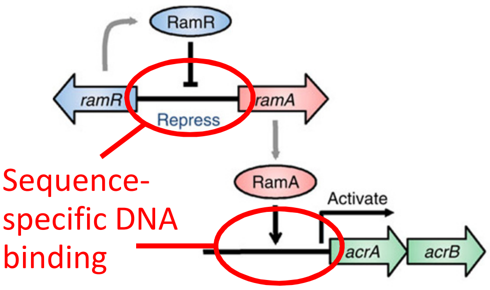
Motifs

BCH394P/364C - Systems Biology / Bioinformatics

Edward Marcotte, Univ of Texas at Austin

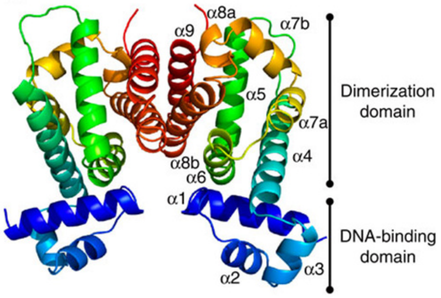
An example transcriptional regulatory cascade

Here, controlling *Salmonella* bacteria multidrug resistance



Sequence-specific DNA binding

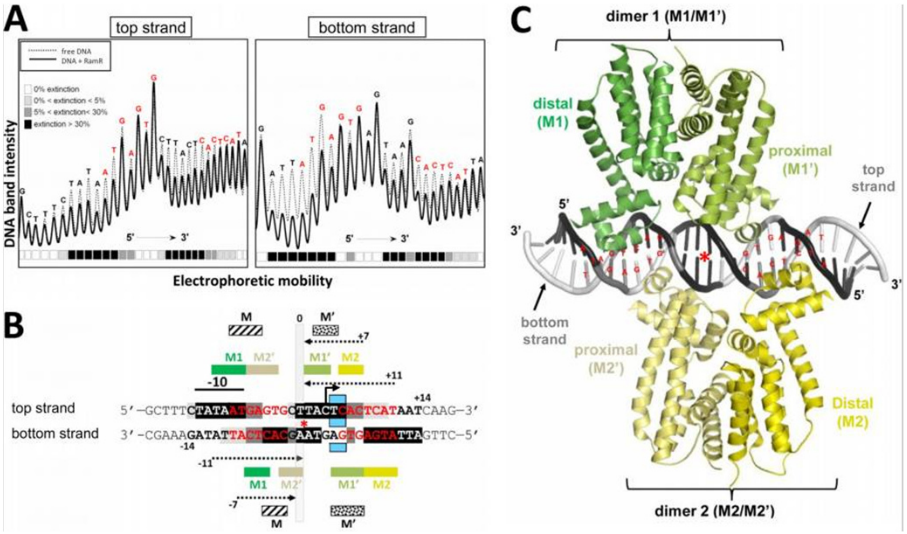
RamR represses the *ramA* gene, which encodes the activator protein for the *acrAB* drug efflux pump genes.



RamR dimer

Nature Communications 4, Article number: 2078 doi:10.1038/ncomms3078

Historically, DNA and RNA binding sites were defined biochemically (DNAse footprinting, gel shift assays, etc.)

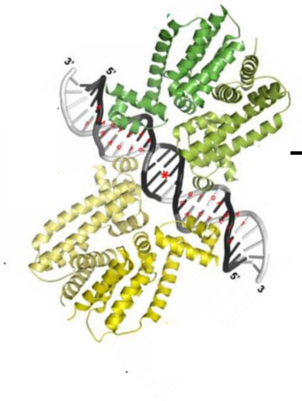


Hydroxyl radical footprinting of *ramR-ramA* intergenic region with RamR

Antimicrob Agents Chemother. Feb 2012; 56(2): 942–948.

Historically, DNA and RNA binding sites were defined biochemically (DNAse footprinting, gel shift assays, etc.)

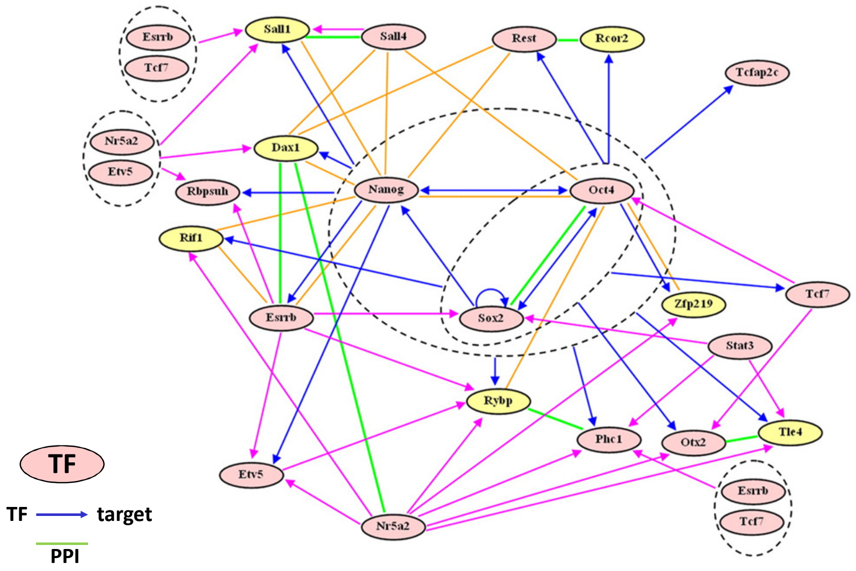
Now, many binding motifs are discovered bioinformatically



Isolate different nucleic acid segments bound by copies of the protein (e.g. all sites bound across a genome) → Sequence → Search computationally for recurring ***motifs***

Image: Antimicrob Agents Chemother. Feb 2012; 56(2): 942–948.

Transcription factor regulatory networks can be highly complex, e.g. as for embryonic stem cell regulators



http://www.pnas.org/content/104/42/16438

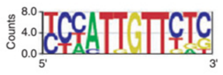
MOTIFS

HEM13	CCCATTGTTCTC
HEM13	TTTCTGGTTCTC
HEM13	TCAATTGTTTAG
ANB1	CTCATTGTTGTC
ANB1	TCCATTGTTCTC
ANB1	CCTATTGTTCTC
ANB1	TCCATTGTTCGT
ROX1	CCAATTGTTTTG

Binding sites of the transcription factor ROX1

YCHATTGTTCTC consensus

A	002700000010
C	464100000505
G	000001800112
T	422087088261

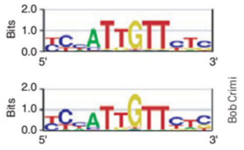


frequencies

frequency of nuc b at position i

$$I_{seq}(i) = -\sum_{b} f_{b,i} \log_2 \frac{f_{b,i}}{p_b}$$

freq of nuc b in genome



scaled by information content

NATURE BIOTECHNOLOGY VOLUME 24 NUMBER 4 APRIL 2006

So, here’s the challenge:

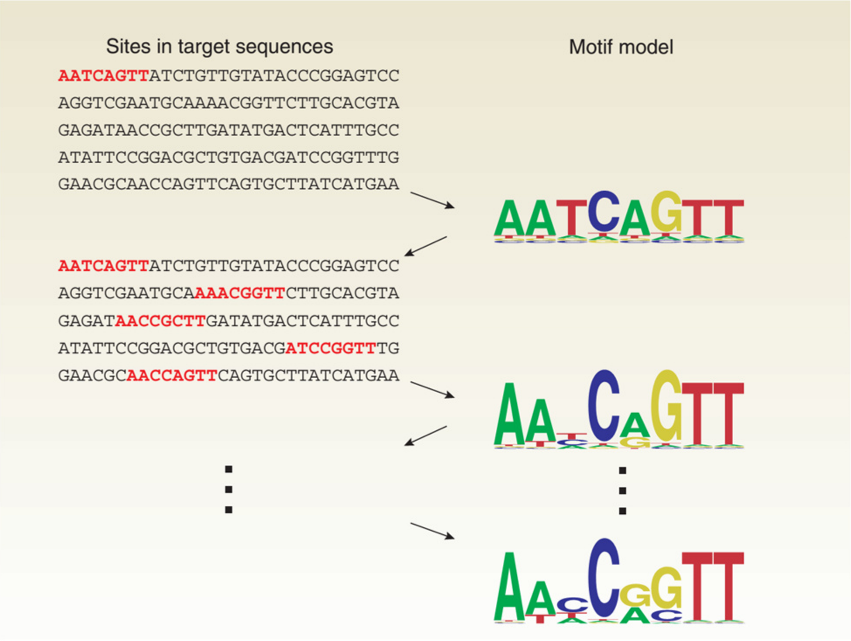
Given a set of DNA sequences that contain a motif (e.g., promoters of co-expressed genes), how do we discover it computationally?

Could we just count all instances of each *k*-mer?

Why or why not?

→ promoters and DNA binding sites are not well conserved

How does motif discovery work?



Sites in target sequences

Motif model

AATCAGTTATCTGTTGTATACCCGGAGTCC
AGGTCGAATGCAAAACGGTTCTTGCACGTA
GAGATAACCGCTTGATATGACTCATTTGCC
ATATTCCGGACGCTGTGACGATCCGGTTTG
GAACGCAACCAGTTCAGTGCTTATCATGAA

AATCAGTTATCTGTTGTATACCCGGAGTCC
AGGTCGAATGCA**AAACGGTT**CTTGCACGTA
GAGAT**AACCGCTT**GATATGACTCATTTGCC
ATATTCCGGACGCTGTGACG**ATCCGGTT**TG
GAACGC**AACCAGTT**CAGTGCTTATCATGAA

⋮

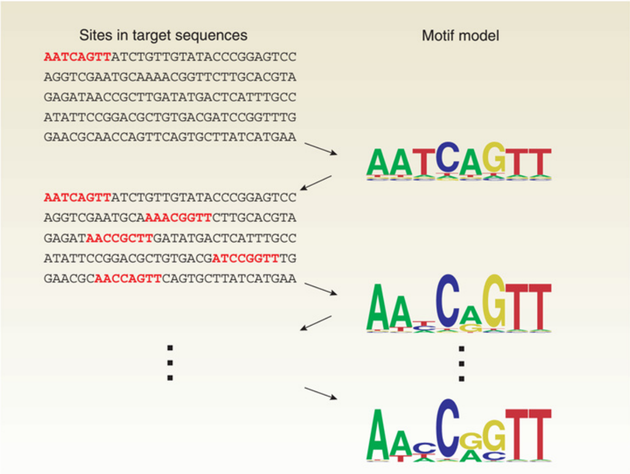
NATURE BIOTECHNOLOGY VOLUME 24 NUMBER 8 AUGUST 2006

How does motif discovery work?

Assign sites to motif

Assign sites to motif

Assign sites to motif



Sites in target sequences

Motif model

AATCAGTTATCTGTTGTATACCCGGAGTCC
AGGTCGAATGCAAAACGGTTCTTGCACGTA
GAGATAACCGCTTGATATGACTCATTTGCC
ATATTCCGGACGCTGTGACGATCCGGTTTG
GAACGCAACCAGTTCAGTGCTTATCATGAA

AATCAGTTATCTGTTGTATACCCGGAGTCC
AGGTCGAATGCA**AAACGGTT**CTTGCACGTA
GAGAT**AACCGCTT**GATATGACTCATTTGCC
ATATTCCGGACGCTGTGACG**ATCCGGTT**TG
GAACGC**AACCAGTT**CAGTGCTTATCATGAA

⋮

Update the motif model

Update the motif model

Update the motif model

etc.

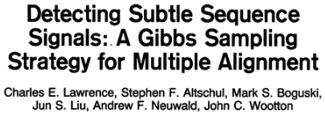
NATURE BIOTECHNOLOGY VOLUME 24 NUMBER 8 AUGUST 2006

How does motif discovery work?

Motif finding often uses *expectation-maximization*
i.e. **alternating between building/updating a motif model and assigning sequences to that motif model.**

Searches the space of possible motifs for optimal solutions without testing everything.

Most common approach = *Gibbs sampling*

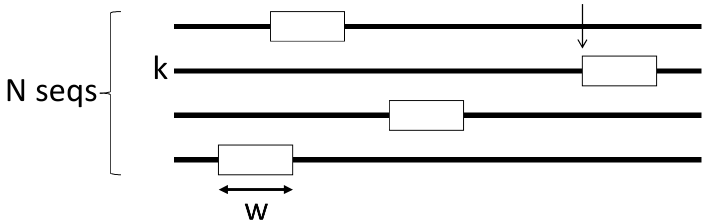


Detecting Subtle Sequence Signals: A Gibbs Sampling Strategy for Multiple Alignment

Charles E. Lawrence, Stephen F. Altschul, Mark S. Boguski, Jun S. Liu, Andrew F. Neuwald, John C. Wootton

We will consider N sequences, each with a motif of length w:

A_k = position in seq k of motif



k

N seqs

w

q_{ij} = probability of finding nucleotide (or aa) j at position i in motif
i ranges from 1 to w
j ranges across the nucleotides (or aa)

p_j = background probability of finding nucleotide (or aa) j

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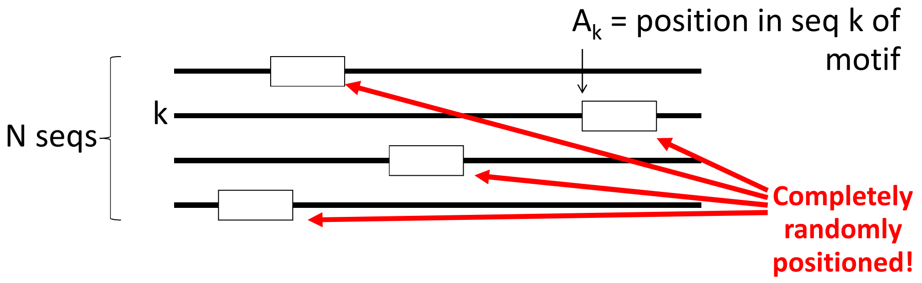
NOTE: You **won't give any information at all** about what or where the motif should be!

Start by **choosing w** and **randomly positioning** each motif:


A_k = position in seq k of motif
N seqs
k
Completely randomly positioned!

q_{ij} = probability of finding nucleotide (or aa) j at position i in motif

i ranges from 1 to w

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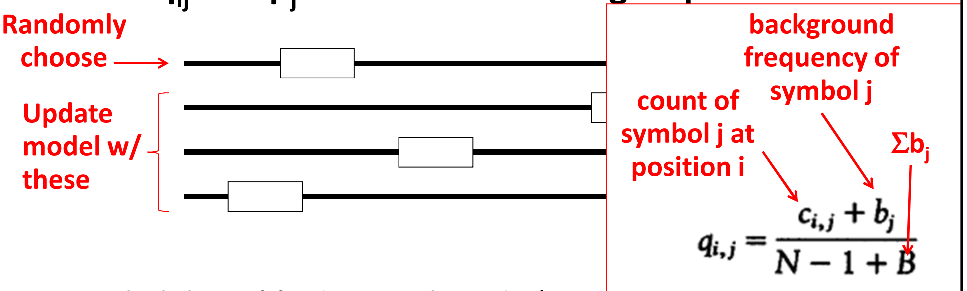
Predictive update step: Randomly choose one sequence, calculate q_{ij} and p_j from N-1 remaining sequences


Randomly choose
Update model w/ these
background frequency of symbol j
count of symbol j at position i
Σb_j

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

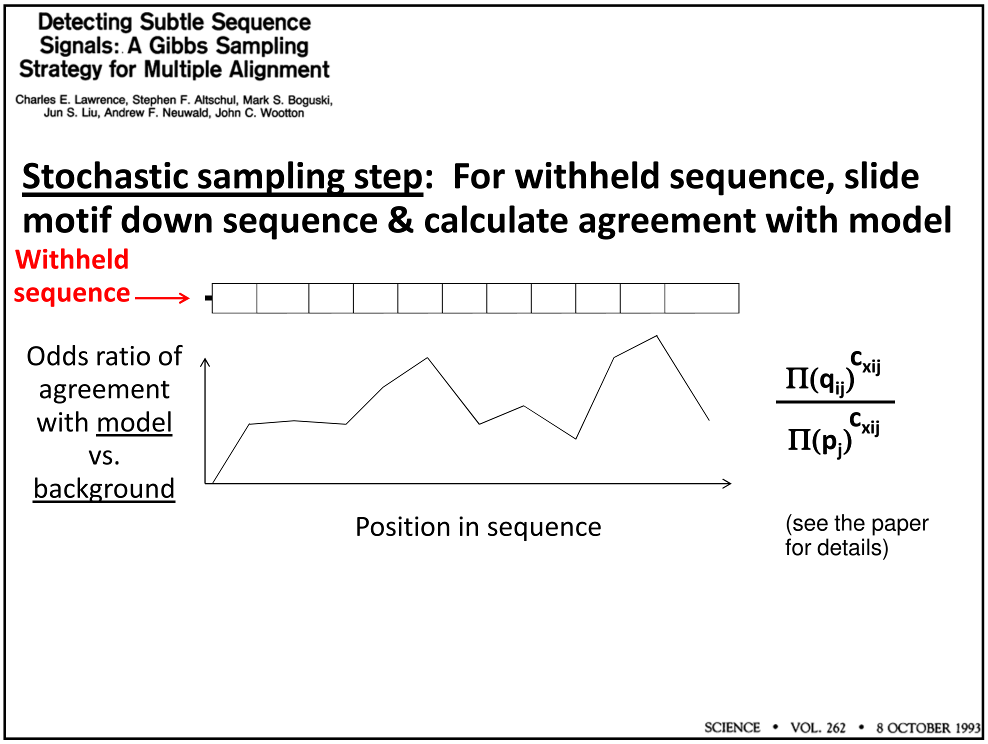
p_j is calculated similarly from the counts **outside** the motifs

q_{ij} = probability of finding nucleotide (or aa

i ranges from 1 to w

j ranges across the nucleotides (or a

p_j = background probability of finding nucleotide (or aa) j



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Stochastic sampling step: For withheld sequence, slide motif down sequence & calculate agreement with model

Withheld sequence →

Odds ratio of agreement with model vs. background

Position in sequence

$$\frac{\Pi(q_{ij})^{c_{xij}}}{\Pi(p_j)^{c_{xij}}}$$

(see the paper for details)

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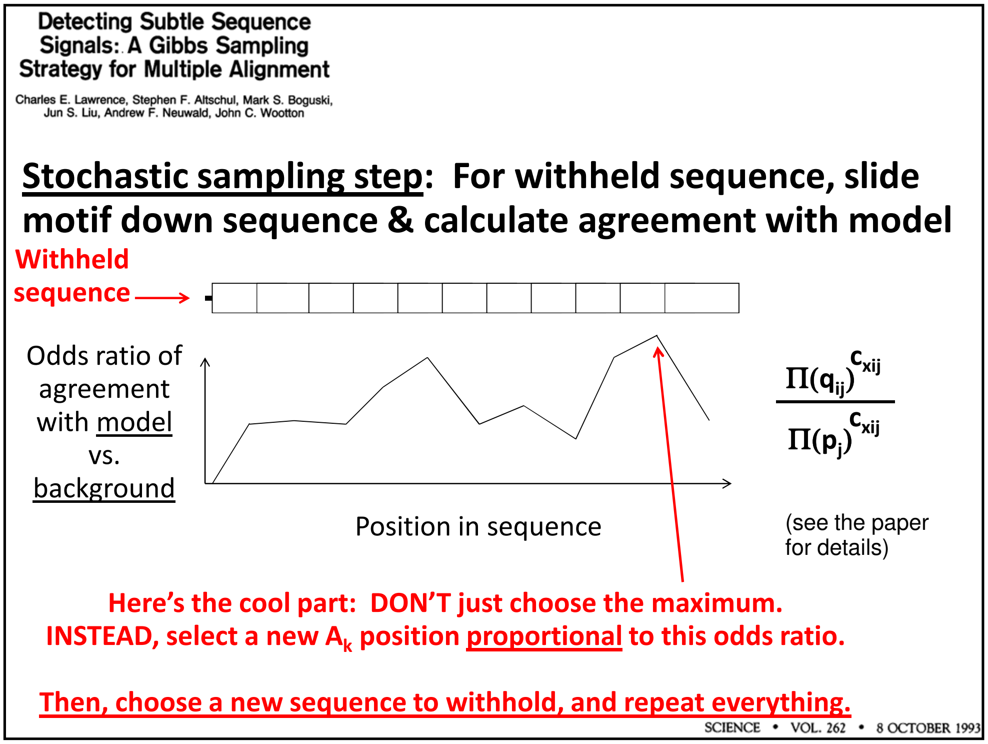

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Withheld sequence →

Odds ratio of agreement with model vs. background

Position in sequence

$$\frac{\Pi(q_{ij})^{c_{xij}}}{\Pi(p_j)^{c_{xij}}}$$

(see the paper for details)

Here's the cool part: DON'T just choose the maximum.
INSTEAD, select a new A_k position proportional to this odds ratio.

Then, choose a new sequence to withhold, and repeat everything.

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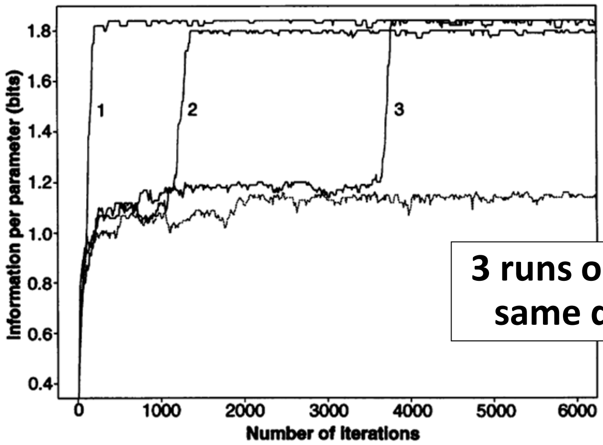
Over many iterations, this magically converges to the most enriched motifs. Note, it's stochastic:



3 runs on the same data

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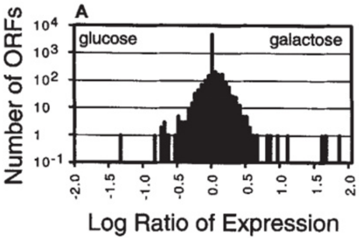
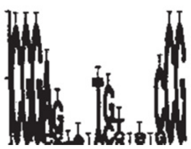
Finding DNA regulatory motifs within unaligned noncoding sequences clustered by whole-genome mRNA quantitation

Frederick P. Roth, Jason D. Hughes, Preston W. Estep, and George M. Church

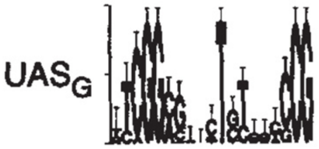


galactose vs. glucose → **Measure mRNA abundances using DNA microarrays** → **Search for motifs in promoters of glucose vs galactose controlled genes**

Discovered motifs



Known motif



Galactose upstream activation sequence

"AlignAce" NATURE BIOTECHNOLOGY VOLUME 16 OCTOBER 1998

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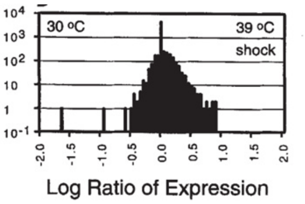


heat shock vs. 30°C → **Measure mRNA abundances using DNA microarrays** → **Search for motifs in promoters of heat-induced and repressed genes**

Discovered motifs

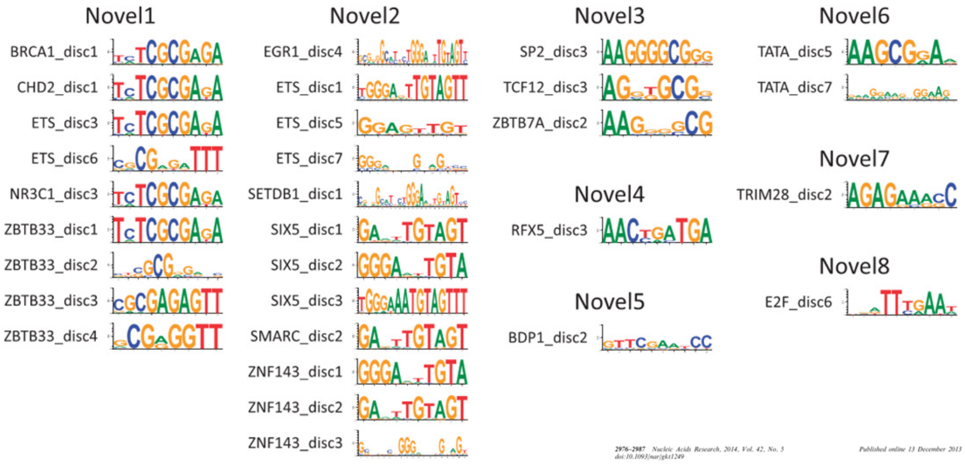
Known motif

Cell cycle activation motif, histone activator

"AlignAce" NATURE BIOTECHNOLOGY VOLUME 16 OCTOBER 1998

If you need them, we now know the binding motifs for 100's of transcription factors at 1000's of distinct sites in the human genome, including many new motifs.

e.g., http://compbio.mit.edu/encode-motifs/

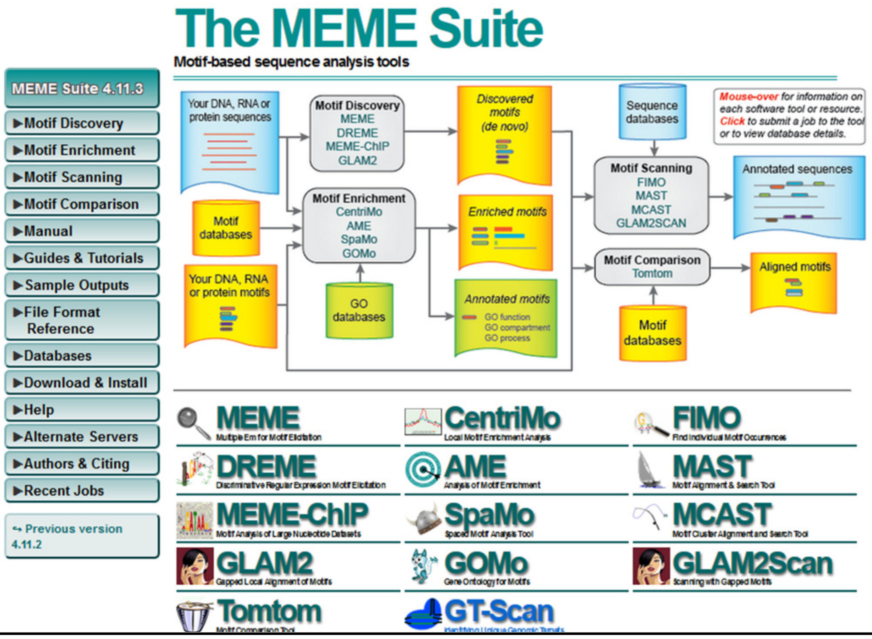


2976–2987 Nucleic Acids Research, 2014, Vol. 42, No. 5 Published online 13 December 2013
doi:10.1093/nar/gkt1249

Systematic discovery and characterization of regulatory motifs in ENCODE TF binding experiments

Pouya Kheradpour and Manolis Kellis

Here's a good place to start if you want to do this practically: http://meme-suite.org/


The MEME Suite
Motif-based sequence analysis tools
MEME Suite 4.11.3
▶Motif Discovery
▶Motif Enrichment
▶Motif Scanning
▶Motif Comparison
▶Manual
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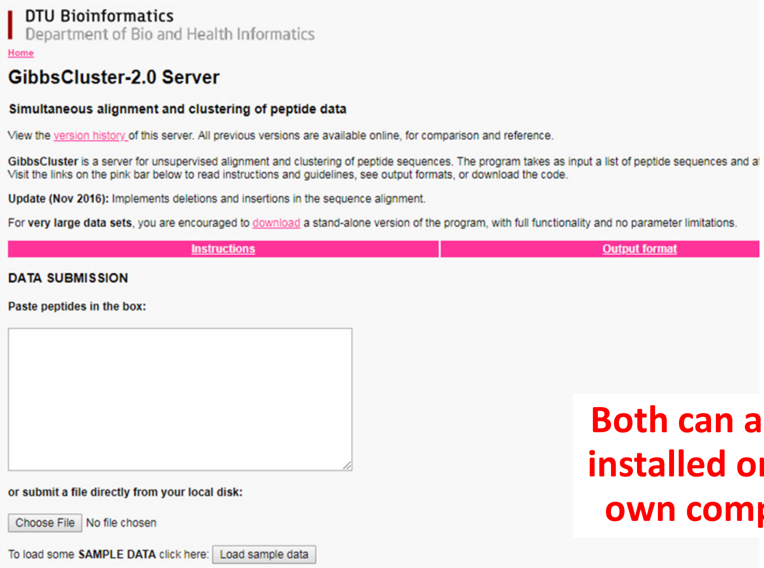
Your DNA, RNA or protein sequences
Motif Discovery
MEME
DREME
MEME-ChIP
GLAM2
Discovered motifs (de novo)
Sequence databases
Mouse-over for information on each software tool or resource. Click to submit a job to the tool or to view database details.
Motif databases
Motif Enrichment
CentriMo
AME
SpaMo
GOMo
Enriched motifs
Motif Scanning
FIMO
MAST
MCAST
GLAM2SCAN
Annotated sequences
Your DNA, RNA or protein motifs
GO databases
Annotated motifs
GO function
GO compartment
GO process
Motif Comparison
Tomtom
Aligned motifs
Motif databases
MEME
Multiple Em for Motif Elicitation
CentriMo
Local Motif Enrichment Analysis
FIMO
Find Individual Motif Occurences
DREME
Discriminative Regular Expression Motif Elicitation
AME
Analysis of Motif Enrichment
MAST
Motif Alignment & Search Tool
MEME-ChIP
Motif Analysis of Large Nucleotide Datasets
SpaMo
Spaced Motif Analysis Tool
MCAST
Motif Cluster Alignment and Search Tool
GLAM2
Gapped Local Alignment of Motifs
GOMo
Gene Ontology for Motifs
GLAM2Scan
Scanning with Gapped Motifs
Tomtom
Motif Comparison Tool
GT-Scan
Identifying Unique Genomic Targets

Note: online MEME suite can sometimes be quite laggy. GibbsCluster is a good alternative for peptide motifs:

http://www.cbs.dtu.dk/services/GibbsCluster/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Home

GibbsCluster-2.0 Server

Simultaneous alignment and clustering of peptide data

View the version history of this server. All previous versions are available online, for comparison and reference.

GibbsCluster is a server for unsupervised alignment and clustering of peptide sequences. The program takes as input a list of peptide sequences and a
Visit the links on the pink bar below to read instructions and guidelines, see output formats, or download the code.

Update (Nov 2016): Implements deletions and insertions in the sequence alignment.

For **very large data sets**, you are encouraged to download a stand-alone version of the program, with full functionality and no parameter limitations.

DATA SUBMISSION

Paste peptides in the box:

or submit a file directly from your local disk:

To load some **SAMPLE DATA** click here:

Both can also be installed on your own computer