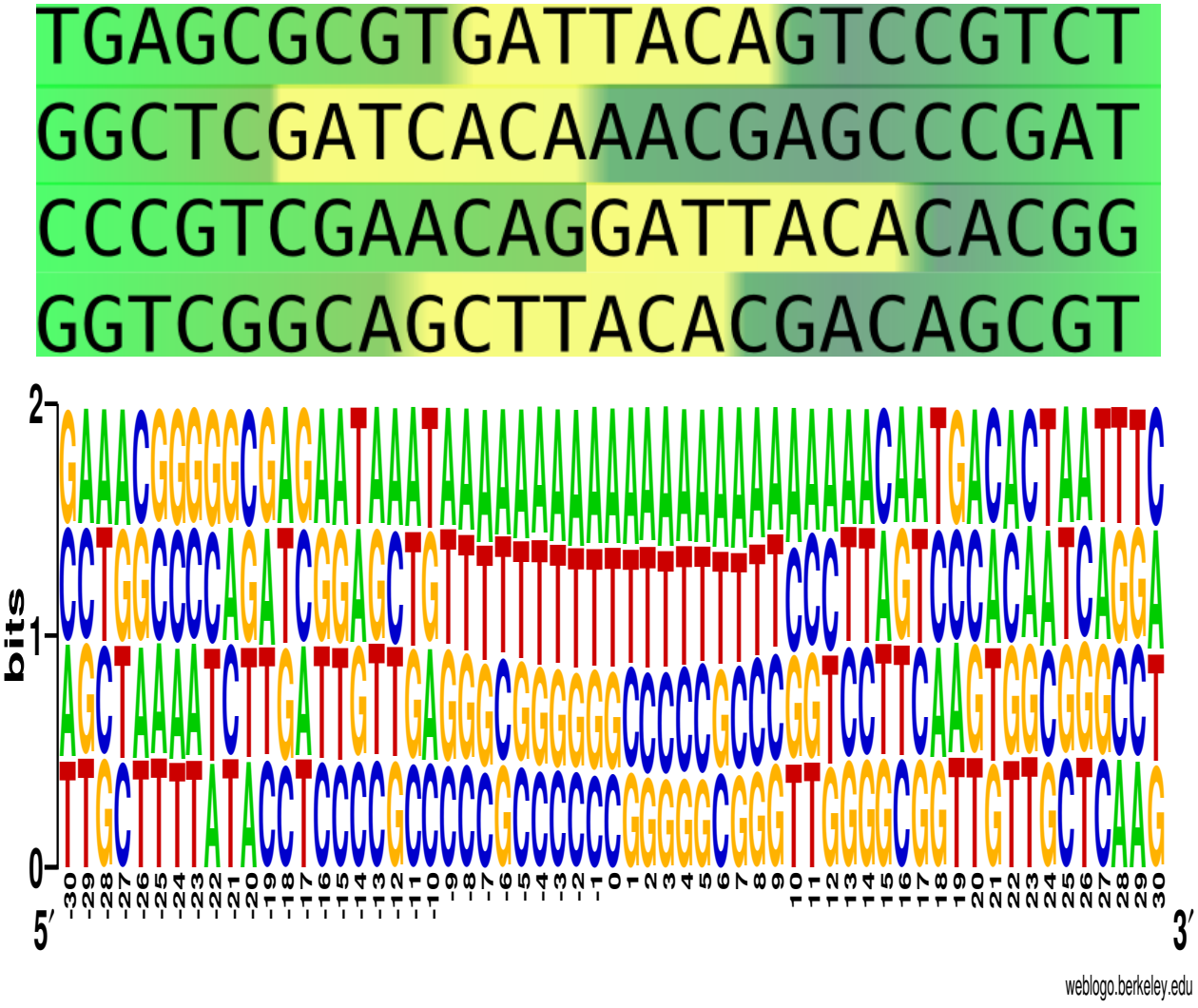


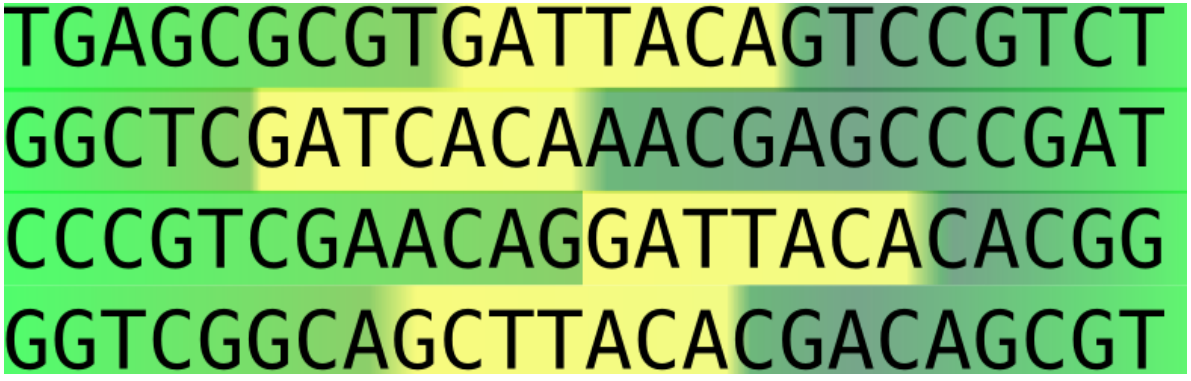
GATTACA at variable positions

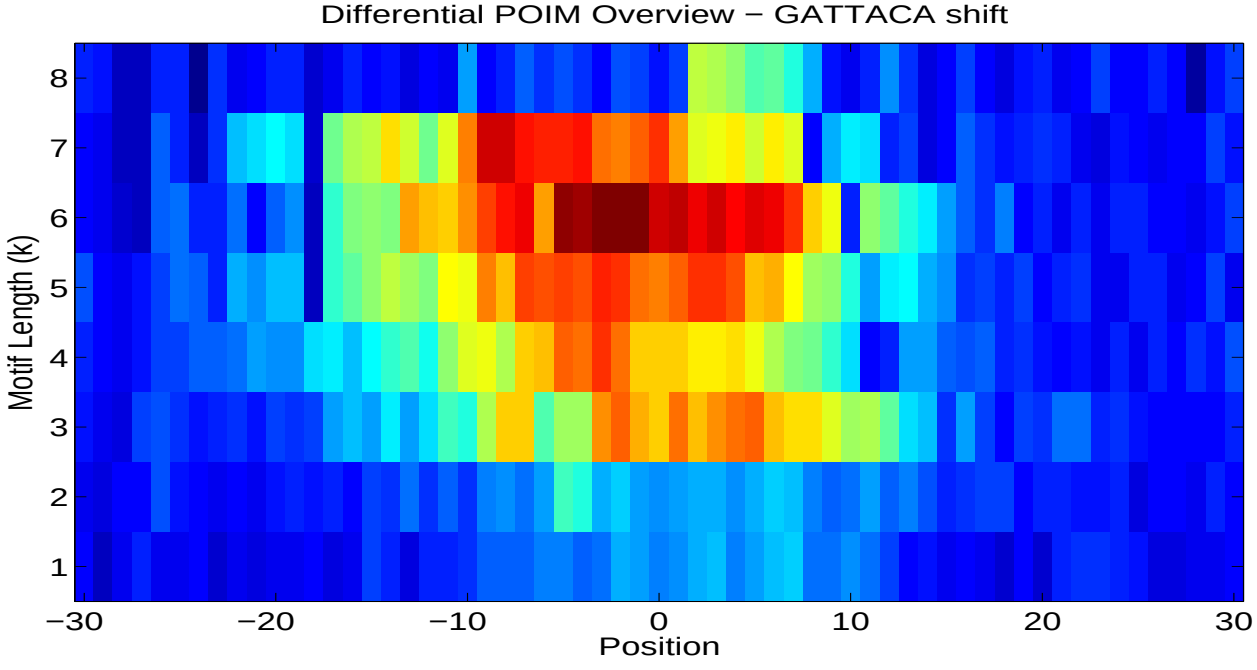


GATTACA at variable positions

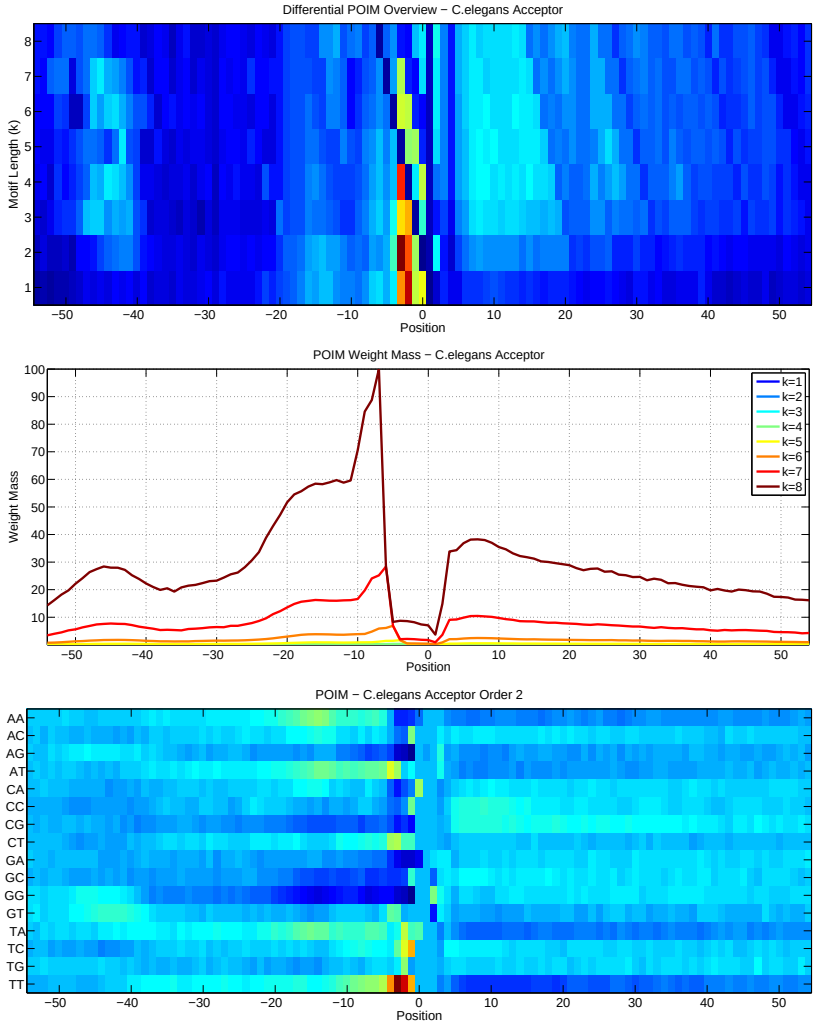


GATTACA at variable positions



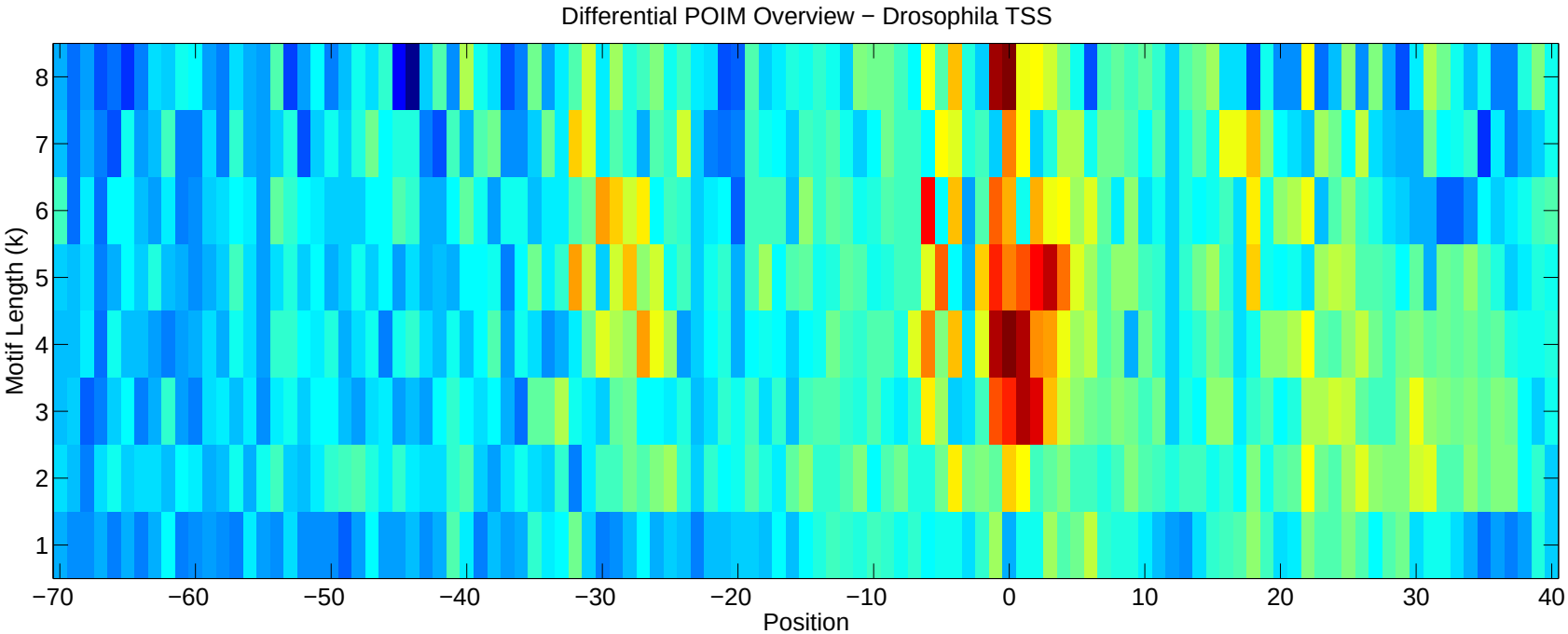


C.elegans Acceptor Splice Site Recognition



- Upstream
  - AG**GT**AAGT -44/++ Donor
  - GGGGGG -16/- - Silencer?
  - **TAAT**AA -16/++ Branch
- Central
  - TTTTTTC -06/+
  - TTTC**AG**$\frac{A}{G}$ -03/++ Acceptor
- Downstream
  - TTTTTTTT +07/- -
  - TTTTT +26/- -

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**	

Outline

Conclusions

Support Vector Machines with string kernels

- General
- Often are state-of-the art signal detectors
- Applicable to genome-sized datasets
- Using POIMs SVMs are interpretable
  - Importances of positional motifs for the expected decision score
  - Useful to rank motifs and for visualization
  - Can even identify motif length
  - Applicable for a large class of popular scores (SVM+Spectrum/WD/Oligo kernel; Markov Chain)

Efficient implementation `http://www.shogun-toolbox.org`
More machine learning software `http://mloss.org`