Supplemental Tables

Supplemental Table 1: Methods for the identification of RNA binding sites of RBPs

CLIP methods are listed detailing how the reads are used to identify binding sites.

Supplemental Table 2: Peak calling tools

Peak calling tools are ordered by date of publication to reflect development in methodologies and technologies. A brief description and web link is given.

Supplemental Table 3: Tools for the analysis and visualisation of CLIP derived binding sites

Other tools relevant for CLIP data analysis are categorised into: i) motif finding, ii) binding site modelling, iii) databases, iv) visualisation and v) miscellaneous with a brief description and web link.

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Data Science Issues in Studying Protein–RNA Interactions with CLIP Technologies
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Supplemental Table 1: Methods for the identification of RNA binding sites of RBPs

Acronym	Full Name	Citation	Analysis based on
BrdU CLIP	Bromodeoxyuridine UV CLIP	(1)	read start
CIMS	Crosslink-induced mutation site analysis	(2)	deletions in read
CLIP	(UV) Crosslinking and immunoprecipitation	(3)	full read
CLIP-seq	Crosslinking immunoprecipitation coupled with high-throughput sequencing	(4)	full read
CRAC	UV cross-linking and analysis of cDNAs	(5)	full read
eCLIP	Enhanced CLIP	(6)	read start
FAST-iCLIP	Fully automated and standardized iCLIP	(7)	read start
FLASH	Fast ligation of RNA after some sort of affinity purification for high-throughput sequencing	(8)	read start
Fr-iCLIP	Fractionation iCLIP	(9)	read start
HITS-CLIP	High-throughput sequencing of RNA isolated by crosslinking immunoprecipitation	(10)	full read

iCLIP	Individual-nucleotide resolution CLIP	(11)	read start
iCLAP	Individual-nucleotide resolution crosslinking and affinity purification	(12)	read start
irCLIP	Infrared-CLIP	(13)	read start
PAR-CLIP	Photoactivatable ribonucleoside-enhanced CLIP	(14)	transitions in read
4SU-iCLIP	4SU-enhanced iCLIP	(15)	read start
RIP-seq	RNP (or RNA) immunoprecipitation followed by sequencing	(16)	full read
RIP-iT-seq	RNA:protein immunoprecipitation in tandem coupled to high-throughput sequencing	(17)	full read
DO-RIP-seq	Digestion optimised RNA immunoprecipitation with deep sequencing	(18)	full read
sCLIP	Simplified CLIP	(19)	read start
uvCLAP	UV crosslinking and affinity purification	(8)	read start

Supplemental Table 2: Peak calling tools

Name	Description	Link
iCount (11, 20)	iCount package includes a peak caller for nucleotide-resolution methods using false discovery rate with local randomisation. It allows adjustments of three variables: 1. Randomisation within local regions (intergenic, UTR3, UTR5, ncRNA, intron, CDS) or within whole genes, 2. The length of the flanking region around each position to define cluster of significantly crosslinked sites. 3. The length of window used to combine proximal crosslink clusters. *Pros: The method exploits the nucleotide resolution of truncated cDNAs, and its enables to search for cluster of a broad size range (variable flank and window regions, as explained in the text).* *Cons: Normalisation by RNA-seq or other control data is not yet implemented. It can be slow because of the randomisation step.*	https://github.com/tomazc/iCount http://icount.biolab.si https://imaps.genialis.com (*under development*)

PARalyzer (21)	For PAR-CLIP only. Uses a kernel density estimator to profile mutations and background. Compares the difference to call binding sites. *Pros: Widely used tool for PAR-CLIP analysis* *Cons: Valid mutations selected by a threshold rather than modelling*	http://www.genome.duke.edu/labs/ohler/research/PARalyzer/.
wavClusteR (22)	Uses a non-parametric, two component mixture model to distinguish crosslink mutations from noise. Uses a coverage-based algorithm, Mini-Rank Norm to identify peak boundaries.	https://bioconductor.org/packages/release/bioc/html/wavClusteR.html
Piranha (23)	Uses zero-truncated negative binomial distribution as the recommended setting. RNA-seq data, or information about covariates can be included in the model. *Pros: Very fast. Can account for confounders or transcript abundance in peak calling process* *Cons: Does not support peak calling based on genomic region.*	http://smithlabresearch.org/software/piranha/

ASPeak (24)	Uses a negative binomial distribution. RNA-seq data can be supplied for normalisation. *Pros: Fast and can be parallelised. Local normalisation by genomic regions together with RNA-seq.* *Cons: For the single nucleotide resolution methods the data needs to be preprocessed to set the right crosslinking positions.*	https://sourceforge.net/projects/as-peak/
CLIP Tool Kit (25, 26)	Defines the crosslink sites using CIMS and CITS analysis. Uses a ‘valley-seeking’ algorithm to delineate adjacent peaks	http://zhanglab.c2b2.columbia.edu/index.php/CTK
MiCLIP (27)	Uses a two-pass hidden Markov model first to identify enriched CLIP clusters and second to identify reliable binding sites within the clusters.	https://cran.r-project.org/src/contrib/Archive/MiClip/
PIPE-CLIP (28)	Uses a zero-truncated negative binomial distribution.	https://github.com/QBRC/PIPE-CLIP

	Pros: Applicable to readthrough, mutation and truncation methods. For mutation methods, models events using a binomial distribution. *Cons: Clusters adjacent reads, rather than specifying a window*	
PyCRAC (29)	Identifies significantly enriched regions by calculating false discovery rates	http://sandergranneman.bio.ed.ac.uk/Granneman_Lab/pyCRAC_software.html
CLIPper (6, 30)	Peak caller using false discovery rate with local randomisation followed by Poisson distribution count modelling. *Pros: Supports normalisation by genomic region and combines two methods used in other tools.* *Cons: Slow and needs annotation.*	https://github.com/YeoLab/clipper
OmniCLIP (31)	In development. Uses a Bayesian model to account for confounding factors	https://github.com/philippdre/omniCLIP
PureCLIP (32)	Uses a hidden Markov model to incorporate RNA abundance and non-specific sequence bias	https://github.com/skrakau/PureCLIP

Supplemental Table 3: Tools for the analysis and visualisation of CLIP-derived binding sites

	Name	Description	Link
Motif finding	MEMERIS (33)	Adapts the MEME expectation maximisation motif finding algorithm by including the single-strandness of the region.	http://www.bioinf.uni-freiburg.de/~hiller/MEMERIS/
	HOMER (34)	Designed for ChIP-seq. Scores occurences of motifs and uses a hypergeometric enrichment calculation	http://homer.ucsd.edu/homer/
	DREME (35)	Designed for ChIP-seq. Uses an expectation maximisation approach	http://meme-suite.org/tools/dreme
	cERMIT (36)	Utilises quantitative data to rank regions then identifies enriched motifs.	https://ohlerlab.mdc-berlin.de/software/PAR-CLIP_motif_analysis_tool_87/
	RNAcontext/	Trains a model that includes secondary structural	http://www.rnamotif.org/

	RBPmotif (37)	context to assess enrichment of a motif.	
	Zagros (38)	Includes sequence, pairing probability and crosslink events and learns these using expectation maximisation	http://smithlabresearch.org/software/zagros/
	RNAmotifs2 (39, 40)	Compares motifs around regulated and control features. Uses a Fisher test and adjusts for the false discovery rate	https://github.com/grexor/rnamotifs2
	*k*pLogo (41)	Focuses on identifying position-specific short motifs based on enrichment	http://kplogo.wi.mit.edu/
	ssHMM (42)	Uses a hidden Markov model and Gibbs sampling to include the relationship between sequence and structure.	https://github.molgen.mpg.de/heller/ssHMM
	SMARTIV (43)	Uses a *k*-mer based approach to extract sequence and structure motifs from ranked	http://smartiv.technion.ac.il/

		regions.	
	SARNAclust (44)	An unsupervised method that uses graph kernels to assess sequence and structure similarities and identify the feature importance.	https://github.com/idotu/SARNAclust
Binding site modelling	GraphProt (45)	Encodes *k*-mer motifs and structural shapes as graph kernel features, including the interedependencies. Fits a model using Support Vector Machine or regression depending on the availability of affinity data.	http://www.bioinf.uni-freiburg.de/Software/GraphProt/
	iONMF (46)	Uses matrix factorisation to integrate multiple factors in order to identify discriminative non-overlapping, class-specific RNA binding patterns of different strengths	https://github.com/mstrazar/iONMF
	Deepnet-rbp (47)	Uses a deep learning framework (multimodal deep belief networks) to to encode sequence, secondary structure and uniquely tertiary	https://github.com/thucombio/deepnet-rbp

		structure predictions to generate RBP binding motifs and predictions	
	iDeep (48)/ iDeepS (49)	Uses a deep learning framework (convolutional neural networks). IDeep can only discover seqeunce preferences whereas IDeepS also identifies structural motifs.	https://github.com/xypan1232/iDeep https://github.com/xypan1232/iDeepS
	DeBooster (50)	Uses a deep boosting machine learning approach to model sequence binding preferences.	https://github.com/dongfanghong/deepboost
Databases	DoRiNA 2.0 (51)	Includes RBP binding and miRNA target sites in a unified database. Includes 100 RBP datasets for human, 30 for M mouse and 6 for *C. elegans*. Integrated with the UCSC genome browser and allows the upload of the user's own data for queries. Does not re-process data.	http://dorina.mdc-berlin.de/
	CLIPdb2:	Includes both experimentally probed (498	http://lulab.life.tsinghua.edu.cn/postar/

	POSTAR (52)	CLIP-seq and 151 eCLIP) and computationally predicted binding sites. Includes systematic re-annotation of regions. Different peak callers used for different CLIP methods.	
Visualisation	iCount (11, 20)	A command-line tool to visualise metaprofiles (RNA maps) of crosslinking at splice sites, gene boundaries, ncRNAs, and other features.	https://github.com/tomazc/iCount http://icount.biolab.si
	rMAPS (53)	A web-server to produce RNA maps around alternatively spliced exons	http://rmaps.cecsresearch.org/
	expressRNA (40)	A web-server to examine RNA motifs and produce RNA maps	http://www.expressrna.org/
Miscellaneous analysis	iCount (11, 20)	Apart from the peak caller, the iCount package also includes tools to demultiplex and map sequence data to the genome to define cross-link sites, quantify cDNAs at these sites based on UMIs, annotate the site, provide summary	https://github.com/tomazc/iCount http://icount.biolab.si https://imaps.genialis.com (*under development*)

		statistics, identify enriched sequence motifs and analyse motif distribution around crosslink sites, and visualise metaprofiles (RNA maps) of crosslinking at splice sites, gene boundaries, ncRNAs, and other features.	
	CLIP Tool Kit (25, 26)	Apart from the peak caller, the CLIP Tool Kit provides a set of tools for analysis of CLIP data including pipelines to filter and map reads, collapse PCR duplicates to obtain unique CLIP tags, and define CLIP tag clusters.	http://zhanglab.c2b2.columbia.edu/index.php/CTK
	CapR (54)	Calculates probabilities that an RNA base position is located within secondary structural context.	https://github.com/fukunagatsu/CapR
	dCLIP (55)	dCLIP analyses differential binding regions in two CLIP experiments. As a hidden Markov model is used to detect common or unique binding	http://qbrc.swmed.edu/software/

		regions, this is more appropriate for assessing relative binding at a common site, rather than the presence or absence of binding.	
	PAR-CLIP HMM (56)	Uses a Bayesian hidden Markov model to identify PAR-CLIP mutation sites by establishing a joint distribution of read and mutation counts.	https://qbrc.swmed.edu/softwares.php
	PyCRAC (29)	A suite of Python scripts which can be used to analyze HITS-CLIP, PAR-CLIP or CRAC data and many other types of data.	http://sandergranneman.bio.ed.ac.uk/Granneman_Lab/pyCRAC_software.html
	BackCLIP (57)	Identifies common non-specific background in PAR-CLIP data.	https://github.com/phrh/BackCLIP
	iCLIPro (58)	Can be used to control for systematic mis-assignments in iCLIP data by visualising coinciding and non-coinciding fragment start sites in order to examine the best way to analyze iCLIP data.	http://www.biolab.si/iCLIPro/doc/

	BMix (59)	Uses a constrained three-component binomial mixture model to identify high confidence mutations in PAR-CLIP reads.	https://github.com/cbg-ethz/BMix

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