A General Pairwise Interaction Model Provides an Accurate Description of *In Vivo* Transcription Factor Binding Sites

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Supporting Figures

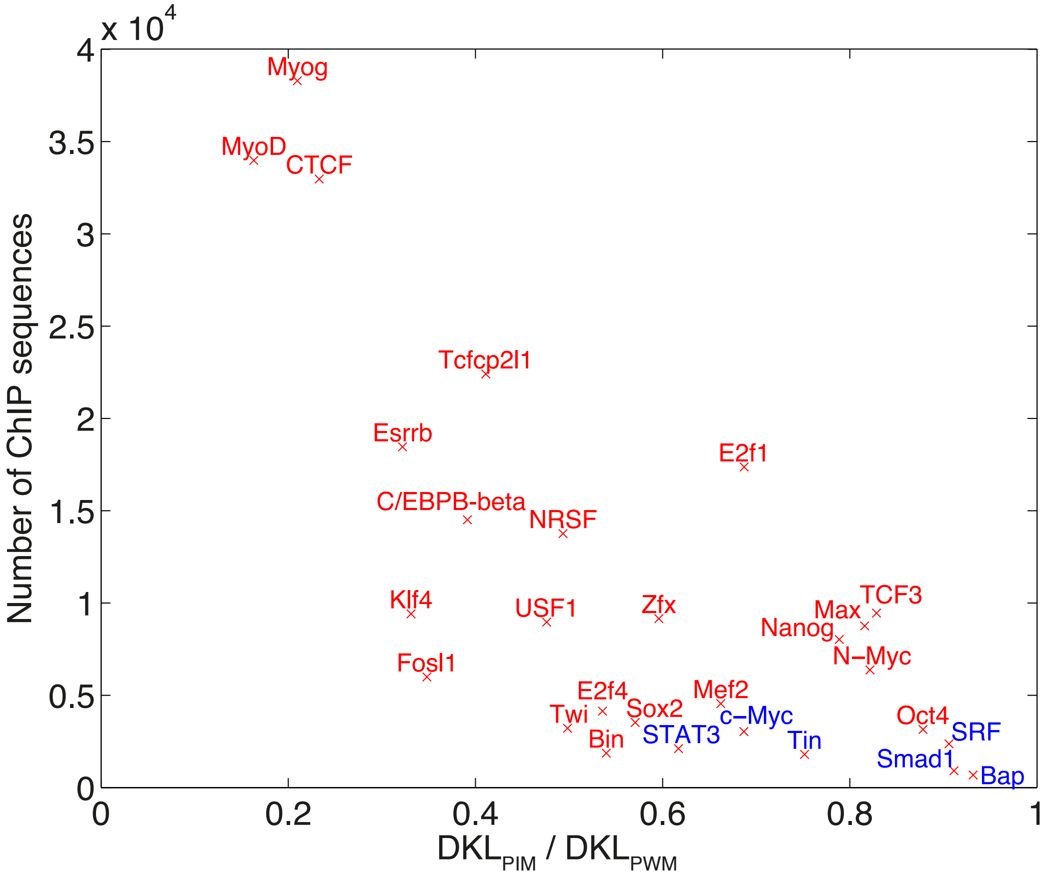


Figure S1. Dependence of the fit on the number of ChIP sequences. For each TF, the number of available ChIP sequences is plotted *vs.* the improvement in the description of its TFBS statistics, provided by the he PIM as compared to the PWM model. The latter is quantified by the ratio of DKL between the respective model probability distributions and the experimental ones provided by the ChIP data, $\mathrm{DKL}_{\mathrm{PIM}}/\mathrm{DKL}_{\mathrm{PWM}}$. The improvement afforded by the PIM is clearly seen to be correlated to the number of ChIP sequences available.TFs for which the PWM description appears satisfactory (see Figure 2 of the main text) are shown in blue.

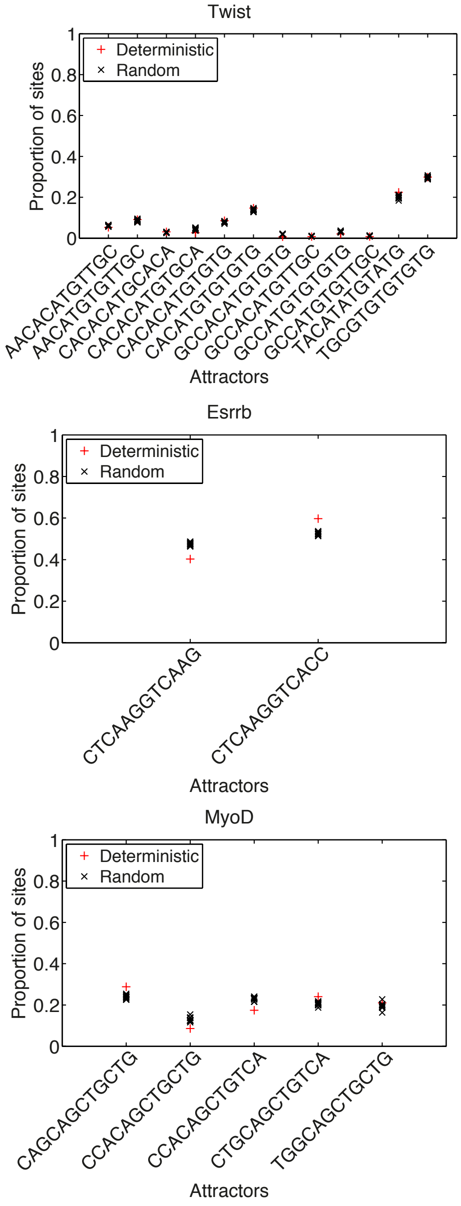
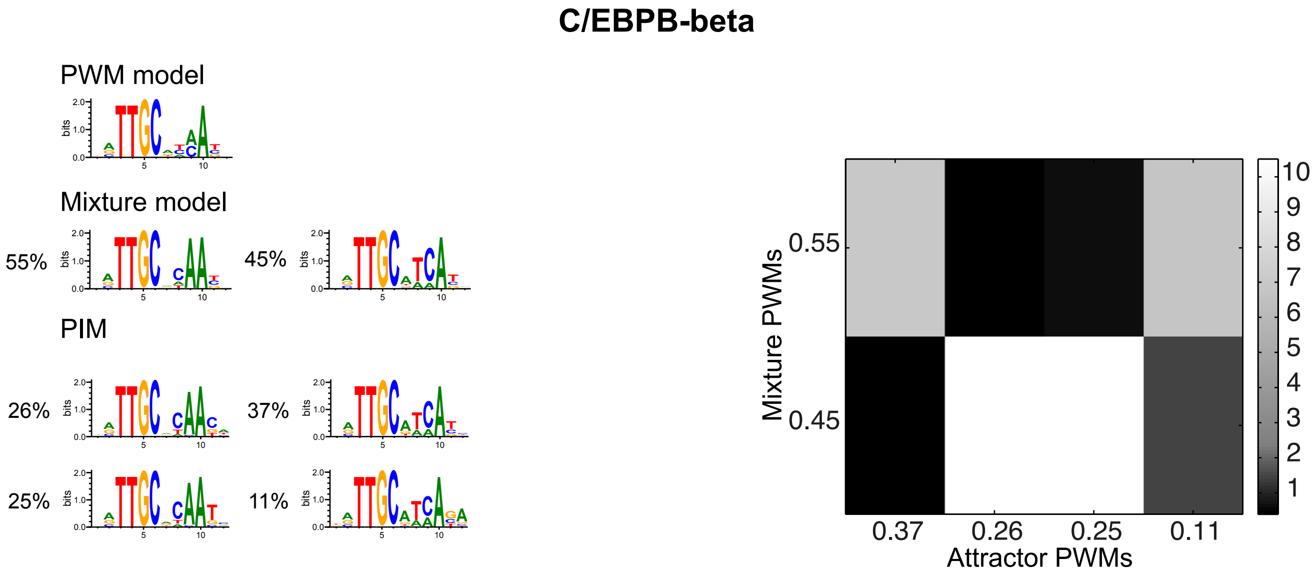
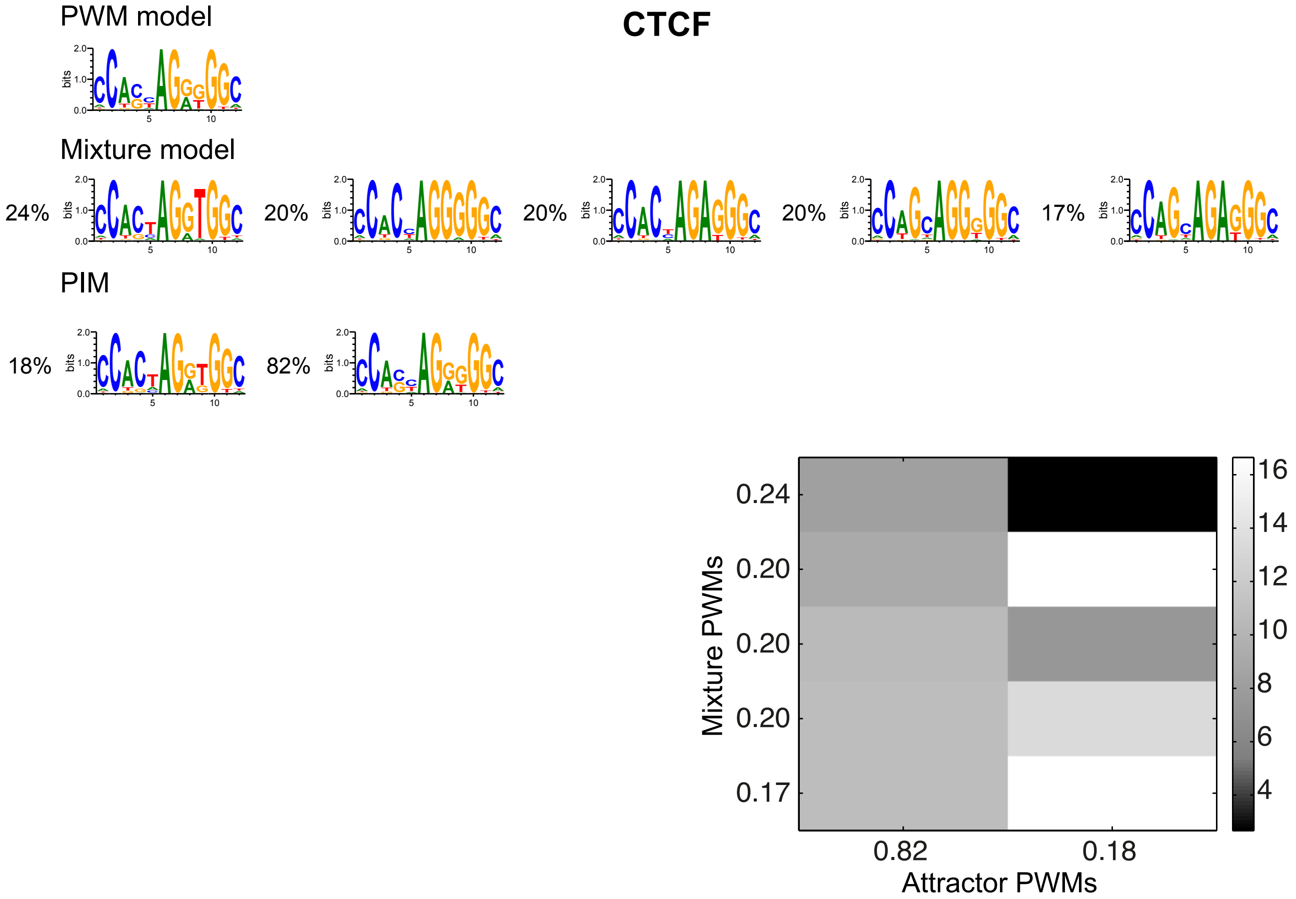
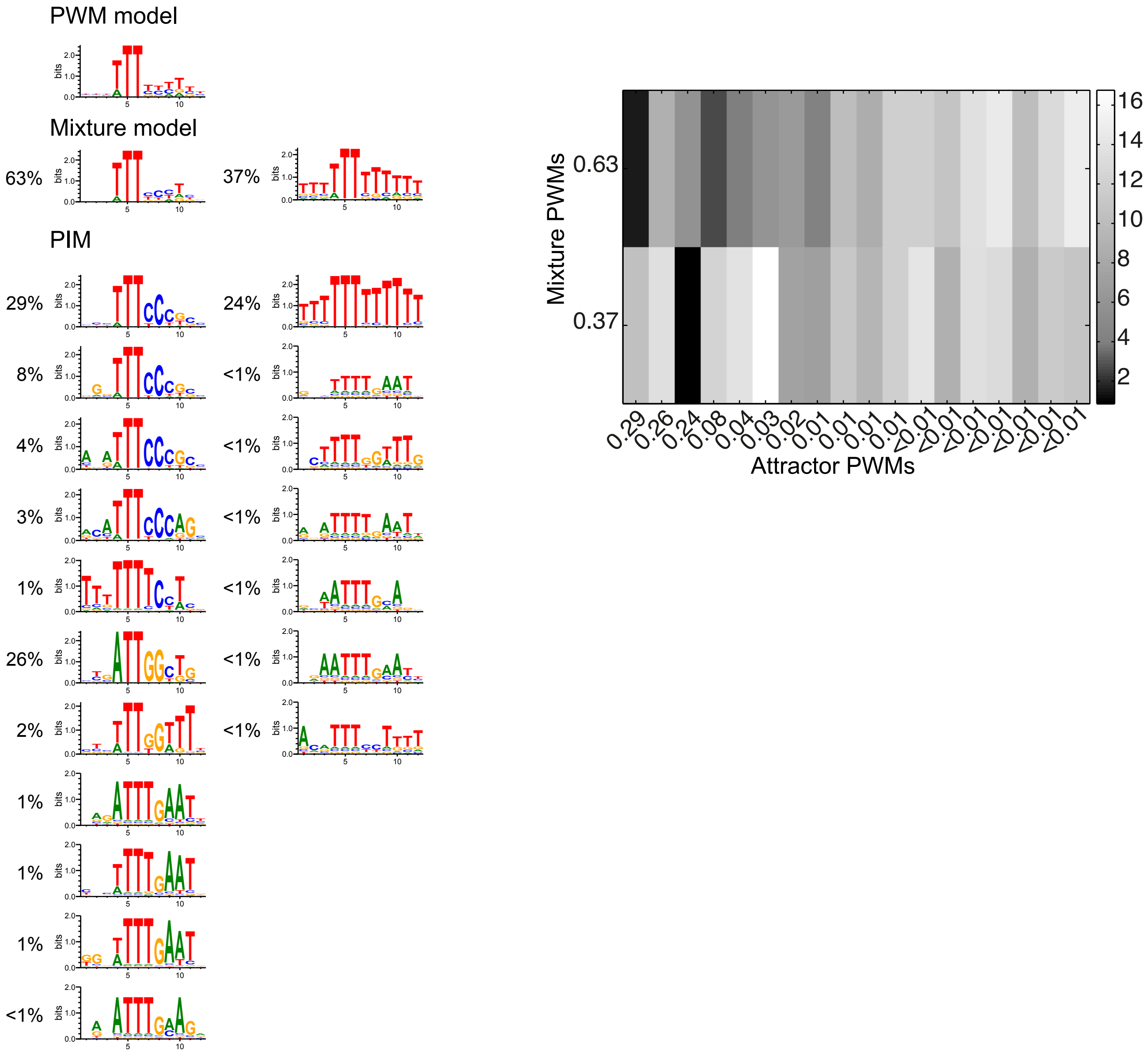


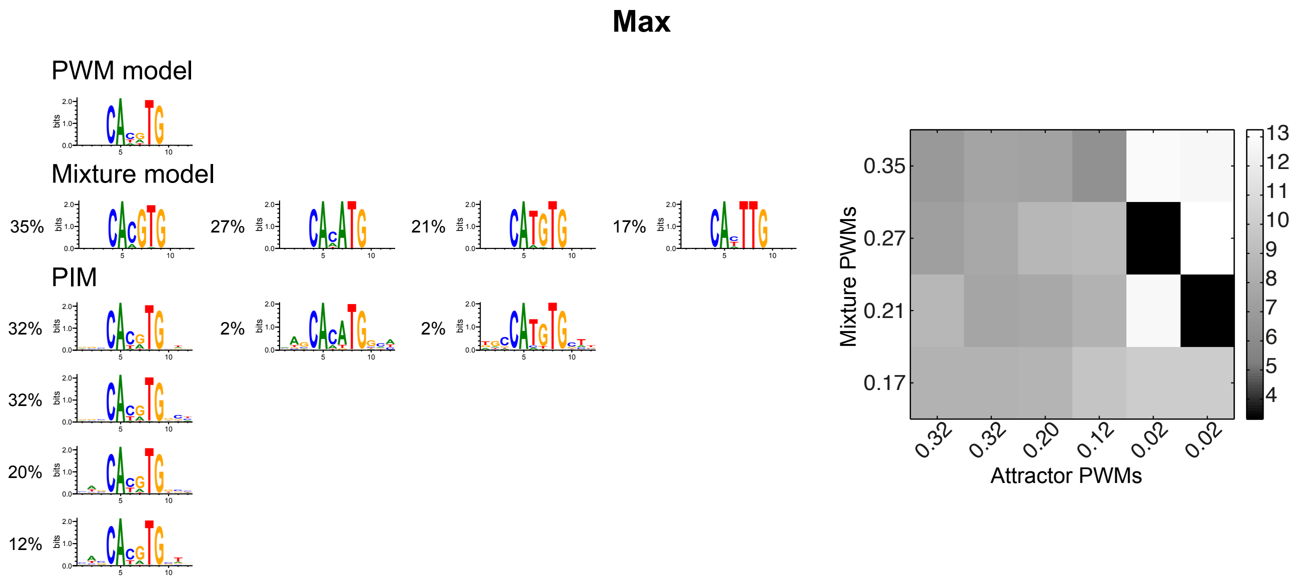
Figure S2. Comparison of the different methods to define the basins of attraction. We compare two methods that allow to define the basins of attraction of the PIM model. Given an initial sequence, the attractor is found by changing iteratively either the nucleotide providing the strongest decrease in energy (deterministic method) or a random nucleotide providing a strict decrease of energy (random method). We show for the 3 factors studied in the main text the proportion of sites falling in each of the basins of attraction using the deterministic method or 10 trials of the random method. For these factors we observed that the number of basins of attraction was not changing, and that the proportion of sites falling in each basin was well conserved.

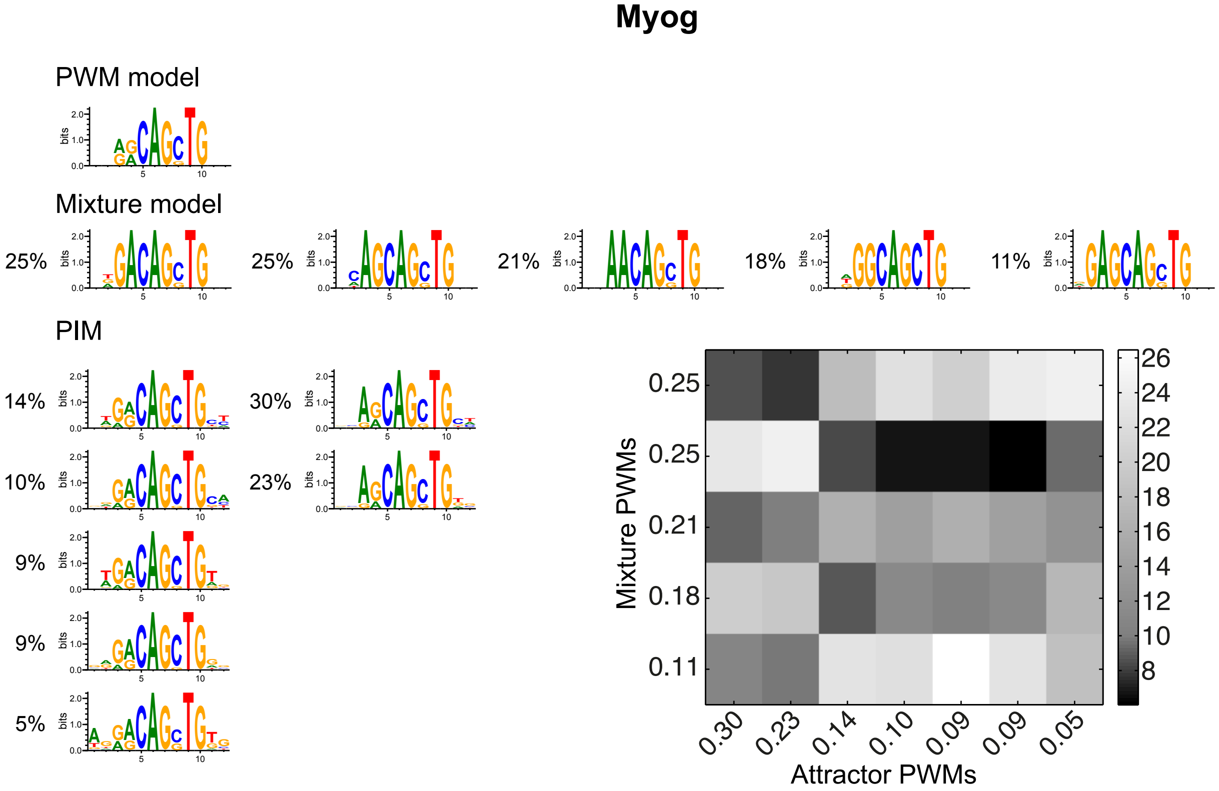

C/EBPB-beta
PWM model
Mixture model
55%
45%
PIM
26%
37%
25%
11%
bits
2.0
1.0
0.0
5
10
Mixture PWMs
0.55
0.45
Attractor PWMs
0.37
0.26
0.25
0.11
10
9
8
7
6
5
4
3
2
1

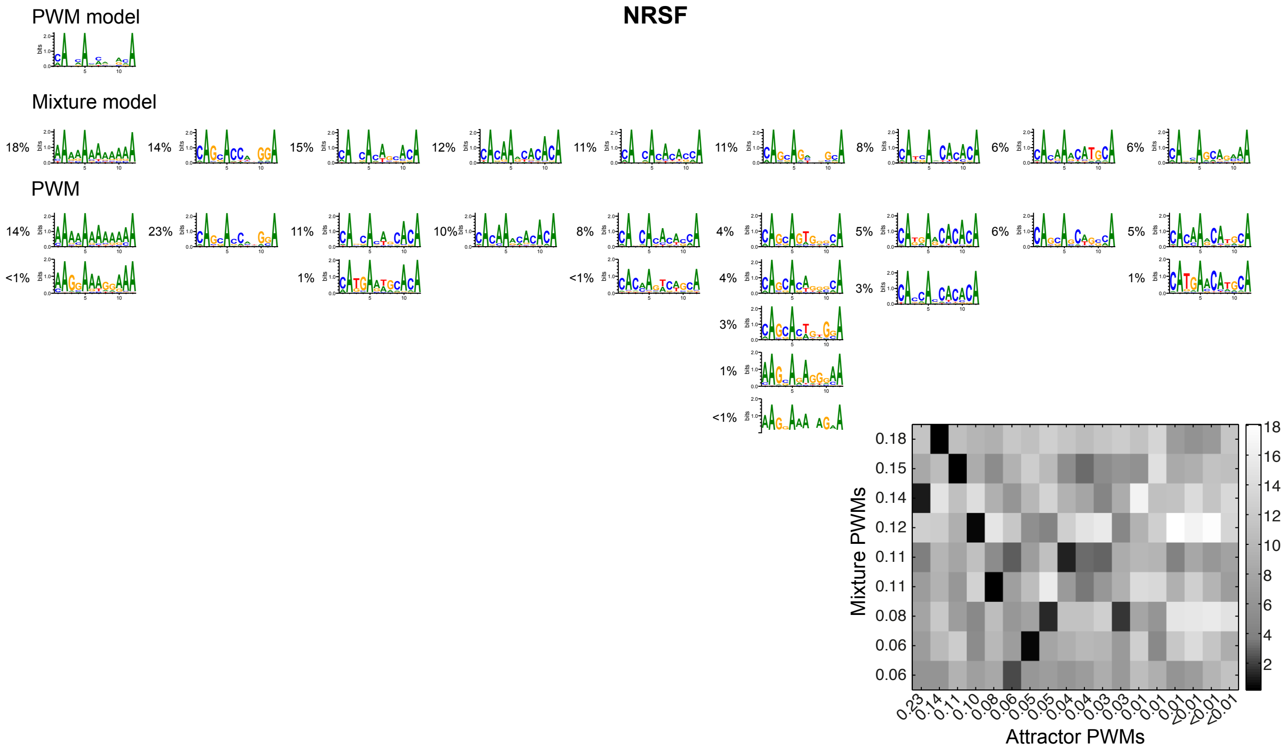

CTCF
PWM model
Mixture model
24%
20%
20%
20%
17%
PIM
18%
82%
bits
2.0
1.0
0.0
5
10
Mixture PWMs
0.24
0.20
0.20
0.20
0.17
Attractor PWMs
0.82
0.18
16
14
12
10
8
6
4

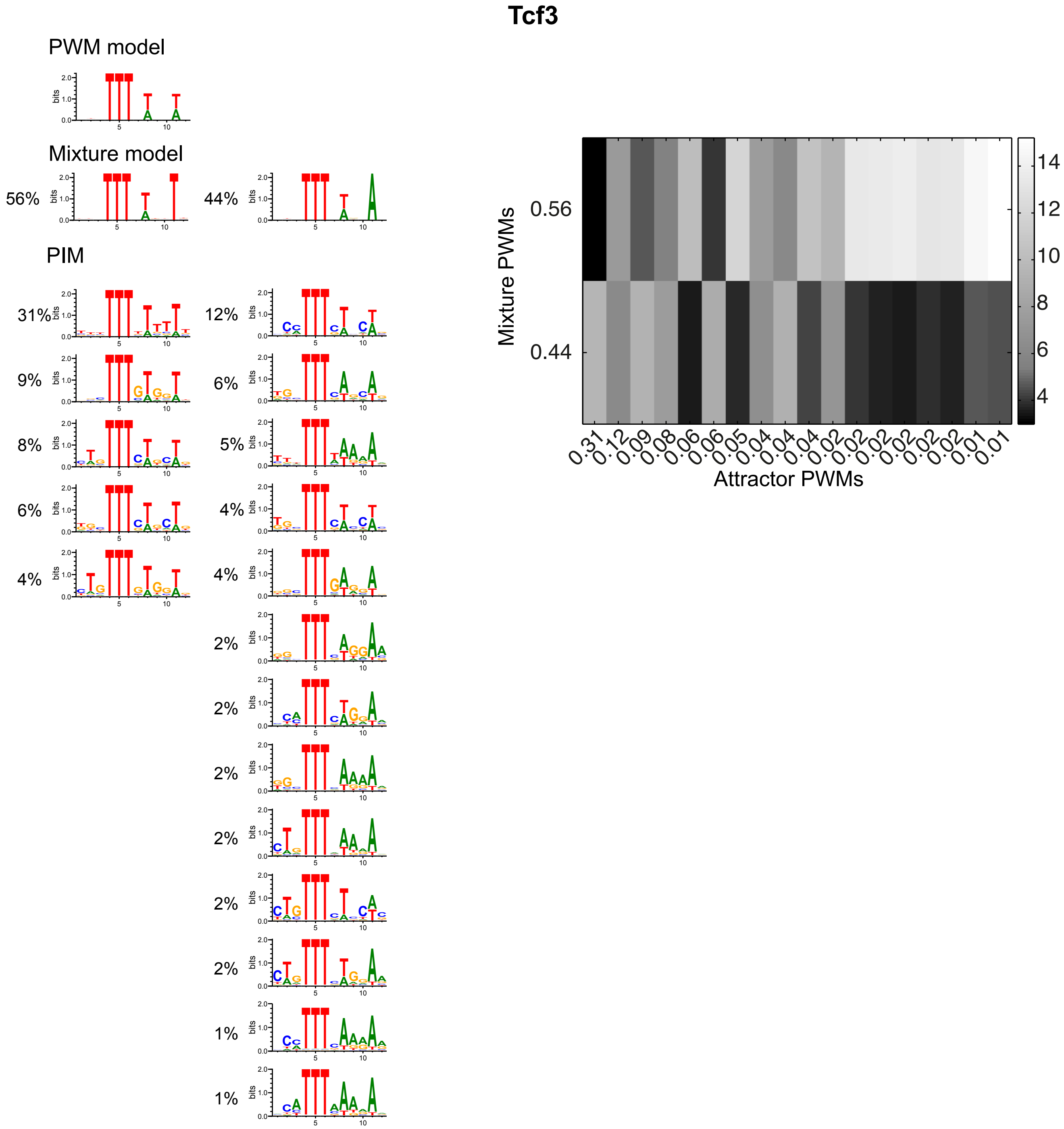
E2f4


PWM model
Mixture model
63%
37%
PIM
29%
24%
8%
<1%
4%
<1%
3%
<1%
1%
<1%
26%
<1%
2%
<1%
1%
1%
1%
<1%
bits
2.0
1.0
0.0
5
10
Mixture PWMs
0.63
0.37
Attractor PWMs
0.29
0.26
0.24
0.08
0.04
0.03
0.02
0.01
0.01
0.01
0.01
<0.01
<0.01
<0.01
<0.01
<0.01
<0.01
<0.01
16
14
12
10
8
6
4
2


Max
PWM model
Mixture model
35%
27%
21%
17%
PIM
32%
2%
2%
32%
20%
12%
bits
2.0
1.0
0.0
5
10
Mixture PWMs
0.35
0.27
0.21
0.17
Attractor PWMs
0.32
0.32
0.20
0.12
0.02
0.02
13
12
11
10
9
8
7
6
5
4


Myog
PWM model
Mixture model
25%
25%
21%
18%
11%
PIM
14%
30%
10%
23%
9%
9%
5%
bits
2.0
1.0
0.0
5
10
Mixture PWMs
0.25
0.25
0.21
0.18
0.11
Attractor PWMs
0.30
0.23
0.14
0.10
0.09
0.09
0.05
26
24
22
20
18
16
14
12
10
8


NRSF
PWM model
Mixture model
18%
14%
15%
12%
11%
11%
8%
6%
6%
PWM
14%
23%
11%
10%
8%
4%
5%
6%
5%
<1%
1%
<1%
4%
3%
1%
3%
1%
<1%
Mixture PWMs
0.18
0.15
0.14
0.12
0.11
0.11
0.08
0.06
0.06
Attractor PWMs
0.23
0.14
0.11
0.10
0.08
0.06
0.05
0.05
0.04
0.04
0.03
0.03
0.01
0.01
0.01
<0.01
<0.01
<0.01
18
16
14
12
10
8
6
4
2


Tcf3
PWM model
Mixture model
56%
44%
PIM
31%
12%
9%
6%
8%
5%
6%
4%
4%
4%
2%
2%
2%
2%
2%
2%
1%
1%
bits
2.0
1.0
0.0
5
10
Mixture PWMs
0.56
0.44
Attractor PWMs
0.31
0.12
0.09
0.08
0.06
0.06
0.05
0.04
0.04
0.04
0.02
0.02
0.02
0.02
0.02
0.02
0.01
0.01
14
12
10
8
6
4

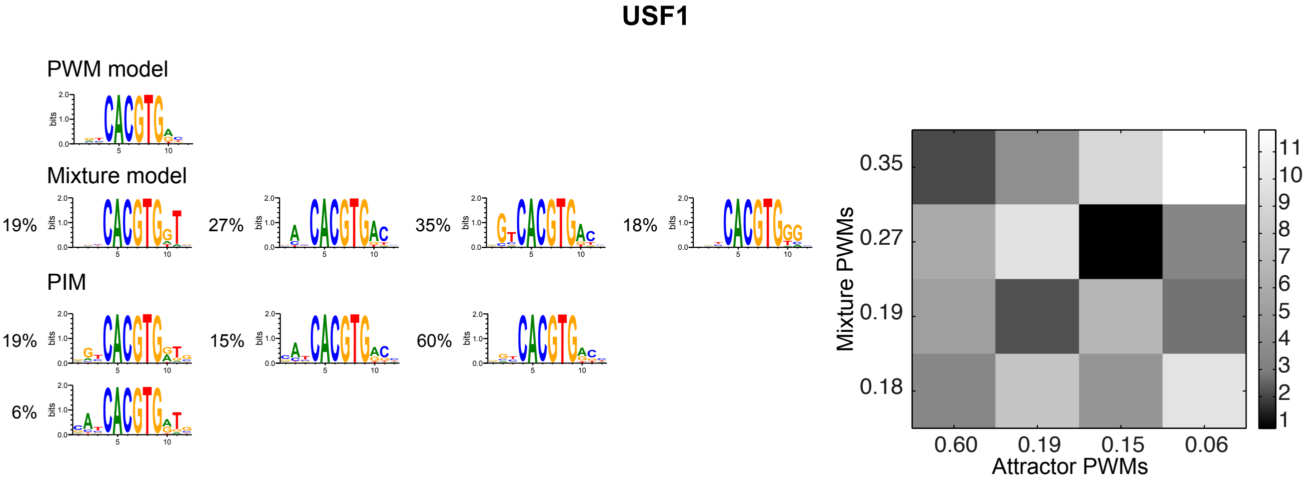
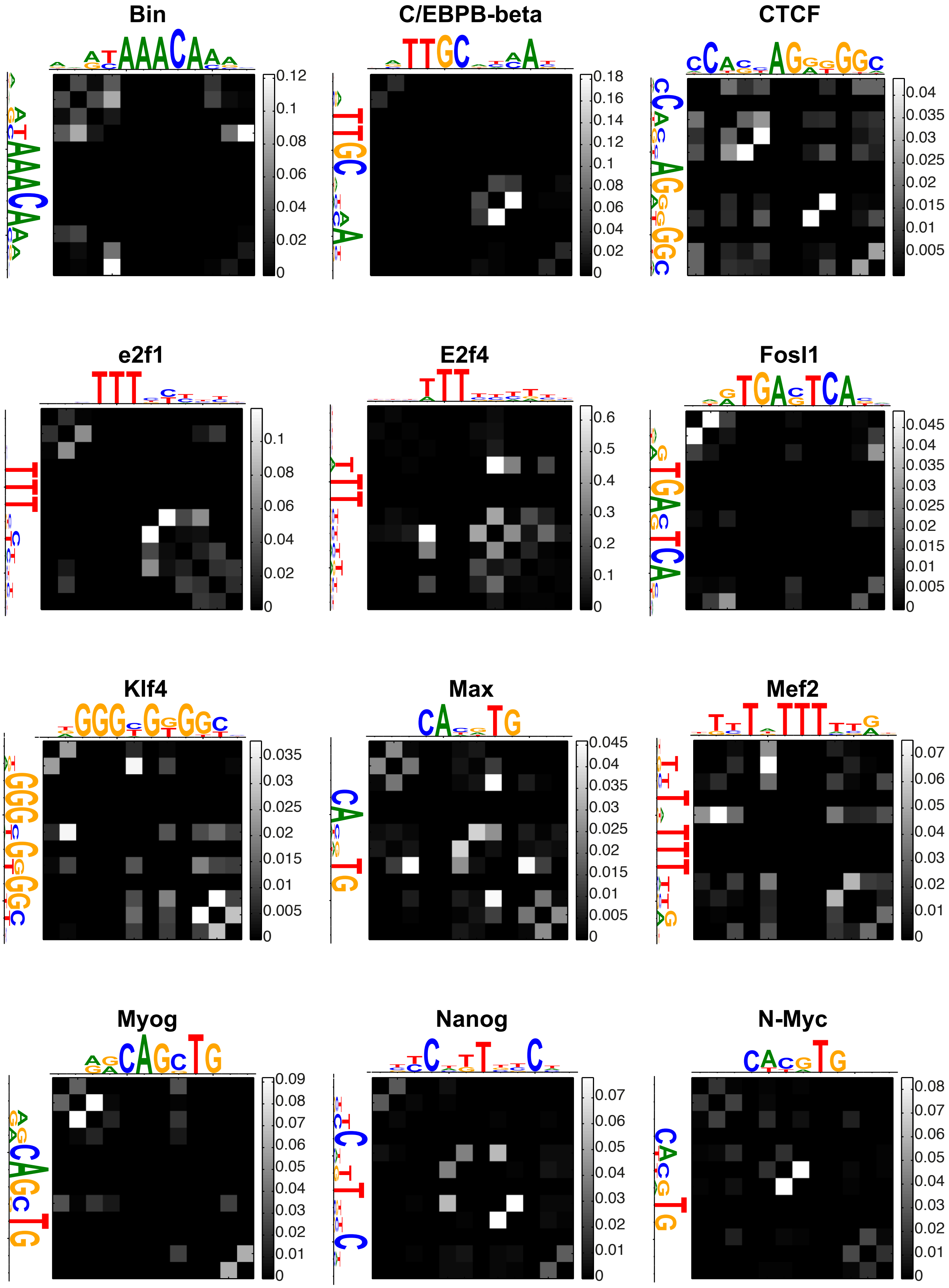


Figure S3. Same as Figure 6 of the main text for all considered factors described by a mixture model with two or more PWMs.


Bin
0.12
0.1
0.08
0.06
0.04
0.02
0
C/EBPB-beta
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
CTCF
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
e2f1
0.1
0.08
0.06
0.04
0.02
0
E2f4
0.6
0.5
0.4
0.3
0.2
0.1
0
Fosl1
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
Klf4
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
Max
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
Mef2
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Myog
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Nanog
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
N-Myc
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0

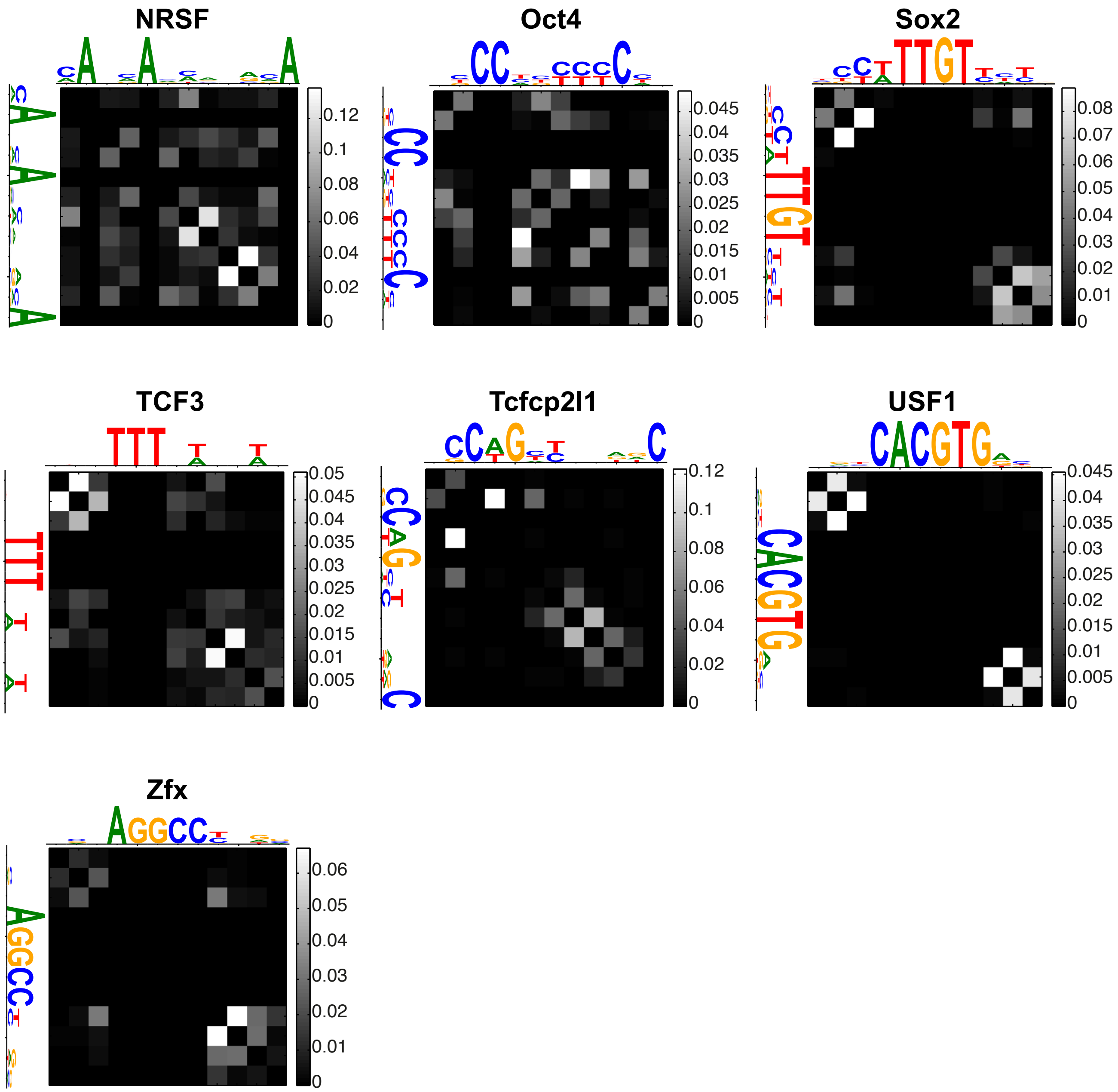


Figure S4. Same as Figure 7A of the main text for the other considered factors.

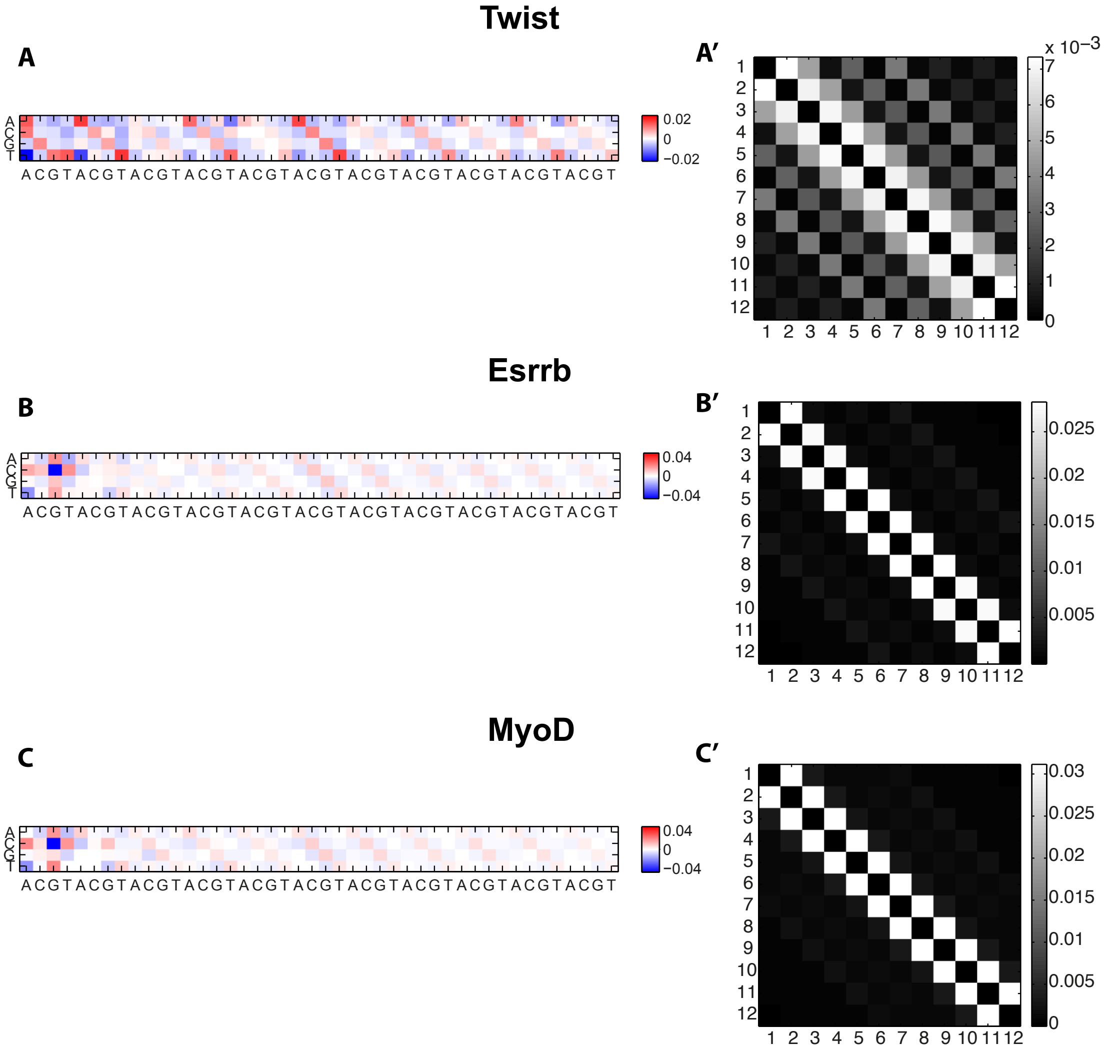


Figure S5. Background correlations. (A,B,C) Heat maps showing the correlations between nucleotides in the ChIP data of the 3 factors from the main text. Because of translation invariance, we only show the correlations between a nucleotide (rows) and the next nearest (first four columns) to farthest (last four columns) nucleotides, using the binding site length of $L = 12$. We see in the Drosophila data the appreciable presence of repeated sequences (of type AA, TT, CC, and GG). In the mammalian data sets, we observe the known CpG depletion. (A',B',C') Corresponding heat maps showing the values of the Normalized Direct Information between pairs of nucleotides.

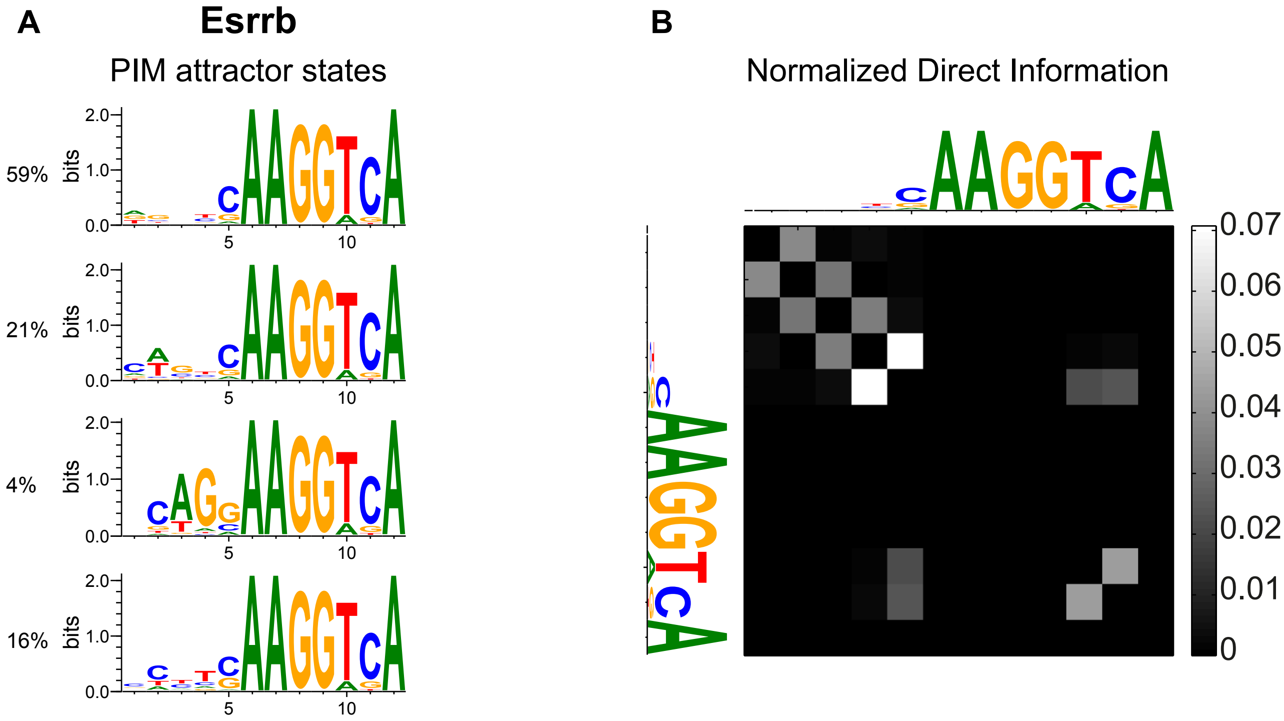


Figure S6. Variable spacer length We learned a PIM for Esrrb including the 4 flanking nucleotides on the left of the main motif. (A) The metastable states of this model show a feature not captured in the main text where binding sites are defined symmetrically around the center of mass of the information content: namely a 'CAG' trinucleotide with variable spacer length from the main motif. This feature is apparent in the first 3 logos shown here. (B) The contribution of this trinucleotidic interaction to the Direct Information is captured through strong direct links between the 4 flanking nucleotides, showing that the PIM is implicitly able to capture higher order correlations. Logos from the PWM model are surrounding the heatmap for clarity.

Supporting Tables

Table S1. Comparison between initial PWMs and $L = 12$ PWMs. Bottom rows correspond to the 6 factors that are satisfactorily described by the PWM model. Information content is in bits.

Name	Reference	Initial length	Initial info	Final info	Loss of info
Bin	Ref. [32] of the main text	12	12.3038	12.3038	0
Mef2	Ref. [32] of the main text	11	9.802	9.802	0
Twi	Ref. [32] of the main text	12	10.766	10.766	0
E2f1	JASPAR_MA0024.1_E2F1	8	10.6909	10.6909	0
Esrrb	JASPAR_MA0141.1_Esrrb	12	14.2211	14.2211	0
Klf4	JASPAR_MA0039.2_Klf4	10	11.358	11.358	0
Nanog	TRANSFAC_V$NANOG_01	12	13.1735	13.1735	0
N-Myc	TRANSFAC_V$NMYC_01	12	10.4726	10.4726	0
Oct4	TRANSFAC_V$OCT4_01	15	17.9438	15.649	-2.29476
Sox2	TRANSFAC_V$SOX2_Q6	16	11.2259	10.7835	-0.442423
Tcfcp2l1	JASPAR_MA0145.1_Tcfcp2l1	14	11.9982	9.00071	-2.99754
Zfx	TRANSFAC_V$ZFX_01	16	9.71554	9.18774	-0.527802
C/EBP-beta	TRANSFAC_V$CEBPB_02	14	8.47114	8.35577	-0.115366
CTCF	TRANSFAC_V$CTCF_01	20	15.5422	13.4622	-2.08002
E2f4	TRANSFAC_V$E2F4DP2_01	8	11.036	11.036	0
Fosl1	JASPAR_MA0099.1_Fos	8	10.2943	10.2943	0
Max	JASPAR_MA0058.1_MAX	10	11.3238	11.3238	0
MyoD	TRANSFAC_V$MYOD_Q6	10	9.25668	9.25668	0
Myog	TRANSFAC_V$MYOGENIN_Q6	8	9.50246	9.50246	0
NRSF	TRANSFAC_V$NRSF_01	21	23.3918	15.0718	-8.31997
TCF3	TRANSFAC_V$TCF3_01	12	12.9923	12.9923	0
USF1	JASPAR_MA0093.1_USF1	7	10.5008	10.5008	0
c-Myc	JASPAR_MA0147.1_Myc	10	10.5487	10.5487	0
SRF	JASPAR_MA0083.1_SRF	12	18.1745	18.1745	0
STAT3	JASPAR_MA0144.1_Stat3	10	14.5568	14.5568	0
Bap	Ref. [32] of the main text	12	10.3746	10.3746	0
Tin	Ref. [32] of the main text	10	10.623	10.623	0
Smad1	TRANSFAC_V$SMAD1_01	12	11.0164	11.0164	0