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TRANSPARENT: a Python tool for designing transcription factor regulatory networks

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Abstract

Transcription factors are proteins able to selectively bind DNA short traits, namely Transcription Factors Binding Sites, in order to regulate gene expression both in terms of repression and activation. Despite plenty of studies focusing on Transcription Factors and on the role they play in specific biological tasks or diseases, is available in literature, to our knowledge there is no tool able to automatically provide a list of Transcription Factors involved in this task and the associated interaction network through a solid computational analysis.

TRANSPARENT (TRANScRiPtion fActor REgulatory NeTwork) is a user-friendly python tool designed to help researchers in studying given biological tasks or given diseases in human, by identifying Transcription Factors controlling and regulating the expression of genes associated with that task or disease. The list of Transcription Factors, that are significantly associated with a gene pool and the correspondent P-value are provided together with the related Transcription Factors network that can be directly visualized through STRING database.

The effectiveness and reliability of the tool was assessed by applying it to two different test-cases: Schizophrenia and Autism disorders. The obtained results clearly show that identified TFs, for both datasets, are significantly associated with those disorders, both in terms of gene enrichment and coherence with literature. The proposed tool TRANSPARENT can be a useful instrument to investigate transcription factor networks and unveil the role that TFs play in given biological tasks and diseases.

Keywords: Transcription Factors, Transcription Factors Binding Sites, protein Networks, Gene regulation, Disease associated genes

1 Introduction

Transcription Factors (TFs) are proteins involved in the regulation of gene expression. They are able to selectively bind DNA short traits, namely Transcription Factors Binding Sites (TFBSs), often located in the promoter regions of genes, to regulate gene expression both in terms of repression

and activation. A large collection of experimental datasets related to TFBSs ([Zhang *et al.*, 2020, Yevshin *et al.*, 2017]) - mainly coming from Chip-seq experiments - is available as well as a large amount of prediction data coming from computational tools designed and trained on experimental data ([Tan and Lenhard, 2016, Jayaram *et al.*, 2016]). TFs often act together and their binding to DNA sites of given promoters

is tightly orchestrated in order to facilitate or impede gene expression depending on the need of the cell at a given time [Cumbo *et al.*, 2018]. The design of TF regulatory networks is a key point to understand the complex mechanisms underlying regulation of gene expression in biological tasks and pathways [Wilkinson *et al.*, 2017, Neph *et al.*, 2012].

The study of TFs networks can also play a crucial role in designing therapeutic intervention to identify specific targets as shown by Karamouzis and Papavassiliou in the context of Breast cancer [Karamouzis and Papavassiliou, 2011].

Chen and colleagues studied how TFs coordinate gene expression in a combinatorial fashion, through cliques of self-regulated core TFs controlling cell identity and cell state. They also studied the complex and interconnected feed-forward transcriptional loops building core transcriptional regulatory circuitry in cancer [Chen *et al.*, 2020].

Lots of studies focused on identifying TFs and their interaction networks in different contexts such as self-renewability and pluripotency of embryonic stem cells ([Nakai-Futatsugi and Niwa, 2013]), haematopoiesis [Wilson *et al.*, 2011], environmental stress response [Song *et al.*, 2016], T-cell development and differentiation [Collins *et al.*, 2009] among the others.

Cui and colleagues ([Cui *et al.*, 2010]) developed a software package to identify TFs involved in biological processes using both gene expression data and existing knowledge base.

Despite a large number of studies, focusing on TFs and on the role they play in specific biological tasks or diseases, is available in literature, to our knowledge there is no tool able to automatically provide a list of TFs involved in those tasks, through a solid computational analysis and the corresponding interaction networks exclusively basing on promoter TFBS enrichment.

Indeed MEME suite ([Bailey *et al.*, 2015]) faces up a similar task but from a different point of view and so far it was not thought and focused on TFs and promoter sequences. Given a set of sequences (promoter sequences of given genes in this case), it is able to provide, if any, common consensus sequences occurring more than expected. The user can also provide his own consensus to look for in the sequences, but the software is not structured so that one can provide

a Position Weight Matrix (PWM), as the one characterizing TFBSs of given TFs, and it does not use ad hoc algorithm designed to find similarity based on PWMs like the software we used (matchPWM of the Biostring R library see Section 2). Anyway to use MEME to this aim the user should provide any single consensus for each known TF (TRANSPARENT analyzes 626 different TFs) to identify significant TFs.

TRANSPARENT is implemented so that all available PWMs related to known and reliable TFs are considered and automatically included in the analysis, moreover the tool also include and manage the different transcripts associated to the genes in the considered list. The user has just to upload his own gene list and the computational analysis is completely *transparent* providing final results in textual mode and with a link to furtherly customize transcription factor network analysis through STRING web site ¹.

TRANSPARENT is a user-friendly python tool, designed to help researchers to analyze TFs involved in the regulation of specific genes associated to a given task or a given disease in human, is presented. The tool was successfully applied to two different test-cases: Schizophrenia and Autism disorders, identifying a set of TFs involved in the considered diseases and their interaction networks.

2 Materials and Methods

TRANSPARENT (TRANScRiPtion fActor REgulatory NeTwork) is a Python tool designed to identify TFs associated to a pool of genes responsible for a given task or associated to a given disease and to build an interaction network of selected TFs. The pipeline of the tool is depicted in Fig 1. Step 1-3 (red boxes) are precomputed and data are already included in the package in order to minimize computational time and resources. Step 4-6 are computed on sample instance providing as a result a list of TFs associated to the uploaded gene list and an interaction network that can be directly visualized and managed through STRING site.

¹<https://string-db.org/>

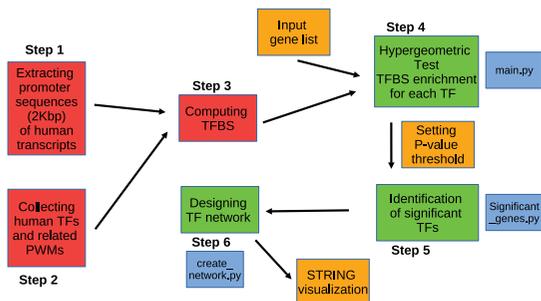


Fig. 1 TRANSPARENT pipeline. Red boxes represent precomputed steps, green boxes represent core steps of the tool computed through python scripts (cyan boxes). Yellow boxes represent input data provided by users and instruments for the visualization (STRING database)

The six steps TRANSPARENT pipeline are reported in the following:

- **Step 1 - Extracting human promoter sequences**
A complete list of human genes and related transcripts, linked to the different isoforms of gene products, are selected. A number of 23,459 genes and 73,432 transcripts are collected. Promoter sequences (2,000 base pairs upstream the Transcription Start Site) are considered according to [Cumbo *et al.*, 2018] of those gene/transcripts were retrieved through the package "TxDb Hsapiens UCSC.hg19.KnownGene" version 3.2.2 of R software.
- **Step 2 - Collecting human TFs and related PWMs**
The set of available 626 human TFs is selected and the related consensus pattern sequences, expressed in terms of Position Weight Matrices (PWMs), are retrieved through JASPAR database ([Fornes *et al.*, 2020]).
- **Step 3 - Computing TFBSs**
TFBS associated to each considered human TF are computed through the `matchPWM()` function, integrated into the Biostrings R library², setting a threshold of 0.90.
- **Step 4 - TFBS enrichment for each TF and hypergeometric test**

Statistical tests are performed to assess the association between a given TF and the input gene set. Input file must contain a list of Entrez gene IDs, one ID for each line; an input file sample is included in the directory `testset` of the package. A hypergeometric test is performed for each considered TF, by comparing the number of genes in the pool set showing at least one TFBS in the promoter region (over all the transcripts) and the expected number, computed on the whole gene set. Obtained P-values are then adjusted using Bonferroni's correction. A complete list of TF and their associated P-value and adjusted P-value is made available in the output directory.

- **Step 6 - Designing TF network**
A link to STRING database [Szkarczyk *et al.*, 2021] visualizing the network of significant TFs is provided in the output directory. Default view is designed with a stringent interaction threshold but can be changed by the user in the STRING database. STRING visualization allows an at-a-glance view of connected significant TFs associated to the considered gene pool. The network of TFs and linked genes, initially submitted by the user, is also available through STRING database (when the `-l` flag is set).

3 Results

Several gene sets associated to given diseases were considered as test-cases to assess the effectiveness and reliability of the tool. In this Section results associated to two sample gene lists are reported: the former is made of genes associated to Schizophrenia disorder, the latter is made of genes associated to Autism disorder.

Gene lists were obtained through DisGeNET [Piñero *et al.*, 2017], setting a threshold of 0.3 on the score associated to the likelihood of the link between gene and disease.

3.1 First case-study: Schizophrenia disorder

A list of 1026 genes associated to Schizophrenia disorder was downloaded from Disgenet

²<https://bioconductor.org/packages/release/bioc/html/Biostrings.html>

(likelihood-score higher than 0.3). The software identified 76 TFs (80 PWM models) showing a significant TFBS enrichment - adjusted P-value smaller than 10^{-2} - in the promoter sequences of the 1026 Schizophrenia-associated genes (101 TFs - 107 PWM models - when considering an adjusted P-value smaller than 5×10^{-2}). Potential interactions among the 76 identified TFs were analysed through STRING database ([Szkarczyk *et al.*, 2021]). 28 TFs, out of the initial 76 ones, were found to be connected considering a stringent threshold on interaction likelihood ($T = 0.9$). The network, made available by TRANSPARENT software through STRING, is reported in the Fig. 2. The number of connected TFs considering a smaller threshold on interaction likelihood is 38 for $T = 0.7$ and 66 for $T = 0.4$. The extended network, considering first (or second) neighbour nodes can be analyzed through STRING database both in terms of biological composition and clusters of the networks and can be customized setting the interaction likelihood threshold.

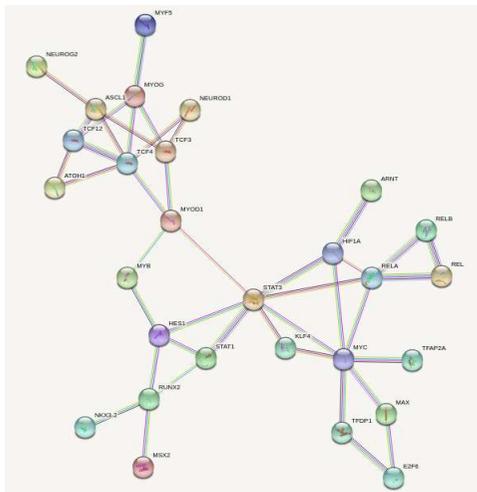


Fig. 2 TF network associated to Schizophrenia.

Enrichment disease analysis of identified TFs (adjusted P-value smaller than (5×10^{-2}) was performed through DAVID tool ([Jiao *et al.*, 2012]). Several classes, coming from GAD Disease database ([Becker *et al.*, 2004]), were found to be significantly enriched; among them: Schizophrenia disorder (8 TFs - P-value 6.9×10^{-2} considering best 76 TFs), Parkinson's disease (6 TFs P-value

2×10^{-3}), Depression (5 TFs - P-value 1.7×10^{-2}), Neurological Disease Class (27 TFs - P-value 3.1×10^{-2}), Antisocial behavioral traits (2 TFs - P-value 6.1×10^{-2}), PSYCH disease Class (19 TFs - P-value 6.6×10^{-2}) and Schizophrenia/bipolar disorder (2 TFs - P-value 9.1×10^{-2}) considering best 101 TFs. The 8 identified TFs belonging to the GAD Disease class Schizophrenia are reported in Tab 1.

MAZ (adjusted P-value $< 10^{-21}$), KLF5 (adjusted P-value $< 10^{-18}$), KLF15 (adjusted P-value $< 10^{-17}$), VEZF1 (adjusted P-value $< 10^{-16}$) and ZNF148 (adjusted P-value $< 10^{-15}$) are the identified TFs with the lowest adjusted P-values. Remarkably 29 TFs showed an adjusted P-value lower than 10^{-5} . The table with all the TFs with P-value smaller than 5×10^{-2} is reported as Supplemental Material (TabS1). Interestingly KLF5 (adjusted P-value $< 10^{-18}$), KLF15 (adjusted P-value $< 10^{-17}$), KLF4 (adjusted P-value $< 10^{-13}$) and KLF2 (adjusted P-value $< 10^{-11}$), belonging to the family Kruppel-like factor, were identified as highly significant, in particular KLF5 was found to be highly related to Schizophrenia and down-regulated in Schizophrenic subjects ([Yanagi *et al.*, 2008]). Moreover 5 TFs, belonging to the TCF family, TCF3 (P-value $< 10^{-6}$), TCF12 (P-value $< 10^{-6}$), TCF5 (P-value $< 10^{-3}$), TCF7 (P-value $< 10^{-3}$) and TCF4 (P-value $< 10^{-2}$) were found as highly significant. Particularly a TCF4 was found to regulate genes involved in neuronal development and schizophrenia risk ([Xia *et al.*, 2018, Zakharyan, 2016]). Also FOS (adjusted P-value $< 10^{-2}$) is known to be involved in Schizophrenia disorder ([Zakharyan, 2016]).

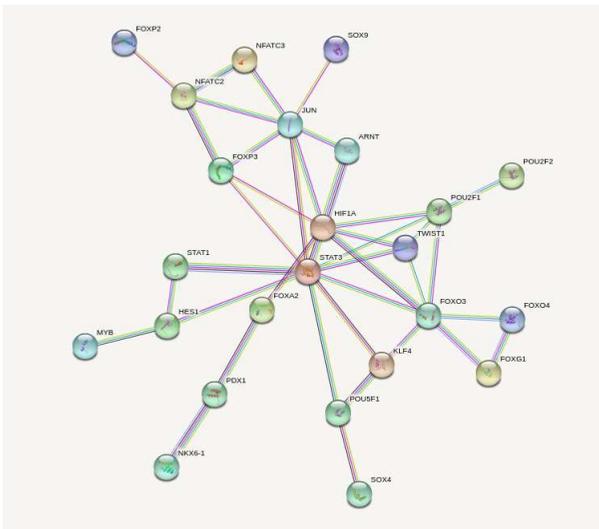
3.2 Second case-study: Autism disorder

A list of 1112 genes associated to Autism disorder was downloaded from Disgenet (no threshold on the likelihood was set). The software identified 181 TFs showing a significant TFBS enrichment - adjusted P-value smaller than 0.01 - in the promoter sequences of the 1112 Autism-associated genes (214 TFs when considering an adjusted P-value smaller than 0.05). Potential interactions among the 181 identified TFs were analysed through STRING database

Table 1 Identified TFs associated to Schizophrenia in GAD disease database.

Gene symbol	Gene name
ASCL1	achaete-scute family bHLH transcription factor 1
FOXP2	forkhead box P2
KLF5	Kruppel like factor 5
RUNX2	runt related transcription factor 2
TBX3	T-box 3
TCF4	transcription factor 4
TFAP2A	transcription factor AP-2 alpha
TFAP2B	transcription factor AP-2 beta

([Szkarczyk *et al.*, 2021]). 24 TFs, out of the initial 181, were found to be in the first connected component, considering a stringent threshold on interaction likelihood ($T = 0.9$). The related network, made available by TRANSPARENT software, is reported in the Fig. 3. The number of TSs in the connected network considering a smaller threshold on interaction likelihood is 97 for $T = 0.7$ and 172 for $T = 0.4$.

**Fig. 3** TF network associated to Autism disorder in GAD disease database.

Enrichment analysis of the 214 identified TFs (adjusted P-value smaller than 0.05) was performed through DAVID tool ([Jiao *et al.*, 2012]). Several classes, coming from GAD Disease database ([Becker *et al.*, 2004]), were found to be significantly enriched; among them: Autism (8 TFs - P-value $< 9.5 \times 10^{-2}$ considering best 181 TFs), Neurodevelopmental psychiatric disorders (3 TFs - P-value $< 1.7 \times 10^{32}$), Parkinson's Disease (7 TFs - P-value $< 1.2 \times 10^{-2}$) and Depression (7 TFs - P-value $< 1.6 \times 10^{-2}$) considering best 214 TFs. The 8 identified TFs belonging to the GAD Disease class Autism are reported in Tab 2.

VEZF1 (P-value $< 10^{-17}$), MZF1 (P-value $< 10^{-17}$), KFL15 (P-value $< 10^{-15}$), MAZ (P-value $< 10^{-15}$) and ZNF148 (P-value $< 10^{-14}$) are the identified TFs with the lowest adjusted P-values. 45 TFs showed an adjusted P-value lower than 10^{-5} . The table with all the TFs with P-value smaller than 10^{-2} is reported as Supplemental Material (TabS2). Interestingly many TFs - 19 - belonging to the family FOX (forkhead box), were identified as highly significant; among them: FOXP2 (adjusted P-value $< 10^{-8}$), FOXH1 (adjusted P-value $< 10^{-8}$), FOXK2 (adjusted P-value $< 10^{-7}$), FOXP1 (adjusted P-value $< 10^{-7}$), FOXA3 (adjusted P-value $< 10^{-6}$), FOXO3 (P-value $< 10^{-5}$), FOXD1 (adjusted P-value $< 10^{-5}$). Those findings are consistent with related literature, providing a strong evidence of the link between FOX genes (expressed in the central nervous system

Table 2 Identified TFs associated to Autism disorder in GAD disease database.

Gene symbol	Gene name
CUX2	cut like homeobox 2
EN2	engrailed homeobox 2
FOXP2	forkhead box P2
HES1	hes family bHLH transcription factor 1
HOXA1	homeobox A1
MAZ	Myc associated zinc finger protein
NFIL3	nuclear factor, interleukin 3 regulated
POU6F2	POU class 6 homeobox 2

that are involved in brain development as well as the evolution of language) and autism spectrum disorder, regulating genes implicated in this disorder ([Bowers and Konopka, 2012]). Interestingly a significant association between FOXP2 single nucleotide polymorphisms and autistic disorder was found in [Gong *et al.*, 2004]. Moreover FOXO subfamily is known to be involved in ageprogressive axonal degeneration and associated to several neurological and neurodevelopmental disorders, such as epilepsy, microcephaly, and autism ([Hwang *et al.*, 2018]). Similarly, several TFs belonging to the homeobox family (HOX) and to Basic Helix-Loop-Helix (BHLH), in particular ASCL1, were identified by the software as highly significant in line with previous works claiming the association between those TF families and autism disorders ([Rylaarsdam and Guemez-Gamboa, 2019]).

4 Conclusion

The tool presented in this work is a user-friendly software designed to help researchers in analysing gene sets associated to a given task or a given disease. It allows to extract useful information regarding Transcription Factors involved in the expression regulation of given gene sets providing the related TF network that can be directly visualized and furtherly customized through STRING web resource. The effectiveness and reliability of the tool was assessed through two different test-cases: Schizophrenia and Autism disorder.

Obtained results clearly show that identified TFs, for both datasets, are significantly associated with given disorders, both in terms of gene enrichment and coherence with literature. TRANSPARENT is based on a simple but straight computational analysis; to the best of our knowledge there is no available tool able to provide clear and easy to use data associated to Transcription Factor regulation of a given gene set. In conclusion we are confident that TRANSPARENT can be a useful instrument to investigate transcription factor networks and unveil the role that TFs play in given biological tasks and diseases.

Declarations

Data used in the present work can be found at the following link:

- Available PWMs associated to human Transcription Factors are available in the JASPAR repository through the site <https://jaspar.genereg.net/>.
- The gene list associated to Schizophrenia and Autism disorders are available in the DisGeNet repository through the site <https://www.disgenet.org/>.
- Authors' contributions: DS: conception and design of the work, acquisition, analysis, interpretation of data, draft of the work and revision. CD: creation of new software used in the work, acquisition, analysis, interpretation

of data, draft of the work and revision.

- Project name: TRANSPARENT
- Project homepage: <https://github.com/carlodere/Transparent.git>
- Operating system (s): Linux, macOS, and Windows 10 Subsystem for Linux.
- Programming language: Python 3, Other requirements: Python 3.x., including packages Mygene, Numpy, Pandas, Requests and Scipy.
- License:GNU GPL-2.
- Conflict of interest/Competing interests: The authors have no relevant financial interests to disclose. One of the author Daniele Santoni serves as Associate Editor for Soft Computing journal.

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Supplementary Files

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- [TabS1.csv](#)
- [TabS2.csv](#)