

**Supplementary Table 2:**  
**Overview on TF co-occurrence tools and evaluation on comparability**

<b>Tool name</b>	<b>Maintained</b>	<b>Chosen for comparison</b>	<b>Year</b>	<b>Last updated</b>	<b>Source</b>	<b>Note</b>
coTRaCTE	yes	no	2018	-	[1]	Precalculated data needed
PC-TraFF	yes	no	2015	-	[2]	Predefined motifs only
TACO	yes	no	2014	2016	[3]	Replicated data needed
CIS Miner	no	no	2014	2016	[4]	No input example
INSECT 2.0	yes	no	2015	2015	[5]	Disregarded ( too different approach)
SpaMo	yes	yes	2012	2021	[6]	<b>Comparable</b>
iTFs	no	no	2013	-	[7]	Link not reachable
COPS	no	no	2012	2012	[8]	Limited to Drosophila & Mus musculus
CENDIST	no	no	2011	-	[9]	Link not reachable
TICA	no	no	2018	-	[10]	Link not reachable
Nautica	no	no	2020	-	[11]	Link not reachable
MCOT	yes	yes	2019	2021	[12]	<b>Comparable</b>

**Supplementary Table 3:**  
**Feature comparison of MCOT, SPAMO and TF-COMB**

Tool name	MCOT	SPAMO	TF-COMB
<b>Overview</b>			
Input	ChIP-seq; Anchor motif; Partner motif(s);	ChIP-seq; Meme motifs	ChIP-seq; Meme motifs; Peaks with regions of interest
Type	One-against-all	One-against-all	All-against-all
ChIP-seq mandatory	Yes	Yes	No
Genome reference free	No	Yes	Yes
Programming language	C++	C	Python, Cython
Output	plethora of result files (intermediate files, different files for metrics)	.html summary, result .tsv	result tsv, optional plots
<b>Features</b>			
Scoring	Yes	Yes	Yes
Differential analysis	No	No	Yes
Finding Hubs	No	No	Yes
Preferred Distance analysis	No	(Yes)	Yes
Dynamic parameters for distance analysis	(Yes)	No	Yes
Orientation analysis	forced	forced	optional
Anchor free motif prediction	No	No	Yes
Deriving networks	No	No	Yes
Network clustering	No	No	Yes
Overlapping motifs	Yes	No	Yes
<b>Plotting</b>			
Weighted networks	No	No	Yes
Network substructures	No	No	Yes
Preferred spacing	No	Yes	Yes
Paired footprint visualization	No	No	Yes

## Supplementary Table 4:

### Literature search for top 10 exclusively found pairs for MCOT, SPAMO and TF-COMB

Mcot Only			weak evidence
Anchor	Partner	Sources	no evidence
ATF2	SREBF2	[13]	strong evidence
NR2C1	ESRRA	-	
MEF2A	SMAD5	[14]	
SMAD5	MEF2B	[14]	
BHLHE40	MYC	[15]	
SPI1	ETS1	[16]	
NR2F1	USF1	-	
STAT3	STAT5A	[17]	
USF2	SREBF1	[18]	
STAT3	STAT1	[16]	
Spamo Only			
Anchor	Partner	Sources	
MEF2C	PBX3	[18]	
PAX5	ZNF384	-	
ZNF384	PBX3	-	
NFYB	MXI1		
MEF2C	EGR1	-	
NFYB	MAX	[19]	
NFIC	ZNF384	-	
PBX3	CEBPB	-	
PAX5	CEBPB	-	
ZNF384	MAZ	-	
TF-COMB Only			
Anchor	Partner	Sources	
JUNB	BATF	[20],[21],[22]	
JUNB	NFIC	[23]	
NFATC3	TBX21	[24]	
IRF4	CREM	[25]	
JUNB	ATF2	[26]	
NFIC	BATF	*	
MEF2B	EBF1	[27]	
CREM	ETV6	-	
JUNB	IRF4	[20]	
SP1	CREM	[16]**	
* We found the pairs NFIC-JUNB and JUNB-BATF (top2) with strong evidence. This hints on a connection between BATF-NFIC connected by JUNB			
** Only reported in <i>C. familiaris</i> (BioGrid)			

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