CSE 527

Autumn 2006

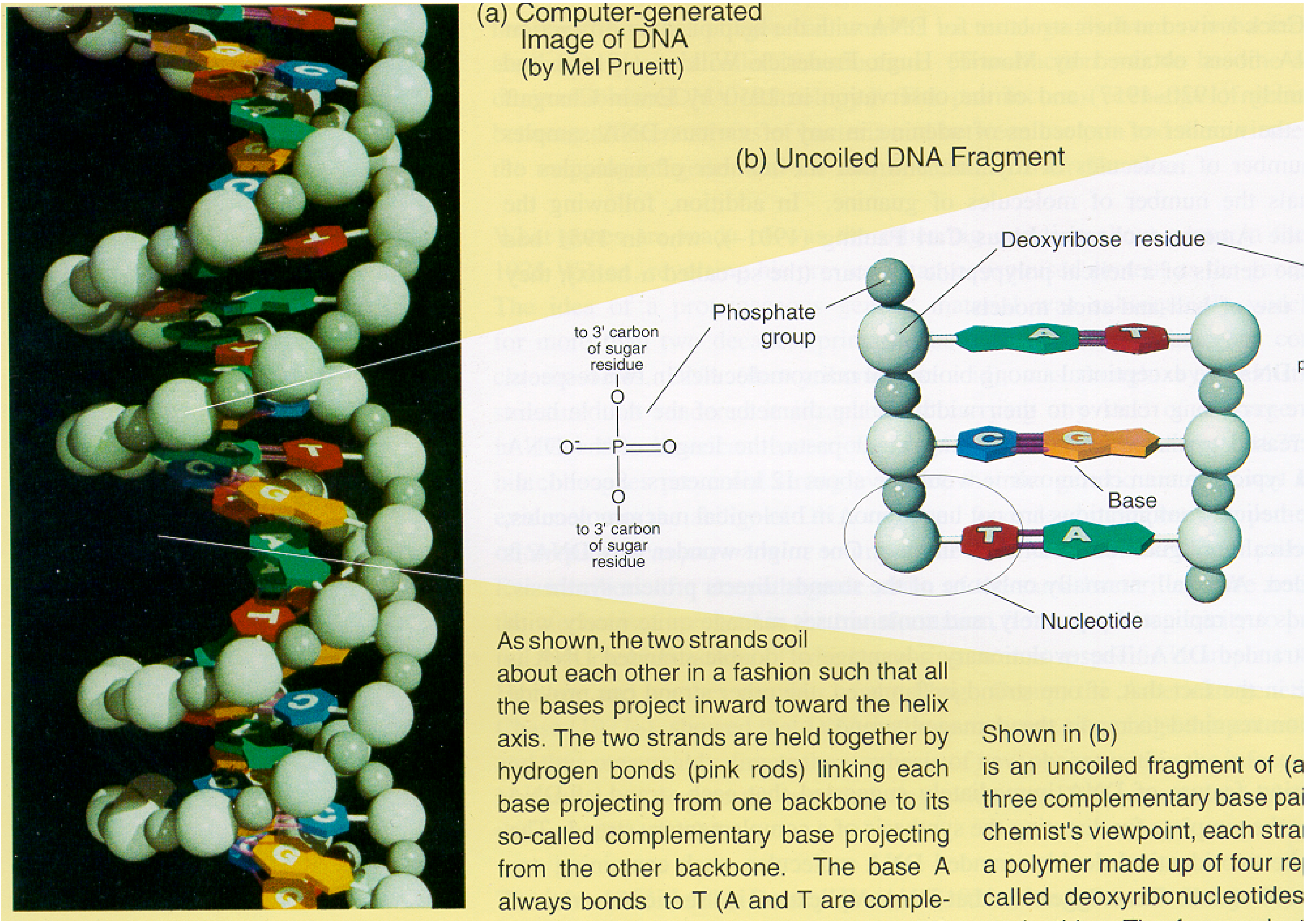
Lectures 8-9 (& part of 10)

Motifs: Representation & Discovery

DNA Binding Proteins

A variety of DNA binding proteins ("transcription factors"; a significant fraction, perhaps 5-10%, of all human proteins) modulate transcription of protein coding genes

The Double Helix



(a) Computer-generated Image of DNA (by Mel Prueitt)

(b) Uncoiled DNA Fragment

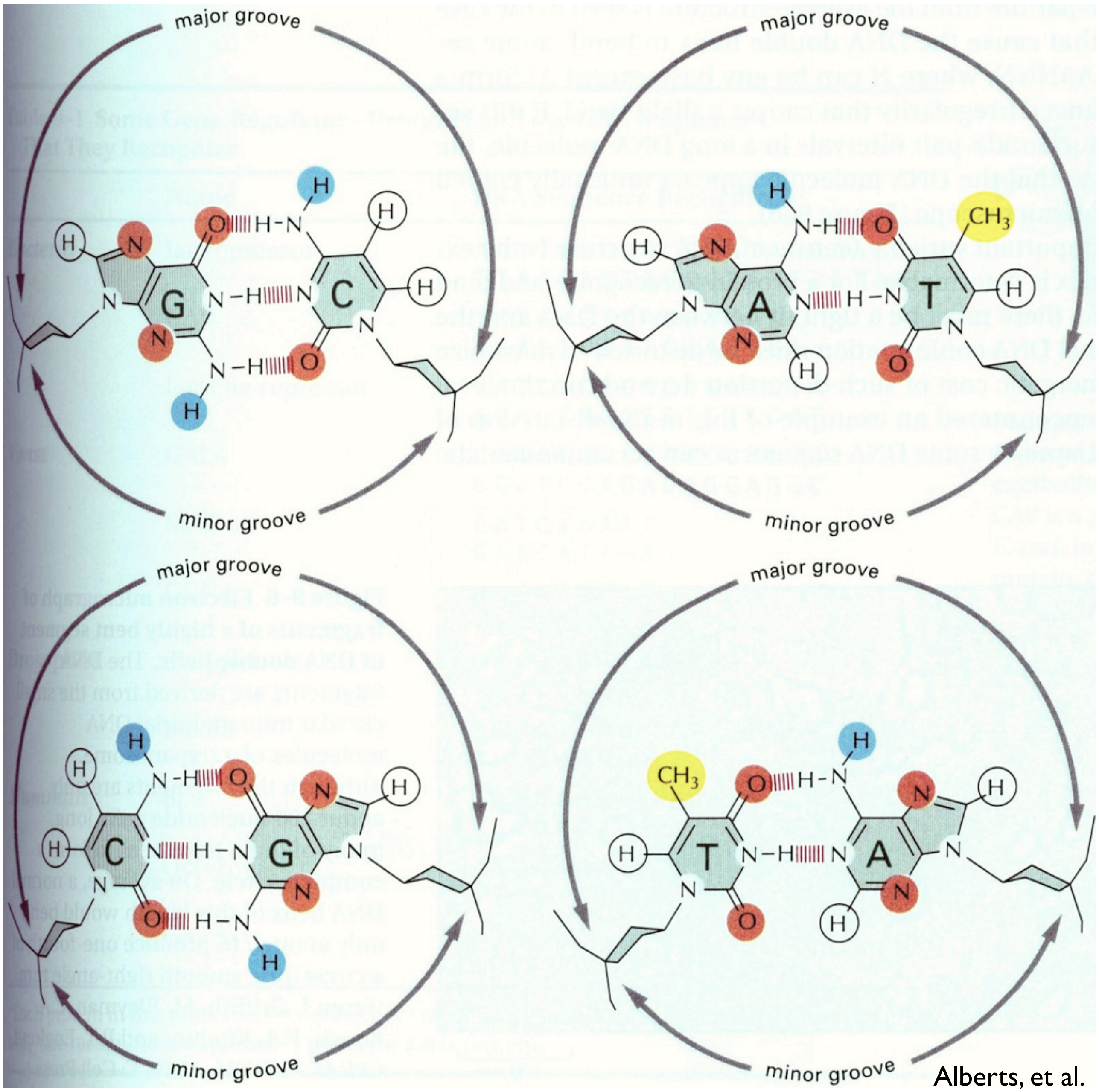
As shown, the two strands coil about each other in a fashion such that all the bases project inward toward the helix axis. The two strands are held together by hydrogen bonds (pink rods) linking each base projecting from one backbone to its so-called complementary base projecting from the other backbone. The base A always bonds to T (A and T are comple-

Shown in (b) is an uncoiled fragment of (a three complementary base pai chemist's viewpoint, each stra a polymer made up of four re called deoxyribonucleotides

Los Alamos Science

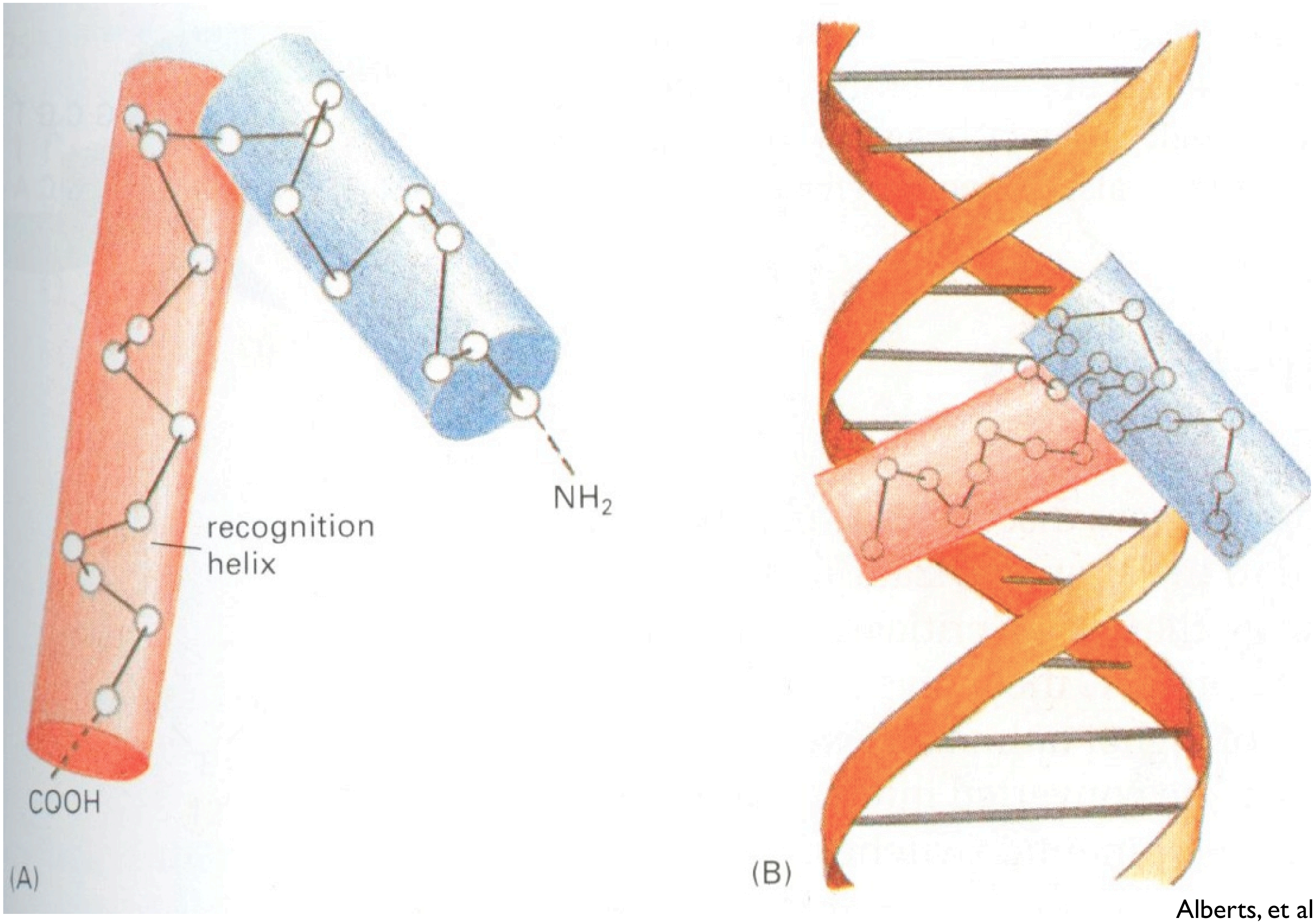
In the groove

Different patterns of potential H bonds at edges of different base pairs, accessible esp. in major groove



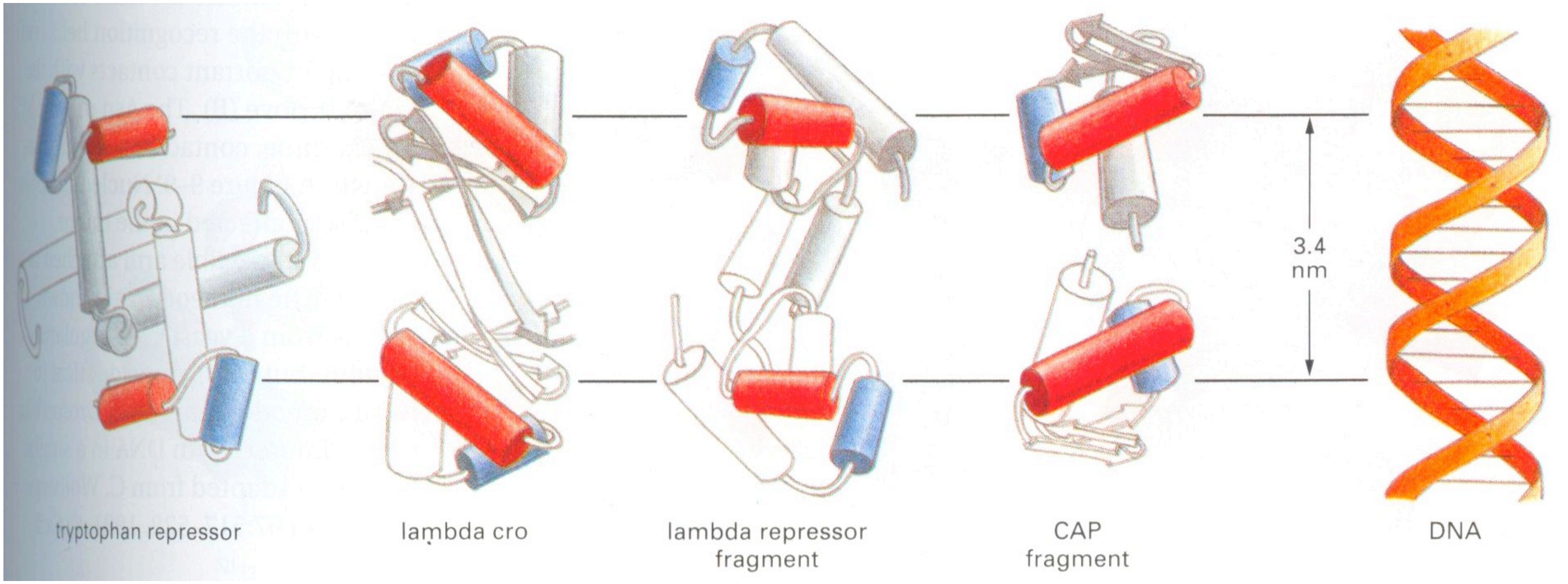
Alberts, et al.

Helix-Turn-Helix DNA Binding Motif



Alberts, et al.

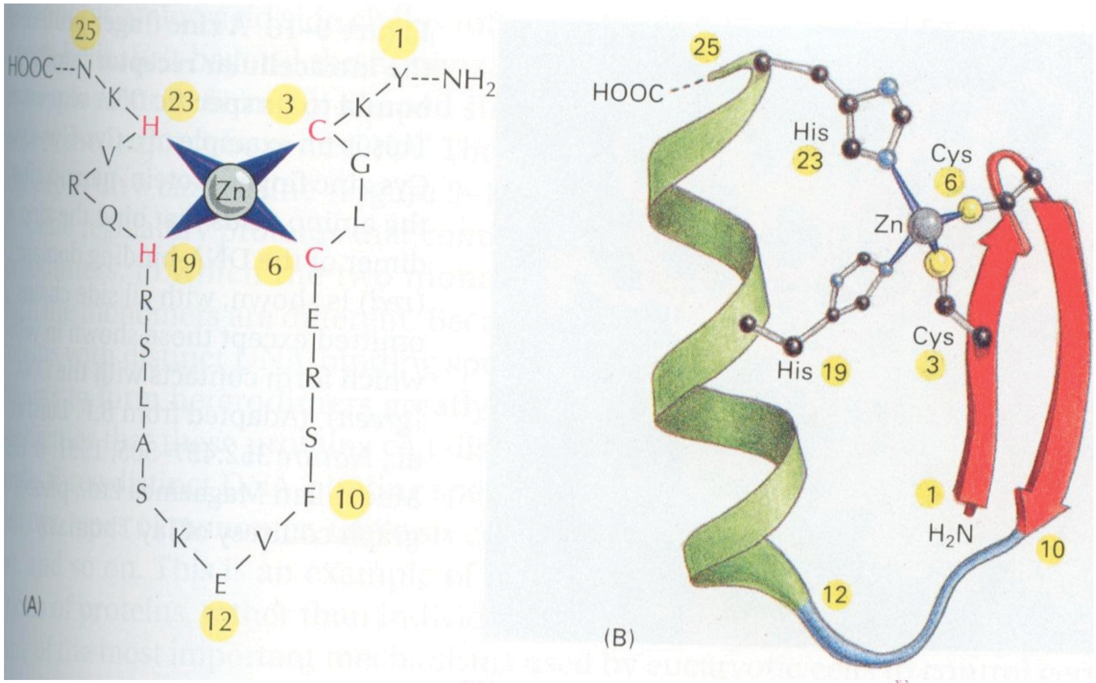
H-T-H Dimers

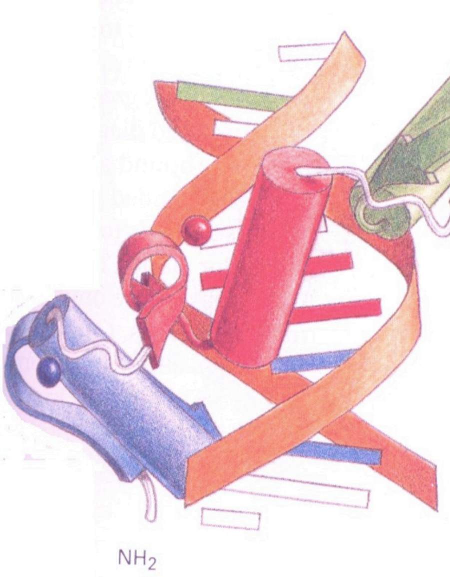


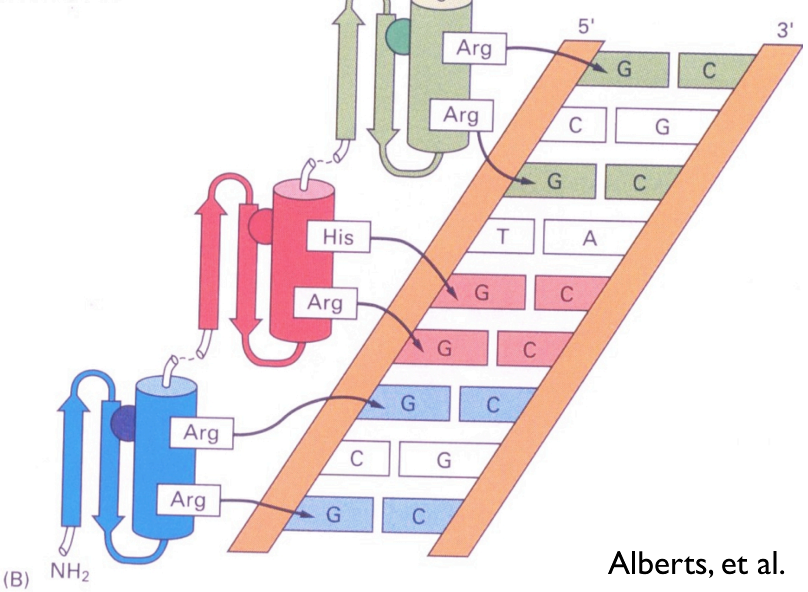
Alberts, et al.

Bind 2 DNA patches, ~ 1 turn apart
Increases both specificity and affinity

Zinc Finger Motif

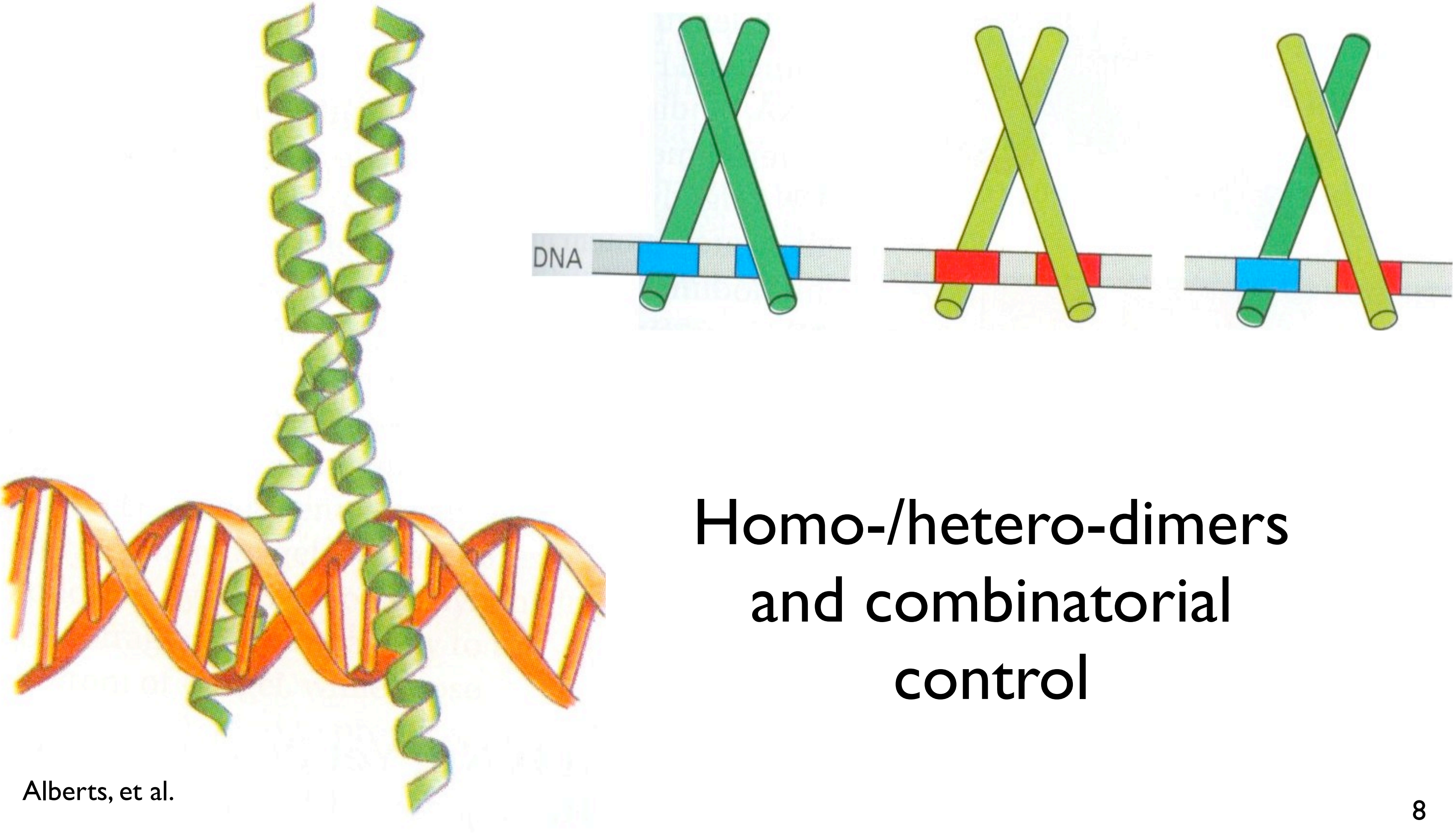






Alberts, et al.

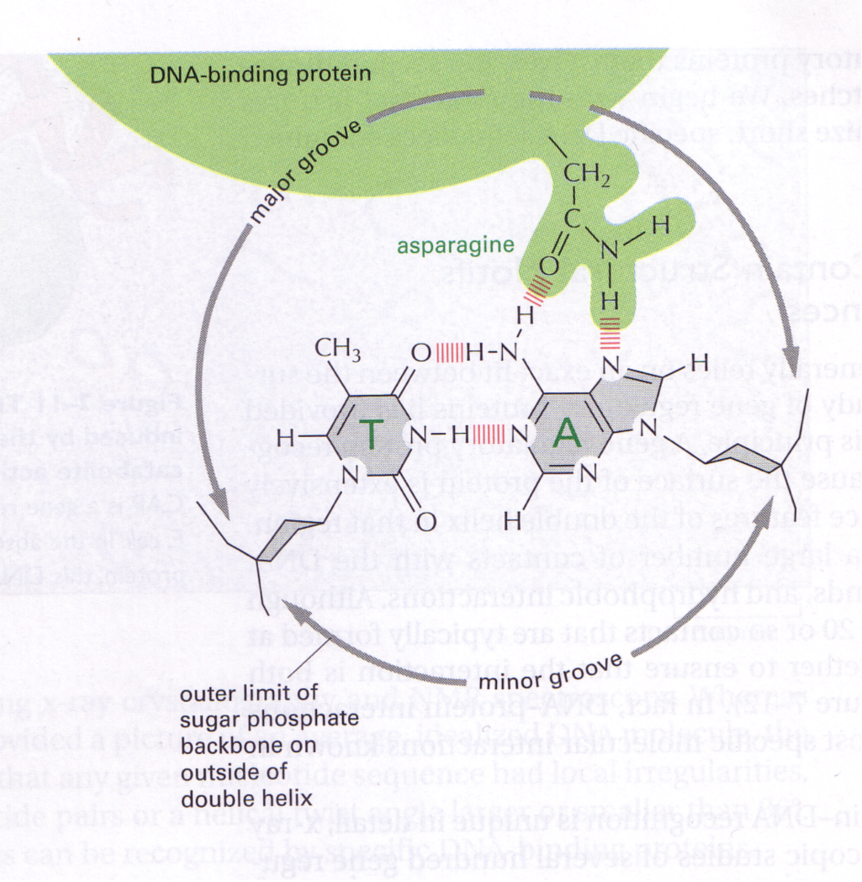
Leucine Zipper Motif

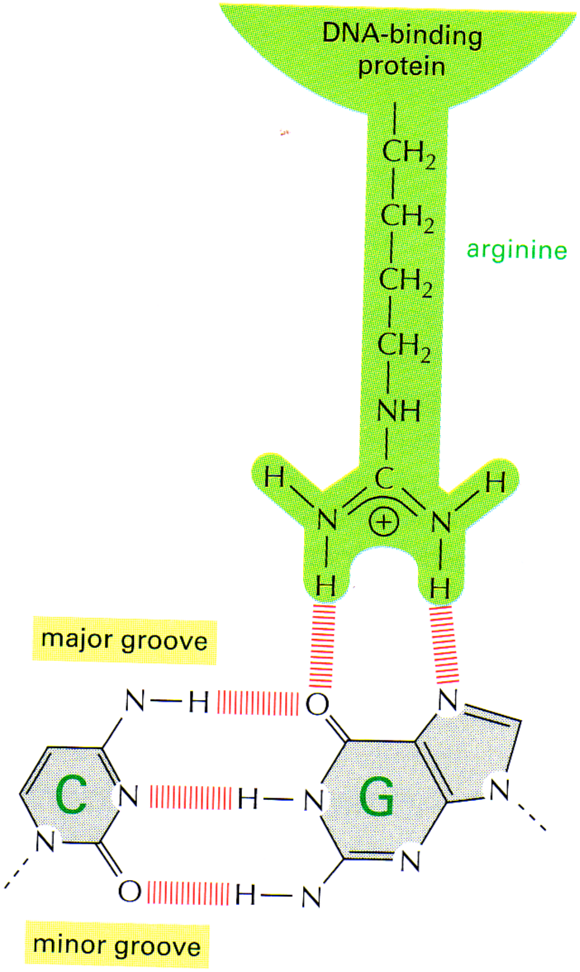


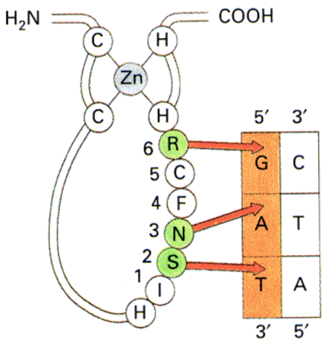
Homo-/hetero-dimers
and combinatorial
control

Alberts, et al.

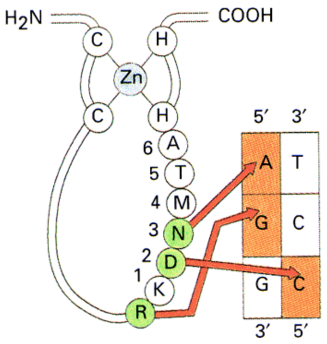
Some Protein/DNA interactions well-understood



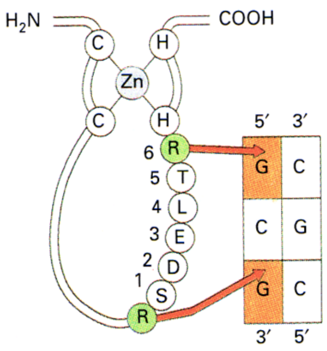




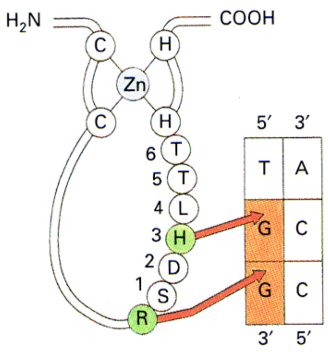
TTK Finger 1



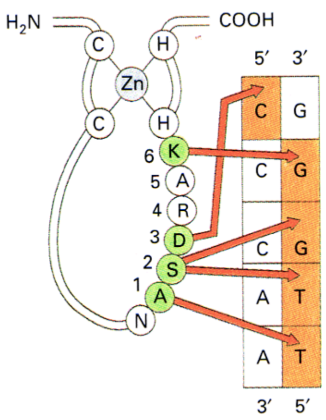
TTK Finger 2



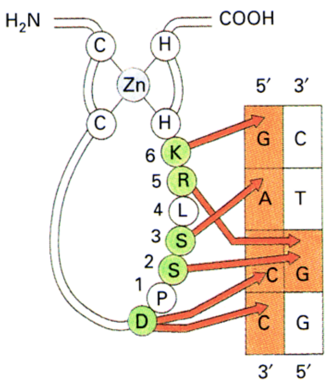
Zif Finger 1



Zif Finger 2

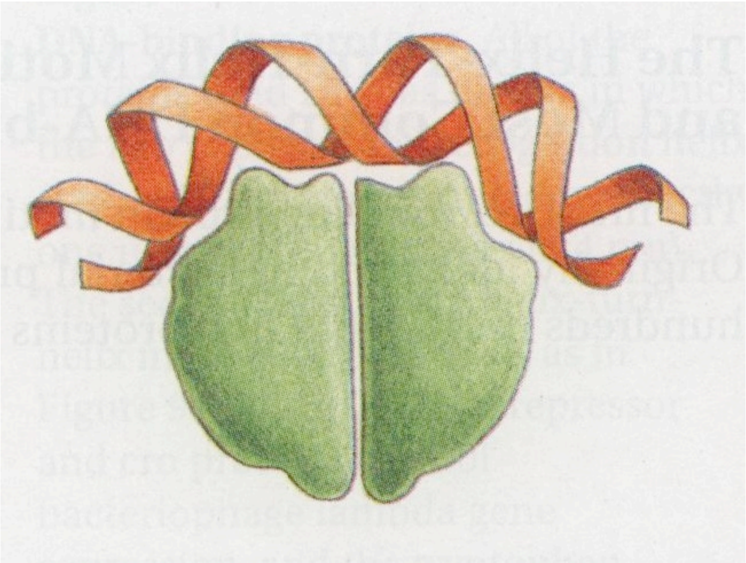


GLI Finger 4



GLI Finger 5

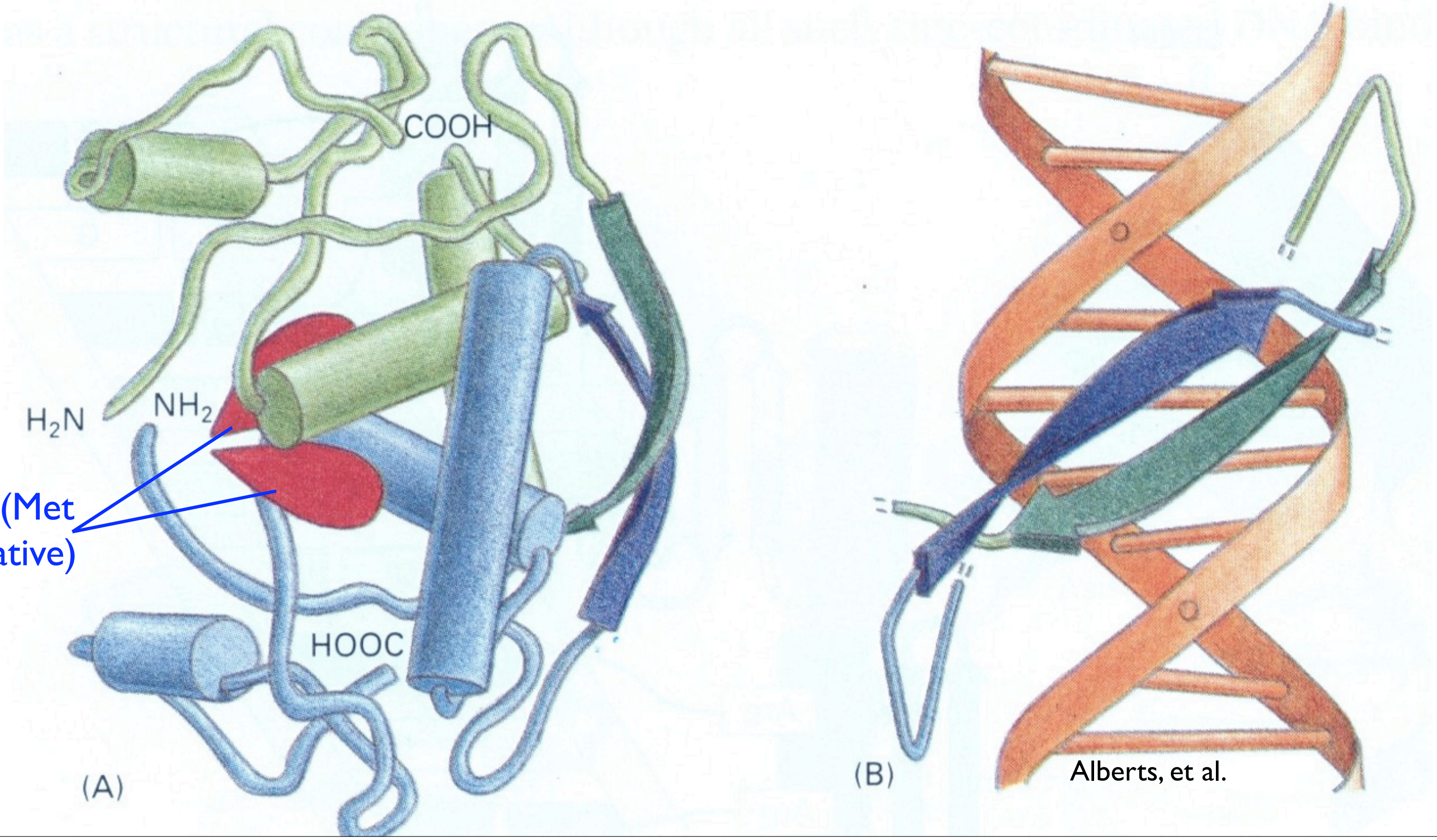
But the overall DNA binding “code” still defies prediction



Bacterial Met Repressor

a beta-sheet DNA binding domain

Negative feedback loop:
high Met level ⇒ repress Met synthesis genes



SAM (Met derivative)

Alberts, et al.

DNA binding site summary

- complex "code"
- short patches (6-8 bp)
- often near each other (1 turn = 10 bp)
- often reverse-complements
- not perfect matches

Sequence Motifs

E. coli Promoters

- "TATA Box" ~ 10bp upstream of transcription start
- How to define it?
  - *Consensus* is TATAAT
  - BUT all differ from it
  - allow k mismatches?
  - equally weighted?
  - wildcards like R,Y? ({A,G}, {C,T}, resp.)

```
TACGAT
TAAAAT
TATACT
GATAAT
TATGAT
TATGTT
```

E. coli Promoters

- "TATA Box" - consensus TATAAT ~ 10bp upstream of transcription start
- *Not* exact: of 168 studied (mid 80's)
  - nearly all had 2/3 of TAxyzT
  - 80-90% had all 3
  - 50% agreed in each of x,y,z
  - no perfect match
- Other common features at -35, etc.

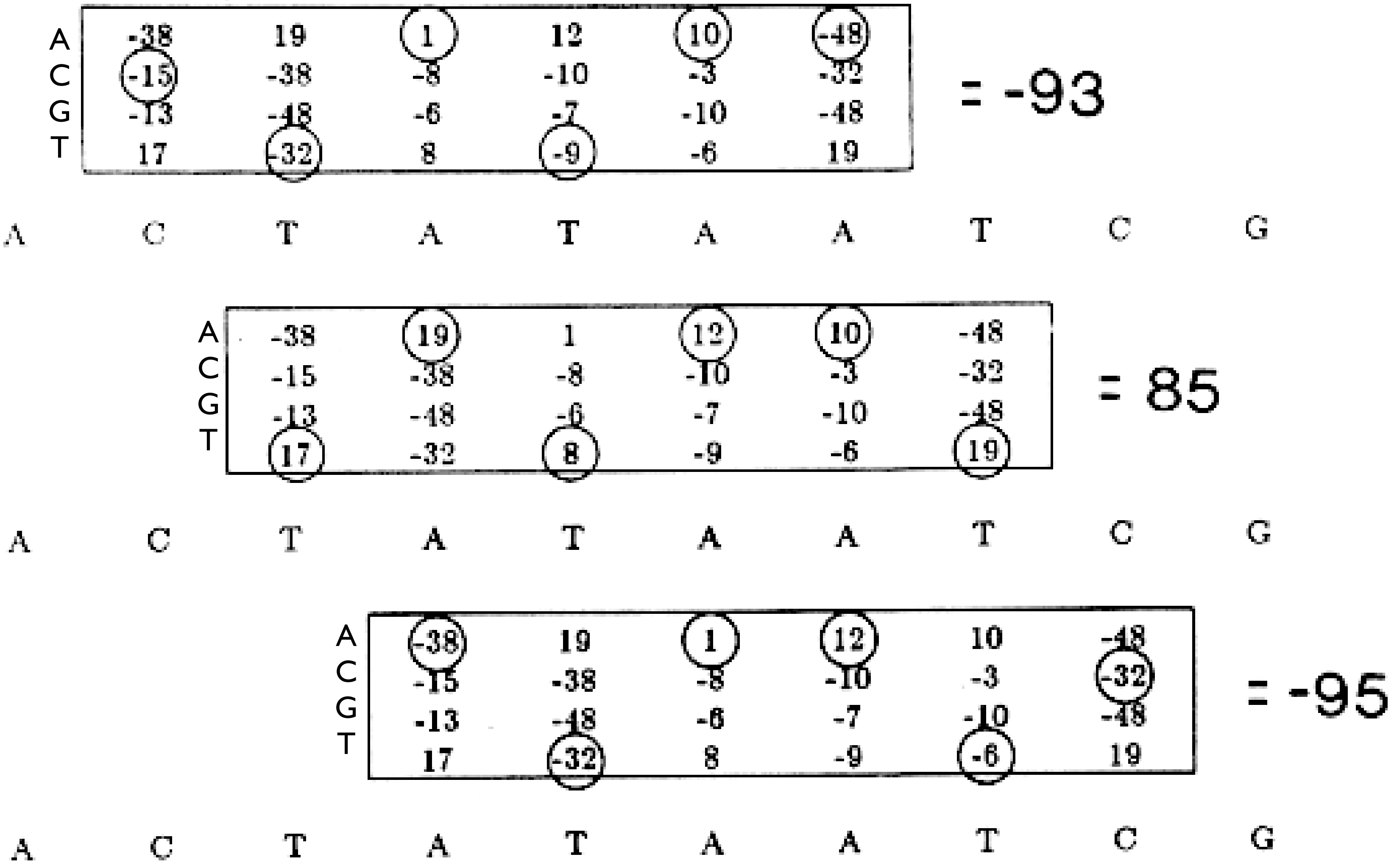
TATA Box Frequencies

pos base	1	2	3	4	5	6
A	2	95	26	59	51	1
C	9	2	14	13	20	3
G	10	1	16	15	13	0
T	79	3	44	13	17	96

TATA Scores

pos base	1	2	3	4	5	6
A	-36	19	1	12	10	-46
C	-15	-36	-8	-9	-3	-31
G	-13	-46	-6	-7	-9	-46(?)
T	17	-31	8	-9	-6	19

Scanning for TATA



A	-38	19	1	12	10	-48
C	-15	-38	-8	-10	-3	-32
G	-13	-48	-6	-7	-10	-48
T	17	-32	8	-9	-6	19

= -93

A C T A T A A T C G

A	-38	19	1	12	10	-48
C	-15	-38	-8	-10	-3	-32
G	-13	-48	-6	-7	-10	-48
T	17	-32	8	-9	-6	19

= 85

A C T A T A A T C G

A	-38	19	1	12	10	-48
C	-15	-38	-8	-10	-3	-32
G	-13	-48	-6	-7	-10	-48
T	17	-32	8	-9	-6	19

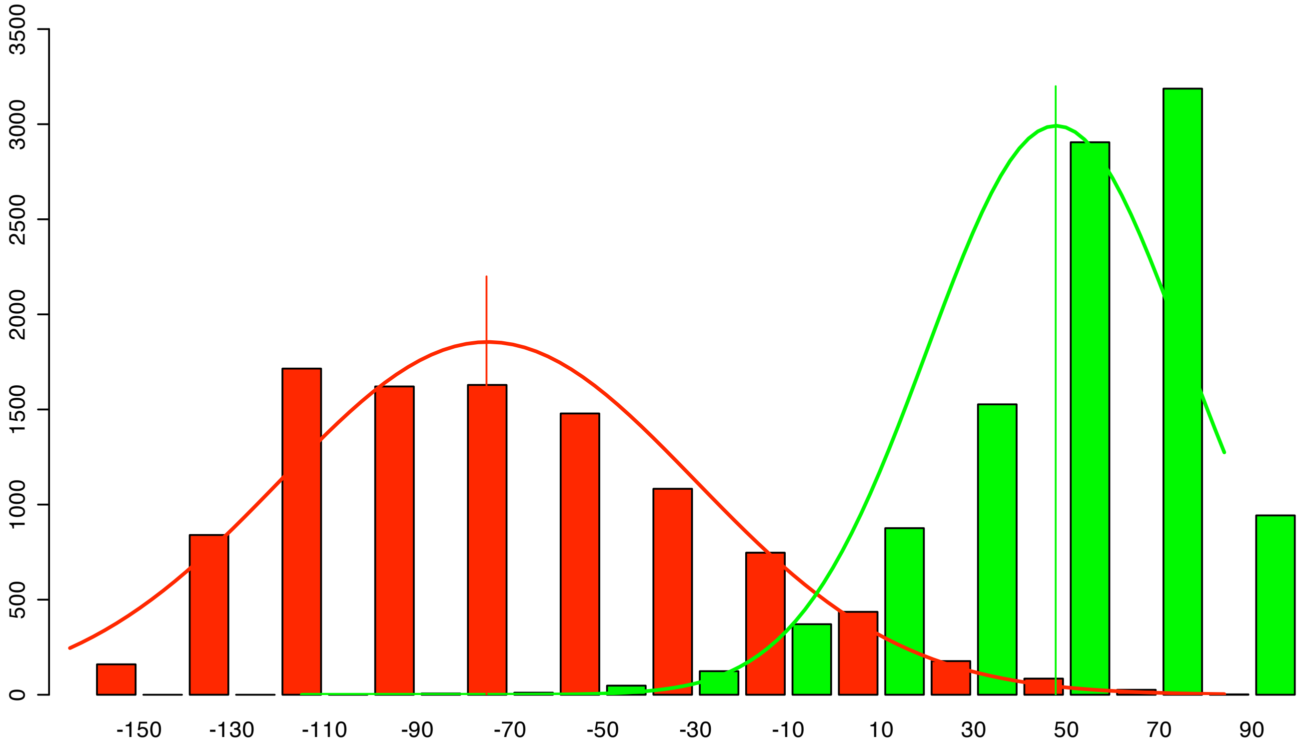
= -95

A C T A T A A T C G

Stormo, Ann. Rev. Biophys. Biophys Chem, 17, 1988, 241-263

Score Distribution

(Simulated)



Weight Matrices: Statistics

- Assume:

  $f_{b,i}$ = frequency of base *b* in position *i in TATA*

  f_b = frequency of base *b* in all sequences

- Log likelihood ratio, given S = $B_1B_2...B_6$:

$$\log\left(\frac{P(S|\text{“tata”})}{P(S|\text{“non-tata”})}\right) = \log\frac{\prod_{i=1}^{6} f_{B_i,i}}{\prod_{i=1}^{6} f_{B_i}} = \sum_{i=1}^{6}\log\frac{f_{B_i,i}}{f_{B_i}}$$

Assumes *independence*

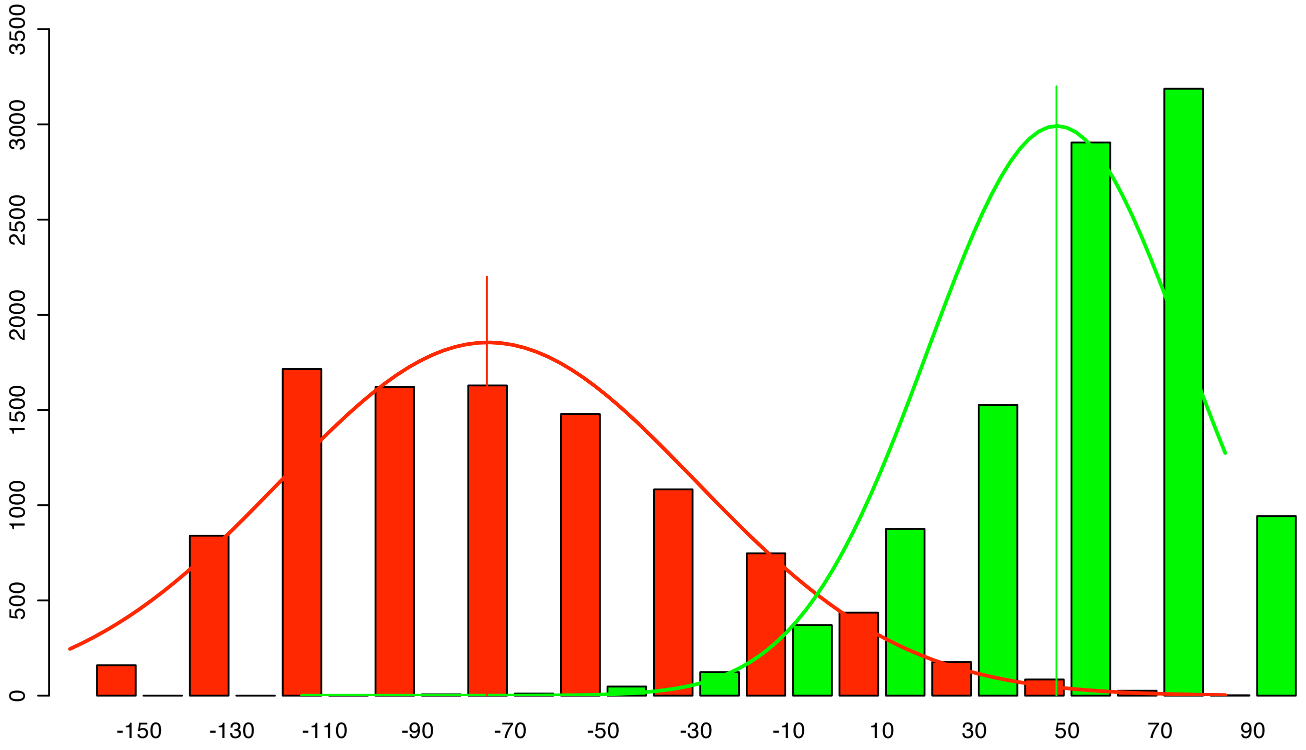
Neyman-Pearson

- Given a sample $x_1, x_2, ..., x_n$, from a distribution $f(...|\Theta)$ with parameter Θ, want to test hypothesis $\Theta = \theta_1$ vs $\Theta = \theta_2$.
- Might as well look at *likelihood ratio:*

$$\frac{f(x_1, x_2, ..., x_n|\theta_1)}{f(x_1, x_2, ..., x_n|\theta_2)} > \tau$$

(or *log likelihood difference*)

Score Distribution (Simulated)



What's best WMM?

- Given 20 sequences $s_1, s_2, ..., s_k$ of length 8, assumed to be generated at random according to a WMM defined by 8 x (4-1) parameters θ, what's the best θ?
- E.g., what's MLE for θ given data $s_1, s_2, ..., s_k$?
- Answer: count frequencies per position.

Weight Matrices: Chemistry

- Experiments show ~80% correlation of log likelihood weight matrix scores to measured binding energy of RNA polymerase to variations on TATAAT consensus
[Stormo & Fields]

Another WMM example

8 Sequences:

ATG
ATG
ATG
ATG
ATG
GTG
GTG
TTG

Freq.	Col 1	Col 2	Col3
A	.625	0	0
C	0	0	0
G	.250	0	1
T	.125	1	0

LLR	Col 1	Col 2	Col 3
A	1.32	$-\infty$	$-\infty$
C	$-\infty$	$-\infty$	$-\infty$
G	0	$-\infty$	2.00
T	-1.00	2.00	$-\infty$

Log-Likelihood Ratio:

$$\log_2 \frac{f_{x_i,i}}{f_{x_i}}, \; f_{x_i} = \frac{1}{4}$$

Non-uniform Background

- *E. coli* - DNA approximately 25% A, C, G, T
- *M. jannaschi* - 68% A-T, 32% G-C

LLR from previous example, assuming

$$f_A = f_T = 3/8$$
$$f_C = f_G = 1/8$$

LLR	Col 1	Col 2	Col 3
A	.74	-∞	-∞
C	-∞	-∞	-∞
G	1.00	-∞	3.00
T	-1.58	1.42	-∞

e.g., G in col 3 is 8 x more likely via WMM than background, so ($\log_2$) score = 3 (bits).

Relative Entropy

- AKA Kullback-Liebler Distance/Divergence, AKA Information Content
- Given distributions P, Q

$$H(P||Q) = \sum_{x \in \Omega} P(x) \log \frac{P(x)}{Q(x)} \quad \geq 0$$

Notes:

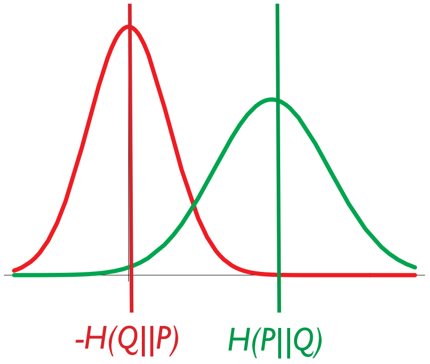
$$\text{Let } P(x) \log \frac{P(x)}{Q(x)} = 0 \text{ if } P(x) = 0 \text{ [since } \lim_{y \to 0} y \log y = 0]$$

$$\text{Undefined if } 0 = Q(x) < P(x)$$

WMM: How "Informative"? Mean score of site vs bkg?

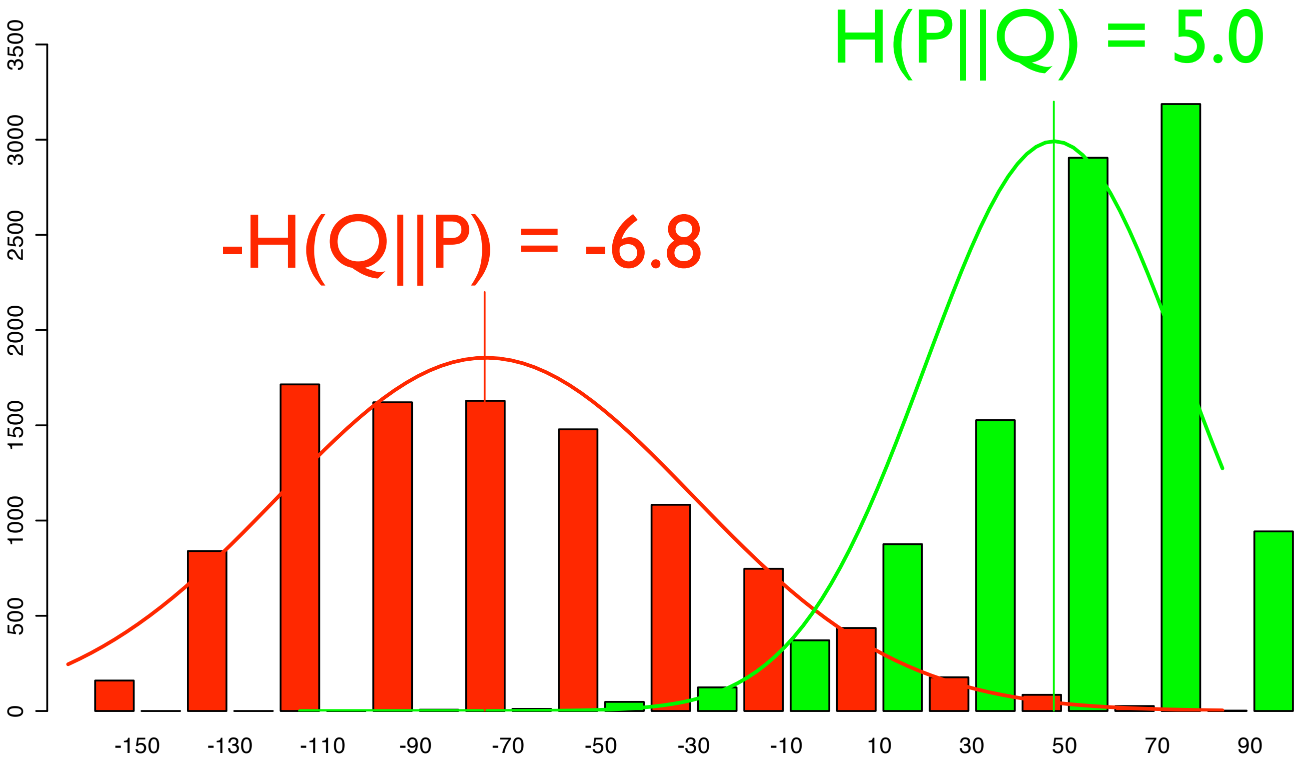
- For any fixed length sequence *x*, let
  P(x) = Prob. of *x* according to WMM
  Q(x) = Prob. of *x* according to background
- Relative Entropy:

$$H(P||Q) = \sum_{x \in \Omega} P(x) \log_2 \frac{P(x)}{Q(x)}$$



- *H(P||Q)* is *expected log likelihood score* of a sequence randomly chosen from *WMM*; *-H(Q||P)* is expected score of *Background*

WMM Scores vs Relative Entropy



For WMM, you can show (based on the assumption of independence between columns), that :

$$H(P||Q) \quad = \quad \sum_i H(P_i||Q_i)$$

where P_i and Q_i are the WMM/background distributions for column i.

WMM Example, cont.

Freq.	Col 1	Col 2	Col3
A	.625	0	0
C	0	0	0
G	.250	0	1
T	.125	1	0

Uniform

LLR	Col 1	Col 2	Col 3	
A	1.32	-∞	-∞	
C	-∞	-∞	-∞	
G	0	-∞	2.00	
T	-1.00	2.00	-∞	
RelEnt	.70	2.00	2.00	4.70

Non-uniform

LLR	Col 1	Col 2	Col 3	
A	.74	-∞	-∞	
C	-∞	-∞	-∞	
G	1.00	-∞	3.00	
T	-1.58	1.42	-∞	
RelEnt	.51	1.42	3.00	4.93

Pseudocounts

- Are the $-\infty$'s a problem?
  - Certain that a given residue *never* occurs in a given position? Then $-\infty$ just right
  - Else, it may be a small-sample artifact
- Typical fix: add a *pseudocount* to each observed count—small constant (e.g., .5, 1)
- Sounds *ad hoc*; there is a Bayesian justification

WMM Summary

- Weight Matrix Model (aka Position Specific Scoring Matrix, PSSM, "possum", 0th order Markov models)
- Simple statistical model assuming independence between adjacent positions
- To build: count (+ pseudocount) letter frequency per position, log likelihood ratio to background
- To scan: add LLRs per position, compare to threshold
- Generalizations to higher order models (i.e., letter frequency per position, conditional on neighbor) also possible, with enough training data

How-to Questions

- Given aligned motif instances, build model?
  - Frequency counts (above, maybe with pseudocounts)
- Given a model, find (probable) instances
  - Scanning, as above
- Given unaligned strings thought to contain a motif, find it? (e.g., upstream regions for co-expressed genes from a microarray experiment)
  - Hard... rest of lecture.

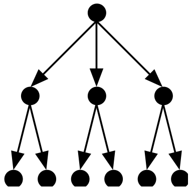
Motif Discovery

Unfortunately, finding a site of max relative entropy in a set of unaligned sequences is NP-hard [Akutsu]

Motif Discovery: 4 example approaches

- Brute Force
- Greedy search
- Expectation Maximization
- Gibbs sampler

Brute Force



Input:

- Sequences $s_1, s_2, ..., s_k$ (length ~n, say); motif length l

Algorithm:

- create singleton set with each length l subsequence of each $s_1, s_2, ..., s_k$ (~nk sets)
- for each set, add each possible length l subsequence not already present (~$n^2k(k-1)$ sets)
- repeat until all have k sequences (~$n^kk!$ sets)
- compute relative entropy of each; pick best

problem: astronomically sloooow

Greedy Best-First Approach

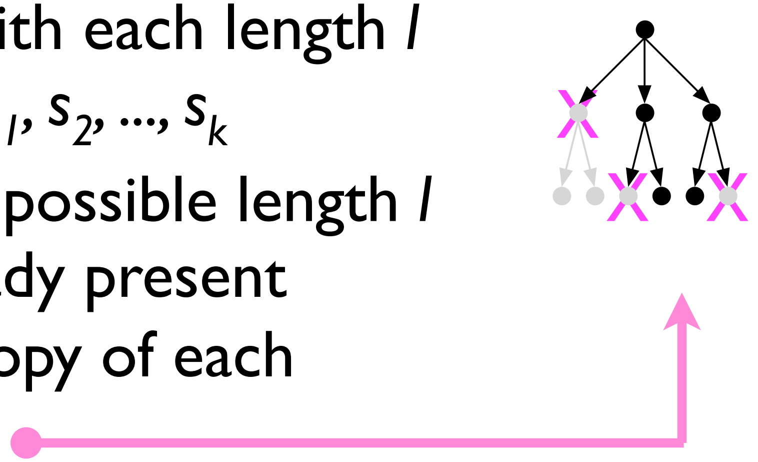
[Hertz & Stormo]

Input:

- Sequence $s_1, s_2, ..., s_k$; motif length l; "breadth" d

Algorithm:

- create singleton set with each length l subsequence of each $s_1, s_2, ..., s_k$
- for each set, add each possible length l subsequence not already present
- compute relative entropy of each
- discard all but d best
- repeat until all have k sequences



usual "greedy" problems

Expectation Maximization

[MEME, Bailey & Elkan, 1995]

Input (as above):

- Sequence $s_1, s_2, ..., s_k$; motif length l; background model; again assume one instance per sequence (variants possible)

Algorithm: EM

- Visible data: the sequences
- Hidden data: where's the motif

$$Y_{i,j} = \begin{cases} 1 & \text{if motif in sequence } i \text{ begins at position } j \\ 0 & \text{otherwise} \end{cases}$$

- Parameters θ: The WMM

MEME Outline

Typical EM algorithm:

- Parameters θ^t at t^{th} iteration, used to estimate where the motif instances are (the hidden variables)
- Use those estimates to re-estimate the parameters θ to maximize likelihood of observed data, giving θ^{t+1}
- Repeat

Key: given a few good matches to best motif, expect to pick out more

Expectation Step

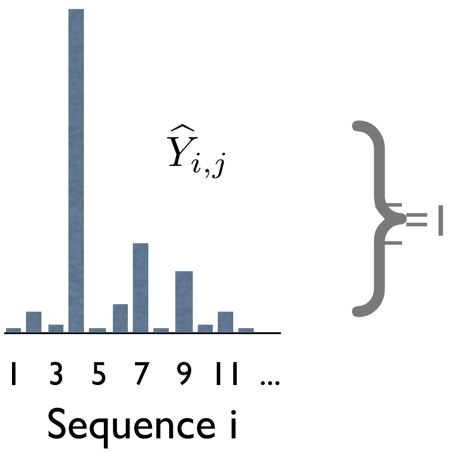
(where are the motif instances?)

$$
\begin{aligned}
\widehat{Y}_{i,j} &= E(Y_{i,j} \mid s_i, \theta^t) \\
&= P(Y_{i,j} = 1 \mid s_i, \theta^t) \\
&= P(s_i \mid Y_{i,j} = 1, \theta^t)\,\frac{P(Y_{i,j}=1|\theta^t)}{P(s_i|\theta^t)} \\
&= cP(s_i \mid Y_{i,j} = 1, \theta^t) \\
&= c' \prod_{k=1}^{l} P(s_{i,j+k-1} \mid \theta^t)
\end{aligned}
$$

$E = 0 \cdot P(0) + 1 \cdot P(1)$

Bayes

where c' is chosen so that $\sum_j \widehat{Y}_{i,j} = 1$.



Maximization Step

(what is the motif?)

Find θ maximizing expected value:

$$
\begin{aligned}
Q(\theta \mid \theta^t) &= E_{Y\sim\theta^t}[\log P(s, Y \mid \theta)] \\
&= E_{Y\sim\theta^t}[\log \textstyle\prod_{i=1}^k P(s_i, Y_i \mid \theta)] \\
&= E_{Y\sim\theta^t}[\textstyle\sum_{i=1}^k \log P(s_i, Y_i \mid \theta)] \\
&= E_{Y\sim\theta^t}[\textstyle\sum_{i=1}^k \sum_{j=1}^{|s_i|-l+1} Y_{i,j} \log P(s_i, Y_{i,j} = 1 \mid \theta)] \\
&= E_{Y\sim\theta^t}[\textstyle\sum_{i=1}^k \sum_{j=1}^{|s_i|-l+1} Y_{i,j} \log(P(s_i \mid Y_{i,j} = 1, \theta) P(Y_{i,j} = 1 \mid \theta))] \\
&= \textstyle\sum_{i=1}^k \sum_{j=1}^{|s_i|-l+1} E_{Y\sim\theta^t}[Y_{i,j}] \log P(s_i \mid Y_{i,j} = 1, \theta) + C \\
&= \textstyle\sum_{i=1}^k \sum_{j=1}^{|s_i|-l+1} \widehat{Y}_{i,j} \log P(s_i \mid Y_{i,j} = 1, \theta) + C
\end{aligned}
$$

M-Step (cont.)

$$Q(\theta \mid \theta^t) \quad = \quad \textstyle\sum_{i=1}^{k} \sum_{j=1}^{|s_i|-l+1} \widehat{Y}_{i,j} \log P(s_i \mid Y_{i,j} = 1, \theta) + C$$

Exercise: Show this is maximized by "counting" letter frequencies over all possible motif instances, with counts weighted by $\widehat{Y}_{i,j}$, again the "obvious" thing.

s_1 : ACGGATT...

...

s_k : GC...TCGGAC

$\widehat{Y}_{1,1}$	ACGG
$\widehat{Y}_{1,2}$	CGGA
$\widehat{Y}_{1,3}$	GGAT
$\vdots$	$\vdots$
$\widehat{Y}_{k,l-1}$	CGGA
$\widehat{Y}_{k,l}$	GGAC

Initialization

1. Try *every* motif-length substring, and use as initial θ a WMM with, say 80% of weight on that sequence, rest uniform
2. Run a few iterations of each
3. Run best few to convergence

(Having a supercomputer helps)

Another Motif Discovery Approach

The Gibbs Sampler

Lawrence, *et al.* "Detecting Subtle Sequence Signals: A Gibbs Sampling Strategy for Multiple Sequence Alignment," *Science* 1993

Sigma-37	223	IIDLTYIQNK	SQKETGDILGISQMHVSR	LQRKAVKKLR	240	A25944	
SpoIIIC	94	RFGLDLKKEK	TQREIAKELGISRSYVSR	IEKRALMKMF	111	A28627	
NahR	22	VVFNQLLVDR	RVSITAENLGLTQPAVSN	ALKRLRTSLQ	39	A32837	
Antennapedia	326	FHFNRYLTRR	RRIEIAHALCLTERQIKI	WFQNRRMKWK	343	A23450	
NtrC (Brady.)	449	LTAALAATRG	NQIRAADLLGLNRNTLRK	KIRDLDIQVY	466	B26499	
DicA	22	IRYRRKNLKH	TQRSLAKALKISHVSVSQ	WERGDSEPTG	39	B24328	(BVECDA)
MerD	5	MNAY	TVSRLALDAGVSVHIVRD	YLLRGLLRPV	22	C29010	
Fis	73	LDMVMQYTRG	NQTRAALMMGINRGTLRK	KLKKYGMN	90	A32142	(DNECFS)
MAT a1	99	FRRKQSLNSK	EKEEVAKKCGITPLQVRV	WFINKRMRSK	116	A90983	(JEBY1)
Lambda cII	25	SALLNKIAML	GTEKTAEAVGVDKSQISR	WKRDWIPKFS	42	A03579	(QCBP2L)
Crp (CAP)	169	THPDGMQIKI	TRQEIGQIVGCSRETVGR	ILKMLEDQNL	186	A03553	(QRECC)
Lambda Cro	15	ITLKDYAMRF	GQTKTAKDLGVYQSAINK	AIHAGRKIFL	32	A03577	(RCBPL)
P22 Cro	12	YKKDVIDHFG	TQRAVAKALGISDAAVSQ	WKEVIPEKDA	29	A25867	(RGBP22)
AraC	196	ISDHLADSNF	DIASVAQHVCLSPSRLSH	LFRQQLGISV	213	A03554	(RGECA)
Fnr	196	FSPREFRLTM	TRGDIGNYLGLTVETISR	LLGRFQKSGM	213	A03552	(RGECF)
HtpR	252	ARWLDEDNKS	TLQELADRYGVSAERVRQ	LEKNAMKKLR	269	A00700	(RGECH)
NtrC (K.a.)	444	LTTALRHTQG	HKQEAARLLGWGRNTLTR	KLKELGME	461	A03564	(RGKBCP)
CytR	11	MKAKKQETAA	TMKDVALKAKVSTATVSR	ALMNPDKVSQ	28	A24963	(RPECCT)
DeoR	23	LQELKRSDKL	HLKDAAALLGVSEMTIRR	DLNNHSAPVV	40	A24076	(RPECDO)
GalR	3	MA	TIKDVARLAGVSVATVSR	VINNSPKASE	20	A03559	(RPECG)
LacI	5	MKPV	TLYDVAEYAGVSYQTVSR	VVNQASHVSA	22	A03558	(RPECL)
TetR	26	LLNEVGIEGL	TTRKLAQKLGVEQPTLYW	HVKNKRALLD	43	A03576	(RPECTN)
TrpR	67	IVEELLRGEM	SQRELKNELGAGIATITR	GSNSLKAAPV	84	A03568	(RPECW)
NifA	495	LIAALEKAGW	VQAKAARLLGMTPRQVAY	RIQIMDITMP	512	S02513	
SpoIIG	205	RFGLVGEEEK	TQKDVADMMGISQSYISR	LEKRIIKRLR	222	S07337	
Pin	160	QAGRLIAAGT	PRQKVAIIYDVGVSTLYK	TFPAGDK	177	S07958	
PurR	3	MA	TIKDVAKRANVSTTTVSH	VINKTRFVAE	20	S08477	
EbgR	3	MA	TLKDIAIEAGVSLATVSR	VLNDDPTLNV	20	S09205	
LexA	27	DHISQTGMPP	TRAEIAQRLGFRSPNAAE	EHLKALARKG	44	S11945	
P22 cI	25	SSILNRIAIR	GQRKVADALGINESQISR	WKGDFIPKMG	42	B25867	(Z1BPC2)
			*****************	***			

B

	Position in site																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Arg	94	222	265	137	9	9	137	137	9	9	9	52	222	94	94	9	265	606
Lys	9	133	442	380	9	71	380	194	9	133	9	9	71	9	9	9	71	256
Glu	53	9	96	401	9	9	140	140	9	9	9	53	140	140	9	9	9	53
Asp	67	9	9	473	9	9	299	125	9	67	9	67	67	9	9	9	9	67
Gln	9	600	224	9	9	9	224	9	9	9	9	9	278	63	278	9	9	170
His	240	9	9	9	9	9	125	125	9	9	9	9	125	125	125	9	9	240
Asn	168	9	9	9	9	9	168	89	9	89	9	248	9	168	89	9	89	89
Ser	117	9	117	117	9	9	9	9	9	9	9	819	63	387	63	9	819	9
Gly	151	9	56	9	9	151	9	9	9	1141	9	151	9	56	9	9	56	9
Ala	9	9	112	43	181	901	43	181	215	9	43	9	43	181	112	43	78	9
Thr	915	130	130	9	251	9	9	9	9	9	9	311	130	70	855	9	130	9
Pro	76	9	9	9	9	9	9	9	9	9	9	9	210	210	9	9	9	9
Cys	9	9	9	9	9	9	9	9	295	581	295	9	9	9	9	9	9	9
Val	58	107	9	9	500	9	9	9	156	9	598	9	205	58	9	746	9	58
Leu	9	121	9	9	149	9	93	149	458	9	149	9	37	37	9	177	9	9
Ile	9	166	114	61	323	9	114	166	9	9	427	9	61	9	61	427	9	61
Met	9	104	9	9	9	9	9	198	198	9	104	9	9	198	9	9	9	9
Tyr	9	9	136	9	9	9	9	262	262	9	9	136	136	9	262	9	262	136
Phe	9	9	9	9	9	9	9	9	9	9	108	9	9	9	9	9	9	9
Trp	9	9	9	9	9	9	9	9	9	9	366	9	9	9	9	9	9	366

Some History

- Geman & Geman, IEEE PAMI 1984
- Hastings, Biometrika, 1970
- Metropolis, Rosenbluth, Rosenbluth, Teller, & Teller, "Equations of State Calculations by Fast Computing Machines," J. Chem. Phys. 1953
- Josiah Williard Gibbs, 1839-1903, American physicist, a pioneer of thermodynamics

How to Average

An old problem:

- n random variables: $x_1, x_2, \ldots, x_k$
- Joint distribution (p.d.f.): $P(x_1, x_2, \ldots, x_k)$
- Some function: $f(x_1, x_2, \ldots, x_k)$
- <u>Want</u> Expected Value: $E(f(x_1, x_2, \ldots, x_k))$

How to Average

$$E(f(x_1, x_2, \ldots, x_k)) \quad = \\ \int_{x_1} \int_{x_2} \cdots \int_{x_k} f(x_1, x_2, \ldots, x_k) \cdot P(x_1, x_2, \ldots, x_k) dx_1 dx_2 \ldots dx_k$$

- Approach 1: direct integration
  (rarely solvable analytically, esp. in high dim)
- Approach 2: numerical integration
  (often difficult, e.g., unstable, esp. in high dim)
- Approach 3: Monte Carlo integration
  sample $\vec{x}^{(1)}, \vec{x}^{(2)}, \ldots \vec{x}^{(n)} \sim P(\vec{x})$ and average:
  $E(f(\vec{x})) \approx \frac{1}{n} \sum_{i=1}^{n} f(\vec{x}^{(i)})$

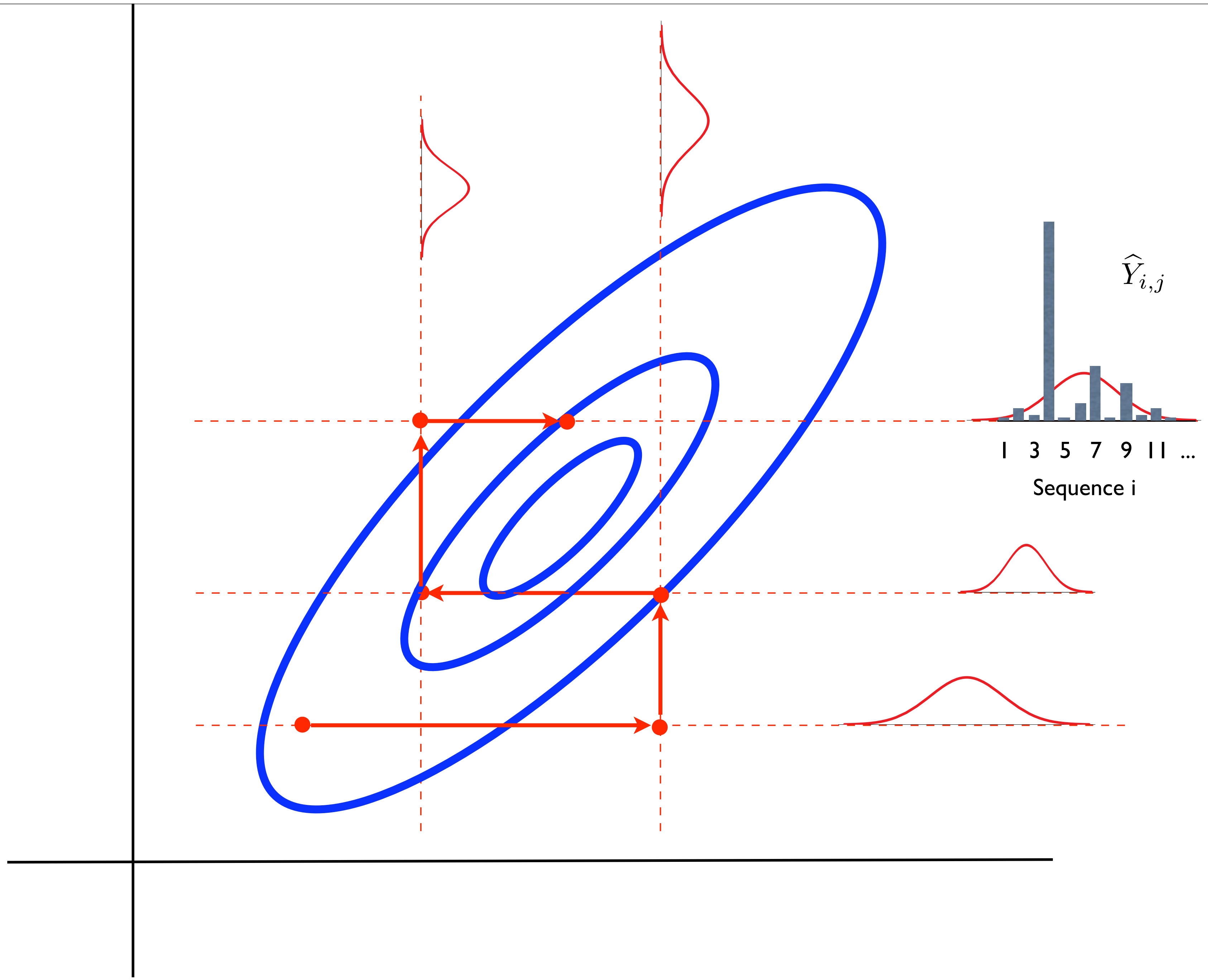
Markov Chain Monte Carlo (MCMC)

- *Independent* sampling also often hard, but *not required* for expectation
- MCMC $\vec{X}_{t+1} \sim P(\vec{X}_{t+1} \mid \vec{X}_t)$ w/ stationary dist = *P*
- Simplest & most common: Gibbs Sampling

$$P(x_i \mid x_1, x_2, \ldots, x_{i-1}, x_{i+1}, \ldots, x_k)$$

- Algorithm

```
for t = 1 to ∞
  for i = 1 to k do :
$x_{t+1,i} \sim P(x_{t+1,i} \mid \overset{t+1}{\underline{x_{t+1,1}, x_{t+1,2}, \ldots, x_{t+1}}}{}_{,i-1}, \overset{t}{\underline{x_{t,i+1}, \ldots, x_{t,k}}})$
```


$\widehat{Y}_{i,j}$
1 3 5 7 9 11 ...
Sequence i

- Input: again assume sequences $s_1, s_2, \ldots, s_k$ with one length w motif per sequence
- Motif model: WMM
- Parameters: Where are the motifs? for $1 \leq i \leq k$, have $1 \leq x_i \leq |s_i|-w+1$
- "Full conditional": to calc $$P(x_i = j \mid x_1, x_2, \ldots, x_{i-1}, x_{i+1}, \ldots, x_k)$$ build WMM from motifs in all sequences except *i*, then calc prob that motif in i^{th} seq occurs at *j* by usual "scanning" alg.

Overall Gibbs Alg

```
Randomly initialize $x_i$'s
for $t$ = 1 to ∞
  for $i$ = 1 to $k$
    discard motif instance from $s_i$;
    recalc WMM from rest
    for $j$ = 1 ... $|s_i|-w+1$
      calculate prob that $i^{th}$ motif is at $j$:
        $P(x_i = j \mid x_1, x_2, \ldots, x_{i-1}, x_{i+1}, \ldots, x_k)$
      pick new $x_i$ according to that distribution
```

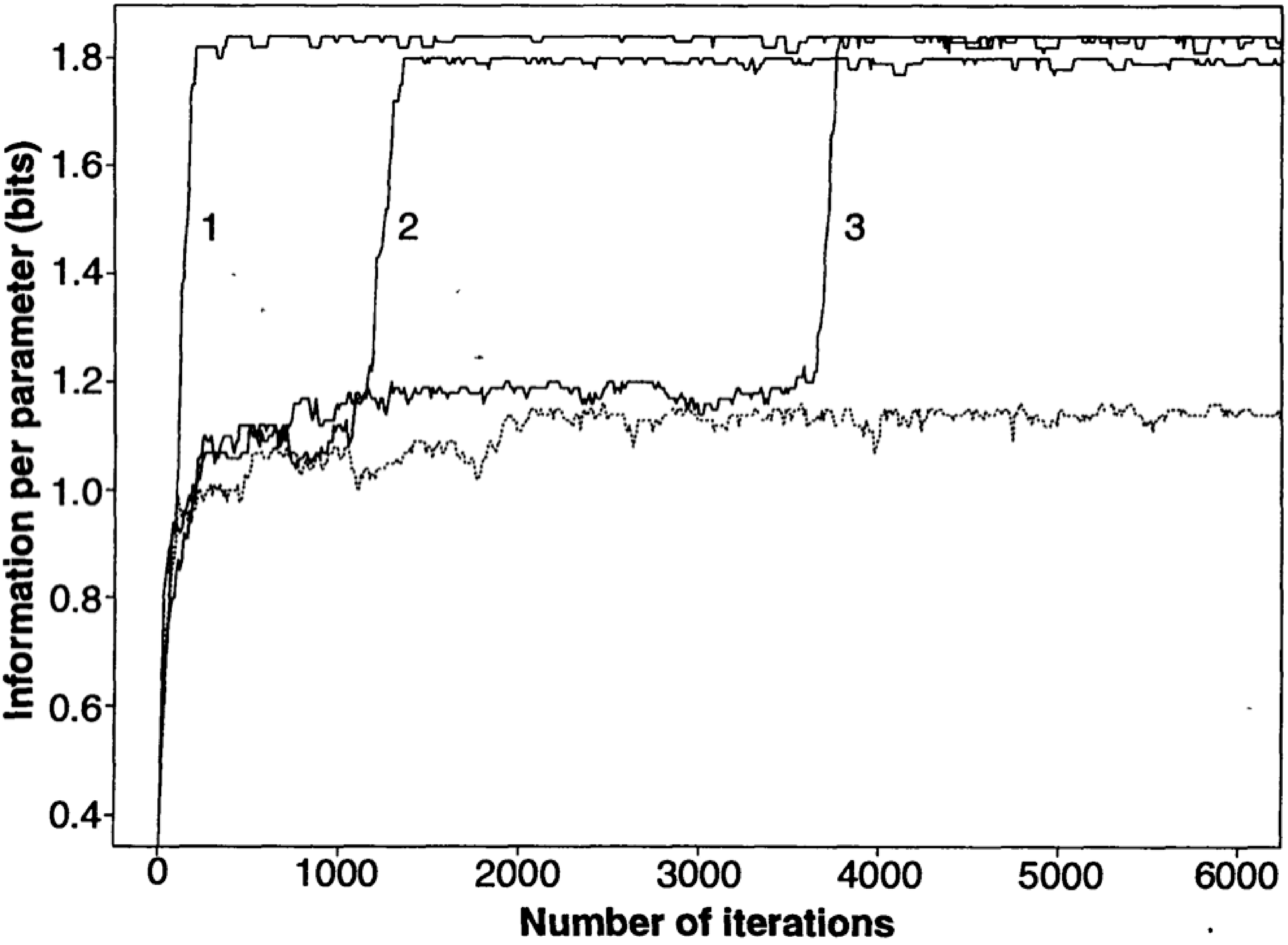
Similar to MEME, but it would average over, rather than sample from

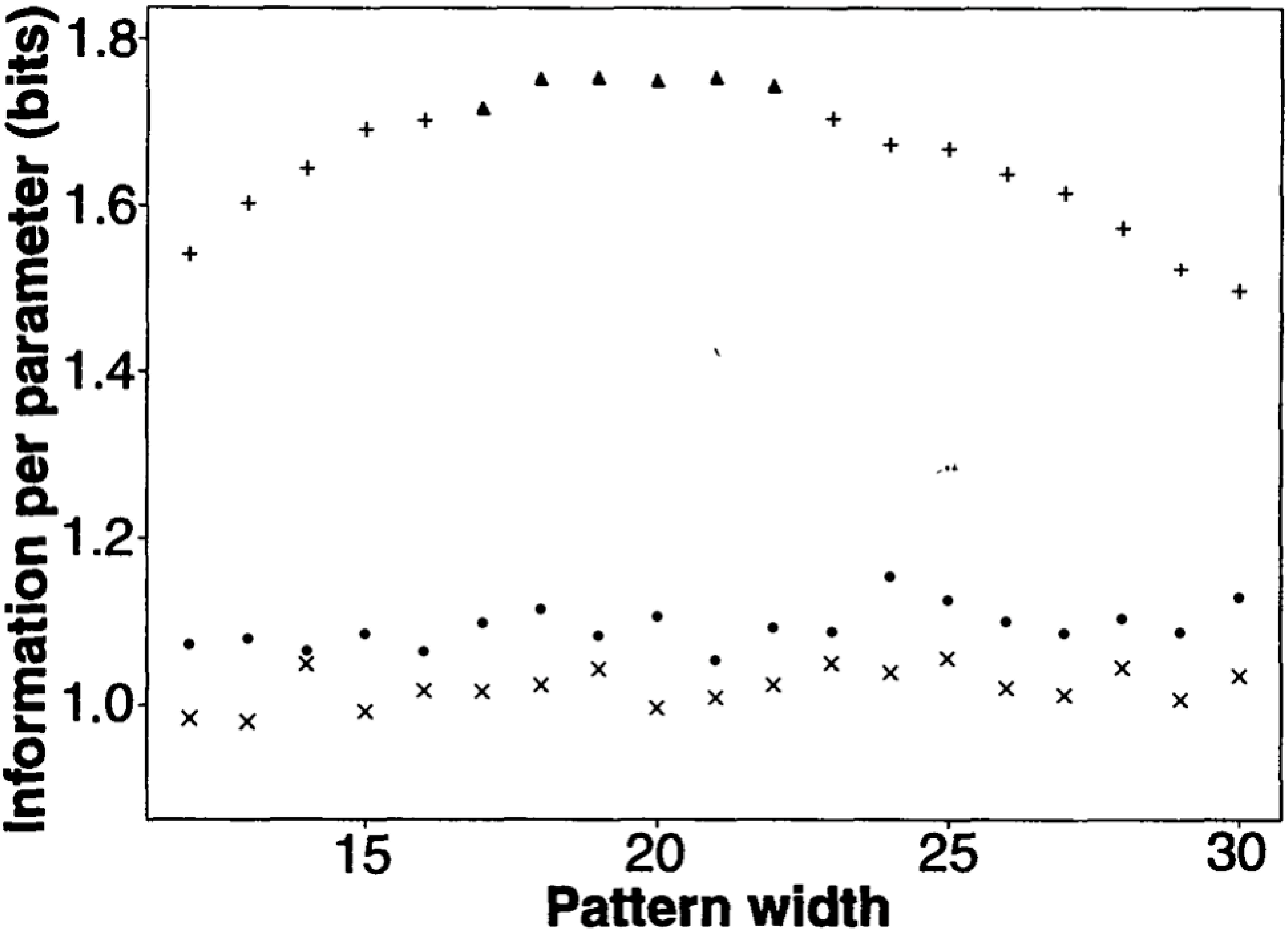
Issues

- Burnin - how long must we run the chain to reach stationarity?
- Mixing - how long a post-burnin sample must we take to get a good sample of the stationary distribution? (Recall that individual samples are not independent, and may not "move" freely through the sample space. Also, many isolated modes.)

Variants & Extensions

- “Phase Shift” - may settle on suboptimal solution that overlaps part of motif. Periodically try moving all motif instances a few spaces left or right.
- Algorithmic adjustment of pattern width: Periodically add/remove flanking positions to maximize (roughly) average relative entropy per position
- Multiple patterns per string


Information per parameter (bits)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
1
2
3
0
1000
2000
3000
4000
5000
6000
Number of iterations


Information per parameter (bits)
1.8
1.6
1.4
1.2
1.0
15
20
25
30
Pattern width

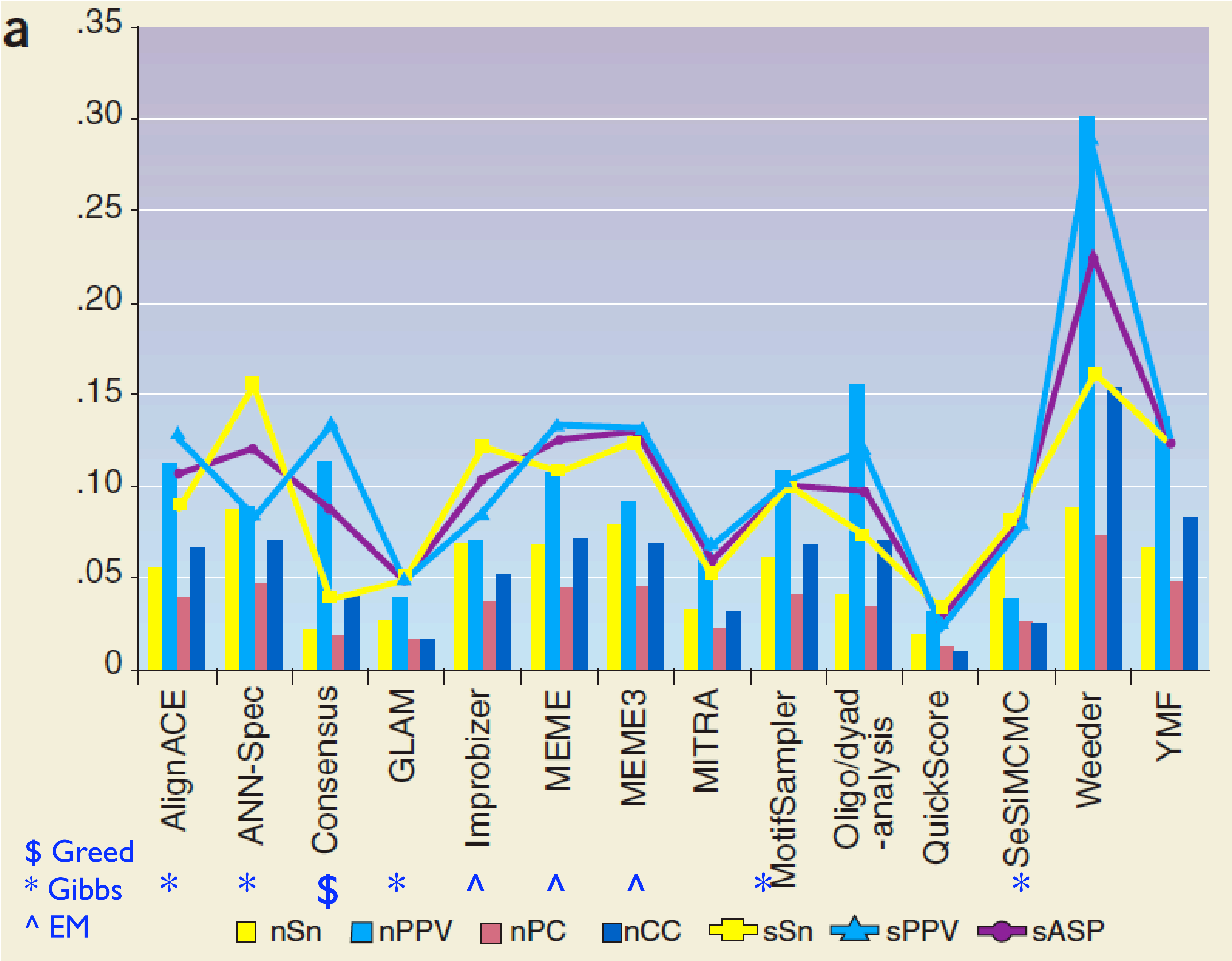
NATURE BIOTECHNOLOGY VOLUME 23 NUMBER 1 JANUARY 2005

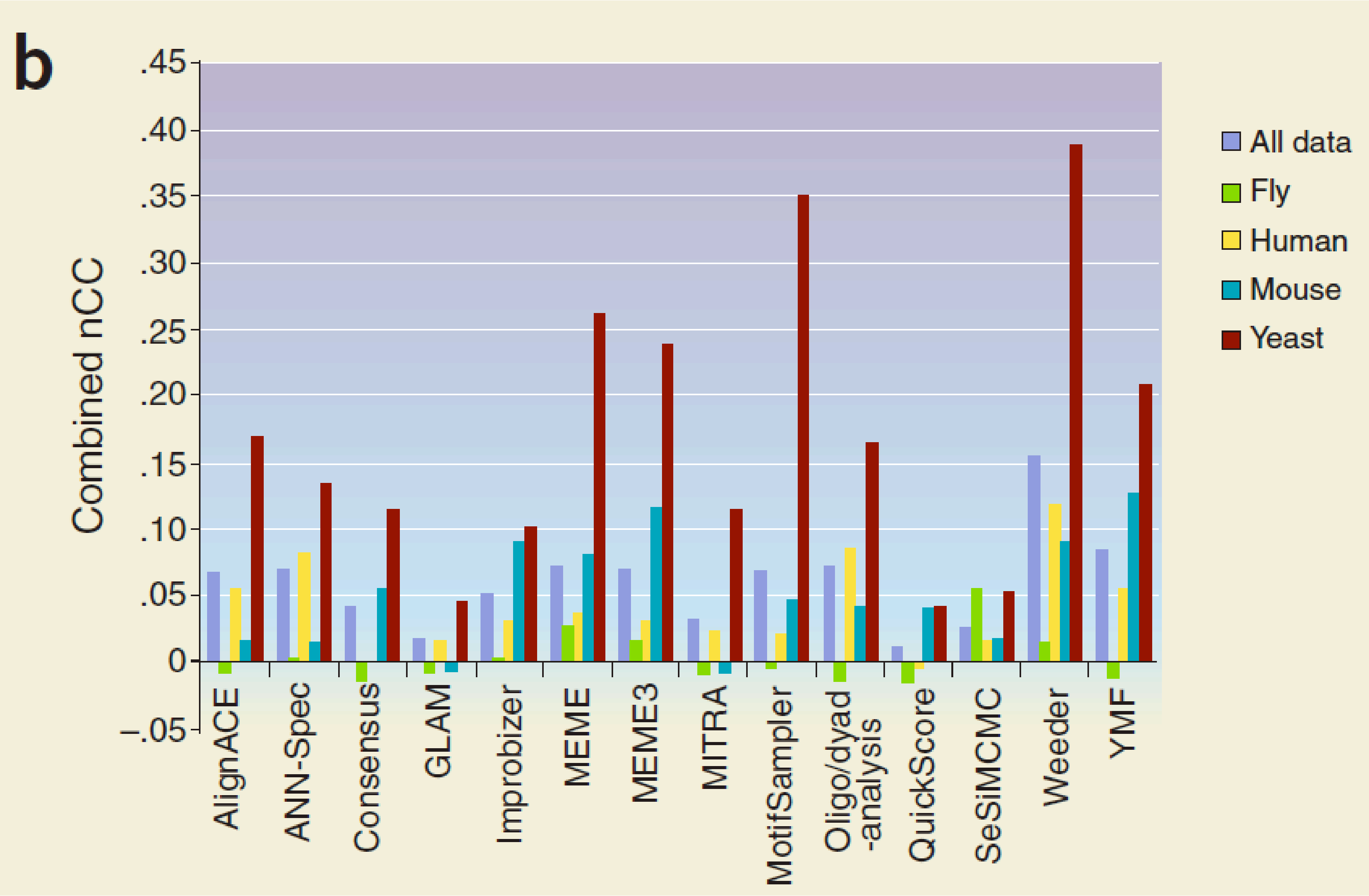
Assessing computational tools for the discovery of transcription factor binding sites

Martin Tompa[1,2], Nan Li[1], Timothy L Bailey[3], George M Church[4], Bart De Moor[5], Eleazar Eskin[6], Alexander V Favorov[7,8], Martin C Frith[9], Yutao Fu[9], W James Kent[10], Vsevolod J Makeev[7,8], Andrei A Mironov[7,11], William Stafford Noble[1,2], Giulio Pavesi[12], Graziano Pesole[13], Mireille Régnier[14], Nicolas Simonis[15], Saurabh Sinha[16], Gert Thijs[5], Jacques van Helden[15], Mathias Vandenbogaert[14], Zhiping Weng[9], Christopher Workman[17], Chun Ye[18] & Zhou Zhu[4]

Methodology

- 13 tools
- Real ‘motifs’ (Transfac)
- 56 data sets (human, mouse, fly, yeast)
- ‘Real’, ‘generic’, ‘Markov’
- Expert users, top prediction only


a
.35
.30
.25
.20
.15
.10
.05
0
AlignACE
ANN-Spec
Consensus
GLAM
Improbizer
MEME
MEME3
MITRA
MotifSampler
Oligo/dyad -analysis
QuickScore
SeSiMCMC
Weeder
YMF
$ Greed
* Gibbs
^ EM
* * $ * ^ ^ ^ * *
nSn
nPPV
nPC
nCC
sSn
sPPV
sASP


b
Combined nCC
.45
.40
.35
.30
.25
.20
.15
.10
.05
0
–.05
All data
Fly
Human
Mouse
Yeast
AlignACE
ANN-Spec
Consensus
GLAM
Improbizer
MEME
MEME3
MITRA
MotifSampler
Oligo/dyad -analysis
QuickScore
SeSiMCMC
Weeder
YMF

Lessons

- Evaluation is hard (esp. when “truth” is unknown)
- Accuracy low
  - partly reflects defects in evaluation methodology (e.g. <= 1 prediction per data set; results better in synth data)
  - partly reflects difficult task, limited knowledge (e.g. yeast > others)
- No clear winner re methods or models

Motif Discovery Summary

- Important problem: a key to understanding gene regulation
- Hard problem: short, degenerate signals amidst much noise
- *Many* variants have been tried, for representation, search, and discovery. We looked at only a few:
  - Weight matrix models for representation & search
  - greedy, MEME and Gibbs for discovery
- Still much room for improvement. *Comparative genomics*, i.e. cross-species comparison is very promising