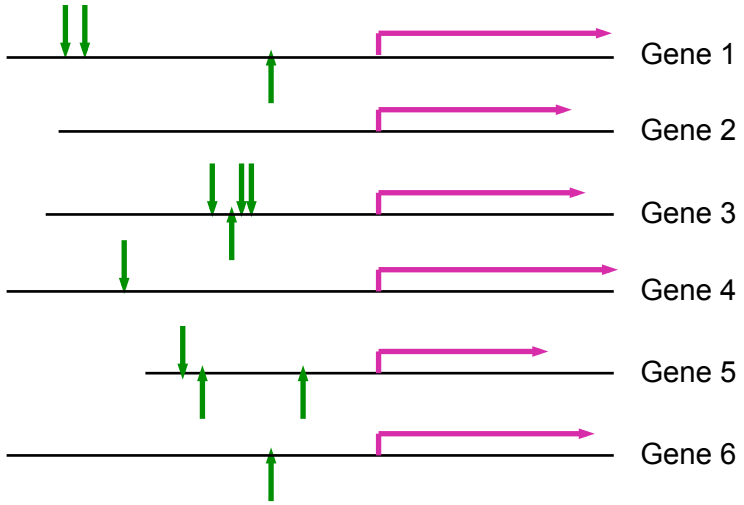
Matrix-based pattern discovery algorithms

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/

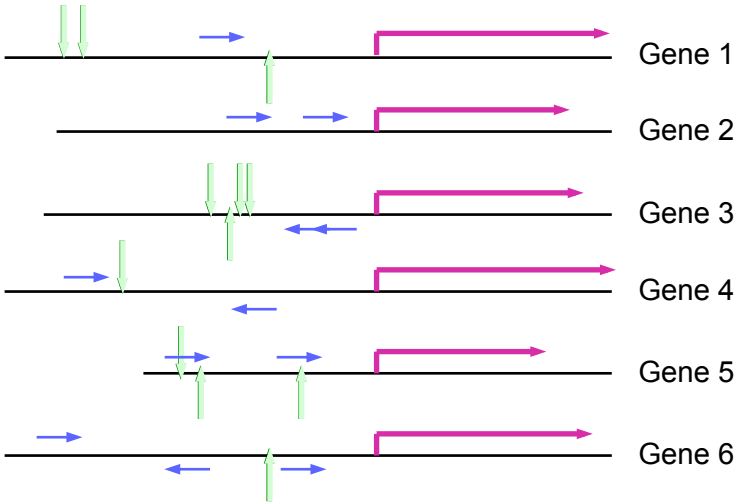
Pattern discovery situation

- Question
  - We dispose of a set of *s* promoter sequences containing *x* instances (sites) of a cis-regulatory motif.
  - Starting from the sequences, we want to discover the motif.
- Hypothesis
  - The motif is over-represented in the sequence set.



Building a matrix from an arbitrary set of sites

- A simple procedure
  - Select *x* sites of length *w* in the input sequences.
  - Align them at their first position.
  - Build a matrix.
- If the sites are selected at random, the motif is likely to be non informative.



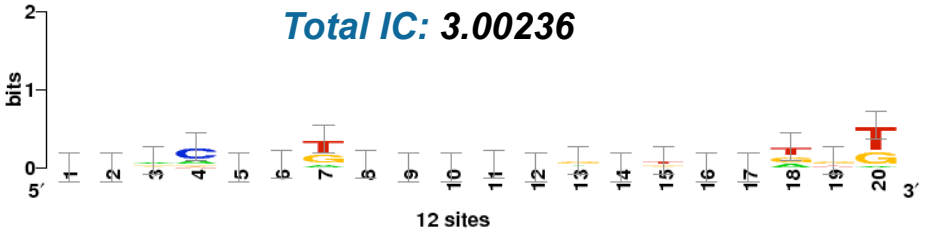
Site sequences

```
→ G C A C C A T C C G T T T A G A C T T A
→ C G G C G A T G C T G A G G T T G G A T
→ G A A A C A G A A T A C G C G A G T G T
→ C T T C T A G G G T C C T T T T G G G T
→ C G A C T C A G A G G A A T T C A T C G
→ A T A C A A G T G C A G A C A C T A C G
→ A C C T C G A T G A G A C T T C T A G T
→ G G T G A C T A C C C T G G G G A T T T
→ T C A C A T T T A C A G G G T A A G G T
→ G G G A A C G T T A G A G T C T C T T T
→ A T A A G C T G C A A T G T T A T G G G
→ C T G C T G T T T G G G A C C C G A G G
```

Matrix build from those sites

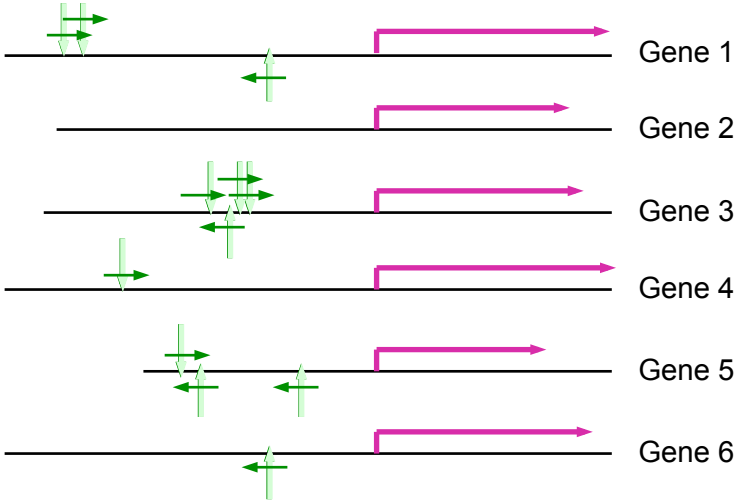
A	|	3	1	6	3	4	5	2	2	3	3	4	4	3	1	1	4	3	3	1	1
C	|	4	3	1	7	3	4	0	1	4	3	2	2	1	3	2	4	2	0	2	0
G	|	4	4	3	1	2	2	4	4	3	3	5	3	6	3	3	1	4	4	6	4
T	|	1	4	2	1	3	1	6	5	2	3	1	3	2	5	6	3	3	5	3	7

Total IC: 3.00236



Building a matrix from an arbitrary set of sites

- A simple procedure
  - Select *x* sites of length *w* in the input sequences.
  - Align them at their first position.
  - Build a matrix.
- If the matrix is build with the « correct » sites, we expect to observe a high information content.



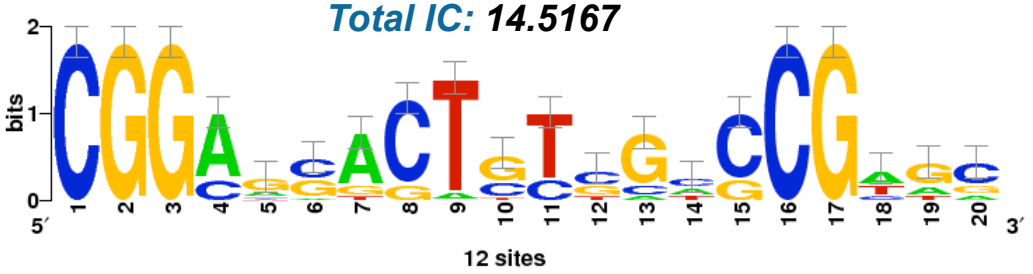
Site sequences

```
C G G C G C A C T C T C G C C C G A A C
C G G A G G G C T G T C G C C C G C T C
C G G A G G G C T G T C G C C C G C T C
C G G A G C A G T G C G G C G C G A G G
C G G A G C A G T G C G G C G C G A G G
C G G A A G A C T C T C C T C C G T G C
C G G A A G A C T C T C C T C C G T G C
C G G A G C A C T G T T G A G C G A A G
C G G C G G T C T T T C G T C C G T G C
C G G C A C A C A G T G G A C C G A A C
C G G A C A A C T G T T G A C C G T G A
C G G A T C A C T C C G A A C C G A G A
```

Matrix build from those sites

```
A |  0  0  0  9  3  1  9  0  1  0  0  0  1  4  0  0  0  6  3  2
C | 12  0  0  3  1  6  0 10  0  4  3  6  2  5  9 12  0  2  0  7
G |  0 12 12  0  7  5  2  2  0  7  0  4  9  0  3  0 12  0  7  3
T |  0  0  0  0  1  0  1  0 11  1  9  2  0  3  0  0  0  4  2  0
```

Total IC: 14.5167



Finding the optimal matrix – a straightforward algorithm

- Straightforward approach
  - Test all possible motifs that can built from the sequence by aligning *x* sequence fragments of length *w*.
  - Compute a score (e.g. information content, log-likelihood, P-value) associated to each motif.
  - Report the highest-scoring motif.
- Is this approach tractable ?

Pattern discovery: typical dimensionality for a very small dataset

- Typical case 1: GAL genes
  - s 6 sequences (promoters of the annotated GAL genes)
  - L average promoter size (yeast) 500 bp
  - sps expected sites per sequences: 2 (multiple sites are frequent in yeast)
  - x expected number of sites: sps*s=12
  - w matrix width = 20
- Let us assume that
  - A signal can be found on any strand of any sequence
  - Number of possible site positions: $n=2s(L-w+1)=5772$
  - Each sequence contains 0 or several occurrences -> the number of possible alignments equals the number of ways to choose 12 among the 5772 possible sites.

$$N_{alignments} = C_n^x = C_{2s(L-w+1)}^x = C_{5772}^{12} = 2.9 \cdot 10^{36}$$

Pattern discovery: typical dimensionality for a reasonable dataset

- **Typical case 2:** yeast promoters bound by a TF in a ChIP-chip experiment (e.g. Harbison et al. 2004)
  - s 50 sequences
  - L average promoter size (yeast) 500 bp
  - sps expected sites per sequences: 2 (multiple sites are frequent in yeast)
  - occ_e expected sites: sps*s=100
  - w matrix width = 20
- Let us assume that
  - A signal can be found on any strand of any sequence
  - Number of possible site positions: $n=2s(L-w+1)=48100$
  - Each sequence contains 0 or several occurrences -> the number of possible alignments equals the number of ways to choose 100 among the 48100 possible sites.

$$N_{alignments} = C^{occ_e}_{2s(L-w+1)} = C^{100}_{48100} \approx \infty$$

sites	positions	alignments
1	962	4.62E+05
2	1924	5.69E+11
3	2886	7.98E+17
4	3848	1.18E+24
5	4810	1.81E+30
6	5772	2.82E+36
7	6734	4.46E+42
8	7696	7.13E+48
9	8658	1.15E+55
10	9620	1.86E+61
15	14430	2.19E+92
20	19240	2.75E+123
25	24050	3.55E+154
30	28860	4.69E+185
35	33670	6.27E+216
40	38480	8.48E+247
45	43290	1.16E+279
50	48100	Inf

Matrix-based pattern discovery

- Problem: the number of possible matrices is too large to be tractable
- Approaches: define heuristics to extract a matrix with highest possible information content (lowest probability to be due to random effect) → optimization techniques
- Two approaches working with regulatory sequences
  - greedy algorithm
  - gibbs sampling

The greedy algorithm "consensus"

Jacques.van.Helden@ulb.ac.be
Université Libre de Bruxelles, Belgique
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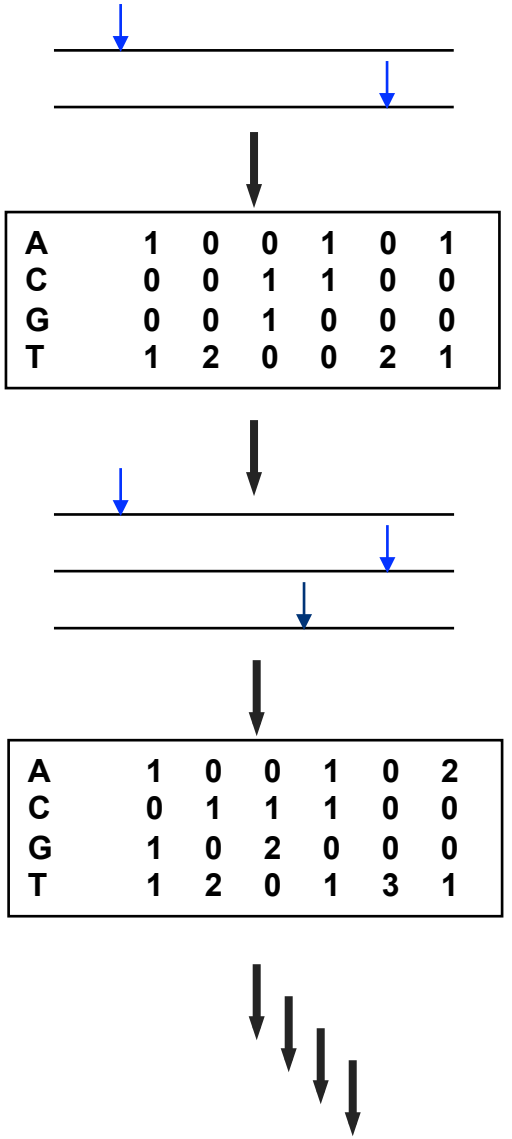
Pattern discovery: greedy algorithm (consensus, by Jerry Hertz)

1. Create all possible matrices with two sites taken from the two first sequences (*n*n* possibilities).
   - Typically 1000*1000=1.000.000 possible matrices, each made of 2 sites.
2. Retain the most informative matrices only
   - E.g. the 1000 matrices with the highest information content
3. Create all possible combinations between each of these matrix and each possible site in the next sequence.
   - Typically 1000 previous matrices x 1000 new sites.
4. Iterate from previous steps until all sequences are incorporated
5. Return the most significant matrices



Greedy algorithm: weaknesses

- Returns multiple matrices, but they are generally slight variants of the same pattern
- Time-consuming
- Sensitive to sequence ordering in the input data set
- Takes into account prior residue frequencies, but not oligonucleotide bias
- References
  - Hertz et al. (1990). Comput Appl Biosci 6(2), 81-92.
  - Hertz, G. Z. & Stormo, G. D. (1999). Bioinformatics 15(7-8), 563-77.
  - Stormo, G. D. & Hartzell, G. W. d. (1989). Proc Natl Acad Sci U S A 86(4), 1183-7.

Expectation- Maximization (EM)

Jacques.van.Helden@ulb.ac.be
Université Libre de Bruxelles, Belgique
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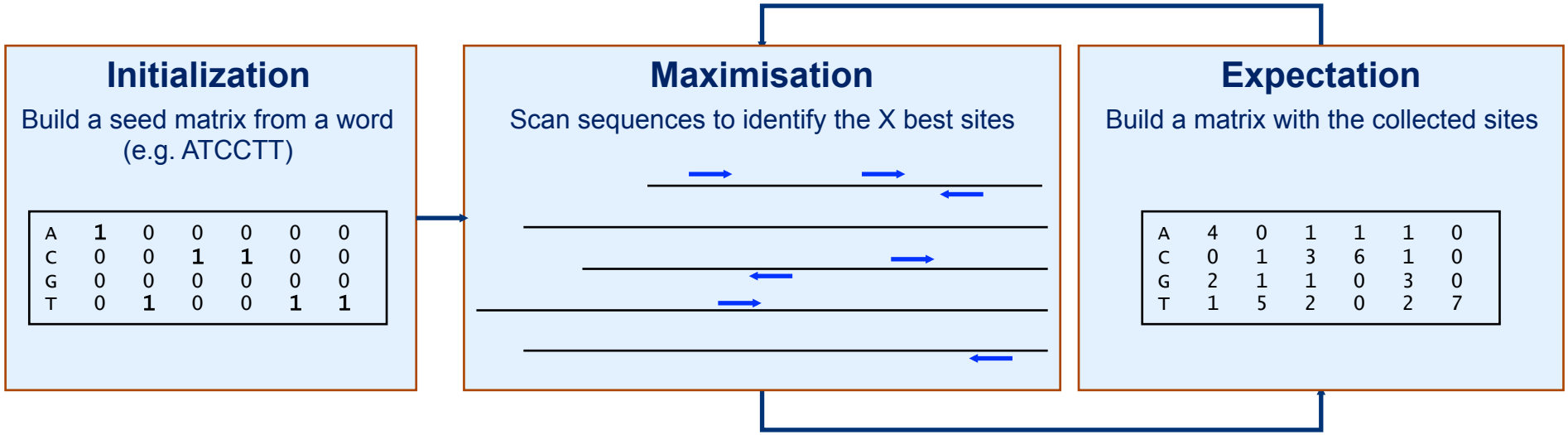
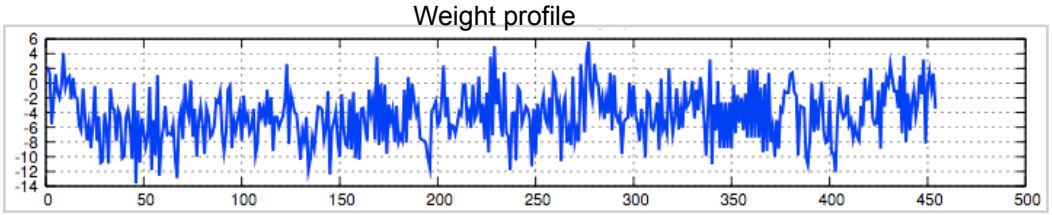
MEME - Multiple EM for Motif Elicitation

- Algorithm
  - Select over-represented k-mers as seeds for several matrices
  - Run an EM (expectation/maximisation) algorithm on each seed in order to optimize the matrix.
  - Return the highest scoring matrices.





MEME - Multiple EM for Motif Elicitation

- Web interface + downloadable program
  - http://meme.nbcr.net/
- Reference
  - Timothy L. Bailey and Charles Elkan (1994). Fitting a mixture model by expectation maximization to discover motifs in biopolymers. Proceedings of the Second International Conference on Intelligent Systems for Molecular Biology, pp. 28-36, AAAI Press, Menlo Park, California.
- Strengths
  - Flexible options
  - Matrices are scored with the E-value (expected number of false positives). Very low E-values are generally indicative of good results.
  - Supports multiple-widths (test various matrix widths and returns the most informative).
  - Supports higher-order background models (Markov chains)
    - This parameter strongly affects the result.
    - In my hands, higher order background models seem to give better results at least with yeast data sets.

Example of MEME result

- We ran MEME with 30 yeast genes involved in methionine metabolism and sulfur assimilation
  - (We actually collected all genes having MEY\d+ or SAMd\+ in their names)
- MEME returned 3 motifs
  - The first ones are uninformative poly-A and polyT motifs.
  - The third one is the motif bound by Met31p or Met32p.

PN

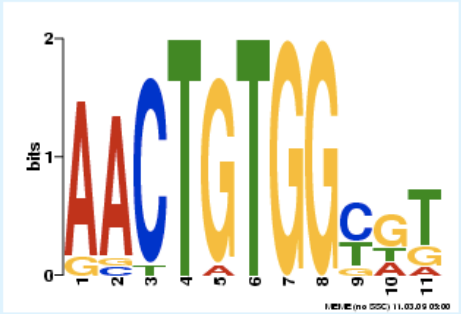
MOTIF 3 width = 11 sites = 34 llr = 394 E-value = 4.2e-023

SEQUENCE LOGO

Information Content
16.1 (bits)

Relative Entropy
16.7 (bits)

Download LOGO
Without SSC:[EPS][PNG]
With SSC:[EPS][PNG]



NAME	STRAND	START	P-VALUE	SITES
SAM2_reverse_complement	-	288	1.16e-07	TGAGCTTGAA AACTGTGGCGT TTTTCCACCG
SAM2	+	278	1.16e-07	TGAGCTTGAA AACTGTGGCGT TTTTCCACCG
MET32_reverse_complement	+	318	1.16e-07	AGAAAATATA AACTGTGGCGT ACTAAGCGTA
MET32	-	218	1.16e-07	AGAAAATATA AACTGTGGCGT ACTAAGCGTA
MET28_reverse_complement	+	145	3.87e-07	TCCCGCCCAA AACTGTGGTGT TAGAAAGTAG
MET28	-	333	3.87e-07	TCCCGCCCAA AACTGTGGTGT TAGAAAGTAG
MET3_reverse_complement	+	245	7.96e-07	TAAGTTGTAA AACTGTGGCTT TGTTATACGG
MET3	-	544	7.96e-07	TAAGTTGTAA AACTGTGGCTT TGTTATACGG
MET28_reverse_complement	+	276	7.96e-07	CGGGCCCCAC AACTGTGGCAT CTTTCAGATC
MET28	-	202	7.96e-07	CGGGCCCCAC AACTGTGGCAT CTTTCAGATC
MET30_reverse_complement	+	154	7.96e-07	TCTCCGCGCA AACTGTGGCTT CCCGATCACG
MET30	-	12	7.96e-07	TCTCCGCGCA AACTGTGGCTT CCCGATCACG
SAM1_reverse_complement	-	265	9.78e-07	TTCACAGGAA AACTGTGGTGG CGCCCTTGCC
SAM1	+	272	9.78e-07	TTCACAGGAA AACTGTGGTGG CGCCCTTGCC
MET17_reverse_complement	-	265	9.78e-07	GATATTGGGG AACTGTGGTGG TTGGCAAATG
MET17	+	524	9.78e-07	GATATTGGGG AACTGTGGTGG TTGGCAAATG
MET13_reverse_complement	+	22	9.78e-07	TTGTAGTAGT AACTGTGGTGG TTCTGTTTGC

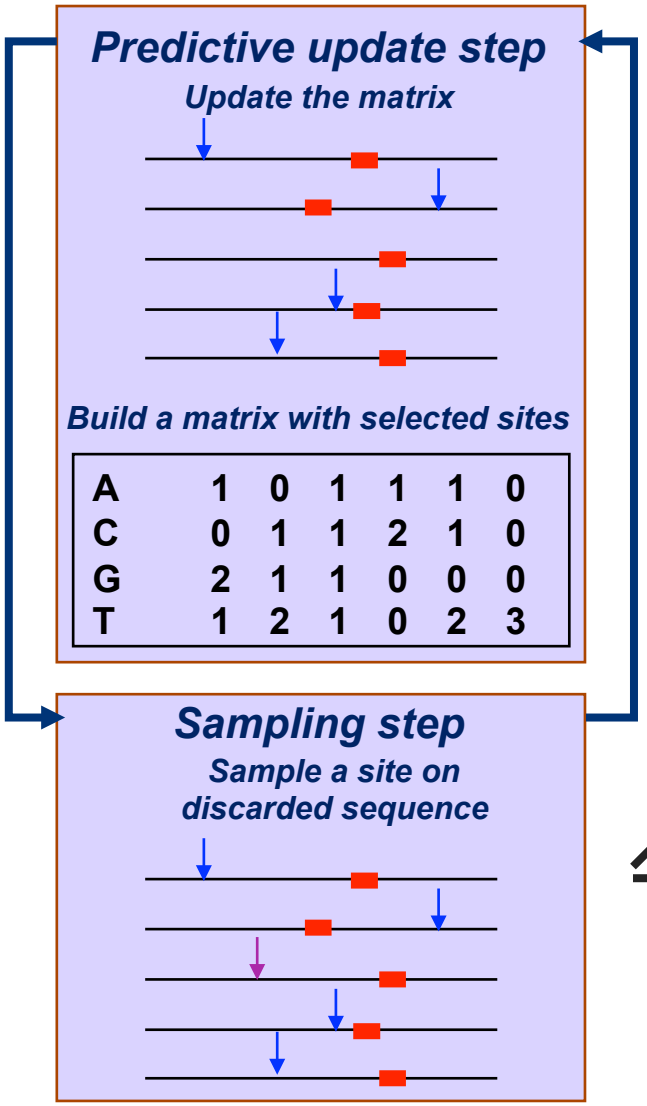
Gibbs sampling (stochastic Expectation - Maximization)

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/

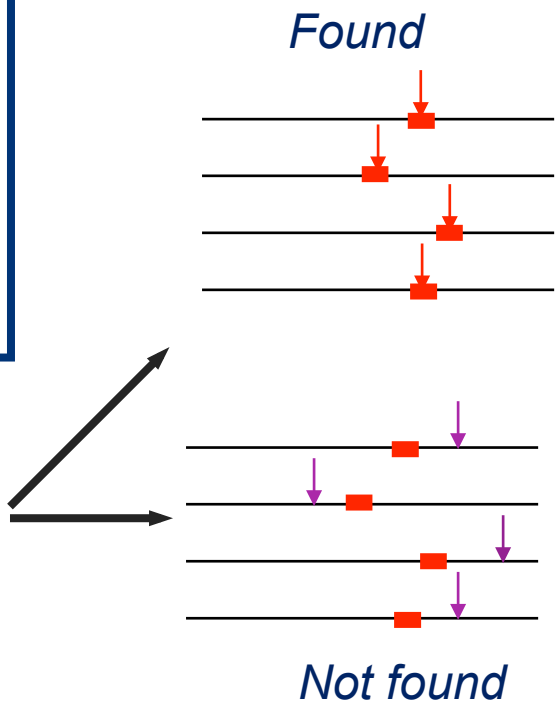
Pattern discovery: The Gibbs sampler (gibbs motif sampler, by Andrew Neuwald)

Pretend you know the motif, this might become true

- Initialization
  - select a random set of sites in the sequence set
  - Create a matrix with these sites
- Sampling (Stochastic Expectation)
  - Isolate one sequence from the set, and score each position (site) of the sequence.
  - Select one “random” site, with a probability proportional to the score (Ax, see next slide).
- Predictive update (Maximization)
  - Replace the old site with a new site, and update the matrix
- Iterate steps 2 and 3 for a fixed number of cycles



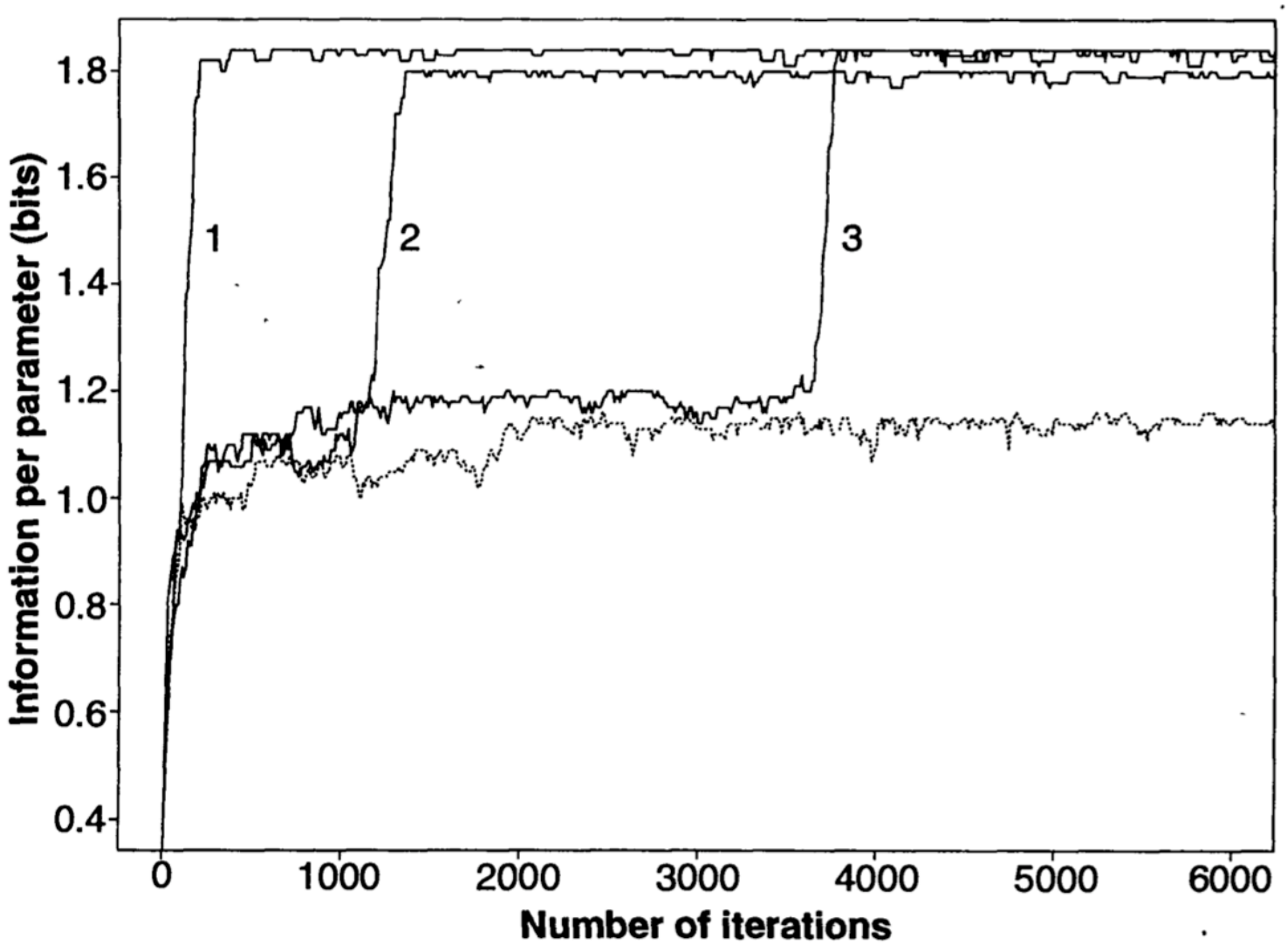
After N iterations



Stochastic vs deterministic behaviour

- Why to select a random site ?
  - A deterministic behaviour would consist in selecting, at each iteration, the highest scoring site (the one which matches best the matrix)
  - This would give poor results because the program is attracted too fast towards local optima.
- Stochastic behaviour
  - At each iteration, the next site is selected in a stochastic rather than deterministic way: the probability of each site to be selected is proportional to its scoring with the matrix
  - This allows to avoid weak local optima, and converge towards better solutions.

Gibbs sampling: optimization of information content



source: Lawrence et al.(1993). Science 262(5131), 208-14.

Some gibbs sampling implementations

- Gibbs 1993
  - The first implementation of the gibbs sampler for finding motifs in biological sequences
  - *Lawrence, C. E., Altschul, S. F., Boguski, M. S., Liu, J. S., Neuwald, A. F. and Wootton, J. C. (1993). Detecting subtle sequence signals: a Gibbs sampling strategy for multiple alignment. Science 262, 208-14.*
- Gibbs 1995
  - 0 or several matches per sequence
  - column sampling (spacings can be admitted between columns of the matrix)
  - *Neuwald, A. F., Liu, J. S. and Lawrence, C. E. (1995). Gibbs motif sampling: detection of bacterial outer membrane protein repeats. Protein Sci 4, 1618-32.*
- AlignACE
  - Specific implementation for DNA (double strand is treated)
  - post-filtering of motifs according to number of matches in the genome, in order to discard frequent motifs
  - *Roth, F. P., Hughes, J. D., Estep, P. W. and Church, G. M. (1998). Finding DNA regulatory motifs within unaligned noncoding sequences clustered by whole-genome mRNA quantitation. Nat Biotechnol 16, 939-45.*
- BioProspector
  - Higher-order Markov-chains to estimate background probabilities.
  - *Liu, X., Brutlag, D. L. and Liu, J. S. (2001). BioProspector: discovering conserved DNA motifs in upstream regulatory regions of co-expressed genes. Pac Symp Biocomput, 127-38.*
- MotifSampler
  - Higher-order Markov-chains to estimate background probabilities.
  - *Thijs, G., Lescot, M., Marchal, K., Rombauts, S., De Moor, B., Rouze, P. and Moreau, Y. (2001). A higher-order background model improves the detection of promoter regulatory elements by Gibbs sampling. Bioinformatics 17, 1113-22.*
- info-gibbs
  - Direct optimization of the information content rather than Qx/Px ratio.
  - Defrance & van Helden (2009). *Submitted manuscript.*

Gibbs sampling - scoring scheme

$$A_x = Q_x / P_x$$

- A_x weight of segment x (used for random selection)
- Q_x probability to generate segment x according to pattern probabilities q_{ij}
- P_x probability to generate segment x according to the background probabilities p_i

$$q_{i,j} = \frac{c_{i,j} + b_j}{N - 1 + B}$$

- i index for the site
- j index for the residue
- $c_{i,j}$ counts for residue j at site i
- N number of sequences
- b_j pseudo-count for residue j
- B sum of pseudo-counts

$$F = \sum_{i=1}^{W} \sum_{j=1}^{R} c_{i,j} \ln\left(\frac{q_{i,j}}{p_j}\right)$$

- W width of the matrix
- R number of distinct residues
- p_j prior probability for residue j

A = Q/P profiles after the first iteration (random seed)

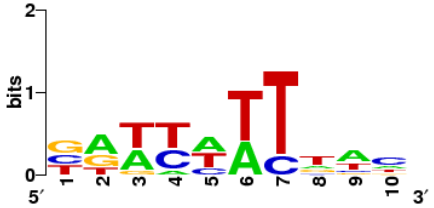
$$A_x = Q_x / P_x$$

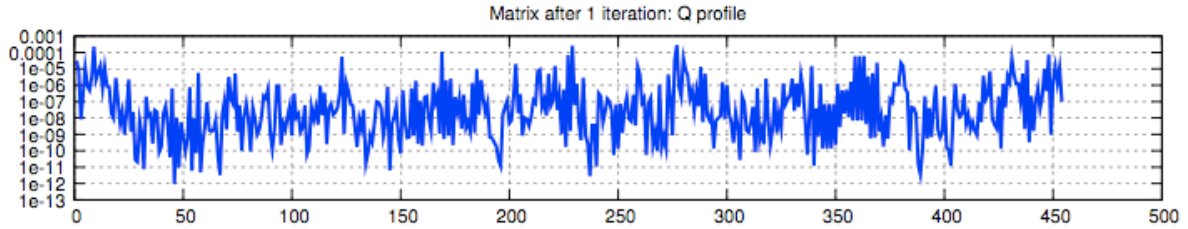
A_x weight of segment x (used for random selection)

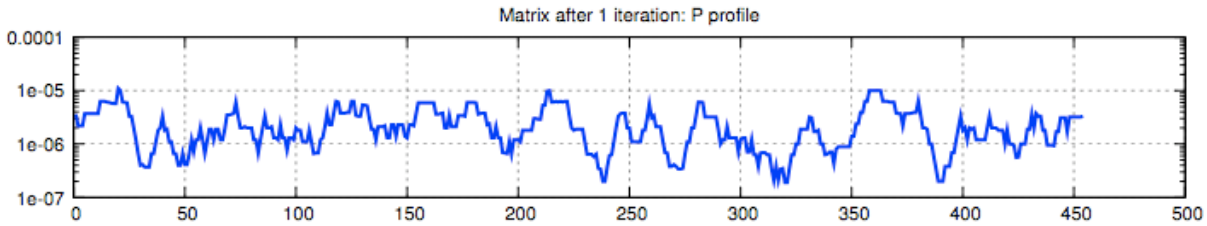
Q_x probability to generate segment x according to pattern probabilities q_{ij}

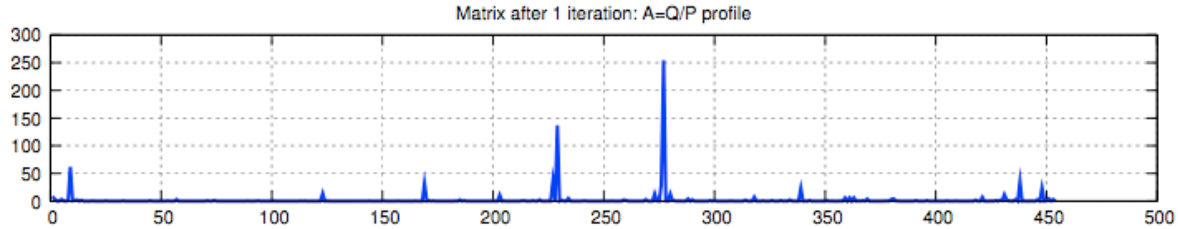
P_x probability to generate segment x according to the background probabilities p_i

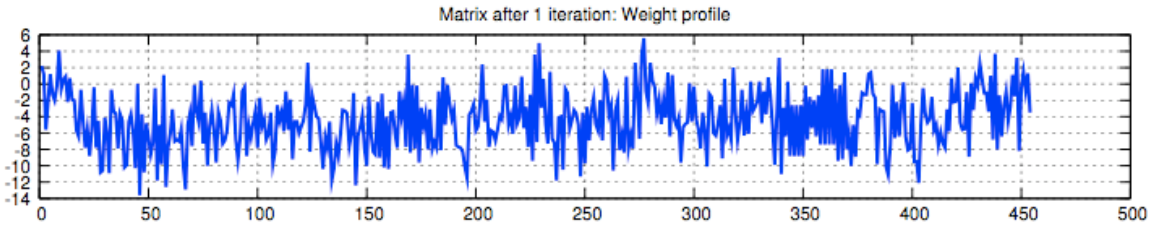
1 iteration, IC per col=0.30











A = Q/P profiles after 1000 iterations (Met4p motif found)

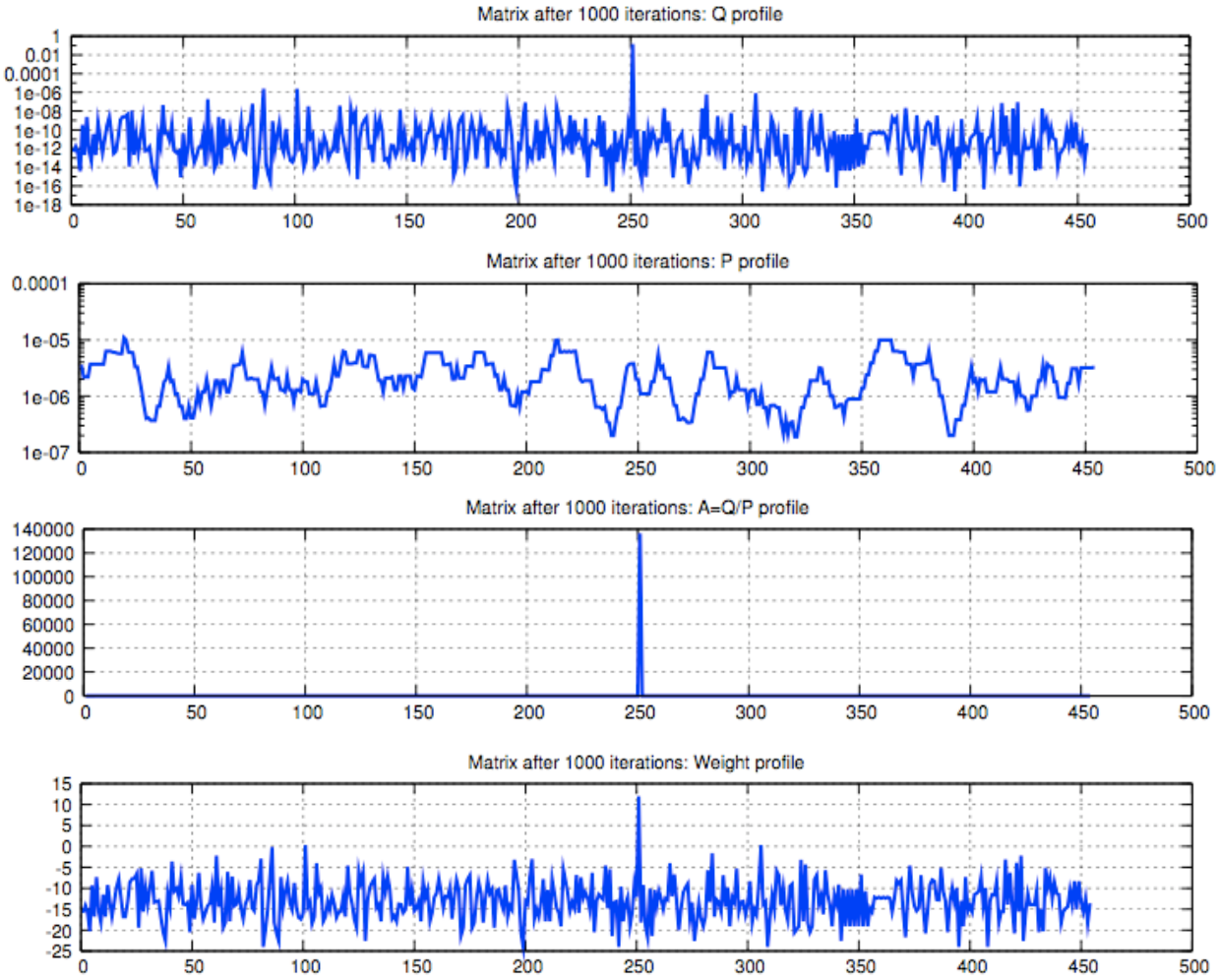
$$A_x = Q_x / P_x$$

A_x weight of segment x (used for random selection)

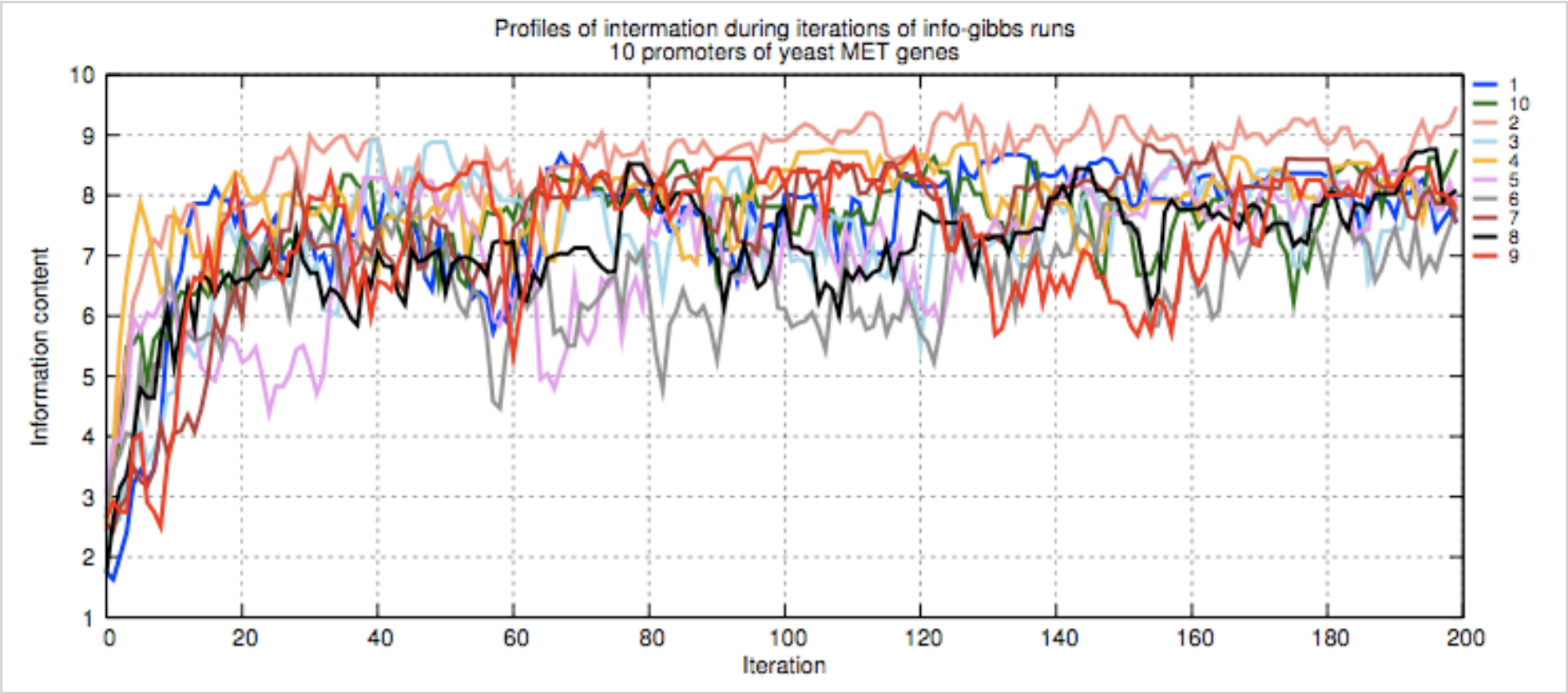
Q_x probability to generate segment x according to pattern probabilities q_{ij}

P_x probability to generate segment x according to the background probabilities p_i

1000 iterations, IC per col=0.95

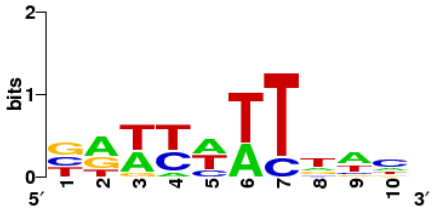


Profiles of information content during iterations of info-gibbs runs

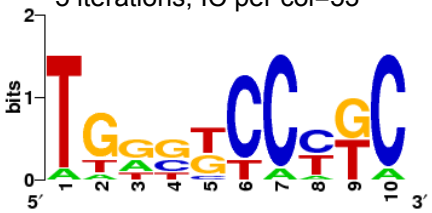


Examples of results

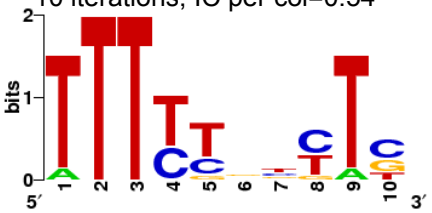
1 iteration, IC per col=0.303332



(another run)
5 iterations, IC per col=53

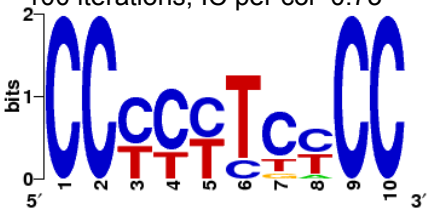


(another run)
10 iterations, IC per col=0.54

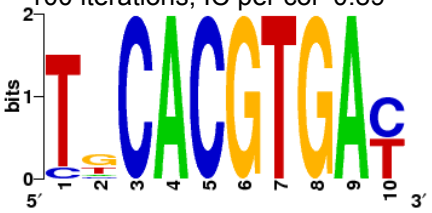


(another run)
100 iterations, IC per col=0.87

(another run)
100 iterations, IC per col=0.73

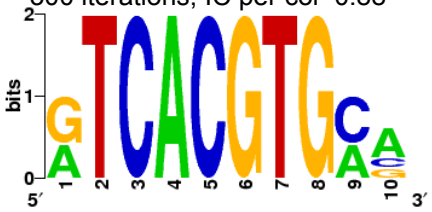


(another run)
100 iterations, IC per col=0.89

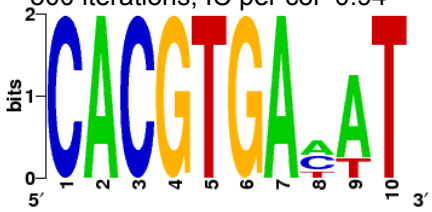


(another run)
200 iterations, IC per col=0.94

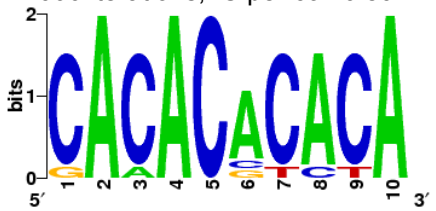
(another run)
300 iterations, IC per col=0.88



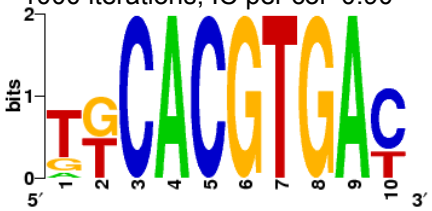
(another run)
500 iterations, IC per col=0.94



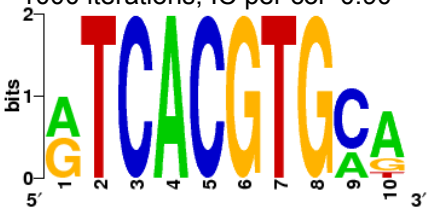
(another run)
1000 iterations, IC per col=0.89



(another run)
1000 iterations, IC per col=0.90

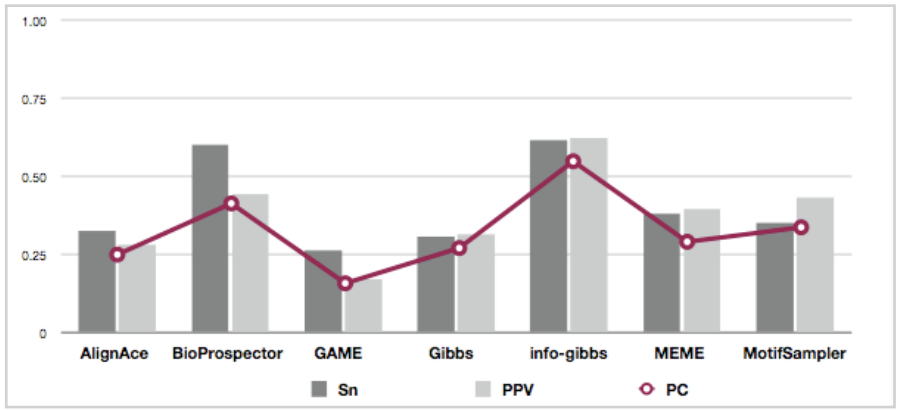


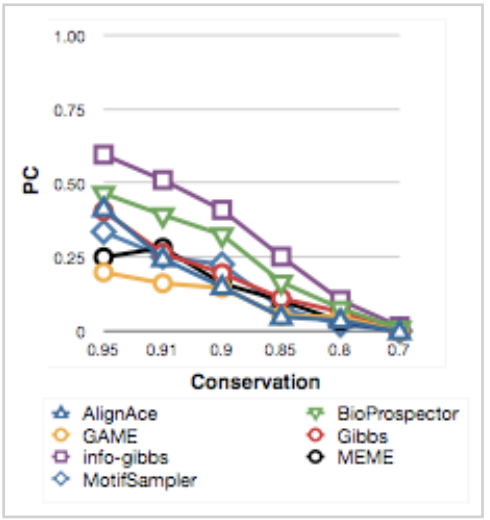
(another run)
1000 iterations, IC per col=0.90



Evaluation on synthetic data

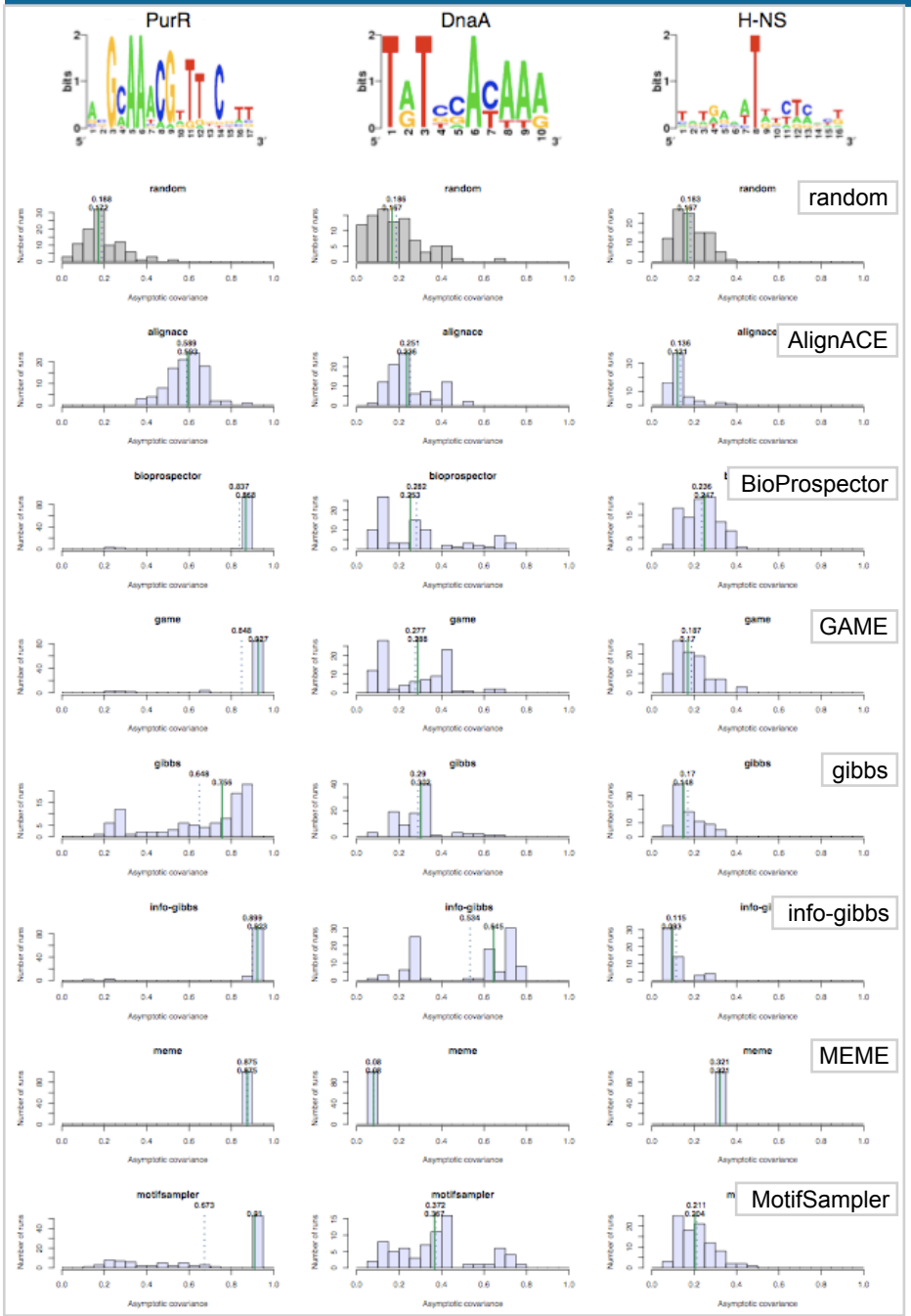
- Synthetic data
  - Generate random sequences (***random-seq***)
  - Generate random PSSMs (***random-motif***)
  - Generate random sites from those random motifs (***random-sites***)
  - Implant random sites at random positions of random sequences (***implant-sites***)
- Motif discovery
  - Those sequences are submitted to various algorithms.
  - The sites used to build the discovered motifs are compared to the implanted sites.
  - The process is run on 100 different artificial data sets.
- Statistics
  - Sensitivity: (correct sites) / (implanted sites)
    - *Sn= TP / (TP + FN)*
  - Positive Predictive Value: (correct sites) / (sites used to build motifs)
    - *PPV = TP / (TP + FP)*
  - Performance Coefficient : (correct sites) / (union of discovered and implanted sites)
    - *PC = TP/ (TP + FP + FN)*
- Advantages of this evaluation protocol
  - The evaluation is accurate, since we control the implanted sites.
  - We can test the impact of various parameters (sequence length, number of sites, degree of conservation of the motifs, ...)
- Weaknesses of the evaluation
  - Performances on synthetic data may differ from performances on real biological sequences.
  - This evaluation is biased since we developed one of the algorithms. Even if we attempt to be as fair as we can, we know better how to handle our algorithm than those developed by other people.





Defrance, M. and Helden, J. V. (2009). Info-gibbs: a motif discovery algorithm that directly optimizes information content during sampling. Bioinformatics 25(20):2715-22.

Evaluation with known regulons



- We took all the regulons annotated in RegulonDB http://regulondb.ccg.unam.mx/
- For each factor, we collect the promoters of all target genes.
- We run each program 100 times, in order to evaluate the intrinsic variability of the results due to the stochasticity of the gibbs sampling.
- We compare discovered and annotated motifs by computing the asymptotic covariance according to Pape et al. (Bioinformatics 2008, 24:350-7).
- We estimate the random expectation by analyzing the distribution of asymptotic covariance for random motifs built by picking up random positions in the input sequences.

Defrance, M. and Helden, J. V. (2009). Bioinformatics 25(20):2715-22.

Evaluation with all regulons from RegulonDB

Fig. 1. Software performances on the RegulonDB data sets. The asymptotic covariance between annotated and predicted regulatory motifs for 32 *Escherichia coli K12* regulons was computed over 100 trials. The mean is reported for a random selection and for each motif discovery software.

Factor	Genes	Sites	IC	random	AlignACE	BioProspector	GAME	Gibbs	info-gibbs	MEME	MotifSampler
AgaR	3	11	9.685	0.270	0.624	0.654	0.462	0.709	0.632	0.535	0.648
AraC	5	13	7.239	0.195	0.295	0.405	0.391	0.371	0.199	0.619	0.372
ArgR	16	18	9.805	0.247	0.824	0.836	0.893	0.796	0.902	0.832	0.872
CpxR	33	42	5.835	0.205	0.170	0.188	0.235	0.235	0.104	0.461	0.197
DeoR	3	7	7.776	0.200	0.278	0.209	0.328	0.243	0.222	0.651	0.423
DgsA	5	7	13.522	0.220	0.815	0.508	0.640	0.799	0.713	0.749	0.622
DnaA	6	8	6.690	0.186	0.251	0.282	0.277	0.290	0.534	0.080	0.372
FadR	9	12	8.609	0.216	0.732	0.807	0.751	0.563	0.825	0.821	0.515
Fis	70	133	5.292	0.176	0.201	0.206	0.321	0.372	0.204	0.312	0.294
FlhDC	20	18	6.816	0.207	0.411	0.580	0.546	0.546	0.387	0.582	0.516
FruR	22	12	10.768	0.167	0.889	0.862	0.830	0.819	0.909	0.878	0.867
GlpR	4	17	7.848	0.213	0.577	0.740	0.659	0.692	0.687	0.394	0.637
GntR	6	10	10.289	0.196	0.575	0.781	0.769	0.576	0.829	0.791	0.766
H-NS	52	35	4.936	0.183	0.136	0.236	0.187	0.170	0.115	0.321	0.211
IHF	77	84	5.267	0.297	0.000	0.359	0.351	0.253	0.259	0.402	0.335
IclR	2	10	4.782	0.227	0.132	0.417	0.081	0.104	0.236	0.427	0.232
LexA	25	23	10.995	0.216	0.659	0.846	0.891	0.855	0.901	0.855	0.892
MalT	5	14	6.048	0.321	0.456	0.638	0.642	0.423	0.710	0.690	0.472
MetJ	9	23	7.099	0.180	0.472	0.705	0.727	0.659	0.664	0.687	0.686
Nac	10	12	6.762	0.224	0.244	0.248	0.238	0.301	0.268	0.365	0.275
NagC	7	10	10.832	0.263	0.323	0.234	0.278	0.332	0.412	0.306	0.302
NanR	3	6	6.497	0.252	0.520	0.569	0.541	0.560	0.666	0.534	0.460
NtrC	15	17	8.886	0.215	0.827	0.839	0.822	0.844	0.895	0.830	0.748
OmpR	12	19	8.103	0.283	0.297	0.149	0.135	0.283	0.118	0.253	0.271
PhoB	14	120	11.411	0.205	0.124	0.699	0.639	0.429	0.115	0.751	0.567
PhoP	20	19	8.162	0.240	0.195	0.275	0.334	0.496	0.611	0.186	0.350
PurR	19	18	10.496	0.188	0.589	0.837	0.848	0.648	0.899	0.875	0.673
RcsAB	10	9	7.870	0.231	0.315	0.293	0.266	0.242	0.156	0.617	0.393
SoxS	18	18	6.753	0.201	0.271	0.288	0.304	0.307	0.344	0.400	0.273
TorR	5	6	6.546	0.170	0.482	0.654	0.357	0.654	0.674	0.188	0.443
TrpR	5	10	14.537	0.213	0.758	0.613	0.856	0.681	0.858	0.878	0.840
TyrR	9	17	9.085	0.229	0.854	0.779	0.282	0.802	0.790	0.746	0.704

Defrance, M. and Helden, J. V. (2009). Bioinformatics 25(20):2715-22.

Gibbs sampling: strength

- Fast
- Probabilistic description of the patterns
- Can run with proteins or DNA

Gibbs sampling: weaknesses

- Returns a different result at each run
- Can be attracted by local maxima
  - solution: run repeatedly and check which motifs come often
- The original Gibbs sampler takes into account prior residue frequencies, but not oligonucleotide bias
  - → in yeast, often returns A/T-rich regions
  - This is however improved in some versions of the Gibbs samplers which use Markov chains for estimating the bacground probabilities (eg the MotifSampler developed by Gert Thijs)
- No threshold on pattern significance
  - → frequent false positive

AlignACE, ScanACE and CompACE
gibbs sampler tools for regulatory sequence analysis

- Single/both strands
- Return multiple matrices, with iterative masking preventing slight variants of the same pattern
- Matrix clustering
- A posteriori evaluation of pattern significance, by analysing the whole-genome frequency of the discovered matrix.
- References
  - Roth et al. (1998). Nat Biotechnol 16(10), 939-45.
  - Tavazoie et al. (1999). Nat Genet 22(3), 281-5.
  - Hughes et al. (2000). J Mol Biol 296(5), 1205-14.
  - McGuire et al. (2000). Genome Res 10(6), 744-57.

Summary: matrix-based pattern discovery

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/

Matrix-based pattern discovery: strengths

- More specific description of degeneracy than with string-based approaches (frequency of each residue at each position).
- The resulting pattern is more accurate than a string for pattern matching (more sensitive scoring scheme)

Matrix-based pattern discovery: weaknesses

- The results strongly depend on parameter setting. Two essential parameters have to be selected :
  - Matrix width
  - Expected number of sites
- The best parameter may change from gene family to gene family. Choosing the appropriate setting requires experience.
- Impossible to evaluate all possible alignments
- Does not take into account higher-order correlation between adjacent positions (oligonucleotide bias)