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
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

- 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)
Introduction and Motivation

Methods

Applications

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Sequence Classification

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**Beauty in Generality**

- Transcription Start (Sonnenburg et al., Eponine Down et al.)
- Acceptor Splice Site (Philips et al.)
- Donor Splice Site (Philips 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!!
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Drawback: SVM solution is hard to interpret!!
Goal

For PWMs we have sequence logos:

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

Why Are SVM’s Hard to Interpret?

SVM decision function is \( \alpha \) weighting of training points

\[
s(x) = \sum_{i=1}^{N} \alpha_i y_i k(x_i, x) + b
\]

\( \alpha_1 \): AAACAAATAAGTAACATATCTTTTAGGAAGAGACGTATTCAACCATTTTGAG
\( \alpha_2 \): AAGATTTAAAAAAACAAAAATTTTAGCATTTACAGATATAATAATCTAATT
\( \alpha_3 \): CACTCCCCAAATCAACGATATTTTAGCTTCAACTAACACATCCGCTCTGTGCC
\( \vdots \)
\( \alpha_N \): TTAATTTTCACTTCCACATACCTTCCAGCATCATCAATCTCCAAAAACCAACAC

But we are interested in \textbf{weights over features}.
### SVM Scoring Function

\[ w = \sum_{i=1}^{N} \alpha_i y_i \Phi(x_i) \]

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

<table>
<thead>
<tr>
<th>k-mer</th>
<th>pos. 1</th>
<th>pos. 2</th>
<th>pos. 3</th>
<th>pos. 4</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+0.1</td>
<td>-0.3</td>
<td>-0.2</td>
<td>+0.2</td>
<td>...</td>
</tr>
<tr>
<td>C</td>
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<td>-0.1</td>
<td>+2.4</td>
<td>-0.2</td>
<td>...</td>
</tr>
<tr>
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<td>-0.7</td>
<td>0.0</td>
<td>-0.5</td>
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</tr>
<tr>
<td>T</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.1</td>
<td>+0.5</td>
<td>...</td>
</tr>
<tr>
<td>AA</td>
<td>+0.1</td>
<td>-0.3</td>
<td>+0.1</td>
<td>0.0</td>
<td>...</td>
</tr>
<tr>
<td>AC</td>
<td>+0.2</td>
<td>0.0</td>
<td>-0.2</td>
<td>+0.2</td>
<td>...</td>
</tr>
<tr>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>TT</td>
<td>0.0</td>
<td>-0.1</td>
<td>+1.7</td>
<td>-0.2</td>
<td>...</td>
</tr>
<tr>
<td>AAA</td>
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<td>0.0</td>
<td>0.0</td>
<td>+0.1</td>
<td>...</td>
</tr>
<tr>
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<td>0.0</td>
<td>-0.1</td>
<td>+1.2</td>
<td>-0.2</td>
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<tr>
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</tr>
<tr>
<td>TTT</td>
<td>+0.2</td>
<td>-0.7</td>
<td>0.0</td>
<td>0.0</td>
<td>...</td>
</tr>
</tbody>
</table>
The Scoring System - Examples

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

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 $\mathbf{w}$

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

**But:** Weights for substrings not independent
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**Definition**

**Interdependence of \( k \)-mer Weights**

- The SVM-w does **NOT** reflect the score for a motif.
Idea:

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

\[
\begin{align*}
&\text{AAAAAAAAAAATACAAAAAAAAAA} \\
&\text{AAAAAAAAAAATACAAAAAAAAAC} \\
&\text{AAAAAAAAAAATACAAAAAAAAAG} \\
&\text{TTTTTTTTTTTTACTTTTTTTTTT}
\end{align*}
\]

- Normalize with expected score over all sequences

POIMs

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

$\Rightarrow$ Needs efficient algorithm for computation
Efficient Computation

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

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

- Number of k-mers grows linearly with size of input
- Only features which are dependent on \((z,j)\) 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 \( z \) from \( Q(z, i) \) (Enhancer or Silencer)

- 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

<table>
<thead>
<tr>
<th>( z )</th>
<th>( i )</th>
<th>( Q(z, i) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATTACA</td>
<td>10</td>
<td>+30</td>
</tr>
<tr>
<td>AGTAGTG</td>
<td>30</td>
<td>+20</td>
</tr>
<tr>
<td>AAAAAAAA</td>
<td>10</td>
<td>-10</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
Comparison with SVM-w

GATTACA and AGTAGTG at Fixed Positions 10 and 30

TGAGCGCGTGATTACAGTCGGTCTTGGGCCAGTAGTGCGTAGTCCGCGGGA
GGCATGGTGCGATTACAAGACAGGCCTCTCGTAGTAGTGGGGAGGCCACGAAA
CCCGTCAAGAGATTACACACGCGGGCGTAGTGAGTCGATTACCGGGGCTC
GGTCGACAGGATTACACGACGCGGTTCAGTAGTAGAACAAGCTGACTCCTC
## GATTACA and AGTAGTG at fixed positions 10 and 30

<table>
<thead>
<tr>
<th>Motif Length (k)</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
</tr>
</tbody>
</table>

### K-mer Scoring Overview – GATTACA (Subst. 0)

![K-mer Scoring Overview](image-url)
Comparison with SVM-\textit{w}

**GATTACA and AGTAGTG at fixed positions 10 and 30**

K-mer Scoring Overview − GATTACA (Subst. 0)

Differential PDIM Overview − GATTACA (Subst. 0)
Comparison with SVM-w

GATTACA and AGTAGTG at fixed positions 10 and 30

TGAGCGCGTGATTACA GTCCGTCTGGGCACGTA GTGCGTCGCCCCGGA GGCATGGTCGATTACA AACGAGCCCTCTCACGTAGTG GGGGAGGCCCACGAAA CCCGTCGAAGATTACA CACCGGGGCTGAGTAGTG GGGGCTATTACCGGGCTC GGTCGGCAGGATTACA CGACGC GTTACGAGTAGTG AAACACTGACTCCTC
GATTACA at variable positions

TGAGCGCGT GATTACAGTCCGTCT
GGCTCGATCAACAAACGAGCCCGAT
CCCGTCAACGAGGATTACACACCGG
GGTCGCGAGCTTACACGACAGCGT
Toy Example motif at Variable Positions

GATTACA at variable positions

TGAGCGCGTGATTACAGTCCGTCT
GGCTCGATCACAACGAGGCCGAT
CCCGTCGAAACAGGATTACACACGG
GGTGGCGCAGCTTACACAGCGT
Toy Example motif at Variable Positions

GATTACA at variable positions
C. elegans Acceptor Splice Site Recognition

- **Upstream**
  - AGGTAAGT -44/++ Donor
  - GGGGGGG -16/- Silencer?
  - TAATAA -16/++ Branch

- **Central**
  - TTTTTTTC -06/+ 
  - TTTCA@G -03/++ Acceptor

- **Downstream**
  - TTTTTTTT +07/- 
  - TTTTTT +26/-
Drosophila Transcription Starts

Differential POIM Overview – Drosophila TSS

- TATAAAAA -29/++
- GTATAAA -30/++
- ATATAAAA -28/++
- CAGTCAGT -01/++
- TCAGTTGT -01/++
- CGTCAGTT -03/++
- CGTCGCGG +18/++
- GCGCGCGG +23/++
- CGCGCGCG +22/++

TATA-box

Inr TCA \( \frac{G}{T} \) \( \frac{T}{C} \)

CpG
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
Efficient implementation http://www.shogun-toolbox.org
Webinterface http://galaxy.fml.tuebingen.mpg.de

Poster P38
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