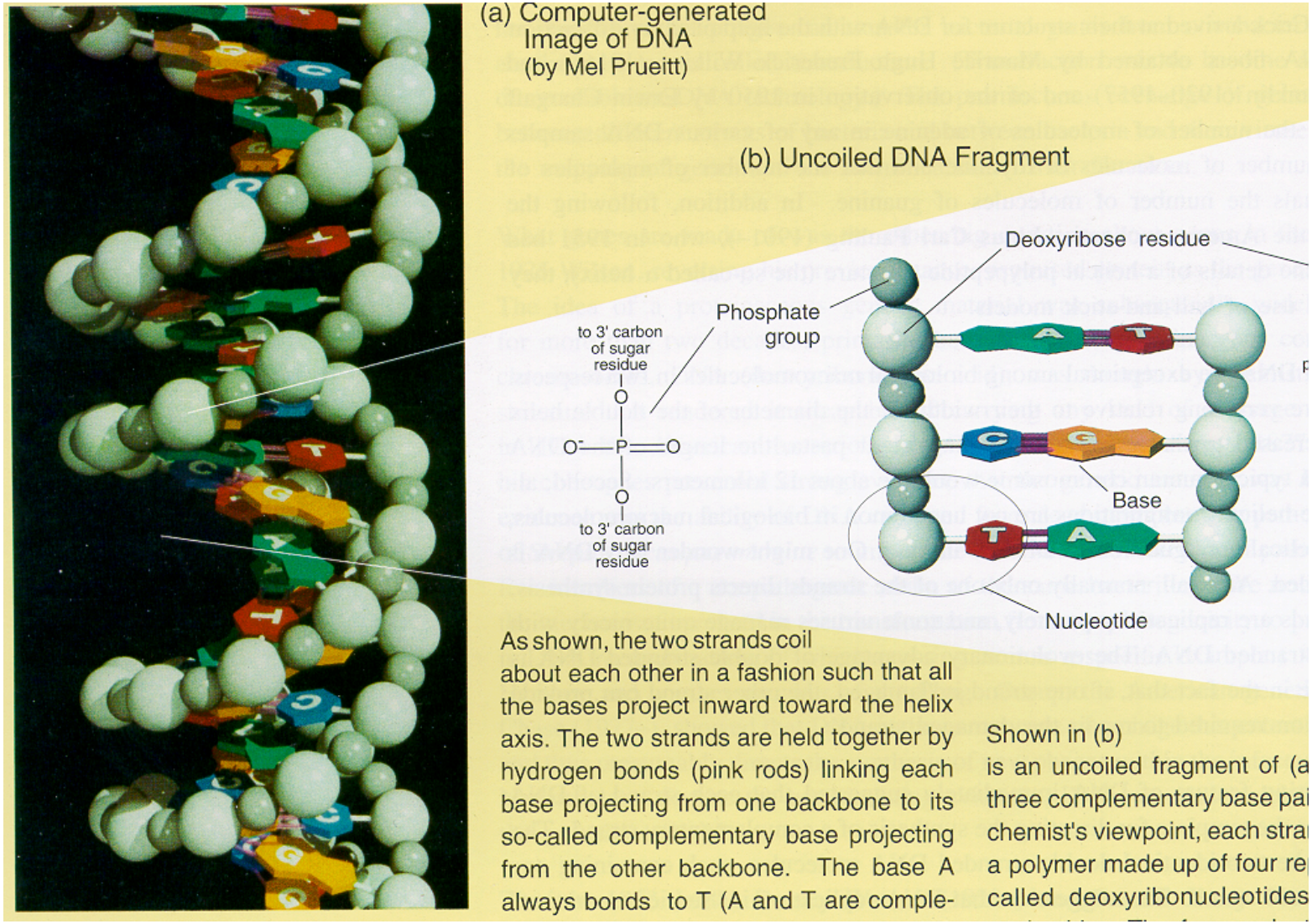
CSE 527
Lecture 9

The Gibbs Sampler

The "Gibbs Sampler"

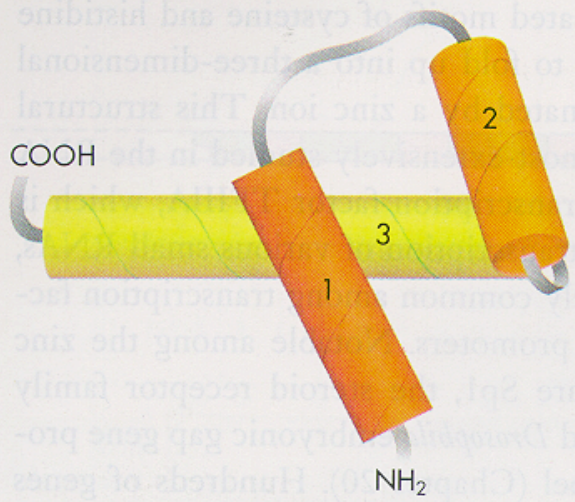
- Lawrence, *et al.*
  "Detecting Subtle Sequence Signals: A Gibbs Sampling Strategy for Multiple Sequence Alignment,"
  Science 1993

The Double Helix

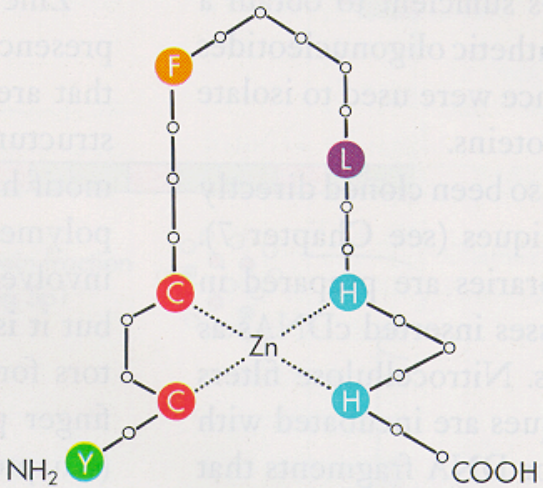


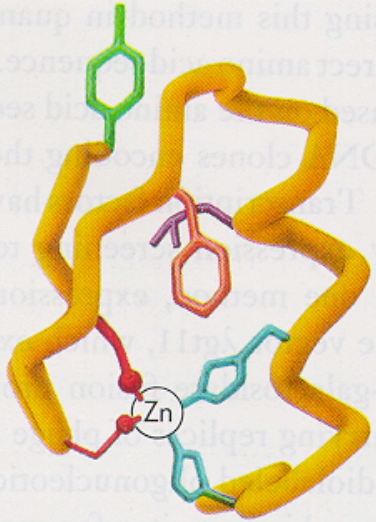
Los Alamos Science

Some DNA Binding Domains

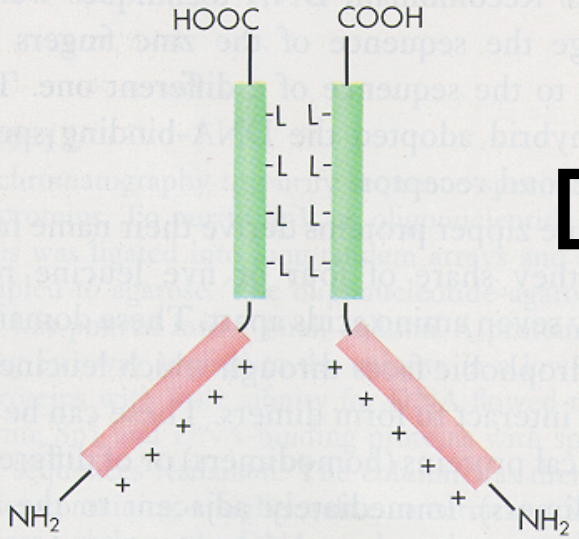


(a) Helix-turn-helix Homeodomain

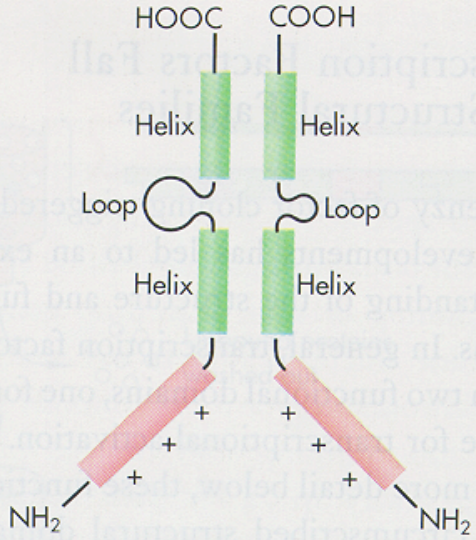




(b) C_2H_2 zinc finger



(c) Leucine zipper



(d) Helix-loop-helix

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: $f(x_1, x_2, \ldots, x_k)$
- Want Expected Value: $E(f(x_1, x_2, \ldots, x_k))$

How to Average

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

- 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

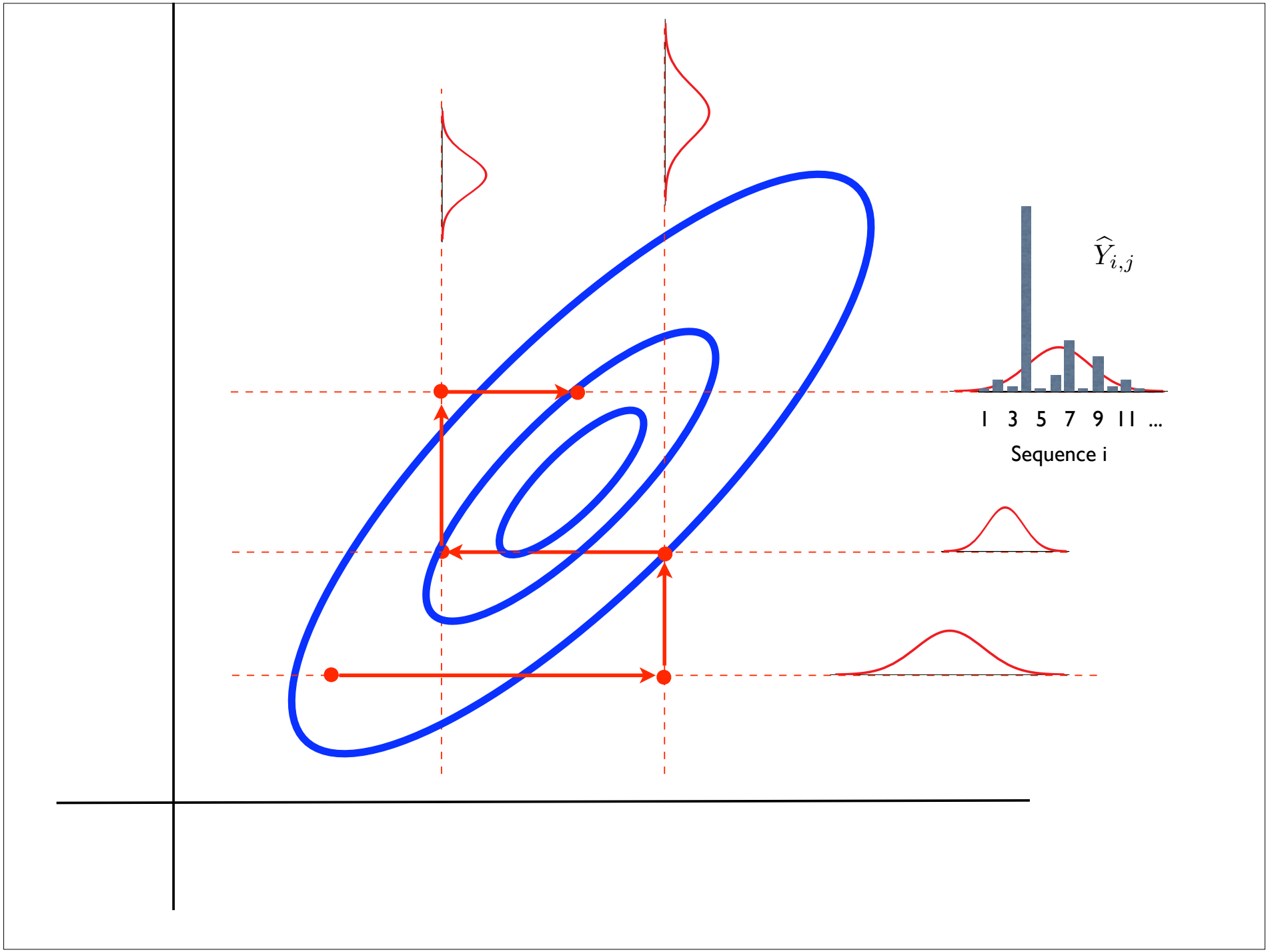
$$P(x_i \mid x_1, x_2, \ldots, x_{i-1}, x_{i+1}, \ldots, x_k)$$

- Algorithm

  for t = 1 to ∞

    for i = 1 to k do :

$$x_{t+1,i} \sim P(x_{t+1,i} \mid \underbrace{x_{t+1,1}, x_{t+1,2}, \ldots, x_{t+1,i-1}}_{t+1}, \underbrace{x_{t,i+1}, \ldots, x_{t,k}}_{t})$$


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

- Input: again assume sequences $s_1, s_2, ..., s_k$ 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.

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

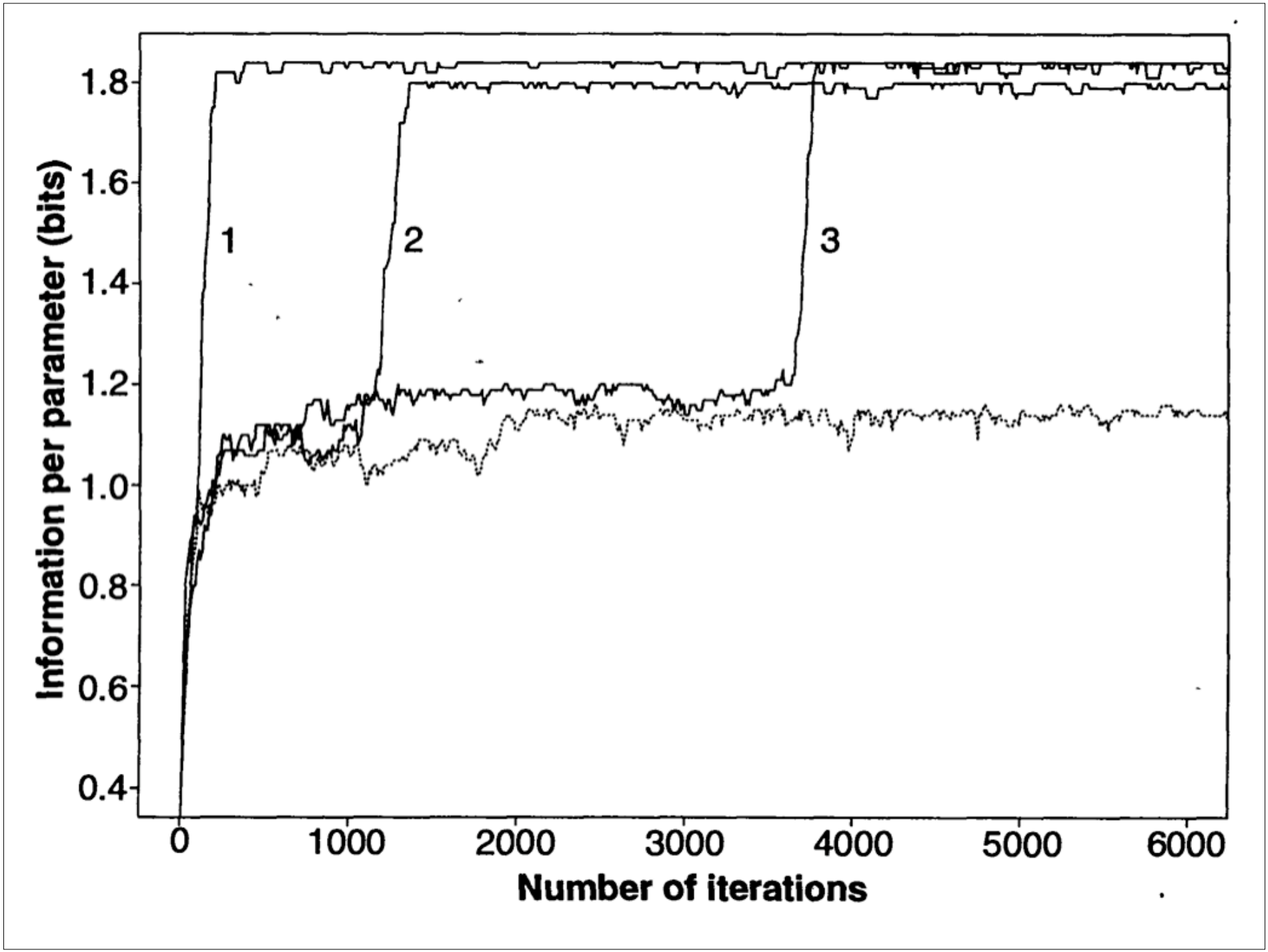
Similar to MEME, but it would average over, rather than sample from

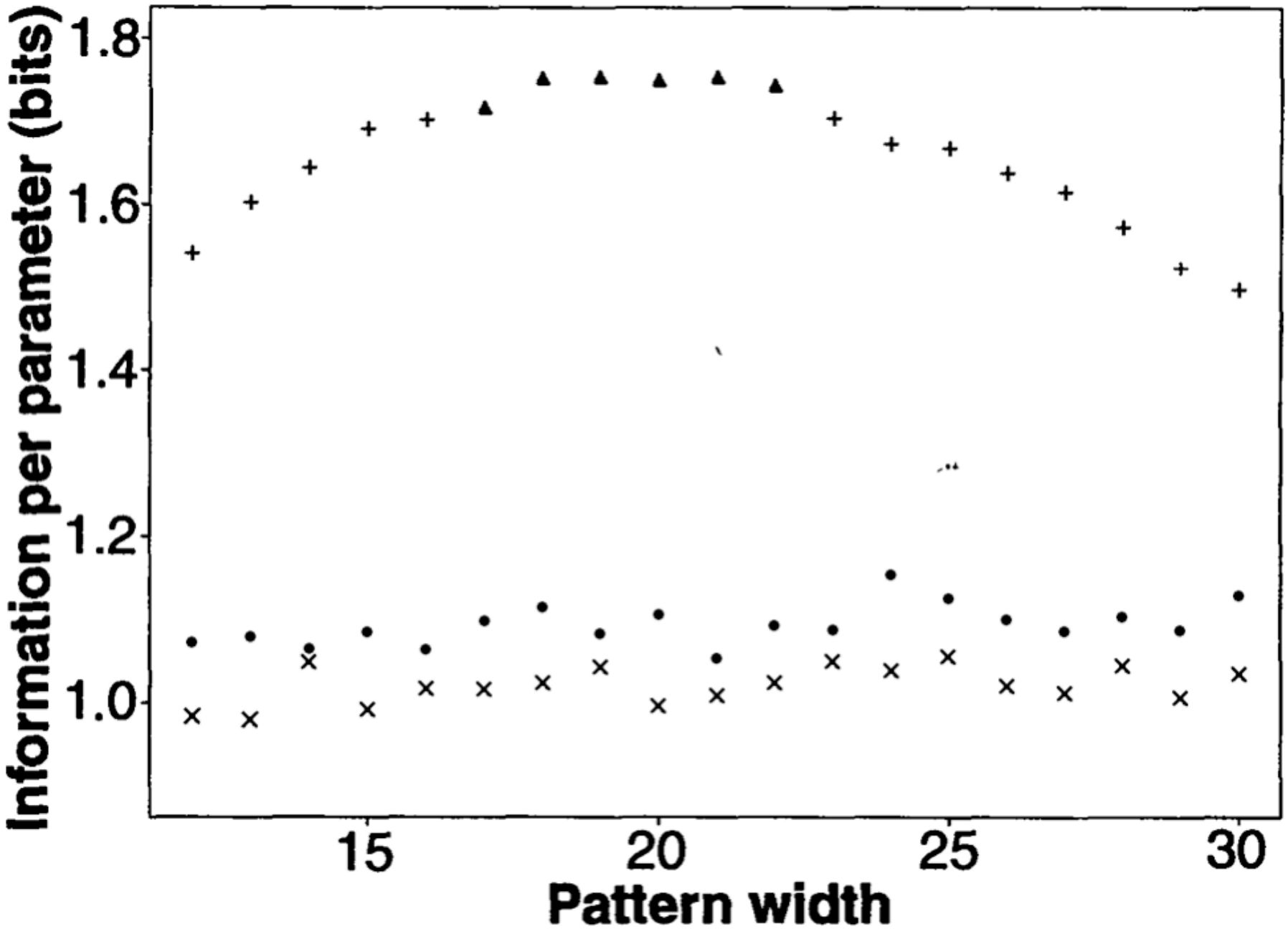
Issues

- 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