Table 1: Summary of computational resources. All methods were run in a Xeon E7-4870 40 CPU (2.4GHz per core). The figures reflect the execution of each method on the `Benchmarking Dataset` (88 TFs; cell types H1-hESC (DU) and K562 (DU)). The table shows the additional steps that the user needs to perform in order to execute the footprinting method, the total CPU time in hours, the maximum memory used during the execution and the total input storage necessary before the execution of each method. Memory comsuption and space requirements of all methods are compatible to a high end desktop. Segmentation based methods, which require a single execution per cell, are four to 200 times faster than the site-centric methods, which require an execution per cell and TF combination. It is important to notice that PIQ is the only site-centric method, which only requires a single exection per cell. The execution of BinDNase and Centipede were particularly time consuming (1 week computing on a 40 core server).

Method	Additional Steps	CPU time (hours)	Max. Memory (GB)	Input Storage (GB)
BinDNase	1,2,4	7034	8	95.7
Boyle	NA*	NA*	NA*	NA*
Centipede	1,2,4	7100	8	157.7
Cuellar	1,2,4	575	32	25.4
DNase2TF	3	31	32	29.3
FLR	2,4	870	16	43.1
HINT-BC	3	56	4	17.7
Neph	3	47	4	14.6
PIQ	-	386	32	18.7
Wellington	3	117	16	14.6

[1] Requires extra BAM file input processing.

[2] Requires extra motif matching.

[3] Requires extra DNase-seq peak calling (HS sites).

[4] Requires execution of method for each TF.

* Implementation not available.

Table 2: Summary of DNase-seq data. DNase-seq datasets used as input for computational footprinting methods are highlighted in bold. The other DNase-seq datasets were used in the DNase-seq sequence bias estimates clustering analysis. The labs are represented by their aliases: DU (Crawford lab) and UW (Stamatoyannopoulous lab).

Cell Type	Lab	UCSC	GEO/NCBI	# Mapped Reads
H1-hESC	**DU**	**wgEncodeEH000556**	**GSM816632**	**110303078**
HeLa-S3	**DU**	**wgEncodeEH000540**	**GSM816643**	**54267867**
HepG2	**DU**	**wgEncodeEH000537**	**GSM816662**	**50838536**
Huvec	**DU**	**wgEncodeEH000548**	**GSM816646**	**31848532**
K562	**DU**	**wgEncodeEH000530**	**GSM816655**	**365820647**
LNCaP	**DU**	**wgEncodeEH001097**	**GSM816637**	**163625945**
MCF-7	**DU**	**wgEncodeEH000579**	**GSM816627**	**89113893**
K562*	**DU**	**–**	**GSM1496625**	**202001412**
MCF-7*	**DU**	**–**	**GSM1496626**	**210715393**
H7-hESC	**UW**	**wgEncodeEH000511**	**GSM736638** **GSM736610**	**302050785**
HepG2	**UW**	**wgEncodeEH000482**	**GSM736637** **GSM736639**	**168883956**
Huvec	**UW**	**wgEncodeEH000488**	**GSM736575** **GSM736533**	**429088276**
K562	**UW**	**wgEncodeEH000484**	**GSM736629** **GSM736566**	**179970820**
m3134	**UW**	**wgEncodeEM001721**	**GSM1014196**	**127594903**
IMR90*	**UW**	**–**	**SRA068503**	**138604440**
H7hESC	DU	wgEncodeEH002554	GSM1008596	433296955
CD14+	DU	wgEncodeEH003466	GSM1008582	287039145
SKNSH	DU	wgEncodeEH003483	GSM1008585	287186739
MCF7/RandshRNA	DU	wgEncodeEH003468	GSM1008603	288004844
K562/SAHACtrl	DU	wgEncodeEH003489	GSM1008580	503410467
MCF7	DU	wgEncodeEH003470	GSM1008565	89113893
IMR90	DU	wgEncodeEH003482	GSM1008586	303769598
HeLaS3/IFNa4h	DU	wgEncodeEH000577	GSM816633	110348694
K562/G2Mphase	DU	wgEncodeEH003472	GSM1008567	431722812
K562/G1phase	DU	wgEncodeEH003469	GSM1008602	426934260
K562/SAHA1um72h	DU	wgEncodeEH003490	GSM1008558	503301111
MCF7/HypLacAc	DU	wgEncodeEH001745	GSM816670	244207602
K562/NaBut	DU	wgEncodeEH002559	GSM1008601	267722720
CD20+RO01794	DU	wgEncodeEH003465	GSM1008588	256442597
GM12878	DU	wgEncodeEH000534	GSM816665	245090730
A549	DU	wgEncodeEH001095	GSM816649	133567925
MCF7/CTCFshRNA	DU	wgEncodeEH003467	GSM1008581	295954052
K562/ZNFP5	UW	wgEncodeEH003016	–	70400755
CD20+RO01778	UW	wgEncodeEH001884	GSM1024765 GSM1024766	71398619

HeLaS3	UW	wgEncodeEH000495	GSM736510 GSM736564	70669968
K562/ZNF4C50C4	UW	wgEncodeEH003009	–	82579252
A549	UW	wgEncodeEH001180	GSM736506 GSM736580	75764710
K562/ZNFb34A8	UW	wgEncodeEH003012	–	95113482
K562/ZNFg54A11	UW	wgEncodeEH003015	–	76873236
CD14+	UW	wgEncodeEH001196	–	33322702
MCF7/EstCtrl0h	UW	wgEncodeEH003018	GSM1024764 GSM1024767	151170759
MCF7/Est100nm1h	UW	wgEncodeEH003017	GSM1024783 GSM1024784	164440980
K562/ZNF4G7D3	UW	wgEncodeEH003010	–	83034668
K562/ZNFe103C6	UW	wgEncodeEH003013	–	78100065
K562/ZNF2C10C5	UW	wgEncodeEH003008	–	173334712
LHCNM2	UW	wgEncodeEH003005	GSM1024786 GSM1024787	89558026
LHCNM2/Diff4d	UW	wgEncodeEH003006	GSM1024771 GSM1024772	120358720
H1hESC	UW	wgEncodeEH000496	GSM736582	24431583
MCF7	UW	wgEncodeEH000502	GSM736581 GSM736588	89482135
K562/ZNFf41B2	UW	wgEncodeEH003014	–	109124535
CD14+/RO01746	UW	wgEncodeEH001196	GSM1024791	67698560
GM12878	UW	wgEncodeEH000492	GSM736496 GSM736620	47899421
K562/ZNFa41C6	UW	wgEncodeEH003011	–	99106989
HepG2	UW	wgEncodeEH000476	GSM646559	69810990
K562	UW	wgEncodeEH000480	GSM646567	71250291
CD20+RO01778	UW	wgEncodeEH002442	GSM1014525	240594387
K562/ZNFP5	UW	wgEncodeEH003153	–	346226678
K562/ZNFa41C6	UW	wgEncodeEH003152	–	372806338
LHCNM2	UW	wgEncodeEH003149	GSM1014524	255134452
LHCNM2/Diff4d	UW	wgEncodeEH003154	GSM1014539	357827356
H7hESC	UW	wgEncodeEH000834	GSM646563	302050785
HUVEC	UW	wgEncodeEH002460	GSM1014528	429088276
A549	UW	wgEncodeEH003146	GSM1014517	350629033

*Naked DNA DNase-seq experiments.

Table 3: **Friedman-Nemenyi hypothesis test results on *AUC at 1% FPR* for all evaluated methods.** The asterisk and the cross, respectively, indicate that the method in the column outperformed the method in the row with significance levels of 0.01 and 0.05

	HINT-BC	HINT-BCN	HINT	DNase2TF	PIQ	Wellington	Neph	Boyle	BinDNase	FLR	Centipede	Cuellar	TC-Rank	PWM-Rank	FS-Rank
HINT-BC															
HINT-BCN															
HINT	*														
DNase2TF	*														
PIQ	*	*													
Wellington	*	*	*	*											
Neph	*	*	*	*	+										
BinDNase	*	*	*	*	*										
Boyle	*	*	*	*	*										
Centipede	*	*	*	*	*	*	*	*							
FLR	*	*	*	*	*	*	*	*	*						
Cuellar	*	*	*	*	*	*	*	*	*						
TC-Rank	*	*	*	*	*	*	*	*	*	*					
PWM-Rank	*	*	*	*	*	*	*	*	*	*	*				
FS-Rank	*	*	*	*	*	*	*	*	*	*	*	+			

Table 4: Friedman-Nemenyi hypothesis test results on *AUC at 10% FPR* for all evaluated methods. The asterisk and the cross, respectively, indicate that the method in the column outperformed the method in the row with significance levels of 0.01 and 0.05

	HINT-BC	HINT-BCN	HINT	DNase2TF	PIQ	Wellington	Neph	Boyle	BinDNase	FLR	Centipede	Cuellar	TC-Rank	PWM-Rank	FS-Rank
HINT-BC															
HINT-BCN															
HINT	*														
DNase2TF	*														
PIQ	*	*	+												
Wellington	*	*	*	*											
Neph	*	*	*	*											
Boyle	*	*	*	*											
BinDNase	*	*	*	*	*										
FLR	*	*	*	*	*	*	*								
Centipede	*	*	*	*	*	*	*	*							
Cuellar	*	*	*	*	*	*	*	*	*						
TC-Rank	*	*	*	*	*	*	*	*	*						
PWM-Rank	*	*	*	*	*	*	*	*	*	*	*	*	+		
FS-Rank	*	*	*	*	*	*	*	*	*	*	*	*	*	*	

Table 5: Friedman-Nemenyi hypothesis test results on *AUC at 100% FPR* for all evaluated methods. The asterisk and the cross, respectively, indicate that the method in the column outperformed the method in the row with significance levels of 0.01 and 0.05

	HINT-BC	HINT-BCN	HINT	DNase2TF	PIQ	Wellington	Neph	Boyle	BinDNase	FLR	Centipede	Cuellar	TC-Rank	PWM-Rank	FS-Rank
HINT-BC															
HINT-BCN															
HINT	*														
DNase2TF	*														
PIQ	*	*	*												
Wellington	*	*	*	*											
Neph	*	*	*	*											
Boyle	*	*	*	*											
BinDNase	*	*	*	*	*	*									
FLR	*	*	*	*	*	*	*								
Cuellar	*	*	*	*	*	*	*	+							
Centipede	*	*	*	*	*	*	*	*							
TC-Rank	*	*	*	*	*	*	*	*	*						
PWM-Rank	*	*	*	*	*	*	*	*	*	*	*	*			
FS-Rank	*	*	*	*	*	*	*	*	*	*	*	*	*		

Table 6: Friedman-Nemenyi hypothesis test results on *AUPR* for all evaluated methods. The asterisk and the cross, respectively, indicate that the method in the column outperformed the method in the row with significance levels of 0.01 and 0.05

	HINT-BC	HINT-BCN	HINT	DNase2TF	PIQ	Wellington	Neph	Boyle	BinDNase	FLR	Centipede	Cuellar	TC-Rank	PWM-Rank	FS-Rank
HINT-BC															
HINT-BCN															
HINT	*														
DNase2TF	*	*													
PIQ	*	*													
Wellington	*	*	*												
Neph	*	*	*	*	+										
Boyle	*	*	*	*	*										
BinDNase	*	*	*	*	*										
Centipede	*	*	*	*	*	*	*	+	+						
FLR	*	*	*	*	*	*	*	*	*						
Cuellar	*	*	*	*	*	*	*	*	*	*					
TC-Rank	*	*	*	*	*	*	*	*	*	*					
PWM-Rank	*	*	*	*	*	*	*	*	*	*		*			
FS-Rank	*	*	*	*	*	*	*	*	*	*	*	+			