

aracne.networks, a data package containing gene regulatory networks assembled from TCGA data by the ARACNe algorithm

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1 Overview of aracne.networks data package

The *aracne.networks* data package provides context-specific transcriptional regulatory networks (also called interactomes or regulons) reverse engineered by the ARACNe algorithm from The Cancer Genome Atlas (TCGA) RNAseq expression profiles.

ARACNe networks This package contains 25 Mutual Information-based networks assembled by ARACNe-AP [1] with default parameters (MI p-value = 10^{-8} , 100 bootstraps and permutation seed = 1). ARACNe is a network inference algorithm based on an Adaptive Partitioning (AP) Mutual Information (MI) approach [1]. In short, ARACNe-AP estimates all pairwise Mutual Information scores between gene expression profiles, then assesses the significance of such Mutual Information by comparison to a null dataset. ARACNe then draws network edges between centroid genes (Transcription Factors and Signaling Proteins) and genes significantly associated with them (i.e. with significant MI). It then calculates Data Processing Inequality (DPI) to reduce the number of indirect connections.

ARACNe-AP was run on RNA-Seq datasets normalized using Variance-Stabilizing Transformation [2]. The raw data was downloaded on April 15th, 2015 from the TCGA official website [3]. We follow the TCGA naming convention (e.g. BRCA = Breast Carcinoma) to name the individual context-specific networks.

```
> library(aracne.networks)
> data(package="aracne.networks")$results[, "Item"]

[1] "regulonblca" "regulonbrca" "reguloncesc" "reguloncoad" "regulonesca"
[6] "regulongbm" "regulohnsc" "regulonkirc" "regulonkirp" "regulonlam1"
[11] "regulonlihc" "regulonluad" "regulonlusc" "regulonnet" "regulonov"
[16] "regulonpaad" "regulonpcpg" "regulonprad" "regulonread" "regulonsarc"
[21] "regulonstad" "regulontgct" "regulonthca" "regulonthym" "regulonucec"
```

Write a network to file The package contains a function to print individual networks into a file. Four columns will be printed: the Regulator id, the Target id, the Mode of Action (MoA, inferred by Spearman correlation analysis [4]) that indicates the sign of the association between regulator and target gene and ranges between -1 and +1, the Likelihood (essentially an edge weight that indicates how strong the mutual information for an edge is when compared to the maximum observed MI in the network, it ranges between 0 and 1). Further details about the *regulon* object as a model for transcriptional regulation are present in the manuscript [4].

In the following example, we print the first 10 interactions from the bladder carcinoma (blca) network. The network genes are identified by Entrez Gene ids.

```
> data(regulonblca)
> write.regulon(regulonblca, n = 10)
```

Regulator	Target	MoA	likelihood
10002	2648	0.994689591270463	0.886774633189913
10002	677827	0.116175345640136	0.707841406455471
10002	80152	0.999770437015603	0.950286744281199
10002	284382	-0.0368424333564396	0.0419762049859333
10002	9866	0.972066598154448	0.442238853411591
10002	283422	-0.574084929385018	0.260828476620346
10002	221613	-0.0959242601820319	0.717904706549976
10002	348174	0.953943934091558	0.814491117578869
10002	373509	0.704691385719852	0.244337186726846
10002	8803	-0.959165656086931	0.831653033754096

The user may want to analyze all the connections of a particular regulator (E.g. "399", the RHOH gene).

```
> data(regulonblca)
> write.regulon(regulonblca, regulator="399")
```

Regulator	Target	MoA	likelihood
399	9595	1	0.999999439751274
399	54440	1	0.999999439753891
399	5788	1	0.999993691255193
399	2124	1	0.999993972431349
399	10563	0.999999999999987	0.999880973084544
399	80342	1	0.999979237947268
399	1840	0.999999959099145	0.994240739975982
399	8875	0.999999999999397	0.999602389369848
399	6689	0.999999999998723	0.999531614767901
399	200186	0.154403590654008	0.948828817305409
399	165631	0.999999999950565	0.998777586463862
399	54509	0.999999981560018	0.997883918024065
399	171389	0.999999994824044	0.996800613785205
399	147929	-0.999154534552766	0.985197674740525
399	23416	0.999929331217517	0.96812145442081
399	26015	-0.992838466368412	0.834785111763068
399	10148	0.999999999999872	0.999729153685544
399	4951	-0.0504647730526015	0.544073601564966
399	57003	-0.0751708929022855	0.714920200879607

References

- [1] Giorgi, F.M. et al. (2016) ARACNe-AP: Gene Network Reverse Engineering through Adaptive Partitioning inference of Mutual Information. *Bioinformatics* doi: 10.1093/bioinformatics/btw216.
- [2] Anders, S and Huber W. (2010) Differential expression analysis for sequence count data. *Genome Biol* 2010;11(10):R106
- [3] Weinstein J.N. et al. (2013) The cancer genome atlas pan-cancer analysis project. *Nature Genetics* 45, 1113-1120 2013

- [4] Alvarez M.J. et al. (2016) Functional characterization of somatic mutations in cancer using network-based inference of protein activity. *Nature Genetics* *in press*.