Positional Oligomer Importance Matrices

(Feature Extraction & Interpretable SVM's)

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Outline

1. Introduction and Motivation
2. Methods
3. Applications
4. Discussion

The Motivating Application - Sequence Classification

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

SVM with string-kernels: State-of-the-art in detecting

- Gene Start/End (Sonnenburg, Zien, Rätsch, 2005)
- Splice Sites (Sonnenburg, Schweikert, Philips, et.al. 2007)
- Trans-splicing, Alternative Splicing (Rätsch, Sonnenburg, Schölkopf 2005)

SVM sensitivity ≈ 2 **times larger at same specificity**

Drawback: We loose interpretability of the result!

Why are SVM's hard to interpret?

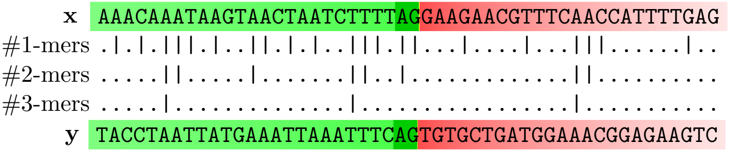
Problem: Learned α weighting of training points
But: One is interested in discriminating features

$$
\begin{aligned}
f(\mathbf{x}) &= \sum_{i=1}^{N} \alpha_i y_i \, \mathrm{k}(\mathbf{x}_i, \mathbf{x}) + b \\
&= \underbrace{\sum_{i=1}^{N} y_i \alpha_i \Phi(\mathbf{x}_i)}_{\mathbf{w}} \cdot \Phi(\mathbf{x}) + b = \mathbf{w} \cdot \Phi(\mathbf{x}) + b
\end{aligned}
$$

Idea: Use SVM's w vector to interpret features

The Weighted Degree Kernel

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



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

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

The SVM normal vector $\mathbf{w}$

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	···

SVM's are interpretable - depending on feature space

Condition:

Feature space enumerable & meaningful, explicitly store w

- linear SVM's
- most of string kernels ($k-$mer based)
  - Spectrum kernel (Leslie, Eskin, Noble, 2002)
  - WD kernels (Rätsch, Sonnenburg, 2005)
  - ...

Problems:

- Feature space may be very high dimensional
- Features not independent

Idea:

- Compute expected SVM output given a certain feature

The Scoring System - Definition

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	⋯
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⋮	⋮	⋮	⋮	⋮	⋱
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	⋯

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

The Scoring System - Examples

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

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)

POIMs

Idea:

- Compute expected score $C(\mathbf{z}, j)$ given that $k-$mer $\mathbf{z}$ appears at position j in the sequence for small k
- Normalize with *expected score* over all sequences

$$C(\mathbf{z}, j) \ := \ \mathbb{E}\left[\, s(\mathbf{x}) \,|\, \mathbf{x}\,[j] = \mathbf{z} \,\right] - \mathbb{E}\left[\, s(\mathbf{x}) \,\right] \qquad (1)$$

Problem:

- Choosing a background distribution for $\mathbf{x}$ (uniform, 0^{th} order MC)
- Naive approach already infeasible for short sequences and small alphabets
- $\mathbf{w}$ may be stored in some sparse data structure (like a tree/forest)

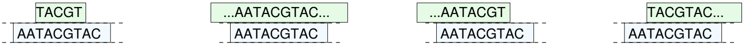
Needs efficient algorithm for computation

Observations

$$
\begin{aligned}
C(\mathbf{z},j) &:= \mathbb{E}\left[\, s(\mathbf{x}) \mid \mathbf{x}\left[j\right] = \mathbf{z}\,\right] - \mathbb{E}\left[\, s(\mathbf{x})\,\right]. \\
&= \sum_{(\mathbf{y},i)\in\mathcal{I}} w(\mathbf{y},i)\left[Pr\left(\,\mathbf{x}\left[i\right] = \mathbf{y} \mid \mathbf{x}\left[j\right] = \mathbf{z}\,\right) - Pr\left(\,\mathbf{x}\left[i\right] = \mathbf{y}\,\right)\right] \\
&= u(\mathbf{z},j) + \sum_{\mathbf{z}\in\Sigma^{|\mathbf{z}|}} u(\mathbf{z},j)
\end{aligned}
$$

- Number of $k-$mers grows only linear with data
- All features which are independent of $(\mathbf{z},j)$ vanish
- Computation can be split in contributions from 4 cases:

$$
\begin{aligned}
u(\mathbf{z},j) &:= \sum_{(\mathbf{y},i)\in\mathcal{I}(\mathbf{z},j)} Pr\left(\,\mathbf{x}\left[i\right] = \mathbf{y} \mid \mathbf{x}\left[j\right] = \mathbf{z}\,\right) w(\mathbf{y},i) \\
&= u^{\vee}(\mathbf{z},j) + u^{\wedge}(\mathbf{z},j) + u^{<}(\mathbf{z},j) + u^{>}(\mathbf{z},j) - w(\mathbf{z},j) \;\;,
\end{aligned}
$$



For AATACGTAC: substring, superstring, left and right partial overlap

Efficient Computation

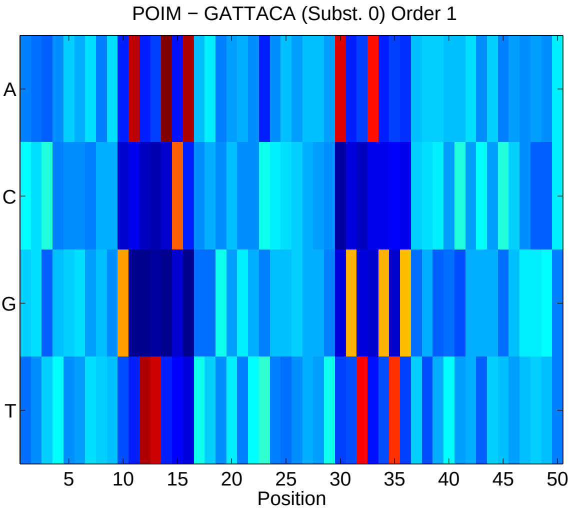
(Zien, Philips, Sonnenburg, 2007)

$$
\begin{aligned}
u^{\vee}(\mathbf{z},j) &= w(\mathbf{z},j) + u^{\vee}(\tau\mathbf{z}',j) + u^{\vee}(\mathbf{z}'\tau',j+1) - u^{\vee}(\mathbf{z}',j+1) \\
u^{\wedge}(\mathbf{z},j) &= w(\mathbf{z},j) - \sum_{(\sigma,\sigma')\in\Sigma^2} Pr\left(\mathbf{x}[j+|\mathbf{z}|]=\sigma'\right) Pr\left(\mathbf{x}[j-1]=\sigma\right) u^{\wedge}(\sigma\mathbf{z}\sigma',j-1) \\
&+ \sum_{\sigma\in\Sigma} Pr\left(\mathbf{x}[j-1]=\sigma\right) u^{\wedge}(\sigma\mathbf{z},j-1) + \sum_{\sigma'\in\Sigma} Pr\left(\mathbf{x}[j+|\mathbf{z}|]=\sigma'\right) u^{\wedge}(\mathbf{z}\sigma',j) \\
u^{<}(\mathbf{z},j) &= \sum_{\sigma\in\Sigma} Pr\left(\mathbf{x}[j-1]=\sigma\right) \sum_{k=1}^{|\mathbf{z}|-1} L(\sigma\mathbf{z}[1]^k,j-1) \\
u^{>}(\mathbf{z},j) &= \sum_{\sigma\in\Sigma} Pr\left(\mathbf{x}[j+|\mathbf{z}|]=\sigma\right) \sum_{k=1}^{|\mathbf{z}|-1} R(\mathbf{z}[|\mathbf{z}|-k+1]^k\sigma,j+|\mathbf{z}|-k) \ ,
\end{aligned}
$$

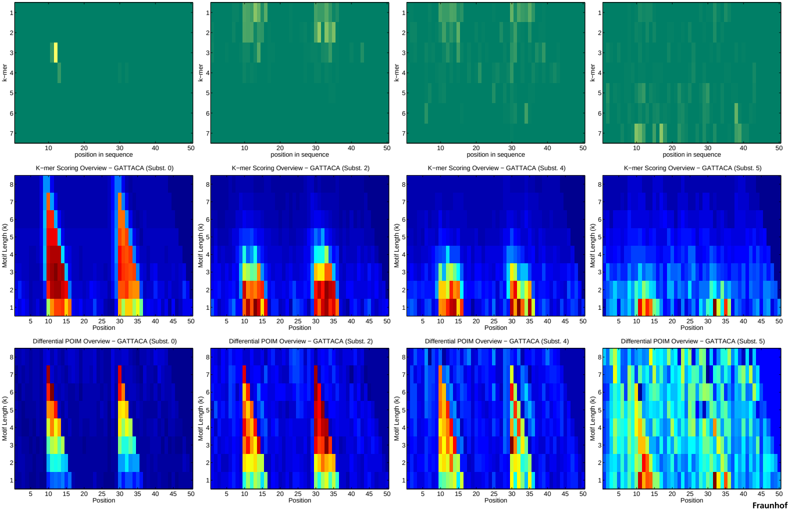
where

$$
\begin{aligned}
L(\mathbf{t},j) &:= \sum_{(\mathbf{y},i)\in\mathcal{L}(\mathbf{t},j)} Pr\left(\mathbf{x}\,[i]=\mathbf{y}\mid\mathbf{x}\,[j]=\mathbf{t}\right) w(\mathbf{y},i) \\
R(\mathbf{t},j) &:= \sum_{(\mathbf{y},i)\in\mathcal{R}(\mathbf{t},j)} Pr\left(\mathbf{x}\,[i]=\mathbf{y}\mid\mathbf{x}\,[j]=\mathbf{t}\right) w(\mathbf{y},i) \ .
\end{aligned}
$$

GATTACA and AGTAGTG at fixed positions 10 and 30



GATTACA and AGTAGTG at fixed positions 10 and 30



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

K−mer Scoring Overview − GATTACA (Subst. 2)

K−mer Scoring Overview − GATTACA (Subst. 4)

K−mer Scoring Overview − GATTACA (Subst. 5)

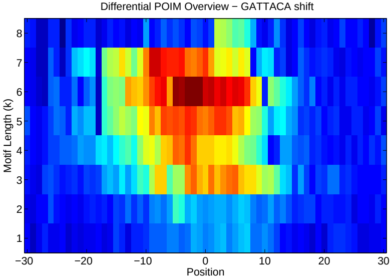
Differential POIM Overview − GATTACA (Subst. 0)

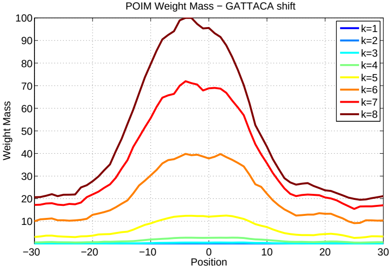
Differential POIM Overview − GATTACA (Subst. 2)

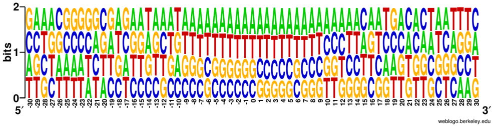
Differential POIM Overview − GATTACA (Subst. 4)

Differential POIM Overview − GATTACA (Subst. 5)

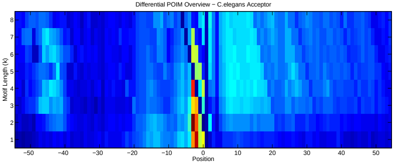
GATTACA at variable positions

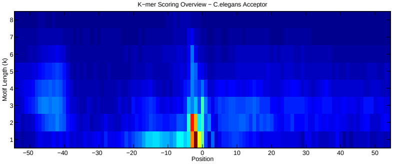


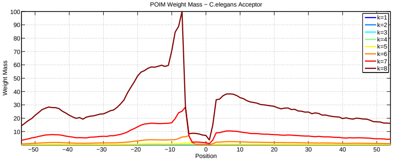


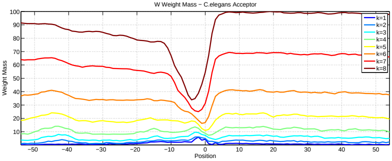


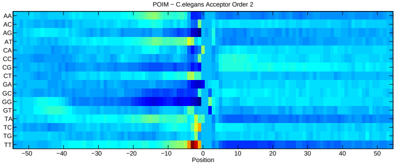
C.elegans Acceptor Splice Site Recognition

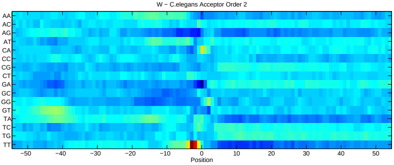

Differential POIM Overview − C.elegans Acceptor


K−mer Scoring Overview − C.elegans Acceptor

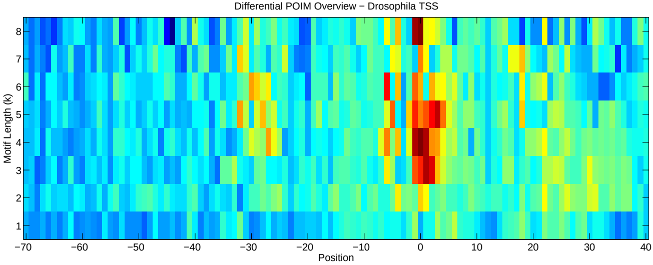

POIM Weight Mass − C.elegans Acceptor

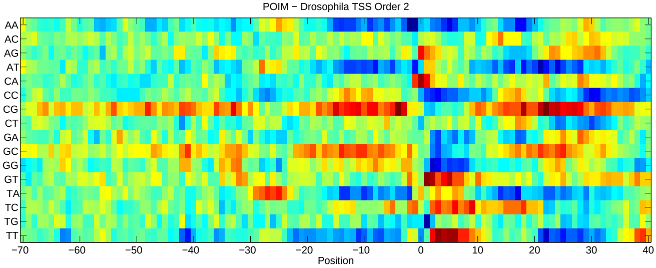

W Weight Mass − C.elegans Acceptor


POIM − C.elegans Acceptor Order 2


W − C.elegans Acceptor Order 2

Drosophila Transcription Starts





Conclusions

Positional Oligomer Importance Matrices

- Developed a method which systematically computes the importances of positional motifs for the expected decision score
    - Feature Ranking in **Feature space**
    - Useful to rank motifs and for visualization
    - Applicable for a large class of popular scores (SVM+Spec/WD/oligo kernel; Markov Chain)
    - Efficiently implemented for spectrum and WD kernels in `http://www.shogun-toolbox.org`
- Nice results on toy and real world data

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- Languages for scientific computing

and should include

- A 4 page description,
- The code,
- A recognised open source license.

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