

GimmeMotifs: an analysis framework for transcription factor motif analysis

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Abstract

Introduction

The regulatory networks that determine cell and tissue identity are robust, yet remarkably flexible. Transcription factors (TFs) control the expression of genes by binding to their cognate DNA sequences, TF motifs, in cis-regulatory elements. To understand how genetic variation affects binding and to elucidate the role of TFs in regulatory networks we need to be able to accurately model binding of TFs to the DNA sequence.

The most widely adopted representation of TF binding is the position frequency matrix (PFM). This matrix, a TF motif, contains (normalized) frequencies of each nucleotide at each position in a collection of aligned binding sites. These PFMs can be derived from high-throughput experiments such as ChIP-sequencing, HT-SELEX or Protein Binding Microarrays (PBMs). Through straightforward transformations PFMs can be expressed as a weight matrix, using log likelihoods, or information content, using the Kullback-Leibler divergence.

Even though the PFM is a convenient representation, it has certain limitations. A PFM cannot model inter-nucleotide dependencies, that are known to affect binding of certain TFs. Multiple different representations have been proposed [1,2,3,4,5], but no single one of these has gained much traction. Ultimately we will need these types of advanced models to accurately represent TF binding. However, PFMs still serve as a useful abstraction that enables an intuitive understanding of TF binding.

Here, we present GimmeMotifs, a Python module and set of command-line tools for TF motif analysis. Amongst other possibilities it can be used to perform *de novo* motif analysis, calculate enrichment statistics and identify differential motifs between two or more experiments. We illustrate the functionality of GimmeMotifs using three different examples.

Findings

We have developed GimmeMotifs to provide an comprehensive framework for transcription factor motif analysis. It includes both command-line tools as well as a Python API to perform all routine motif analysis experiments. Notably, we present maelstrom, a new ensemble approach to determine differential motif activity between two or more experiments. We illustrate the functionality of GimmeMotifs using three examples.

Benchmark of transcription factor motif databases

A variety of transcription factor (TF) motif databases have been published based on different data sources. One of the most established is JASPAR, which consists of a collection of non-redundant, curated binding profiles [6]. The JASPAR website contains many other tools and the underlying databases are also accessible via an API [7]. Other databases are based on protein binding micorarrays [8], HT-SELEX [9] or ChIP-seq profiles [10,11,12,13]. CIS-BP integrates many individual motif databases, and includes assignments of TFs to motifs bases based on DNA binding domain homology [14].

For the purpose of motif analysis, it is beneficial to have a database that is non-redundant (i.e., similar motifs are grouped together), yet as complete as possible (i.e., covers a wide variety of TFs). To establish a quantitative measure of database quality, we evaluated how well motifs from different databases can classify ChIP-seq peaks from background sequences using the GimmeMotifs tool `gimme roc`. We downloaded ChIP-seq peaks from ReMap 2018 [15], and used all TFs with at least 1,000 peaks. We then evaluated 8 motif databases to test how well they could distinguish peaks from random genomic sequences. When a data set contained more than 5,000 peaks we randomly selected 5,000 peaks for the analysis. We included the following databases: JASPAR 2018 vertebrate [6], FANTOM4 [ref], Homer [13], Factorbook [10], the ENCODE motifs from Kheradpour et al [11], HOCOMOCO [12], the RSAT clustered motifs [16] and the motif database created by Madsen et al. [17]. Figure 3A shows distribution of the ROC AUC (area under the curve for the Receiver Operator Curve) of the best motif per database for all 294 transcription factors in a box plot. There is generally a wide distribution of ROC AUCs. For some factors, such as ELK1, CTCF, CBFB and MYOD1, peaks are relatively easy to classify using a single PWM motif. Other factors don't have a peaks with a consistently enriched motif, or do not contain a sequence-specific DNA-binding domain, such as EP300 or CD2 for example.

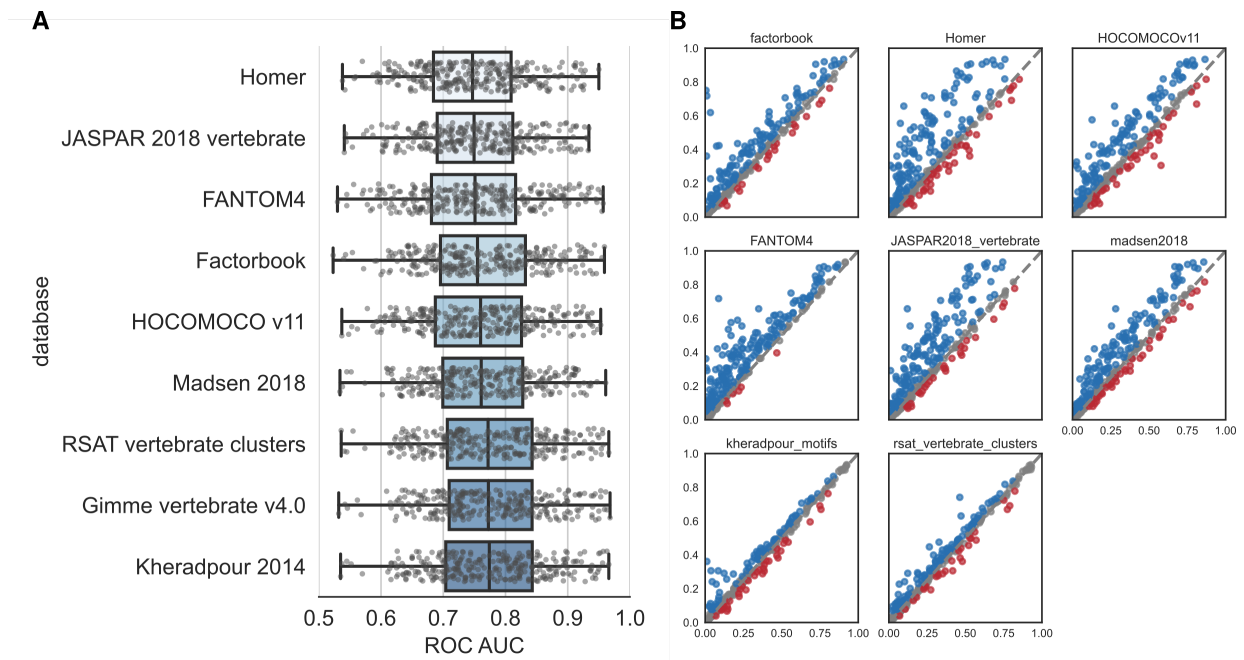


Figure 1: Benchmark of transcription factor motif databases. A) Motif-based classification of binding sites for 294 TFs from the ReMap ChIP-seq database. For all TFs 5000 peaks were compared to background regions using each motif database. The boxplot shows the The ROC AUC of the best motif per database for all TFs. B) Recall at 10% FDR of motif databases compared to the GimmeMotifs vertebrate motif database (v4.0). The same data is used as in A). The X-axis represents the recall for the different databases, the Y-axis represents the recall for the GimmeMotifs vertebrate database. Differences of more than 0.025 are marked blue, and less than -0.025 red.

The difference in maximum ROC AUC between databases is on average not very large, with a mean maximum difference of 0.05. The largest difference (~0.24) is found for factors that were not assayed by ENCODE, such as ONECUT1, SIX2 and TP73, and are therefore not present in the Factorbook motif database. Unsurprisingly, the databases that were based on motif collections of different sources (Kheradpour, Madsen, RSAT and Gimme) generally perform best. It should be noted that, for this task, using motif databases based on motif identification from ChIP-seq peaks is in some sense “overfitting”, as the motifs in these databases were inferred from highly similar data.

While the ROC AUC is often used to compare the trade-off between sensitivity versus specificity, in this context it is not the best metric from a biological point of view. An alternative way of measuring performance is evaluating the recall (ie. how many true peaks do we recover) at a specific false discovery rate. This is one of the criteria that has been used by the ENCODE DREAM challenge for evaluation [18]. Figure 3B shows scatterplots for the recall at 10% FDR for all motif databases compared to the clustered, non-redundant databases that is included with GimmeMotifs. The non-redundant vertebrate motif database included with GimmeMotifs shows better performance than most other databases. The non-redundant RSAT database, which was created in a very similar manner, shows similar performance.

These results illustrate how `gimme roc` can be used for evaluation of motifs. The choice of a motif database can greatly influence the results of an analysis. The default database included with GimmeMotifs shows good performance on the metric evaluated here. However, this analysis illustrates only one specific use case of application of a motif database. In other cases well-curated databases such as JASPAR can be beneficial, for instance when linking motifs to binding proteins.

Performance of *de novo* motif identification varies with motif quality

It has been noted that there is no *de novo* motif prediction algorithm that consistently performs well across different data sets [19]. New approaches and algorithms for *de novo* motif discovery continue to be published, however, many of them are not tested on more than a few datasets. Benchmarks that have been published since Tompa et al. [20,21] typically have tested only a few motif finders or used only a few datasets.

Here, we used the GimmeMotifs framework as implemented in `gimme motifs` to benchmark 14 different *de novo* motif finders. To evaluate the different approaches, we downloaded 495 peak files for 270 proteins from ENCODE (Supplemental Table X; [22]) and selected the 100bp sequence centered on the summit of top 5000 peaks. Of those peaks, half were randomly selected as a prediction set and the other half was used for evaluation. As a background set we selected regions of the same length flanking the original peaks. To assess the performance, we calculated two metrics, the ROC AUC and the recall at 10% FDR. Figure 4a shows the distribution of the ROC AUC scores over all ENCODE peaks in a boxplot, ordered by the mean ROC AUC. The ROC AUC is distributed between 0.58 and 0.98, with a mean of 0.75. All proteins that have low ROC AUC are not sequence-specific transcription factors such as POL2, TAF7 and GTF2B, the PRC2-subunit SUZ12 and the H3K9 methyltransferase SETDB1. The factors with the highest ROC AUC are CTCF and members of the cohesin complex, SMC3 and RAD21, that bind at CTCF sites.

Generally, the ROC AUC distribution of all evaluated motif finders is very similar. However, a few outliers can be observed. Trawler, Posmo and, to a lesser extent, GADEM show an overall lower distribution of ROC AUC scores. Compared to the ROC AUC scores of the next best program, Weeder, this is significant ($p < 1e-5$, Wilcoxon signed-rank). Selecting the best motif for each experiment results in a ROC AUC distribution that is significantly higher than the best single method, BioProspector ($p < 4e-21$, Wilcoxon signed-rank).

As stated in the previous section, the ROC AUC is not the best measure to evaluate motif quality. Therefore, we selected for every peak set the best motif from all motifs predicted by the different motif finders on the basis of the recall at 10% FDR. We then plotted the difference between the best motif from each individual *de novo* approach with this best overall motif (Figure 4b). For this figure, we used only the data sets where at least one motif had a recall higher than 0 at 10% FDR.

In line with previous results [19], there is no single tool that consistently predicts the best motif for each transcription factor. However, the motifs predicted by BioProspector, MEME and Homer are, on basis of this metric, consistently better than motifs predicted by other methods. In 75% of the cases, the motif predicted by BioProspector has a difference in recall smaller than 0.026 compared to the best overall motif. In this benchmark, four programs (Trawler, Improbizer, Posmo and Weeder) generally perform worse than average, with a mean decrease in recall of [5%] to [10], as compared to the best motif. In addition, these programs tend to have a much more variable performance overall.

Predicted motifs identified using MEME with different motif widths show better performance than running MEME with the `minw` and `maxw` options (MEME vs. MEMEW in fig. 4b). Of the best performing algorithms, both MEME and BioProspector were not specifically developed for ChIP-seq data, however, they consistently outperform most methods created for ChIP-seq data. Of the ChIP-seq motif finders Homer consistently shows good performance.

Finally, to gain further insight into *de novo* motif finder performance, we stratified the ChIP-seq datasets by motif “quality”. We divided the transcription factors into five bins on basis of the ROC AUC score of the best motif. For each bin we ranked the tools on basis of the average of three metrics (ROC AUC, recall at 10% FDR and MNCP [23]). The results are visualized as a heatmap in Figure 4c. From this visualization, it is again clear that BioProspector, MEME and Homer produce consistently high-ranking motifs, while the motifs identified by Trawler, Posmo, GADeM and Improbizer generally have the lowest rank. Interestingly, for some motif finders, there is a relation between motif presence and the relative rank. Weeder, XXMotif and MDmodule yield relatively high-ranking motifs when the ROC AUC of the best motif for the data set is low. On the other hand, ChIPMunk shows the opposite pattern. Apparently this algorithm works well when a motif is present in significant fraction of the data set [TODO: check oop param].

These results illustrate that motif finders need to be evaluated along a broad range of data sets with different motif presence and quality. Another interesting observation is that this ChIP-seq benchmark shows a lower-than-average performance for Weeder, which actually was one of the highest scoring in the Tompa et al. benchmark. It should be noted that our metric specifically evaluates how well *de novo* motif finders identify the primary motif in the context of ChIP-seq peaks. It does not evaluate other aspects that might be important, such as the ability to identify many low-abundant motifs. Furthermore, with ChIP-seq data there are usually many peaks available. This allows for other algorithms than those that work well on a few sequences. Interestingly, the original MEME shows consistently good performance, although the running time is longer than most other tools. On the basis of this analysis, BioProspector should be the top pick for a program to identify primary motifs in ChIP-seq data. However, an ensemble program such as GimmeMotifs will report high-quality motifs more consistently than any single tool.

Differential motif analysis of hematopoietic enhancers identifies cell type-specific regulators

While many motif scanners and methods to calculate enrichment exist, there are few methods to compare motif enrichment or activity between two or more data sets. The CentriMo algorithm from the MEME suite implements a differential enrichment method to compare to samples [24]. The regression approach MARA [25], as implemented in ISMARA [26] normalizes between data sets before regression. Here we present the maelstrom algorithm that integrates different methods to determine motif relevance or activity in an ensemble approach (Fig. 5A).

To demonstrate the utility of maelstrom we identified motif activity based on enhancers in hematopoietic cells. We downloaded 72 human hematopoietic DNaseI experiments (Supplemental Table X), called peaks, and created a combined peak set as a collection of putative enhancers. In addition we downloaded 193 hematopoietic H3K27ac ChIP-seq experiments, mainly from BLUEPRINT [27] (Supplemental Table X). We determined the number of H3K27ac reads per enhancer. After log2 transformation and scaling, we selected the 50,000 most dynamic peaks. Figure 5B shows the correlation of the H3K27ac enrichment in these 50,000 enhancers between cell types. For this plot, replicates were combined by taking the mean value and all experiments corresponding to treated cells were removed. We can observe five main clusters 1) non-hematopoietic cells, megakaryocyte and erythrocytes 2), lymphoid cells, 3) neutrophilic cells, 4) macrophages and dendritic cells and 5) monocytes. The lymphoid cluster furthermore separates between B-cells and T- and NK cells and non-hematopoietic cells are distinct from the megakaryocytes and erythroblasts. We can conclude that the H3K27ac profile within this enhancers set recapitulates a cell type-specific regulatory signal.

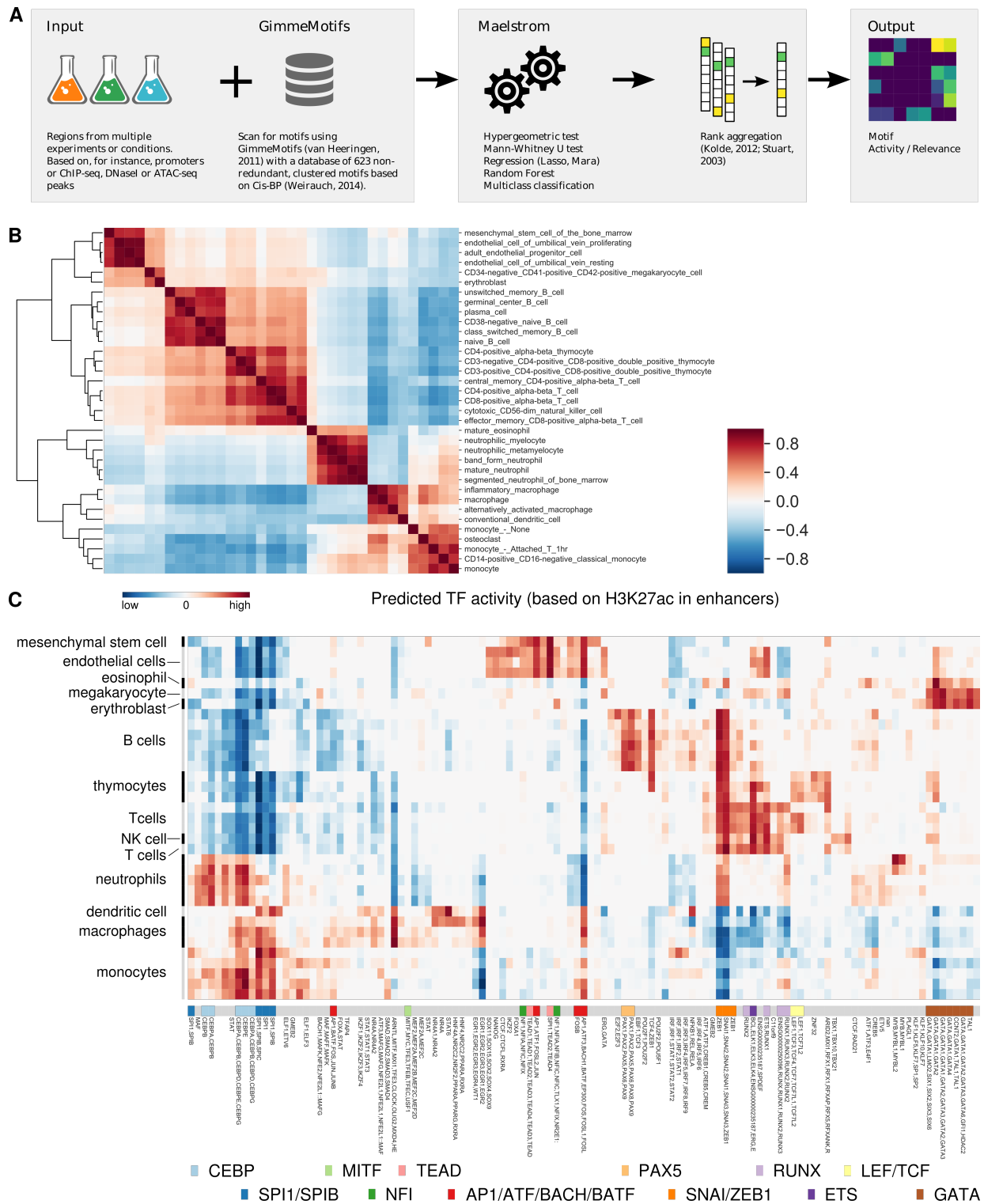


Figure 3: Benchmark of transcription factor motif databases

To determine differential motif activity from these dynamic enhancers we used maelstrom. We combined Bayesian ridge regression, multi-class regression using coordinate descent [28] and regression with boosted trees [29]. The coefficients or feature importances were ranked and combined using rank aggregation [30]. A p-value was calculated for consistently high ranking and consistently low ranking motifs. The results are visualized in Figure 5C.

Two of the most significant motifs are SPI1 (PU.1) and CEBP. The motif activity for SPI1 is consistently high in monocytes and macrophages, consistent with its role in myeloid lineage commitment [refs]. The CEBP family members are important for monocytes and granulocytic cells [ref], and show a high motif activity in neutrophils and monocytes. Other strong motifs include RUNX for T cells and NK cells, GATA1 for erythroid cells.

We identified a strong activity for motifs representing the ZEB1 and Snail transcription factors. The Snail transcription factors play an important role in the epithelial-to-mesenchymal transition (EMT), and their role in hematopoietic cells is less well-described. However, recently Snai2 and Snai3 were found to be required to generate mature T and B cells [31,32] in mice. ZEB1 is expressed in T cells and represses expression of IL-2 [33], as well as other immune genes such as CD4 [34] and GATA3 [35]. ZEB1 knockout mice exhibit a defect in thymocyte development [36]. Together, this suggests that these TFs play an important role in lymphocyte development.

Finally, an interesting observation is the predicted motif activity of NANOG in endothelial cells. NANOG is expressed in embryonic stem cells and is essential for establishment and maintenance of pluripotency [ref]. However, NANOG is indeed expressed in endothelial cells and has been shown to play a role in endothelial proliferation and angiogenesis [37].

Methods

GimmeMotifs

Implementation

GimmeMotifs is implemented in Python, with the motif scanning incorporated as a C module. The software is developed on GitHub (<https://github.com/simonvh/gimmemotifs/>) and documentation is available at <https://gimmemotifs.readthedocs.io>. Functionality is covered by unit tests, which are run through continuous integration. GimmeMotifs can be installed via bioconda [38], see <https://bioconda.github.io/> for details. All releases are also distributed through PyPi [39] and stably archived using Zenodo [40]. For *de novo* motif search, 14 different external tools are supported (Table [X]). All of these are installed when conda is used for installation. By default, [genomepy](#) is used for genome management [41]. In addition, GimmeMotifs uses the following Python modules: numpy [42], scipy [43], scikit-learn, scikit-contrib-lightning [28], seaborn [44], pysam [45,46], xgboost [29] and pandas. In addition to the command line tools, all GimmeMotifs functionality is available through a Python API.

De novo motif prediction pipeline

Originally, GimmeMotifs was developed to predict *de novo* motifs from ChIP-seq data using an ensemble of motif predictors [47]. The tools currently supported are listed in Table [X]. The pipeline is depicted in [Fig X]. An input file (BED, FASTA or narrowPeak format) is split into a prediction and validation set. The prediction set is used to predict motifs, and the validation set is used to filter for significant motifs. All significant motifs are clustered to provide a collection of non-redundant *de novo* motifs. Finally, significant clustered motifs are reported, along with several statistics to evaluate motif quality, calculated using the validation set. These evaluation metrics include ROC AUC, distribution of the motif location relative to the center of the input (i.e., the ChIP-seq peak summit) and the best match in a database of known motifs.

Table [X]: External *de novo* motif prediction tools supported by GimmeMotifs.

Name	Citation
AMD	[48]
BioProspector	[49]
ChIPMunk	[50]
GADEM	[51]
HMS	[52]
Homer	[13]
Improbizer	[53]
MDmodule	[54]
MEME	[55]
MotifSampler	[56]
Posmo	[57]
Trawler	[58]
Weeder	[59]
XXmotif	[60]

Motif activity by ensemble learning: maelstrom

GimmeMotifs implements eight different methods to determine differential motif enrichment between two or more conditions. In addition, these methods can be combined in a single measure of *motif activity* using rank aggregation. Four methods work with discrete sets, such as different peak sets or clusters from a K-means clustering. The hypergeometric test uses motif counts with an empirical motif-specific FPR of 5%. All other implemented methods use the PFM log-odds score of the best match.

The hypergeometric test is commonly used to calculate motif enrichment, for instance by Homer [13]. In GimmeMotifs, motifs in each cluster are tested against the union of all other clusters. The reported value is $-\log_{10}(\text{p-value})$ where the p-value is adjusted by the Benjamini-Hochberg procedure [61].

Using the non-parametric Mann-Whitney U test, GimmeMotifs tests the null hypothesis that the motif log-odds score distributions of two classes are equal. For each discrete class in the data, such as a cluster, it compares the score distributions of the class to the score distribution of all other classes. The value used as activity is the $-\log_{10}$ of the Benjamini-Hochberg adjusted p-value.

The two other methods are classification algorithms: random forest using scikit-learn and a large-scale multiclass classifier using block coordinate descent [28] as implemented in the scikit-contrib-lightning module. The classifier in GimmeMotifs uses a l1/l2 penalty with squared hinge loss where the alpha and C parameters are set using grid search in 10 fold cross-validation procedure.

The other four methods that are implemented relate motif score to an experimental measure such as ChIP-seq or ATAC-seq signal or expression level. These are all different forms of regression. In addition to ridge regression, which is similar to Motif Activity Response Analysis (MARA) [25,26], these methods include regression using boosted trees (XGBoost [29]), multiclass regression [28] and L1 regularized regression (LASSO).

To combine different measures of motif significance or activity into a single score, ranks are assigned for each individual method and combined using rank aggregation based on order statistics [30]. This results in a probability of finding a motif at all observed positions. We use a Python implementation based on the method used in the R package RobustRankAggreg [62]. The rank aggregation is performed twice, once with the ranks reversed to generate both positively and negatively associated motifs.

Clustering

Transcription factor motif database benchmark

We downloaded all ChIP-seq peaks from Remap 2018 v1.2 [15] (<http://tagc.univ-mrs.fr/remap/index.php?page=download>). We removed all factors with fewer than 1000 peaks and created regions of 100 bp centered at the peak summit. Background files were created for each peak set using bedtools shuffle [63], excluding the hg19 gaps and the peak regions. The ROC AUC and Recall at 10% FDR statistics were calculated using `gimme roc`. The motif databases included in the comparison are listed in table X. We only included public databases that can be freely accessed and downloaded.

Name	Version	Citation
Factorbook		
FANTOM4	http://swissregulon.unibas.ch/data/fantom4/WMs.txt.gz	
GimmeMotifs vertebrate clusters		v4.0
HOCOMOCO	http://hocomoco11.autosome.ru/	v11
Homer	http://homer.ucsd.edu/homer/custom.motifs	XX
JASPAR	https://jaspar.genereg.net/	2018
Kheradpour		
Madsen	http://bioinformatik.sdu.dk/solexa/webshare/IMAGE/IMAGE_v1.1.tar.gz	1.1
RSAT vertebrate clusters		

: Table [X]: Motif databases.

The workflow is implemented in snakemake [64] and is available at https://github.com/simonvh/gimme_analysis.

`De novo` motif prediction benchmark

We downloaded all spp ENCODE peaks (January 2011 data freeze) from the EBI FTP (http://ftp.ebi.ac.uk/pub/databases/ensembl/encode/integration_data_jan2011/byDataType/peaks/jan2011/spp/optimal/). We selected the top 5000 peaks and created 100bp regions centered on the peak summit. As background we selected 100 bp regions flanking the original peaks. For the `de novo` motif search default settings for `gimme motifs` were used. The workflow is implemented in snakemake [64] and is available at https://github.com/simonvh/gimme_analysis.

Motif analysis of hematopoietic enhancers

To illustrate the functionality of `gimme maelstrom` we analyzed an integrated collection of hematopoietic enhancers. We downloaded all H3K27ac ChIP-seq and DNase I data from BLUEPRINT (Supplemental Table SX) and hematopoietic DNase I data from ROADMAP (Supplemental Table SX). All DNase I data were processed using the Kundaje lab DNase pipeline version 0.3.0 https://github.com/kundajelab/atac_dnase_pipelines [65]. The ChIP-seq samples were processed using the Kundaje lab AQUAS TF and histone ChIP-seq pipeline https://github.com/kundajelab/chipseq_pipeline. For all experiments from BLUEPRINT we used the aligned reads provided by EBI. All ROADMAP samples were aligned using bowtie2 [66] to the hg38 genome. DNase I peaks were called using MACS2 [67]. We merge all DNase I peak files and centered each merged peak on the summit of the strongest individual peak. H3K27ac reads were counted in a region of 2kb centered at the summit (Supplementary Table SX) and read counts were log2-transformed and scaled. We removed all samples that were treated and averaged all samples from the same cell type. We then selected all enhancers with at least one sample with a scaled log2 read count of 2, sorted by the maximum difference in normalized signal between samples and selected the 50,000 enhancers with the largest difference. Using this enhancer collection as input, we ran `gimme maelstrom` using default settings. The motif analysis workflow is implemented in a Jupyter notebook and is available at https://github.com/simonvh/gimme_analysis.

Conclusions

We demonstrated the functionality of GimmeMotifs with three examples. First, to evaluate different public motif databases, we quantified their performance on distinguishing ChIP-seq peaks from background sequences. The databases that perform best on this benchmark are collections of motifs from different sources. Of the individual databases HOCOMOCO and Factorbook rank highest using this collection of human ChIP-seq peaks. Based on our results it is recommended to use a composite database, such as the RSAT clustered motifs or the GimmeMotifs database (v4.0), for the best vertebrate motif coverage. However, these motifs are less well annotated. For instance, motifs based on ChIP-seq peaks from some sources might be from co-factors or cell

type-specific regulators instead of the factor that was assayed. An example are motifs that associated with the histone acetyl transferase EP300. This transcriptional co-activator lacks a DNA binding domain, and associated motifs depend on the cell type. For instance, in a lymphoblastoid cell line such as GM12878 these include PU.1 and AP1. The lack of high-quality annotation makes it more difficult to reliably link motifs to transcription factors. This can be an advantage of using JASPAR. Although the motifs might not be optimal, JASPAR contains high-quality metadata that is manually curated.

In the second example, we benchmarked 14 different *de novo* motif finders using a large compendium of ChIP-seq data. While performance can vary between different data sets, there are several *de novo* motif finders that consistently perform well, with BioProspector, MEME and Homer as top performers. Interestingly, only Homer was specifically developed for ChIP-seq data. An ensemble approach such as GimmeMotifs still improves on the use of individual tools. This example also illustrates that newly developed *de novo* motif finders should be evaluated on many different data sets, as this is necessary to accurately judge the performance.

Finally, we presented a new ensemble approach, *maelstrom*, to determine motif activity in two or more epigenomic or transcriptomic data sets. Using H3K27ac ChIP-seq signal as a measure for enhancer activity, we analyzed cell-type specific motif activity in a large collection of hematopoietic cell types. We identified known lineage regulators, as well as motifs for factors that are less well studied in a hematopoietic context. This illustrates how `gimme maelstrom` can serve to identify cell type-specific transcription factors.

In conclusion, GimmeMotifs is a flexible and highly versatile framework for transcription factor motif analysis. Both command line and programmatic use in Python are supported. One planned future improvement to GimmeMotifs is the support of more sophisticated motif models. Although PFMs are very informative, it is clear that they represent an oversimplification of TF binding preferences. While several approaches that incorporate positional dependencies have been developed, it is still unclear how well these models perform and their use depends on specific tools. Supporting these different models and benchmarking their performance relative to high-quality PFMs will simplify their use and give insight into their benefits and disadvantages. Second, there is significant progress recently in modeling TF binding using deep neural networks (DNNs). These DNNs can learn sequence motifs, as well as complex inter-dependencies, directly from the data. However, while biological interpretation is possible, it becomes less straightforward. We expect that analyzing and understanding a trained DNN can benefit from high-quality motif databases and comparative tools such as GimmeMotifs.

Availability and requirements

- Project name: GimmeMotifs
- Project home page: <https://github.com/simonvh/gimmemotifs>

- Operating system(s): Linux, Mac OSX
- Programming language: Python 3
- Other requirements: *de novo* motif finders
- License: MIT

Availability of supporting data

Additional files

Competing interests

The authors declare that they have no competing interests.

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