# POIMs: Positional Oligomer Importance Matrices

*(Understanding Support Vector Machine Based Signal Detectors)*

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joint work with
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Friedrich Miescher Laboratory of the Max Planck Society

# The Motivating Application - Splice Site recognition

*Discriminate true signal positions against all other positions*

≈ 150 nucleotides window around dimer

```
CT...GTCGTA...GAAGCTAGGAGCGC...ACGCGT...GA
```

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

```
AAACAAATAAGTAACTAATCTTTTAGGAAGAACGTTTCAACCATTTTGAG
AAGATTAAAAAAAAACAAATTTTTAGCATTACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTTTAGTTCACTAACACATCCGTCTGTGCC
TTAATTTCACTTCCACATACTTCCAGATCATCAATCTCCAAAACCAACAC
```

- Sequences are compared via String-Kernels
  - For each position a Weighted Degree Kernel compares all k-mers up to maximal length K

**SVM ≈ 3 times more accurate than IMCs**
(54.4% vs. 16.2% auPRC)

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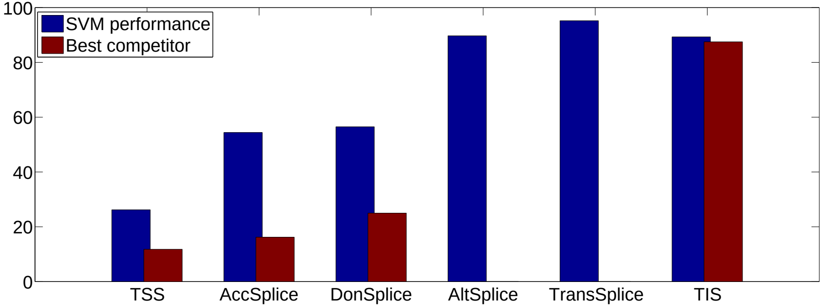
# Beauty in Generality




- Transcription Start (Sonnenburg et al., Eponine Down et al.)
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**Drawback: SVM solution is hard to interpret!!**

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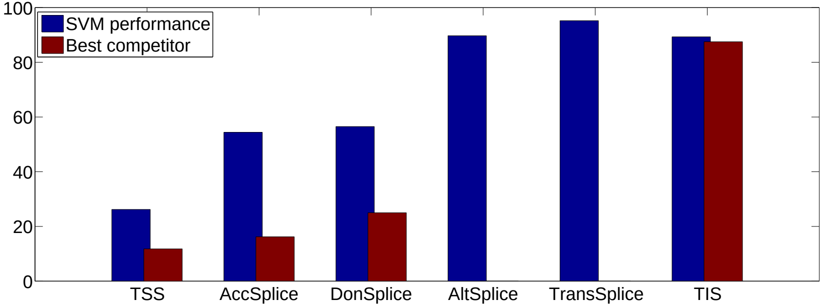


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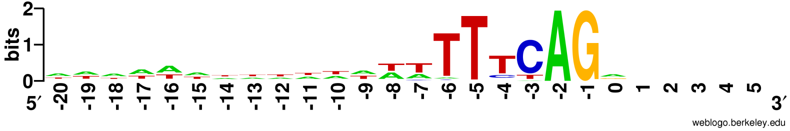
# Understanding Support Vector Machines

## 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 $\alpha$ weighting of training points**

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

$\alpha_1 \cdot$ AAACAAATAAGTAACTAATCTTTTAGGAAGAACGTTTCAACCATTTTGAG

$\alpha_2 \cdot$ AAGATTAAAAAAAAACAAATTTTTAGCATTACAGATATAATAATCTAATT

$\alpha_3 \cdot$ CACTCCCCAAATCAACGATATTTTAGTTCACTAACACATCCGTCTGTGCC

$\vdots$ $\vdots$

$\alpha_N \cdot$ TTAATTTCACTTCCACATACTTCCAGATCATCAATCTCCAAAACCAACAC

**But we are interested in weights over features.**

# SVM Scoring Function

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

| k-mer | pos. 1 | pos. 2 | pos. 3 | pos. 4 | $\cdots$ |
|---|---|---|---|---|---|
| **A** | +0.1 | -0.3 | -0.2 | +0.2 | $\cdots$ |
| **C** | 0.0 | -0.1 | +2.4 | -0.2 | $\cdots$ |
| **G** | +0.1 | -0.7 | 0.0 | -0.5 | $\cdots$ |
| **T** | -0.2 | -0.2 | 0.1 | +0.5 | $\cdots$ |
| **AA** | +0.1 | -0.3 | +0.1 | 0.0 | $\cdots$ |
| **AC** | +0.2 | 0.0 | -0.2 | +0.2 | $\cdots$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\ddots$ |
| **TT** | 0.0 | -0.1 | +1.7 | -0.2 | $\cdots$ |
| **AAA** | +0.1 | 0.0 | 0.0 | +0.1 | $\cdots$ |
| **AAC** | 0.0 | -0.1 | +1.2 | -0.2 | $\cdots$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\ddots$ |
| **TTT** | +0.2 | -0.7 | 0.0 | 0.0 | $\cdots$ |

# The Scoring System - Examples

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

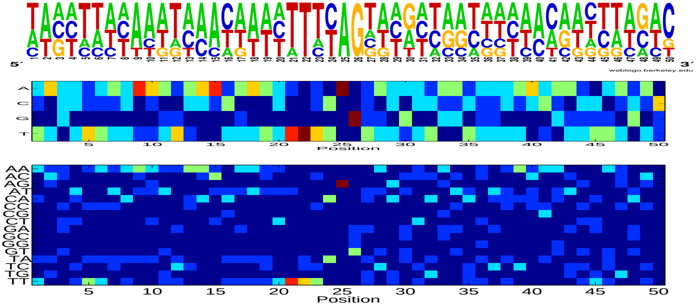
**Examples:**

- 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**

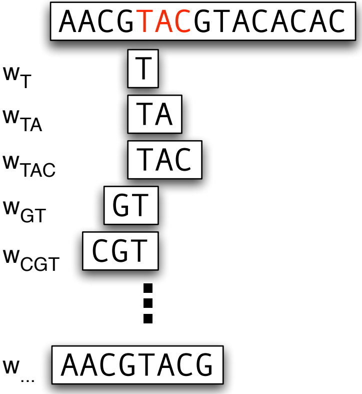



⋮

- 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 $\mathbf{z}$ 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**)

```
AAAAAAAAAATACAAAAAAAAAA
AAAAAAAAAATACAAAAAAAAAC
AAAAAAAAAATACAAAAAAAAAG
           ⋮
TTTTTTTTTTTACTTTTTTTTTT
```

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

**POIMs**

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

$\Rightarrow$ **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

**Main contribution of the paper**

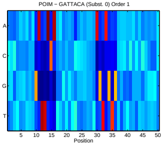
**Efficient Recursive Algorithm:**
**Effort linear in length of input:** $\mathcal{O}(LN + L|\Sigma|^k)$

# Ranking Features and Condensing Information

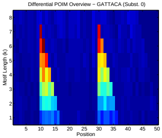
- Obtain highest scoring $\mathbf{z}$ from $Q(\mathbf{z}, i)$ (Enhancer or Silencer)

| $\mathbf{z}$ | 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

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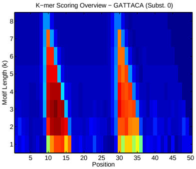
# `GATTACA` and `AGTAGTG` at Fixed Positions 10 and 30

```
TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
GGTCGGCAGGATTACACGACGCGTTTACGAGTAGTGAACACTGACTCCTC
```

# GATTACA and AGTAGTG at fixed positions 10 and 30

```
TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
GGTCGGCAGGATTACACGACGCGTTTACGAGTAGTGAACACTGACTCCTC
```

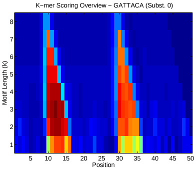
**w**



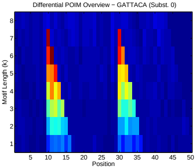
# GATTACA and AGTAGTG at fixed positions 10 and 30

TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
GGTCGGCAGGATTACACGACGCGTTTACGAGTAGTGAACACTGACTCCTC

**w**

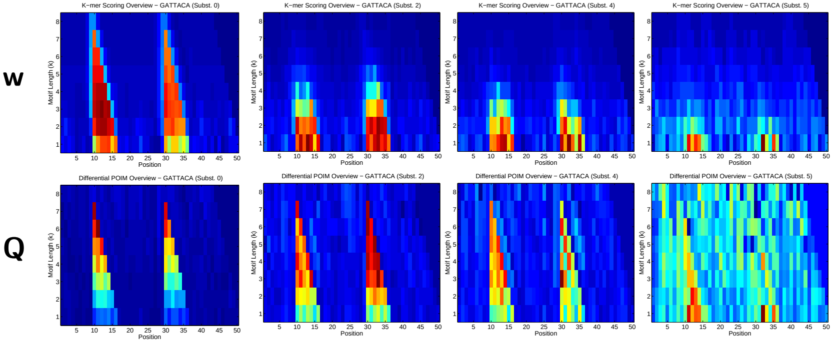



**Q**

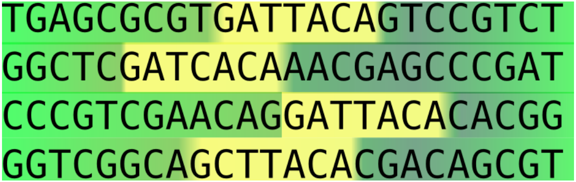


# GATTACA and AGTAGTG at fixed positions 10 and 30

```
TGAGCGCGTGATTACAGTCCGTCTGGGCCAGTAGTGCGTAGTCGCCGGGA
GGCATGGTCGATTACAAACGAGCCCTCTCAGTAGTGGGGAGCCACGAAA
CCCGTCGAAGATTACACACGGGGCGTGGGAGTAGTGGCGATTACGGGCTC
GGTCGGCAGGATTACACGACGCGTTTACGAGTAGTGAACACTGACTCCTC
```

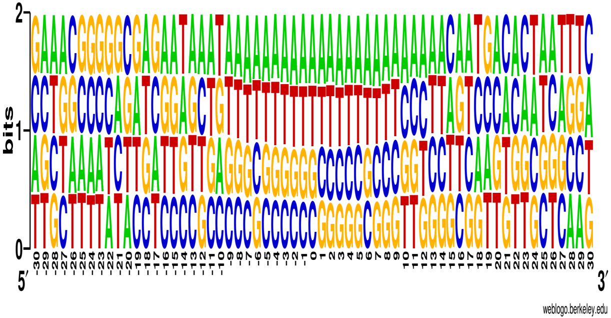


# GATTACA at variable positions



# GATTACA at variable positions

TGAGCGCGTGATTACAGTCCGTCT
GGCTCGATCACAAACGAGCCCGAT
CCCGTCGAACAGGATTACACACGG
GGTCGGCAGCTTACACGACAGCGT



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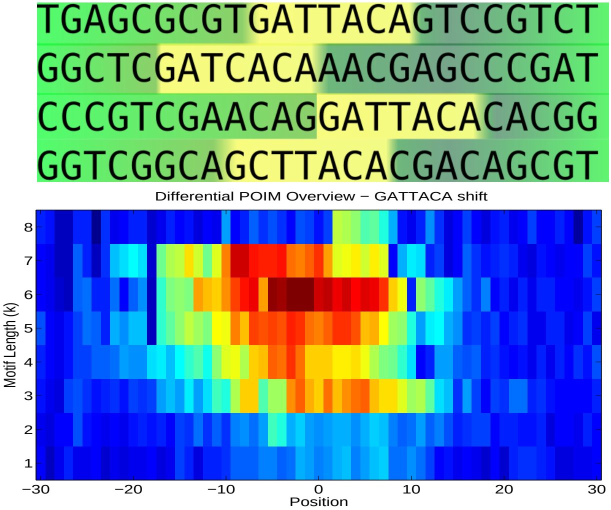
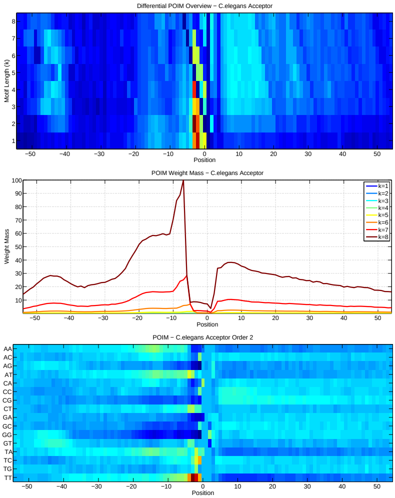


# *C.elegans* Acceptor Splice Site Recognition




- Upstream

| | | |
|---|---|---|
| AG**GT**AAGT | -44/++ | Donor |
| GGGGGG | -16/- - | Silencer? |
| **TAAT**AA | -16/++ | Branch |

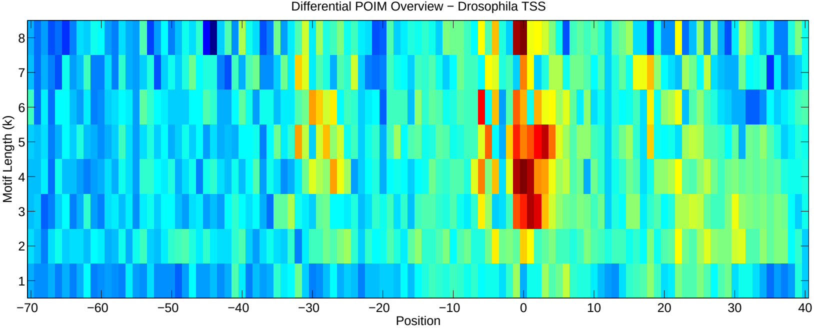
- Central

| | | |
|---|---|---|
| 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**CAGTT** | -03/++ | CGCGCGC | +22/++ |

**TATA-box** **Inr** $\mathbf{TCA}\frac{G}{T}\mathbf{T}\frac{T}{C}$ **CpG**

# Conclusions

## Positional Oligomer Importance Matrices

- Support Vector Machines often are state-of-the art classifiers
- POIMs systematically compute the 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)
- Promising results on toy and **real world data**

**Tables** `http://www.fml.mpg.de/raetsch/projects/POIM`
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