Regulatory Sequence Analysis

Theoretical distribution of PSSM scores

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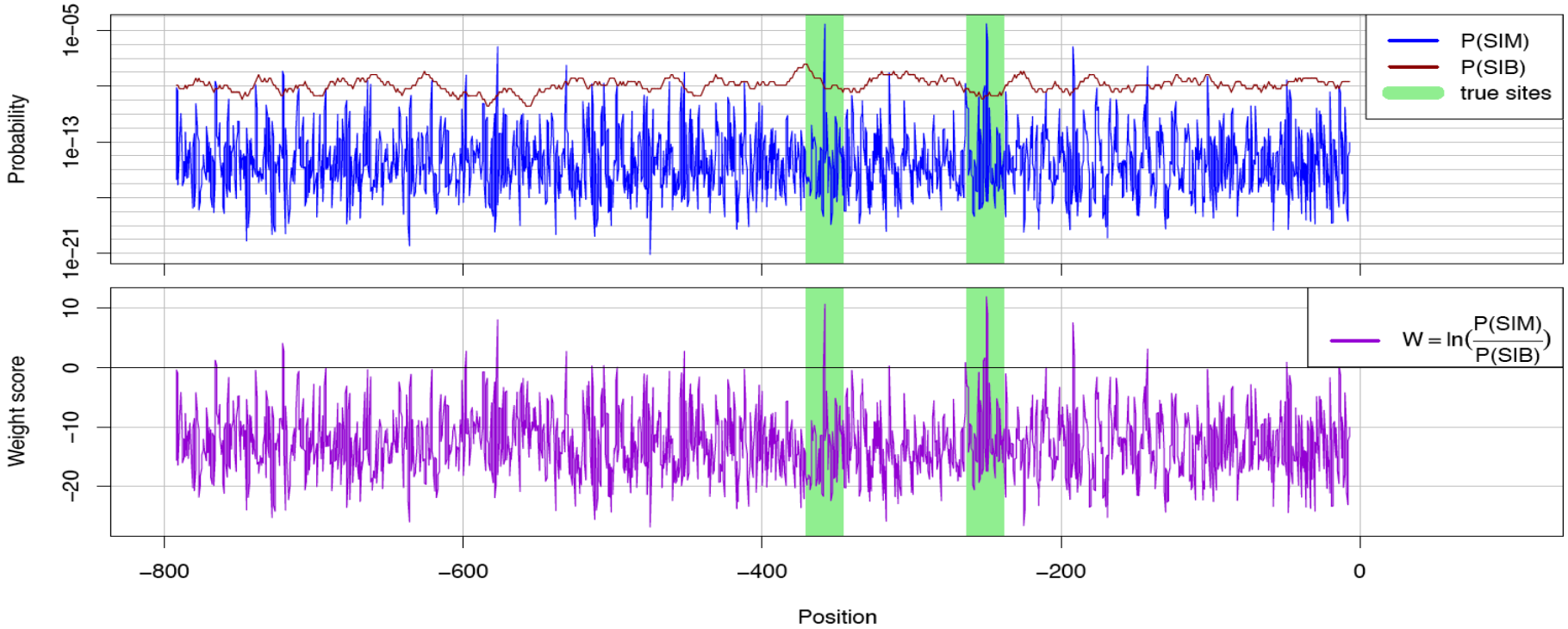
Scanning a sequence with a position-specific scoring matrix

- **P(S|M)** probability for site S to be generated as an instance of the motif.
- **P(S|B)** probability for site S to be generated as an instance of the background.
- **W** weight, i.e. the log ratio of the two above probabilities.
  - A positive weight indicates that a site is more likely to be an instance of the motif than of the background.

$$P(S \mid M) = \prod_{j=1}^{w} f'_{r_j j}$$

$$P(S \mid B) = \prod_{j=1}^{w} p_{r_j}$$

$$W_S = \ln\left(\frac{P(S \mid M)}{P(S \mid B)}\right)$$



Sand, O., Turatsinze, J.V. and van Helden, J. (2008). Evaluating the prediction of cis-acting regulatory elements in genome sequences In Frishman, D. and Valencia, A. (eds.), Modern genome annotation: the BioSapiens network. Springer.

Score distribution: random expectation

- The theoretical distribution of probabilities for position-weight matrices has been discussed in several articles.
  - Staden, R. (1989). Methods for calculating the probabilities of finding patterns in sequences. Comput Appl Biosci 5, 89-96.
  - Hertz, G. Z. & Stormo, G. D. (1999). Identifying DNA and protein patterns with statistically significant alignments of multiple sequences. Bioinformatics 15, 563-77.
- The computation is based on the probability-generating function.
- This function can be used to compute the probability P(W) to obtain exactly a score value of W.
- Each position-weight matrix has its own probability distribution.

$$G_j(x) = \sum f_i x w_{ij}$$

1. Staden, R. (1989). Methods for calculating the probabilities of finding patterns in sequences. *Comput Appl Biosci* 5, 89-96.
2. Bailey, T. L. & Gribskov, M. (1997). Score distributions for simultaneous matching to multiple motifs. *J Comput Biol* 4, 45-59.
3. Hertz, G. Z. & Stormo, G. D. (1999). Identifying DNA and protein patterns with statistically significant alignments of multiple sequences. *Bioinformatics* 15, 563-77.

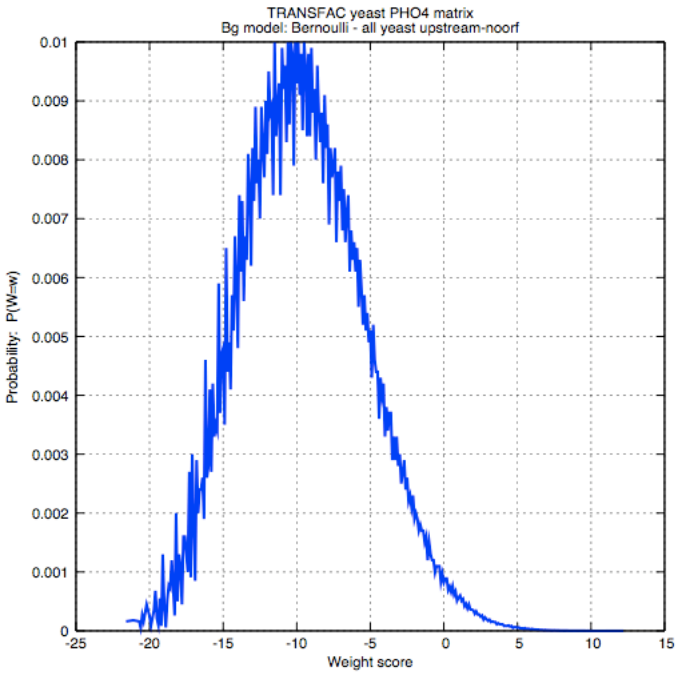
Theoretical distribution of matrix scores

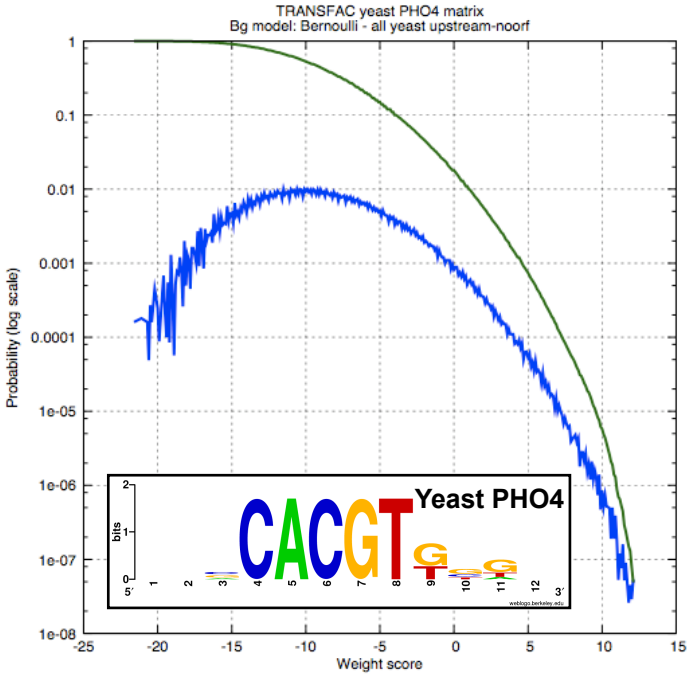
- The RSAT program ***matrix-distrib*** computes the distribution of score probabilities for a given PSSM.
- The distribution is completely determined by
  - Values in the cells of the matrix
  - Prior residue probabilities
- This method can be used to compute
  - ***P(X=x/M)***
    - The probability to obtain by chance a given score x, with a given matrix.
  - ***P(X >= x/M)***
    - The probability to obtain by chance a score higher or equal to x.
    - The inverse cumulative distribution gives a ***P-value***, which indicates the risk of false positive for a given score.
- Computing time increases exponentially with the number of columns, but by rounding values, it is asymptotically linear.
- The original method is based on a Bernoulli assumption for the background model, but we extended it to Markov chains.
- Computing time increases exponentially with Markov order.

Turatsinze, J. V., Thomas-Chollier, M., Defrance, M. and van Helden, J. matrix-scan: predicting transcription factor binding sites and cis-regulatory modules *in prep*.

Theoretical distribution for the PHO matrix

- The program matrix-distrib (RSAT) computes the complete theoretical distribution of scores for a given PSSM, using the algorithm proposed by Staden (1989), and previously implemented in patser (Hertz, 1990, 1999) and MAST (Bailey, 1994, 1997).
- The theoretical distribution P(S) is quite erratic, because each possible value of score has its own probability, depending on
  - the actual weight values in the matrix, and
  - prior residue probabilities.
- Figure below: probability distribution of weight score according to a Bernoulli model.



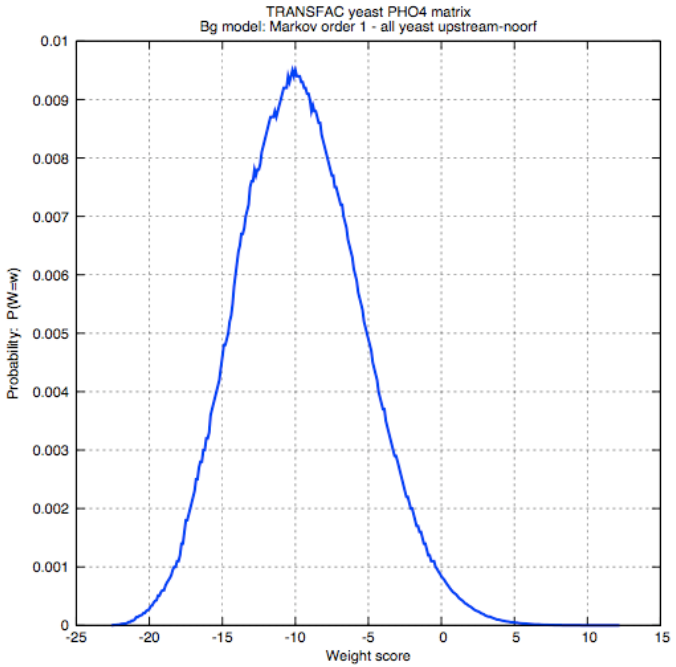


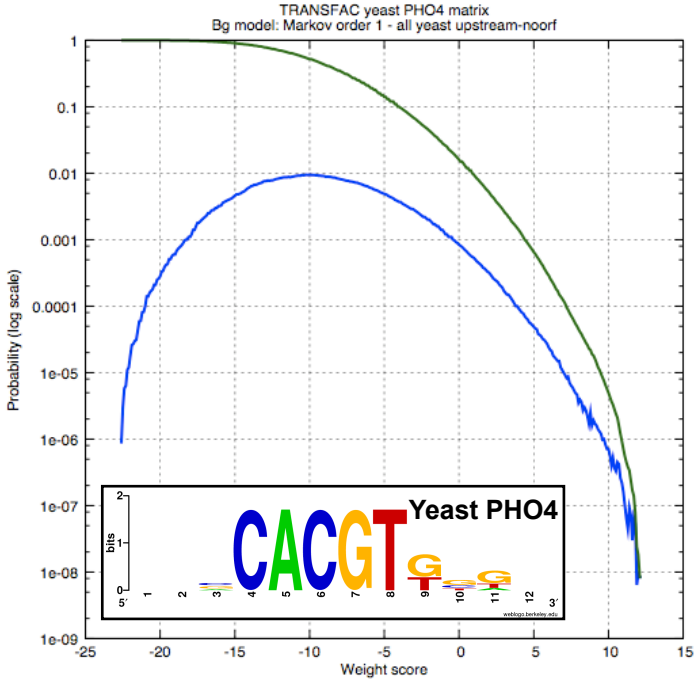
- ***P(W=w|M):*** probability to obtain by chance a precise weight score w, with a given matrix.
- ***P(W >= w|M)***: probability to obtain by chance a weight score higher than or equal to w. This inverse cumulative distribution gives a ***P-value***, which indicates the risk of false positive for a given score.

1. Staden, R. (1989). Methods for calculating the probabilities of finding patterns in sequences. *Comput Appl Biosci* 5, 89-96.
2. Bailey, T. L. & Gribskov, M. (1997). Score distributions for simultaneous matching to multiple motifs. *J Comput Biol* 4, 45-59.
3. Hertz, G. Z. & Stormo, G. D. (1999). Identifying DNA and protein patterns with statistically significant alignments of multiple sequences. *Bioinformatics* 15, 563-77.

Theoretical distribution for the PHO matrix

- matrix-distrib also supports computation of P-values with Markov models of any order (algorithm adapted from Touzet & Varré, 2007).
- Computing time increases exponentially with the number of columns, but by rounding values, it is asymptotically linear.
- The original method is based on a Bernoulli assumption for the background model, but we extended it to Markov chains.
- Computing time increases exponentially with Markov order.
- Figures below: probability distribution of the weight score according to a Markov model of order 1.



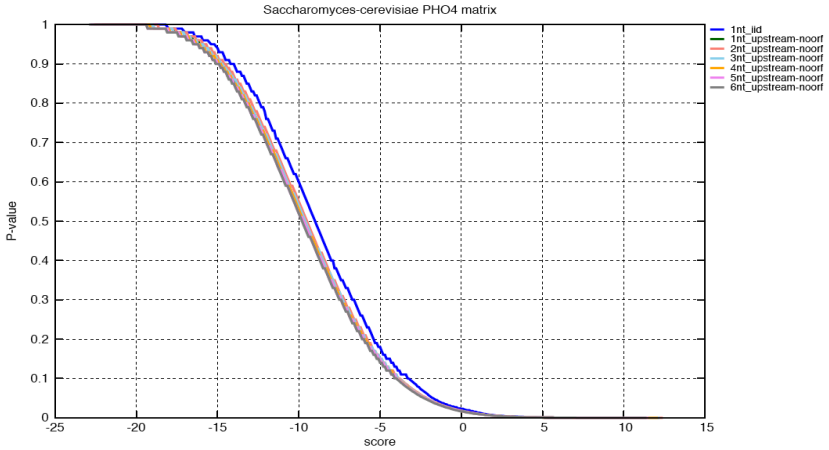


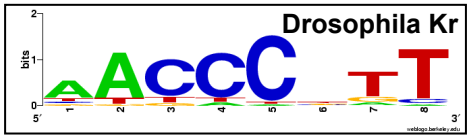
- ***P(W=w|M):*** probability to obtain by chance a precise weight score w, with a given matrix.
- ***P(W >= w|M)***: probability to obtain by chance a weight score higher than or equal to w. This inverse cumulative distribution gives a ***P-value***, which indicates the risk of false positive for a given score.

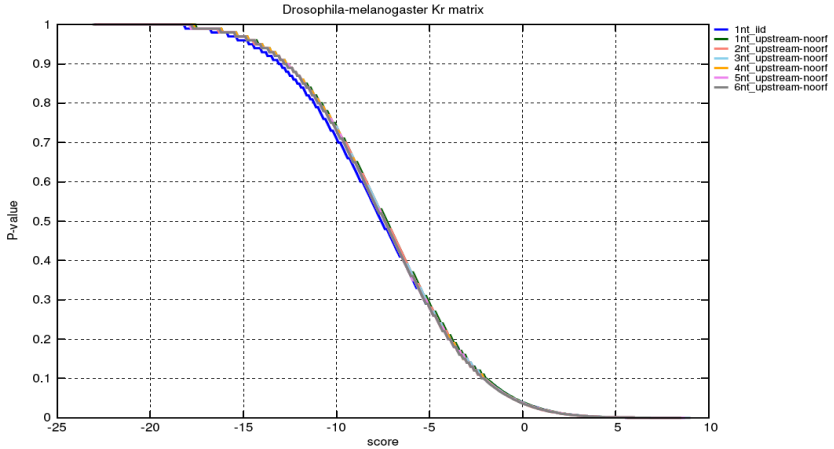
Touzet, H. and Varre, J.S. (2007) Efficient and accurate P-value computation for Position Weight Matrices. Algorithms Mol Biol, 2, 15.
Turatsinze, J. V., Thomas-Chollier, M., Defrance, M. and van Helden, J. matrix-scan: predicting transcription factor binding sites and cis-regulatory modules *in prep* (2008).

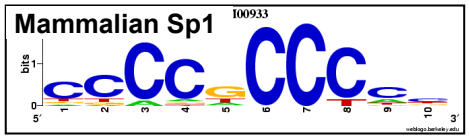
Theoretical distributions

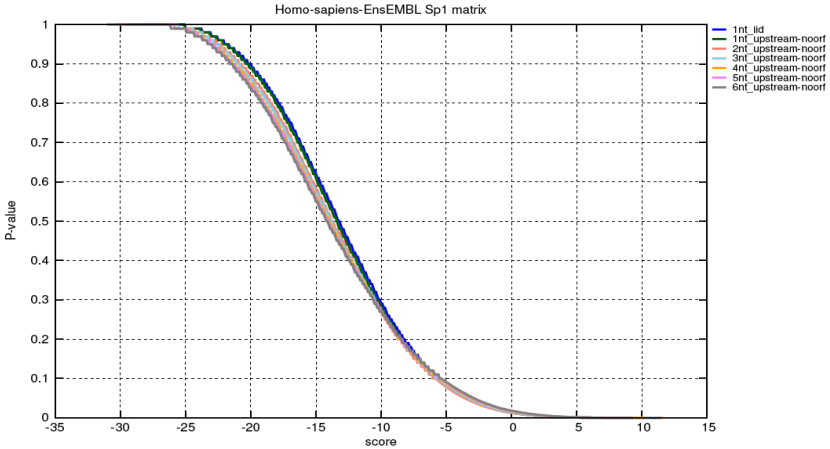
- We used *matrix-distrib* to analyse the theoretical distributions for some matrices according to various BG models.
  - IID (independently and identically distributed) nucleotides (blue)
  - Markov chains of orders 1 to 5, trained on the whole set of upstream sequences of the considered organism.











Impact of Markov order on the right tail of theoretical distributions

- In *Escherichia coli*, using higher-order background model has a weak effect on the core of the distribution, but affects its right tail, which corresponds to high-scoring sites.
- For TrpR, we observe differences for lower-scoring sites, due to the presence of a particular 4nt in the motif.