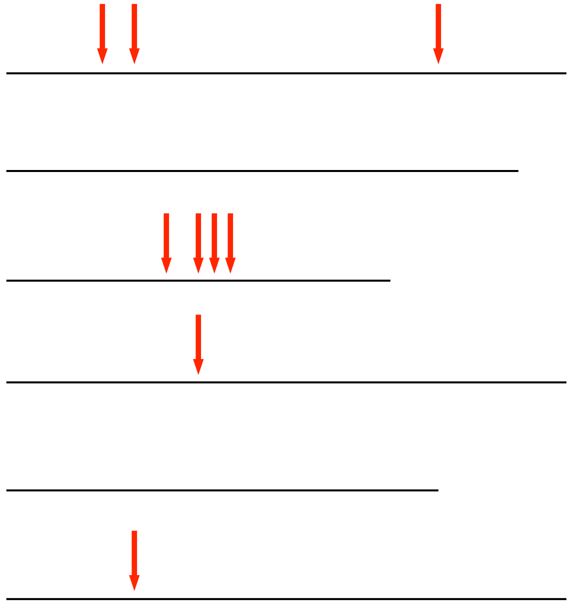
Regulatory Sequence Analysis

String-based pattern matching

Jacques.van.Helden@ulb.ac.be
Université Libre de Bruxelles, Belgique
Laboratoire de Bioinformatique des Génomes et des Réseaux (BiGRe)
http://www.bigre.ulb.ac.be/

Word counting - Occurrences or matching sequences

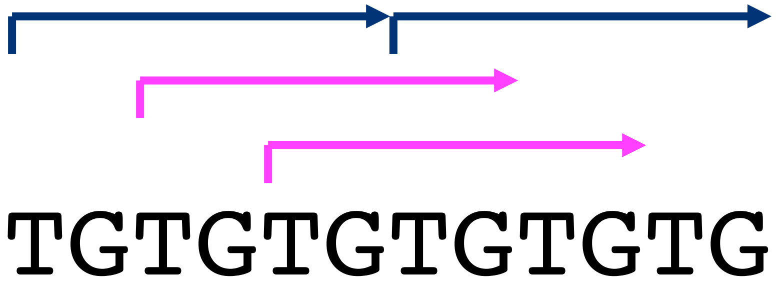
- If a sequence contains multiple occurrences of a given pattern, one can score either
  - all of them, or
  - only count the first occurrence per sequence. In this case, each sequence is scored as "matching" the pattern or not.



	All occurrences	First occurrence
Seq 1	3	true
Seq 2	0	false
Seq 3	4	true
Seq 4	1	true
Seq 5	0	false
Seq 6	1	true
Total	**9 occ**	**4 mseq**

Treatment of self-overlap

- Some words are self-overlapping.
- For such words, one can count
  - either the ***renewing occurrences*** only (2 occurrences in the example below)
  - or all occurrences (2 ***renewing*** and 2 ***overlapping*** in the example below).
- The choice of the counting mode strongly affects the subsequent statistics (dependency/independency).

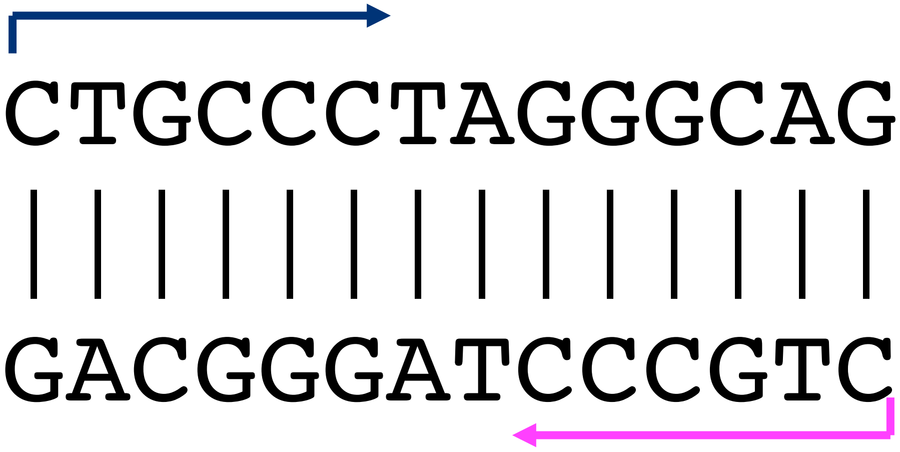


TGTGTGTGTGTG

2 or 4 occurrences of TGTGTG ?

Single or double strand count

- A particularity of DNA sequence is their double-strand structure.
- Words can be counted either on a single strand, or on both, depending on the nature of the expected biological signal.
  - In RNA sequences, single-strand counts are generally suited.
  - In DNA sequences, both-strands counts can be relevant for cis-regulatory signals, because many transcription factor act in an orientation-independent way.



CTGCCCTAGGGCAG
||||||||||||||
GACGGGATCCCGTC

1 or 2 occurrences of CTGCCC ?

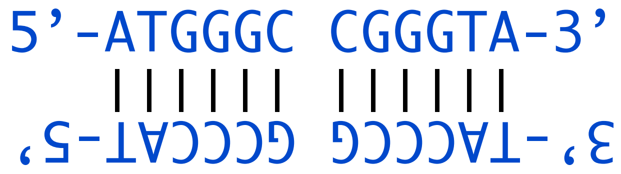
Symmetries in DNA sequences

This English sentence is a palindrome: it is symmetrical relative to the central letter (R). Palindromic sentence have the same succesion of letters when read in either direction. WASITARATISAW

The following sequence contains a textual palindrome

5'-ATGGGC CGGGTA-3'

However, there is no symmetry in the correponding DNA molecule.

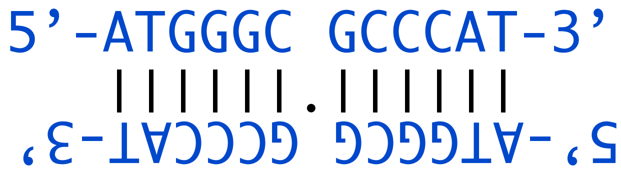


```
5'-ATGGGC CGGGTA-3'
   |||||| ||||||
3'-TACCCG GCCCAT-5'
```

The following sequence contains no textual palindrome

5'-ATGGGC GCCCAT-3'

However, there is a "reverse complementary palindromic" symmetry in the correponding DNA molecule: the molecule has the same succession of nucleotides when "read" on either strands (always from 5' to 3' end).



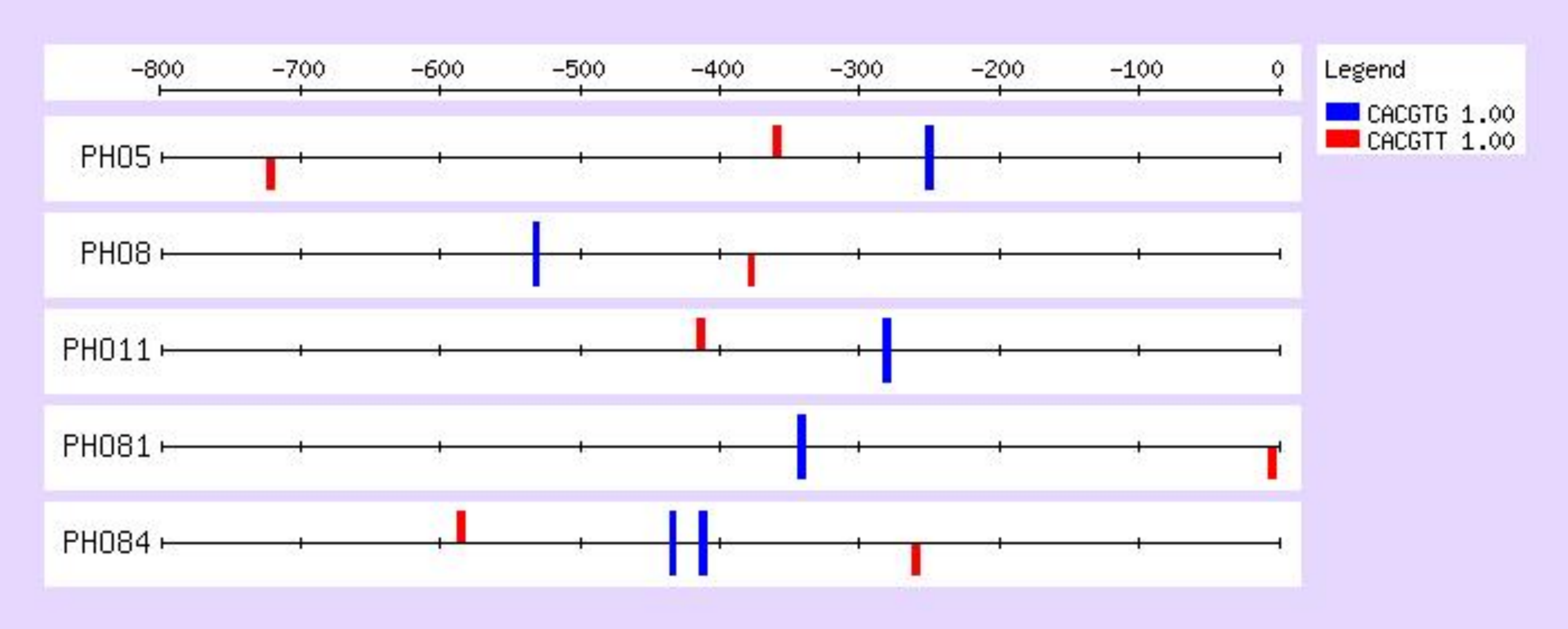
```
5'-ATGGGC GCCCAT-3'
   ||||||.||||||
5'-ATGGGC GCCCAT-3'
```

RSAT tool: dna-pattern

- Specialized program for pattern matching in DNA sequences
  - Supports IUPAC code for partly specified nucleotides (e.g. TSWNATTK)
  - Supports spaces of fixed or variable length within the patterns (e.g. GGGWn{0,30} WCCC)
  - Single or both strands
  - Allow substitutions but no insertion or deletion
- Extract neighbourhood of the match (flanking bases)
- Return
  - matching positions
  - match count per sequence
- Sliding window
  - Detection of regions containing combinations of multiple patterns
  - A specific weight can be associated to each pattern

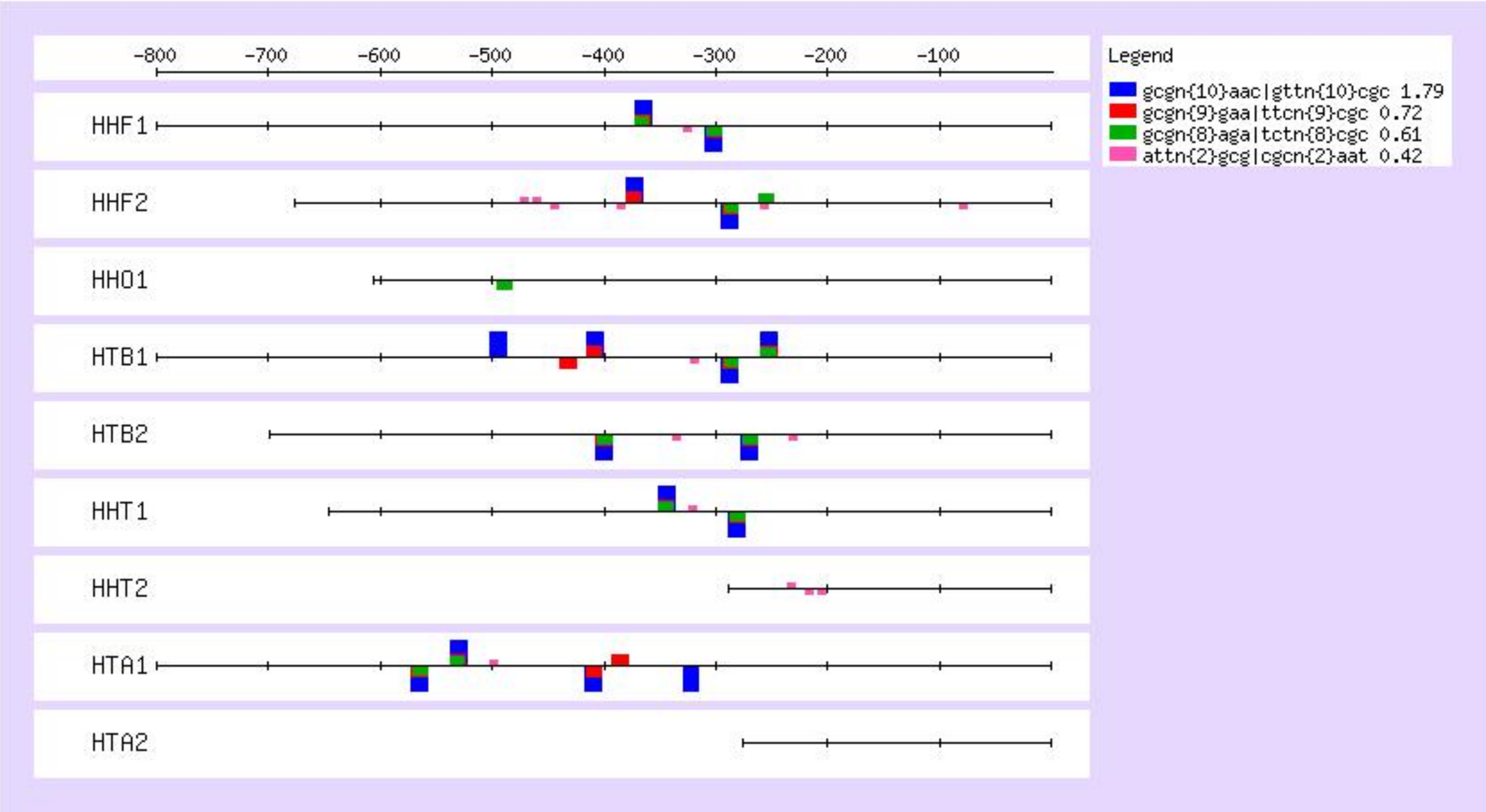
Matching simple patterns

- A simple string-based pattern matching is usually poorly informative.
  - spurious matches are expected to be found anywhere
  - the presence of the consensus does not necessarily mean that the factor binds
  - some patterns have a higher significance than other ones (e.g. the core of the consensus).



Matching a collection of overlapping patterns

- Pattern matching results can be improved by matching a collection of mutually overlapping patterns (words or spaced dyads)
  - Multiple patterns can be used to represent fragments of a larger binding site, or the variants arising from the degeneracy of the consensus.
  - Specific weights can be assigned to the elements of the collection, to represent their relative importance for the binding.



Genome-scale pattern matching

Genome-scale pattern matching

- Knowing the consensus binding site for a given transcription factor, one would be tempted to use this information for predicting its target genes in the whole genome.
- This approach is however very inaccurate, because
  - The consensus poorly reflects the binding specificity
  - Binding is not synonymous of regulation
- As an experiment, we counted the number of occurrences for the consensus of various yeast transcription factors (source: TRANSFAC + our annotations). For each one of the
  - 800bp upstream sequences, clipped to prevent upstream ORFs.
  - For each gene, we counted the number of occurrences of each consensus.

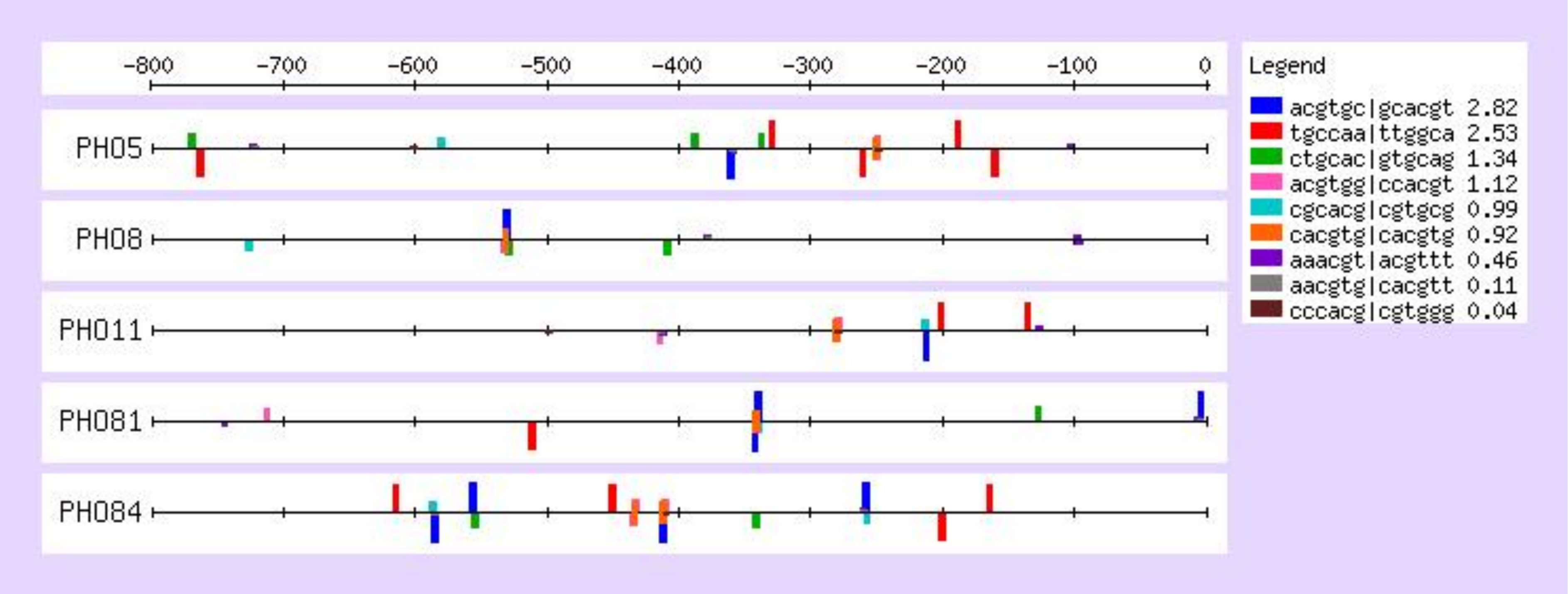
Occurrences of consensus per promoter

- Saccharomyces cerevisiae, 5864 genes, 800bp (clipped if upstream ORF)

factor	**sequence**	**mean**	**>= 1**	**>=2**	**>=3**	**>=4**	**>=5**	**>=6**	**7**
ABF1	TCNNNNNNNACG	0.62	788	196	43	13	5	0	0
ABF1.1	RTCRYYNNNNACG	0.15	61	5	2	0	0	0	0
ADR1	GGRGK	1.52	2187	1283	725	414	230	113	72
CBF1	RTCACRTG	0.07	70	10	6	0	0	0	0
CCBF	RNNYCACGAAAA	0.01	1	1	1	1	1	0	0
GAL4	CGGNNNACWNTCSTCCGARS	0.00	0	0	0	0	0	0	0
GATA_L5	GATAA	1.63	2588	1322	685	322	168	89	40
GATA_L6	GATAAG	0.28	266	46	14	7	2	1	0
GCN4	SKRTGASTCAYMS	0.00	2	0	0	0	0	0	0
GCN4.1	SNSNNNNNRTGACTCATNS	0.00	0	0	0	0	0	0	0
GCR1	RGCTTCCWC	0.03	14	1	0	0	0	0	0
GFII	RTCACRTG	0.07	70	10	6	0	0	0	0
HAP1	aaCttCCGWTAWCtCCNtNCNNNNT	0.00	0	0	0	0	0	0	0
HAP2	YCNNCCAATNANM	0.01	0	0	0	0	0	0	0
HAP3	YCNNCCAATNANM	0.01	0	0	0	0	0	0	0
HAP4	YCNNCCAATNANM	0.01	0	0	0	0	0	0	0
MATa1	TGATGTANNT	0.04	4	0	0	0	0	0	0
MATalpha2	CRTGTNNW	0.74	1088	345	87	15	6	2	1
MCM1	WTWCCYAAWNNGGTAA	0.00	0	0	0	0	0	0	0
MET4_core	CACGTG	0.16	401	49	49	8	8	2	2
MET4_L8	TCACGTGA	0.04	101	2	2	0	0	0	0
MIG1	KANWWWWATSYGGGGW	0.00	0	0	0	0	0	0	0
PHO4	CACGTKBG	0.04	17	2	0	0	0	0	0
PHO4_both	CACGTK	0.32	460	118	61	28	10	3	3
PHO4_high	CACGTG	0.16	401	49	49	8	8	2	2
PHO4_medium	CACGTT	0.16	74	5	0	0	0	0	0
RAP1	aCAcCCataCAt	0.00	0	0	0	0	0	0	0
REB1	YNNYYACCCG	0.11	22	2	0	0	0	0	0
repr of CAR1	TAGCCGCCRANR	0.01	2	0	0	0	0	0	0
TAF	RTCRYNNNNNACG	0.22	130	10	2	0	0	0	0
YAP1	TGASTMA	0.23	282	56	8	0	0	0	0

Assigning scores to patterns

- Pattern-specific scores can improve the interpretation by highlighting the most significant patterns.
- Scores can be assigned arbitrarily (e.g. on the basis of prior biological knowledge) or reflect the significance calculated by pattern discovery programs.



Sliding windows - scoring mutually overlapping matches

Sliding windows - scoring successions of matches