Large Scale Machine Learning for Genomic Sequence Analysis

(Support Vector Machine Based Signal Detectors)

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Outline

1. Introduction
2. Large Scale Learning
3. TSS recognition
Recognizing Genomic Signals

*Discriminate true signal positions against all other positions*

≈ 150 nucleotides window around dimer

CT...GTCGTA...GAAGCTAGGAGC..ACGCGT...GA

- **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,

```
AACAACACCGTAACCTATCCTTTTGAAGAGAACGTTCACCCATTTTGAG
AAGATTAACCTCACTACAGATTTCATTACATACAGATATAATTCAAAAAATT
CACTCCCCAAATCAACGATATTTAAAAATCACATACACATCCGTCTGTC
```

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
- CACTCCCCAAATCAACGATATTTTTATTCACTAACACATCCGTCTGTGCC

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

```
AAACAAATAAGTAACTAATCTTTTTAAAGAGAACGTTTCAACCATTGGAG
AAGATTTTTTTTTTTTTTACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTAAATTTGACTAAACACATCCGTCTGTC
```
Classification - Learning based on examples

**Given:**

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

```
AAACAAATAAGTAACTAATCTTTTGAAGAAGAACGTTTCAACCATTTTGAG
AAGATTTTAAAAAAACAAAAATTTTTACATTACAGATATAATAATCTAATT
CACTCCCCAAATCAACGATATTTTAGTTCACTAACCACATCCGTCCTGTGCC
TTAATTTTCACTTCCACATACCTCCAGATCATCAATCTCCAAAACCAACAC
TTGTTTTTATATATGTACTTTTACTAGTAAGTTGCCAATTCAATGTCCAC
TACCTAATTATAGAAATTATCTACGTGTGCTGATGGAAACGGAGAAGTC
```

**Wanted:**

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

\[ f(x) = \text{sign} \left( \sum_{i=1}^{N} y_i \alpha_i k(x, x_i) + b \right), \]

Spectrum Kernel (with mismatches, gaps)

\[ K(x, x') = \Phi_{sp}(x) \cdot \Phi_{sp}(x') \]

- AACAAAAACGTAACCTAATCTTTTAGAGAGAAACGTTTCAACCATTGGAG
- AAGATTAACTCATCACAGATTTTCATTACATACAGATATAATTCAAAAATT
- CACTCCCCAAATCAACGATATTTTAAAAATCACTAACACATCCGTCTGTGC
The Weighted Degree Kernel

Support Vector Machine

\[ f(x) = \text{sign} \left( \sum_{i=1}^{N} y_i \alpha_i k(x, x_i) + b \right), \]

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

Example: \( K = 3 \) : \( k(x, x') = \beta_1 \cdot 21 + \beta_2 \cdot 8 + \beta_3 \cdot 3 \)
The Weighted Degree Kernel with *shifts*

**Support Vector Machine**

\[ f(x) = \text{sign} \left( \sum_{i=1}^{N} y_i \alpha_i k(x, x_i) + b \right), \]

\[
k(s_1, s_2) = w_7 + w_1 + w_2 + w_2 + w_3
\]

\[
k(x_1, x_2) = w_{6,3} + w_{6,3} + w_{3,4}
\]
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

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

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

**Effort:** $O(NL) \Rightarrow$ speedup of factor $N$

$\Rightarrow$ Training on millions of examples, evaluation on billions.
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 $w \leftarrow w + \alpha \Phi(x)$ and $w \cdot \Phi(x)$ required.
- Compute $\Phi(x)$ on-the-fly and parallelize!

Results

- Computations are simple “table lookups” of $k$-mers weights
- Allows training on 50 million examples
Incorporating Prior Knowledge

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 ($\approx -30$ bp upstream)
- Exon content in UTR 5” region
- Distance to first donor splice site

**Idea:**

Combine weak features to build strong promoter predictor

$$k(x, x') = k_{TSS}(x, x') + k_{CpG}(x, x') + k_{coding}(x, x') + k_{energy}(x, x') + k_{twist}(x, x')$$
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 (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 $z$ at position $j$ in the sequence, compute expected score $\mathbb{E}[s(x) \mid x[j] = z]$ (for small $k$)

\[
\begin{array}{c}
\text{AAAAA ATAC}
\hline
\text{AAAAA ATAC}
\end{array}
\]

- Normalize with expected score over all sequences

POIMs

\[
Q(z, j) := \mathbb{E}[s(x) \mid x[j] = z] - \mathbb{E}[s(x)]
\]
### Example: Drosophila Transcription Starts

<table>
<thead>
<tr>
<th>Motif Length (k)</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>-70</td>
<td>-60</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

**TATA-box**

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

**CpG**

- **TATAAAAA** -29/++
- **GTATAAA** -30/++
- **ATATAAA** -28/++
- **CAGTCAGT** -01/++
- **TCAGTTGT** -01/++
- **CGTCGCG** +18/++
- **CGCGCG** +23/++
- **CGCGCGC** +22/++
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](http://www.mgene.org)
- Positional Oligomer Importance Matrices help making SVMs interpretable

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