Chromatin Conformation Prediction from ChIPseq Signal

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Contents

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- **Main Question**: Can we use transcription factor (TF)-ChIPseq to predict protein complexes (direct and indirect bindings) on chromatin?

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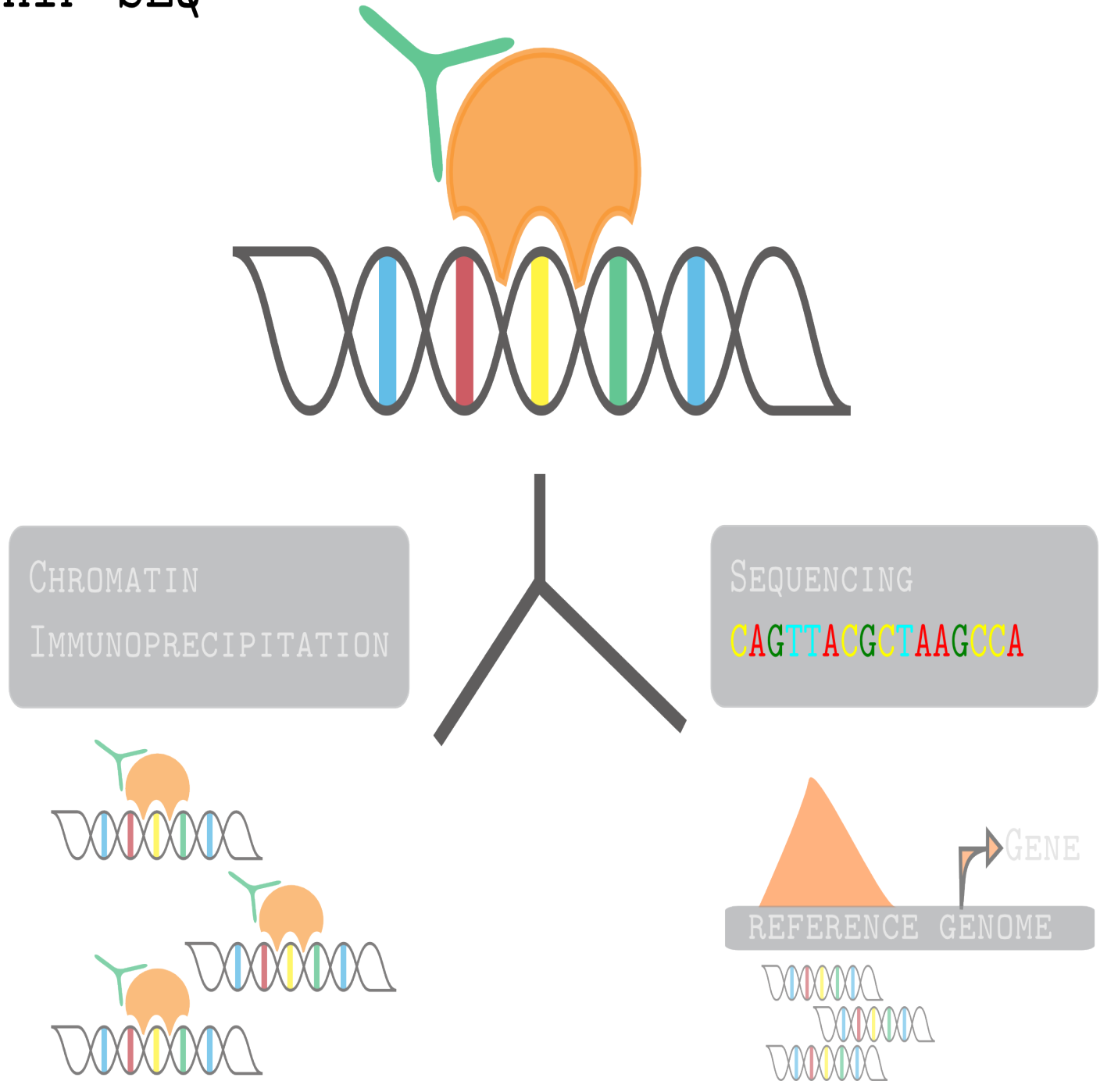
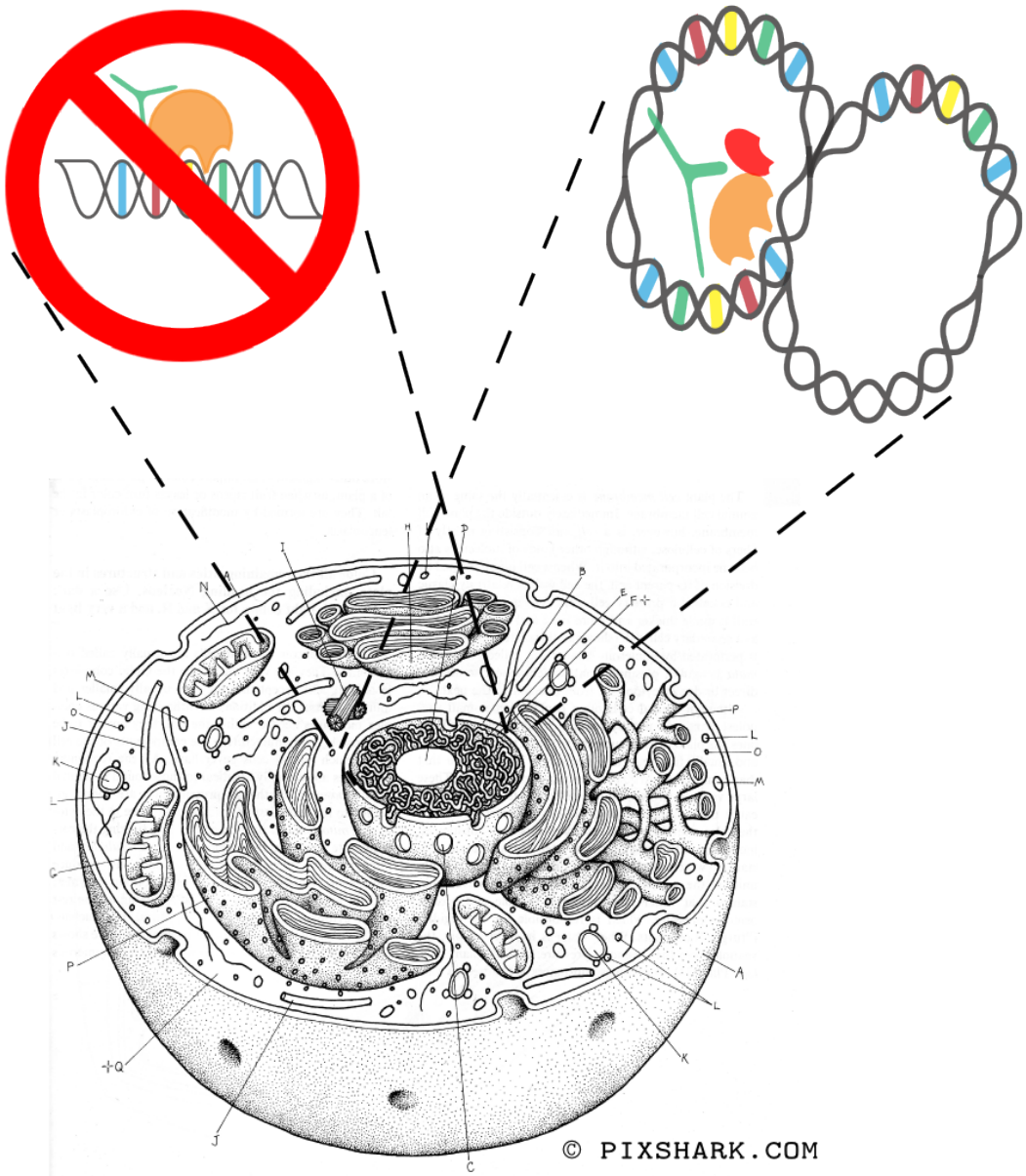
- **Main Question**: Can we use transcription factor (TF)-ChIPseq to predict protein complexes (direct and indirect bindings) on chromatin?
- **Strategy**: Model ChIPseq signal using Mixture Models to cluster the direct and indirect bindings.

What is ChIPseq?

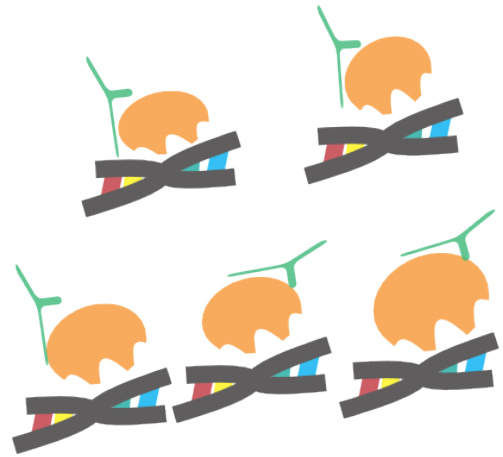
CHIP-SEQ


Chromatin
Immunoprecipitation
Sequencing
CAGTTACGCTAAGCCA
Gene
Reference genome

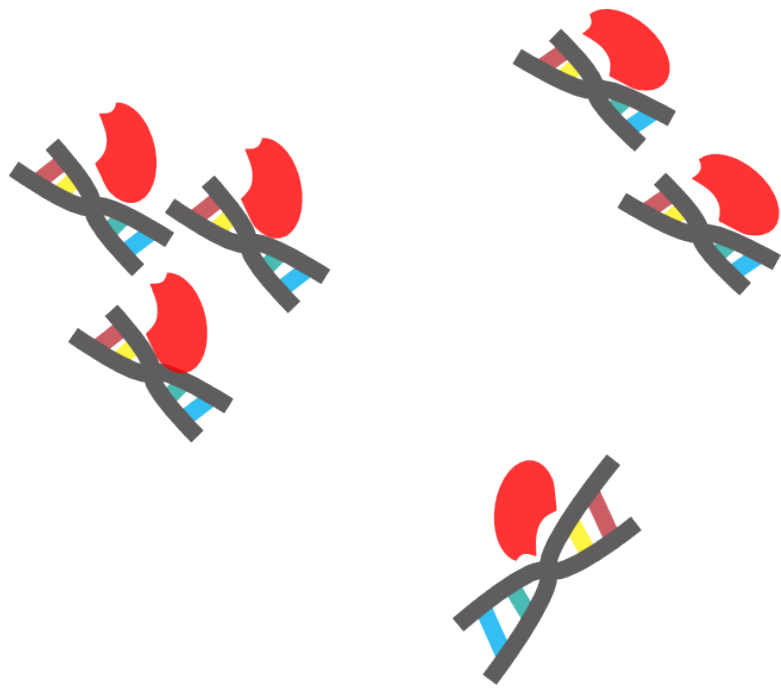
Chromatin Conformation



DIRECT BINDING SITES



INDIRECT BINDING SITES



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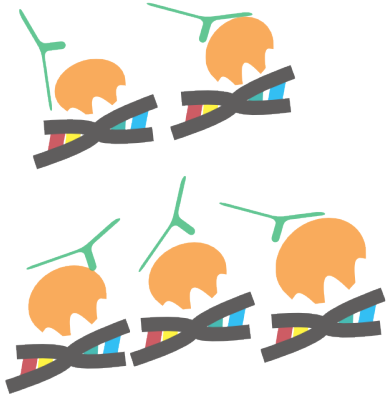
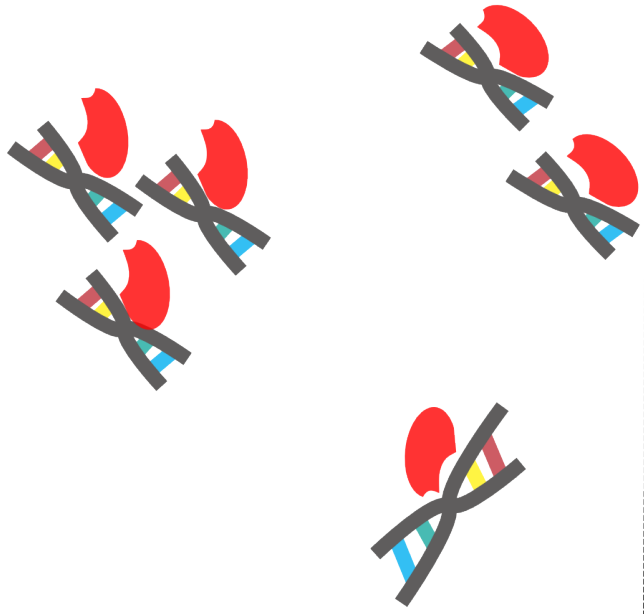
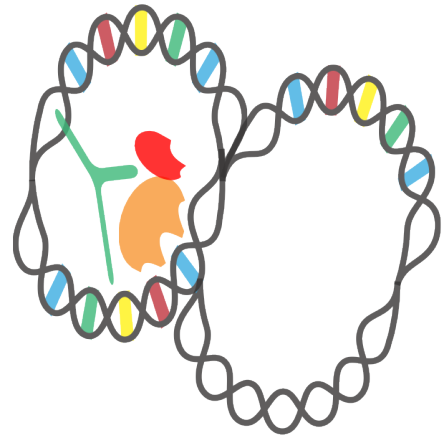
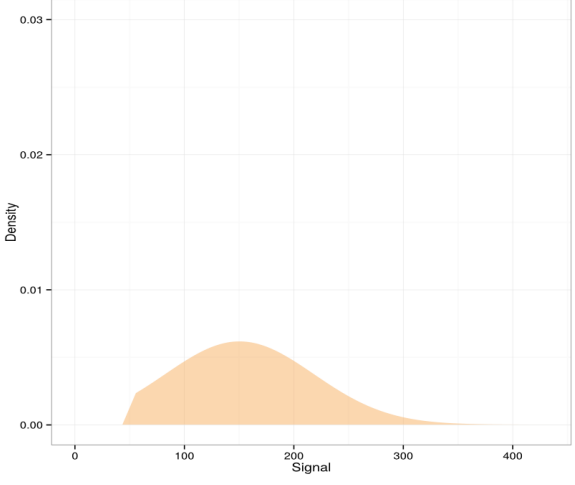
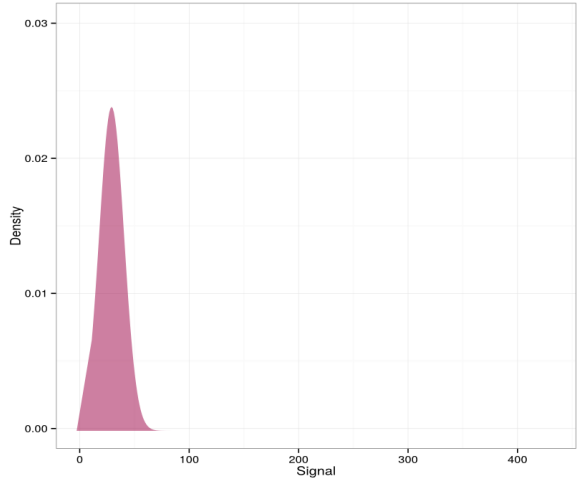
INDIRECT BINDING SITES

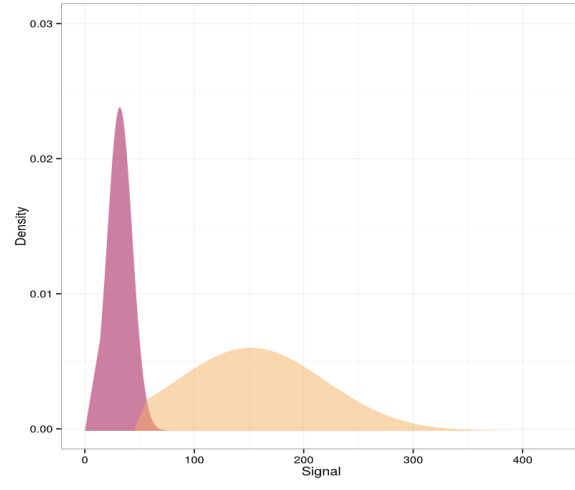












What is Mixture Model (MM)?

Mixture Model: Revisited

Types of clustering methods:

- Hard clustering: non-overlapping clusters
- Soft clustering: overlapping clusters

Mixture Model: Revisited

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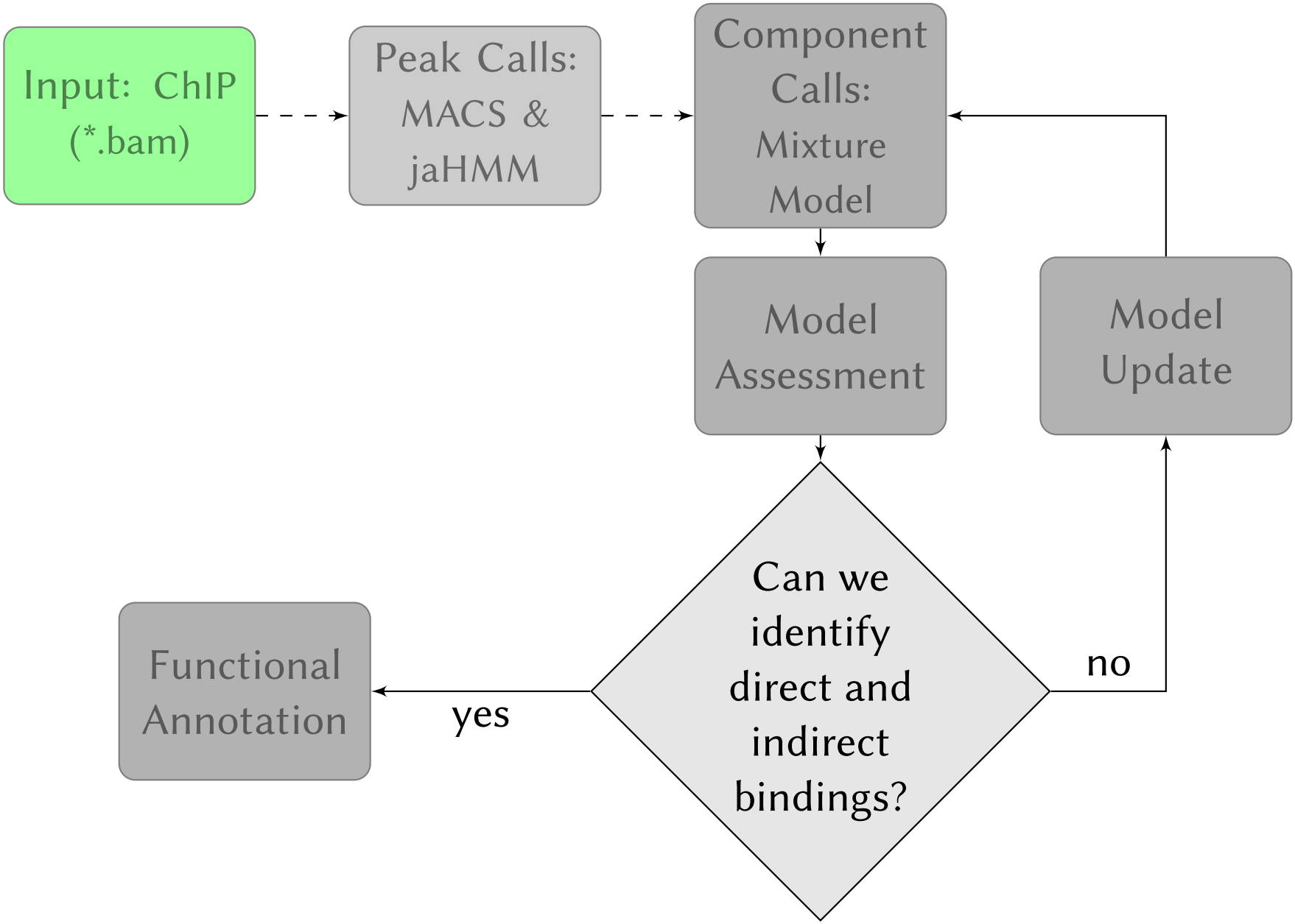
Mixture model is a probabilistic way of soft clustering. Each cluster is a generative mixture model with its parameters.

Gaussian Mixture Model

Key Assumption:

- ChIP-seq signals are drawn from a finite set of gaussian distributions.
- ChIPseq signals are fit with gaussian mixture models, with mixing λ parameter.
- Each gaussian corresponds to a cluster of signals with μ and σ parameters.


Input: ChIP (*.bam)
Peak Calls: MACS & jaHMM
Component Calls: Mixture Model
Model Assessment
Model Update
Can we identify direct and indirect bindings?
yes
no
Functional Annotation

Input: ChIP-seq of Cebpϵ from Koeffler-BM

```
##FastQC 0.10.1
>>Basic Statistics pass
#Measure Value
Encoding Illumina 1.5
Total Sequences 41586141
Sequence length 40
#Summary
PASS  Basic Statistics
PASS  Per base sequence quality
PASS  Per sequence quality scores
WARN  Per base sequence content
PASS  Per base GC content
PASS  Per sequence GC content
PASS  Per base N content
PASS  Sequence Length Distribution
PASS  Sequence Duplication Levels
PASS  Overrepresented sequences
WARN  Kmer Content
```

Peak Calls: MACS2 vs jaHMM

[1] Zhang et al. Model-based Analysis of ChIP-Seq (MACS). Genome Biol (2008) vol. 9 (9) pp. R137

[2] Filion et al. jahmm: A tool for discretizing multiple ChIP seq profiles. arXiv (2014)

Peak Calls: MACS2 vs jaHMM

- **MACS2**: *poisson* model-based analysis of Peak calls [1]

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Peak Calls: MACS2 vs jaHMM

- **MACS2**: *poisson* model-based analysis of Peak calls [1]
- **jaHMM**: *negative binomial* model-based analysis of Peak calls [2]

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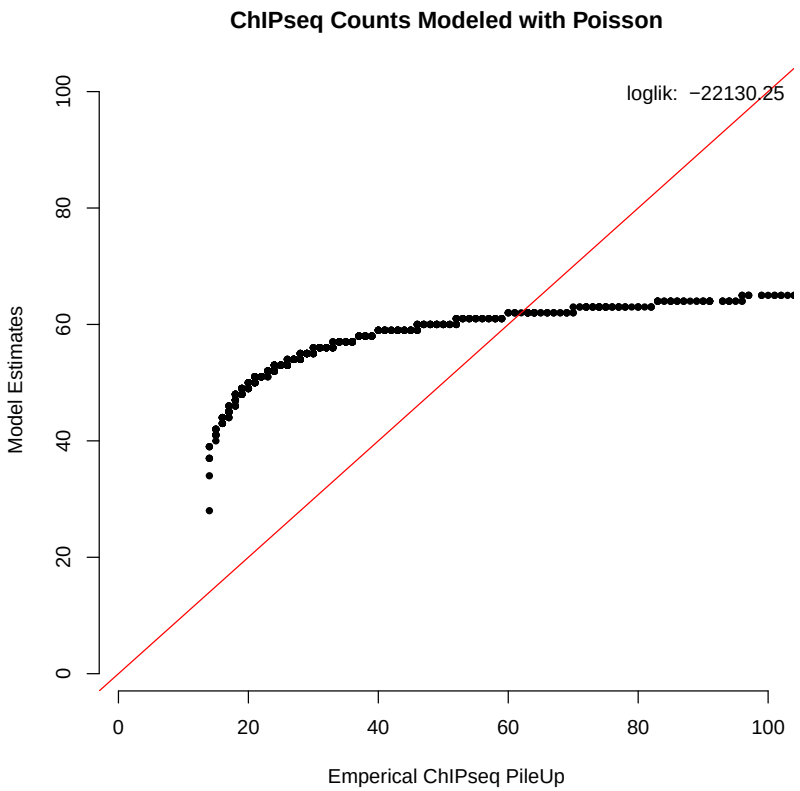
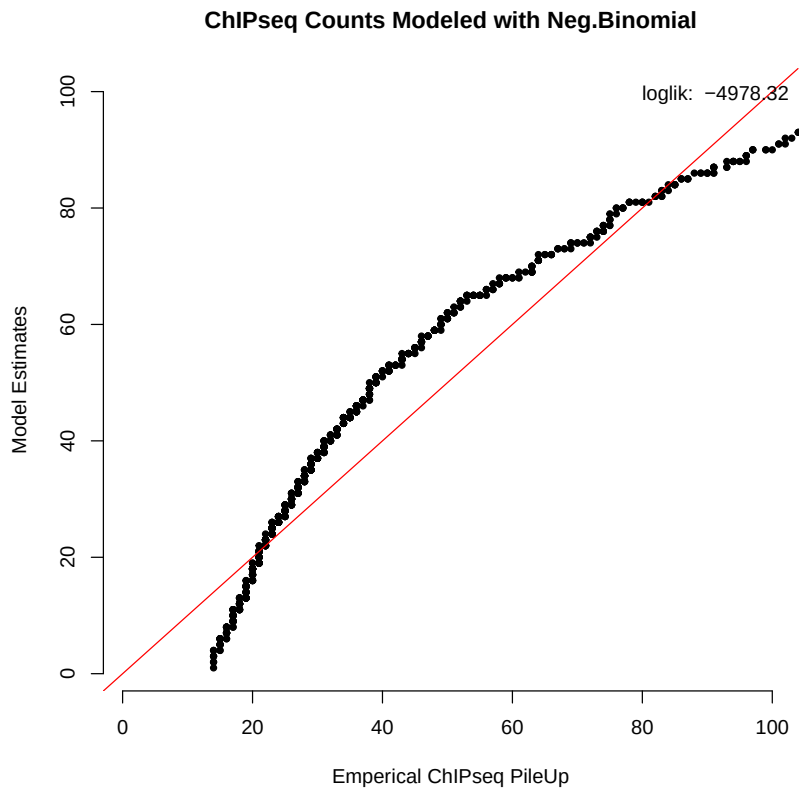
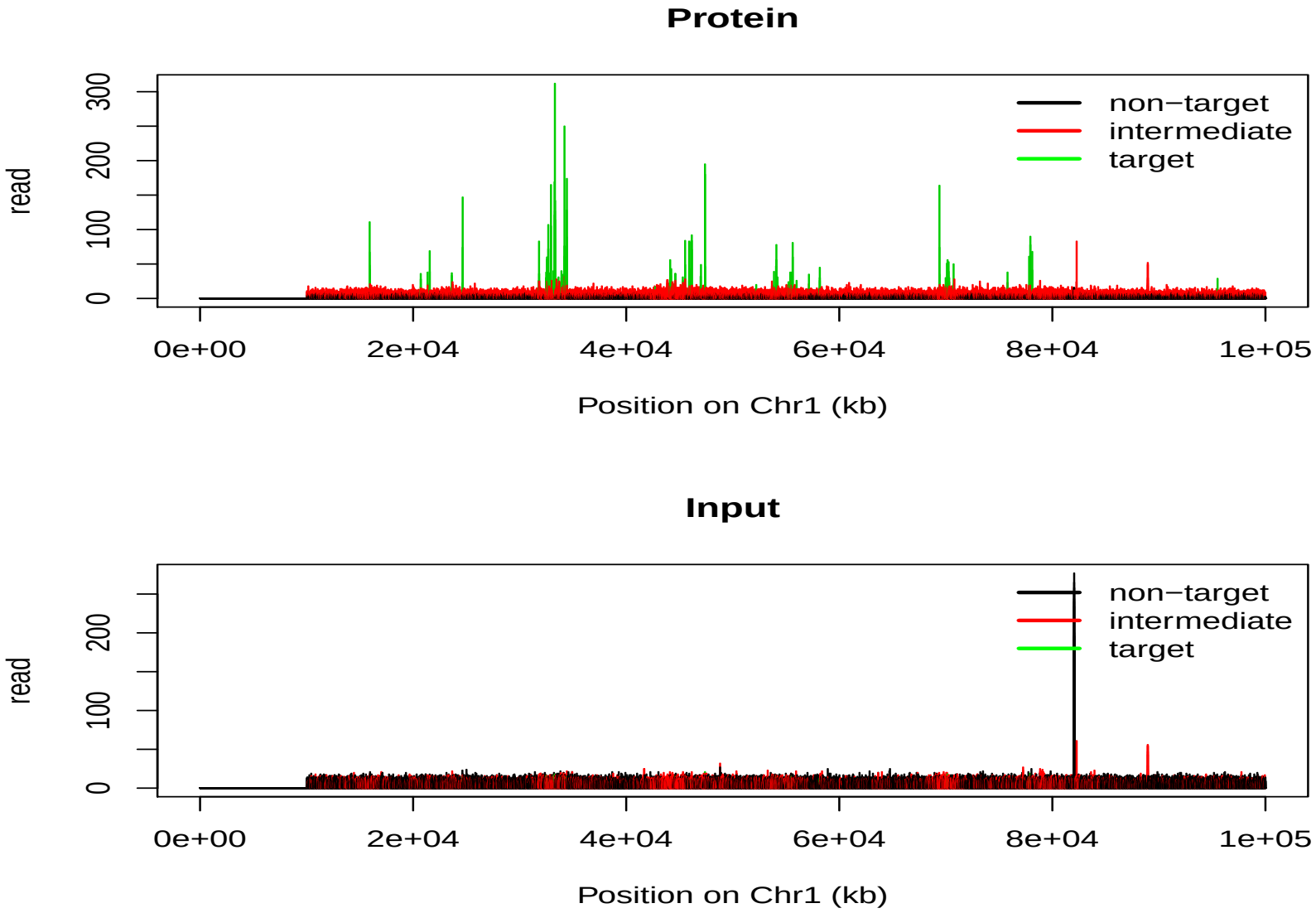
jaHMM fits ChIPseq Signals better than MACS2

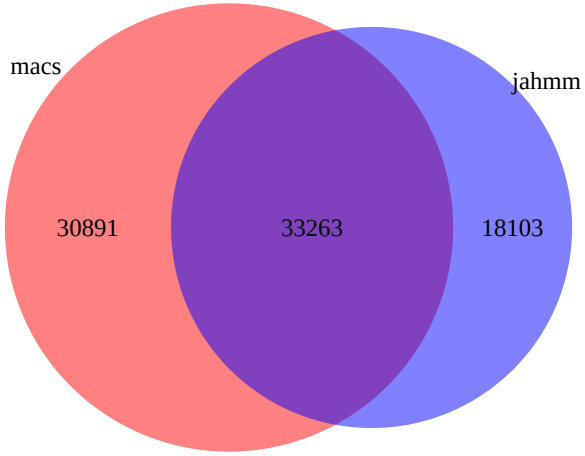


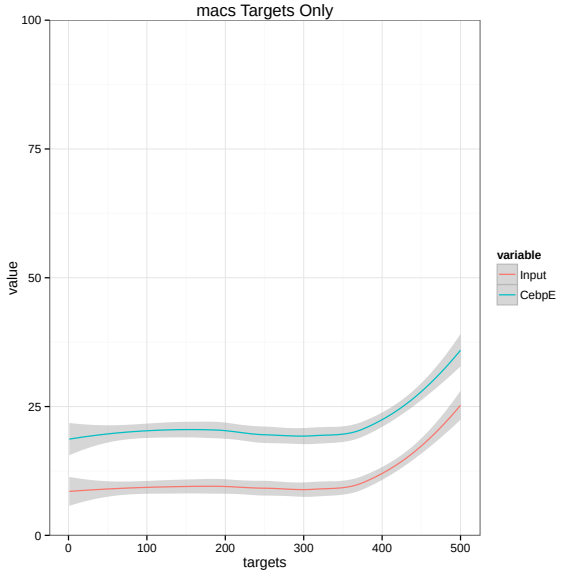


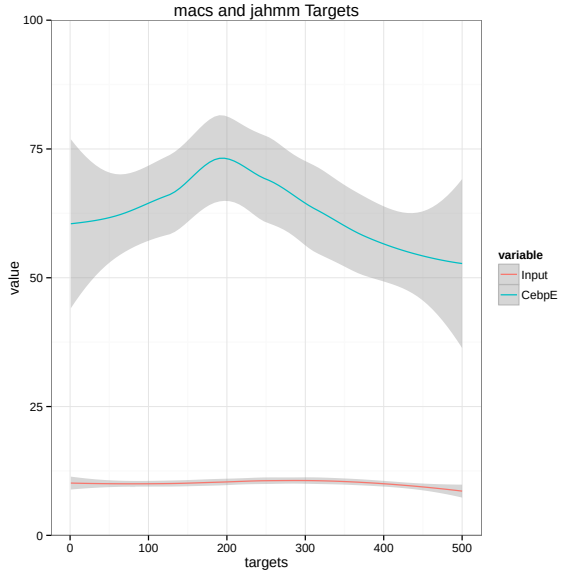
Peaks Called by jahmm

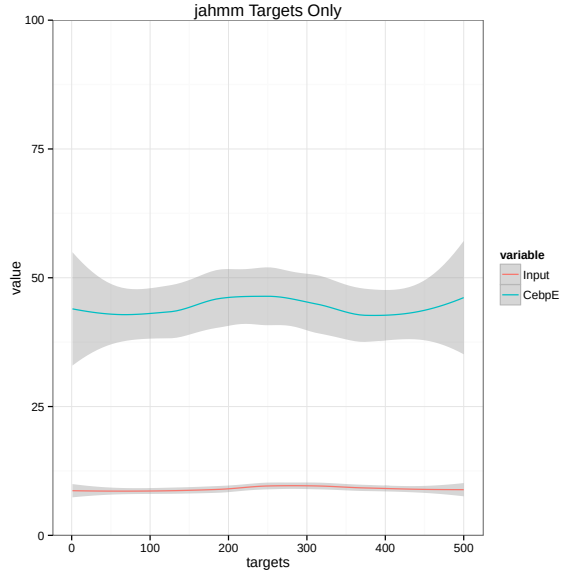


Peaks Called by MACS2 vs jahmm









Summary: Peak Calls

- Given our dataset, MACS2 is able to call peaks however, the estimated scores are less fit than JAHMM

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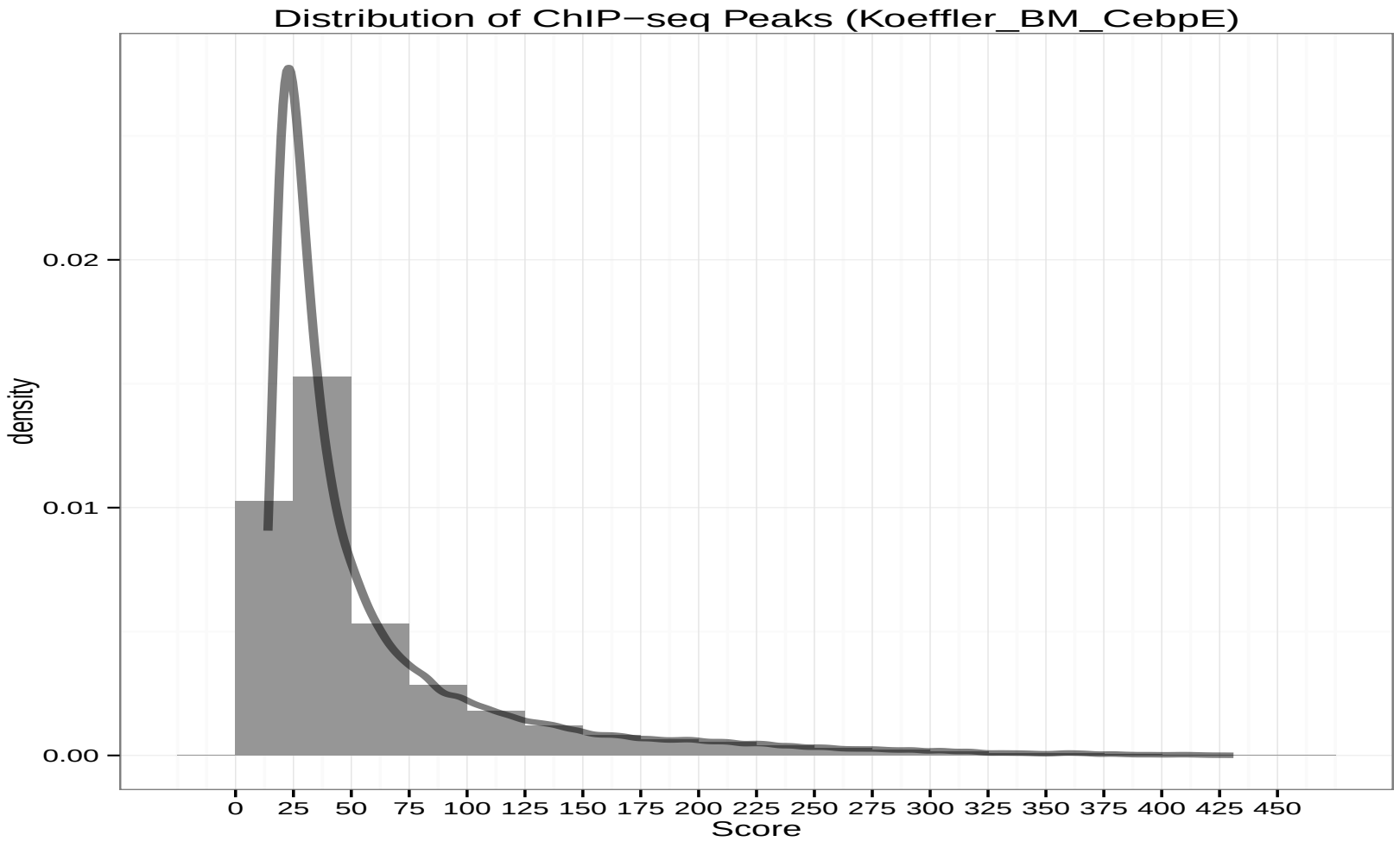
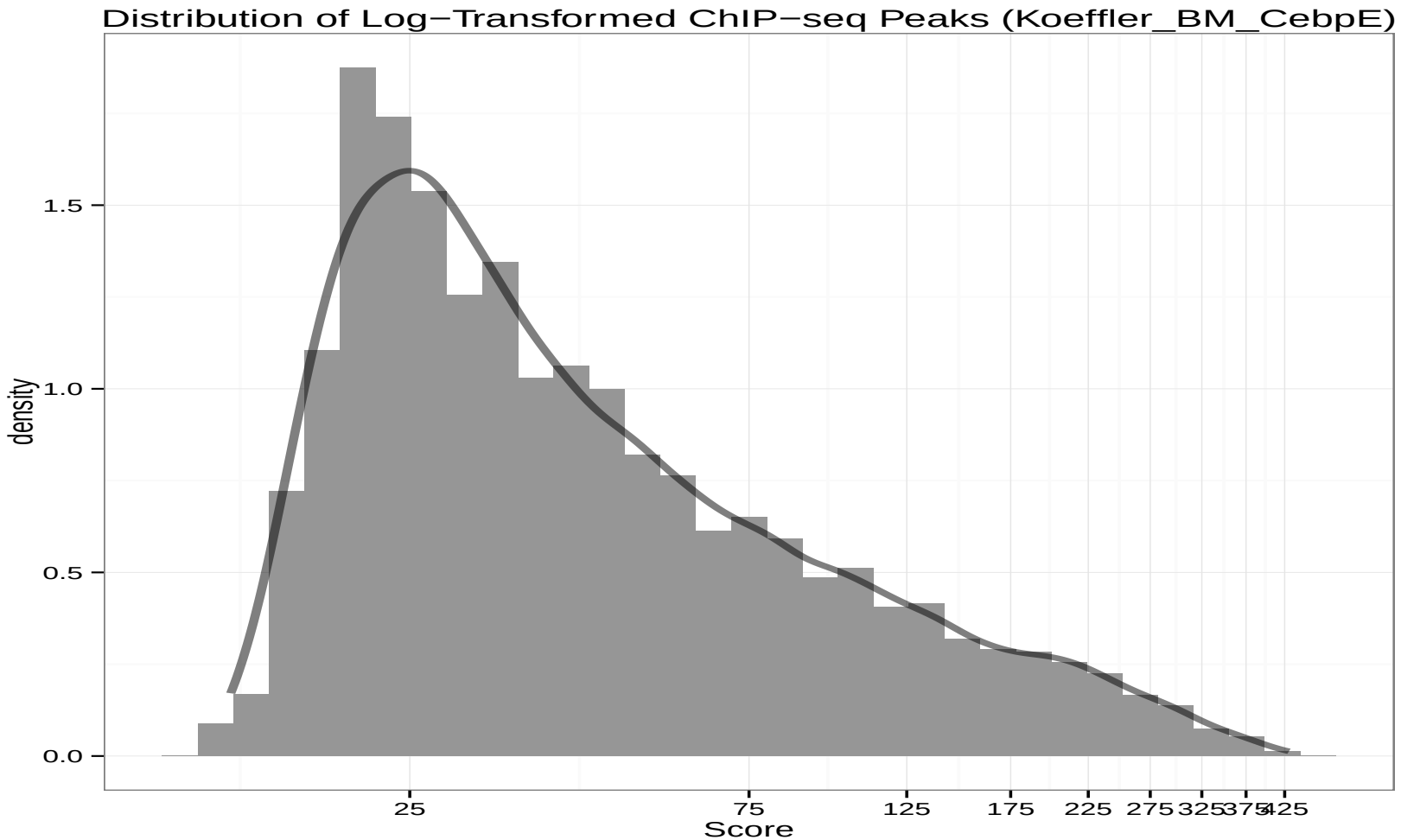
- Given our dataset, MACS2 is able to call peaks however, the estimated scores are less fit than JAHMM
- Peaks identified solely by jaHMM have scores higher with respect to their input (higher ratio) than solely by MACS2

Can we model ChIPseq using components of MMs?

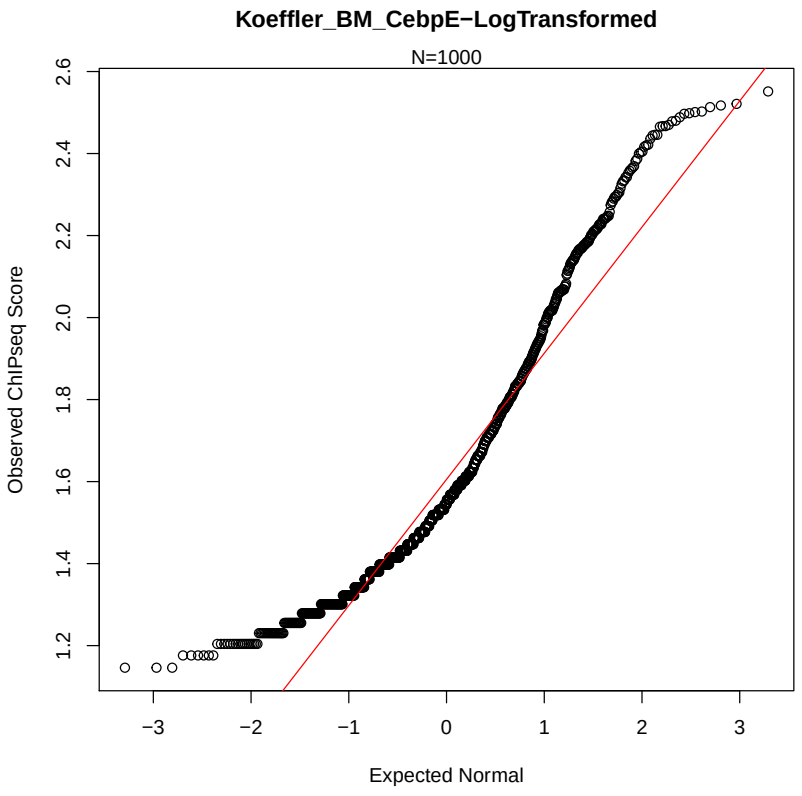
Input: ChIP-seq of Cebpϵ from Koeffler-BM

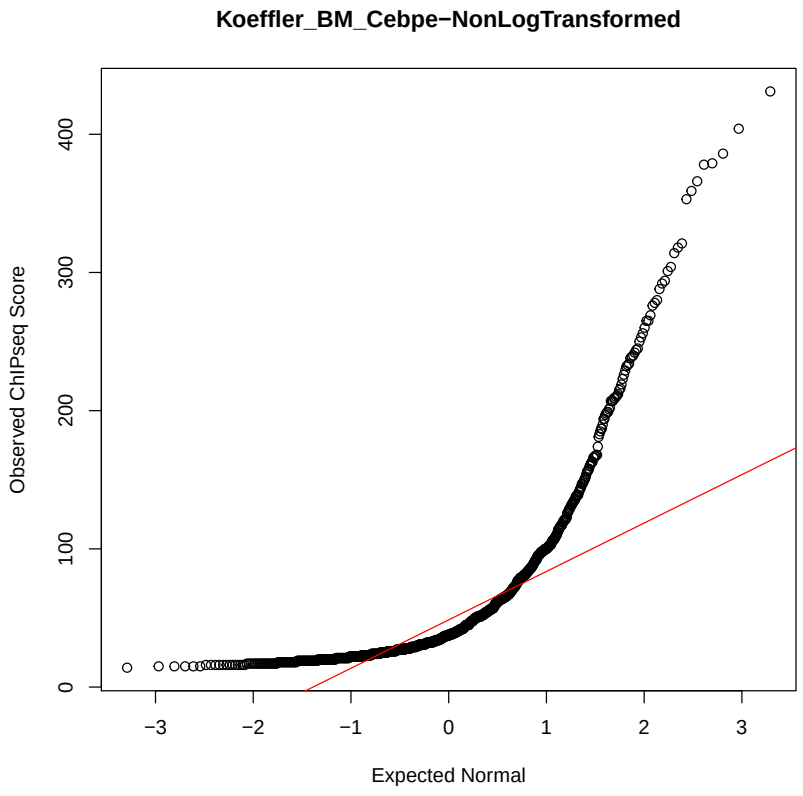


Log Transformation of ChIP-seq Input

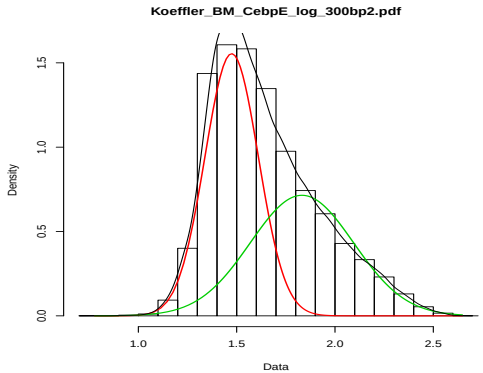


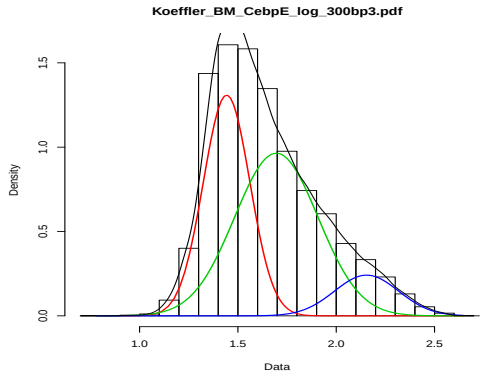
Check the Gaussian Normality

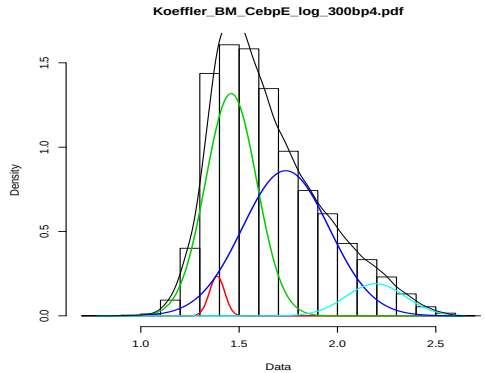


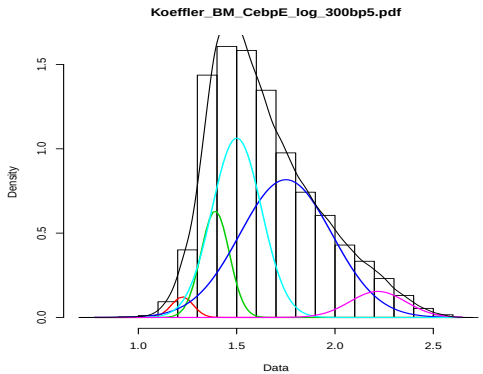


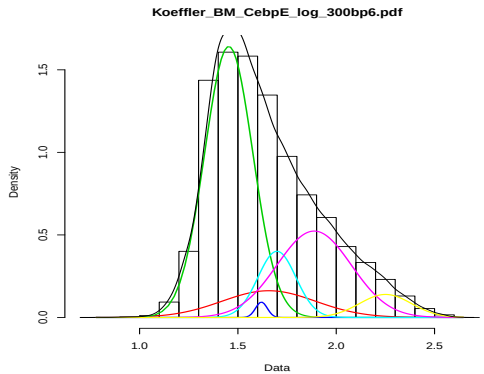
ComponentCalls: Fit ChIPseq Peaks with GMMs

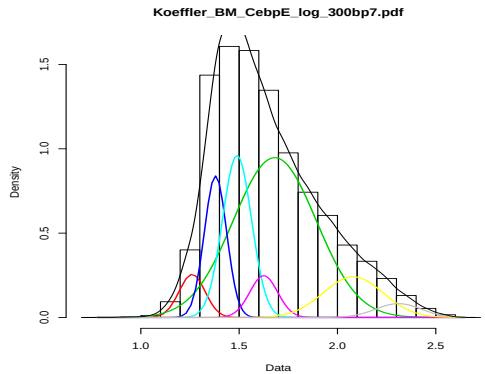


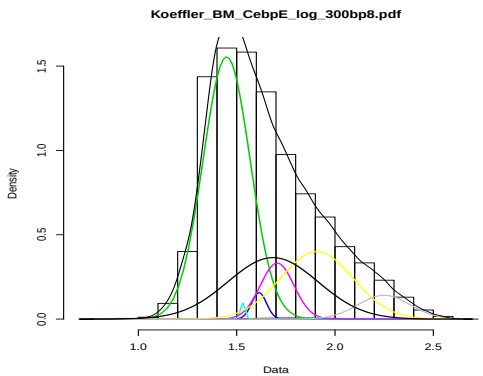


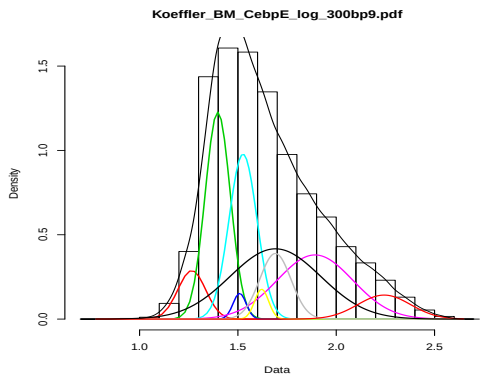


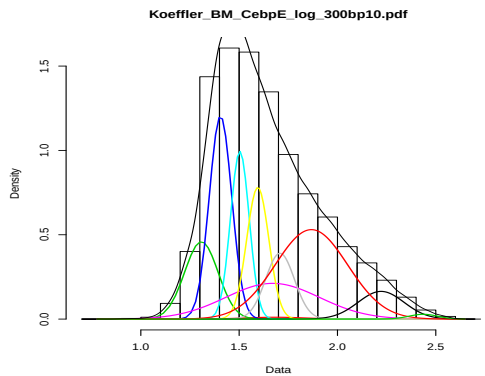




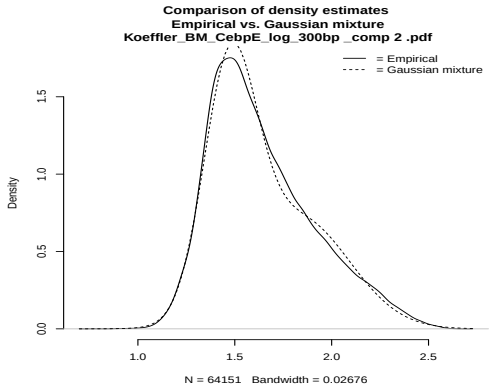


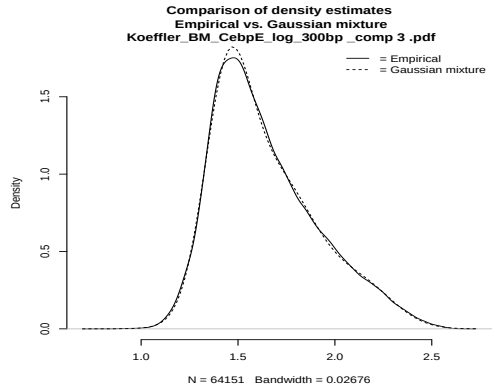


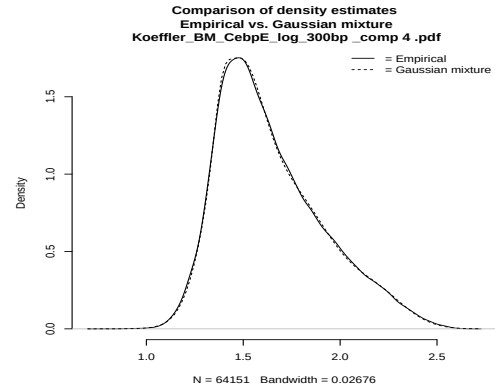


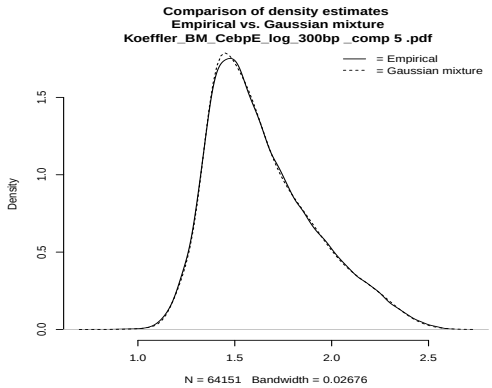


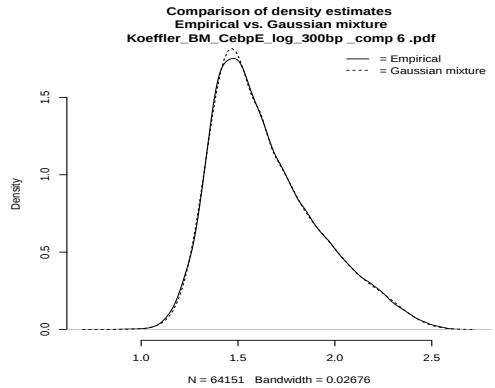
GMM-ModelAssessment: Overfit

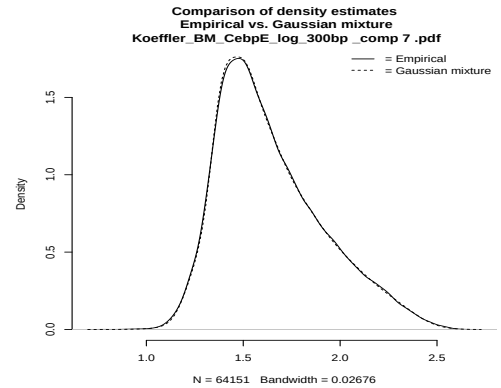


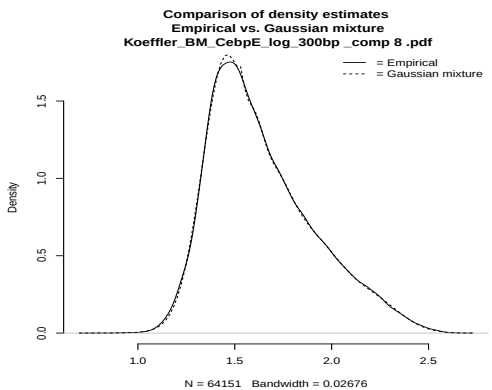


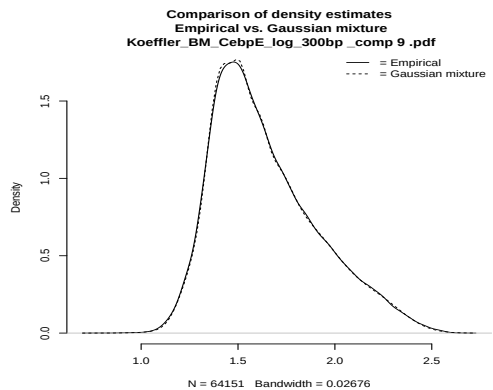


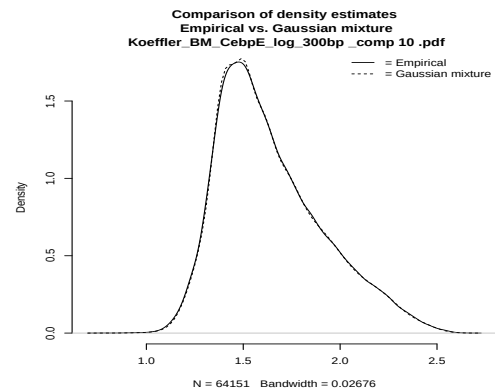












Model Assessment: BIC-AIC

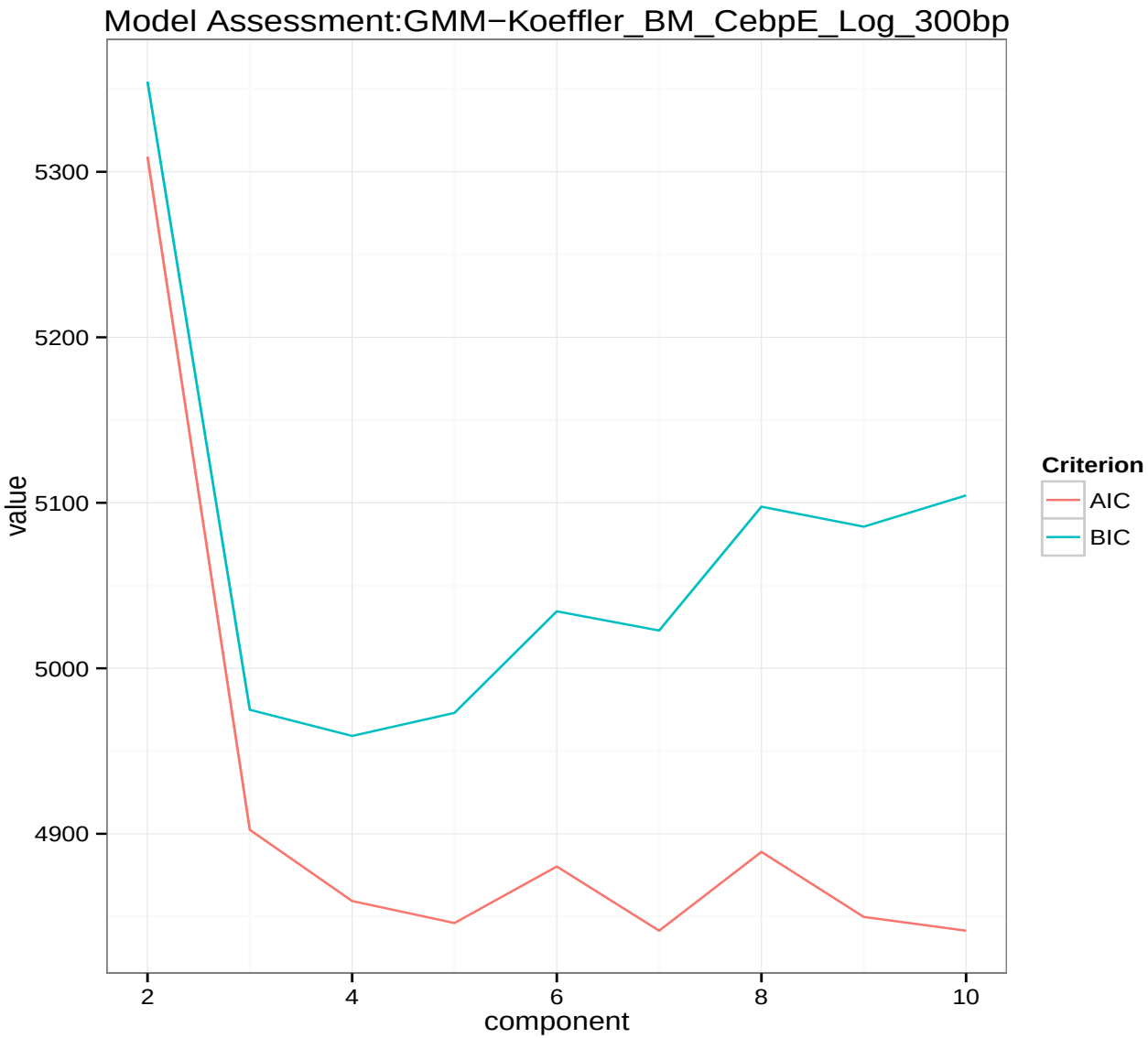
AIC [1] and BIC [2] is based on Occam's razor principle, i.e, the simplest the better.

$$\text{AIC} = -2 \times \log L + 2 * P$$
$$\text{BIC} = -2 \times \log L + \log(n) * P$$

L is likelihood
P is the number of parameters

[1] Akaike information criterion
[2] Bayesian information criterion

Model Assessment: BIC-AIC



Summary: Gaussian Mixture Models (GMMs)

- **Can we model ChIPseq using several components of MMs?**
  Yes, our ChIPseq Peaks identified by jaHMM can be fit with GMMs.

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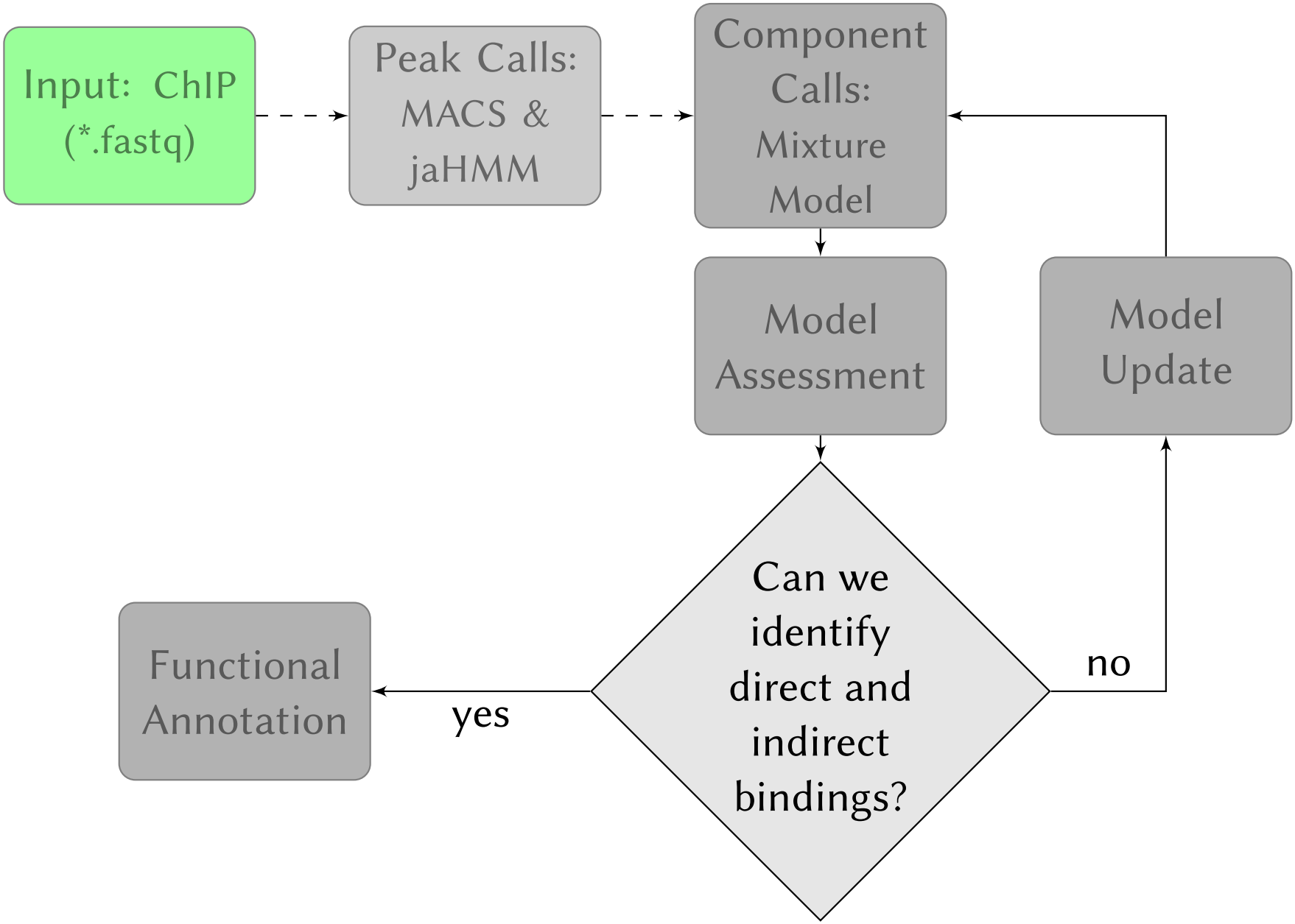
  Yes, our ChIPseq Peaks identified by jaHMM can be fit with GMMs.
- **How many components are required?**
  From AIC-BIC model assessment, 3 components are sufficient to fit ChIPseq signals.
  Note: the lower the AIC and BIC values, the better the fitting.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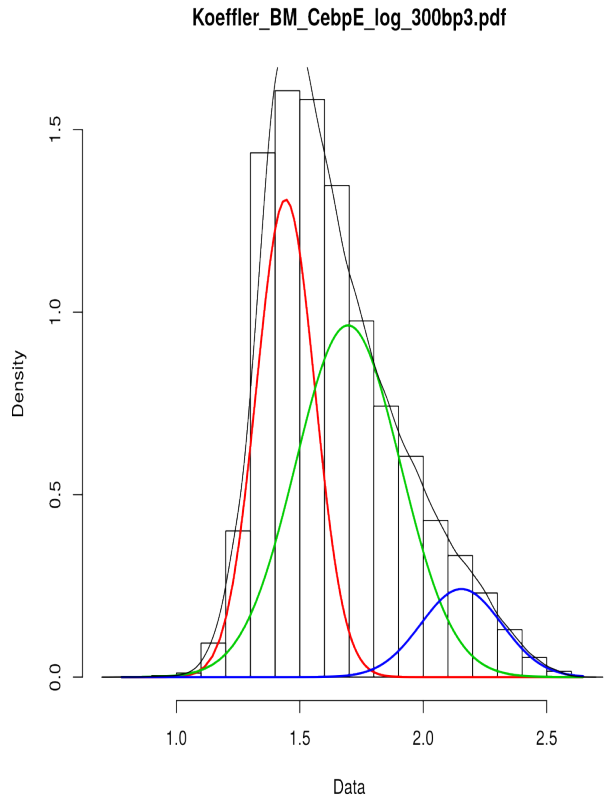
Component Calls: Mixture Model
Model Assessment
Model Update
Can we identify direct and indirect bindings?
yes
no
Functional Annotation

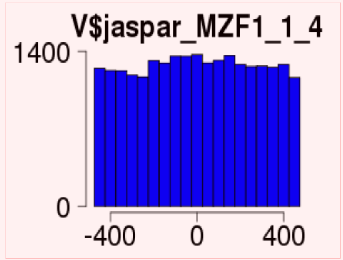
Motif Calls using Centdist [1]

[1] Zhang et al. CENTDIST: discovery of co-associated factors by motif distribution. Nucleic Acids (2011)

Component 1: low peak score (29559 peaks)

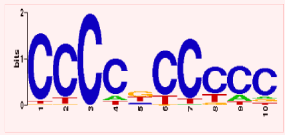


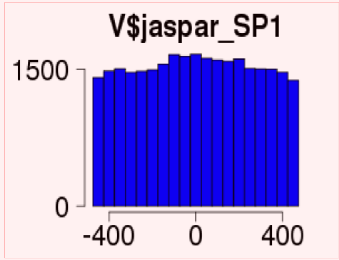
MZF



7.79e-13

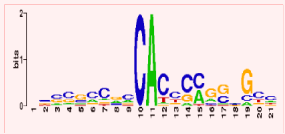
SP1

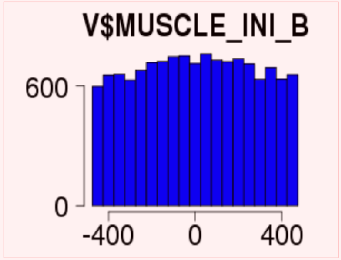




2.0e-11

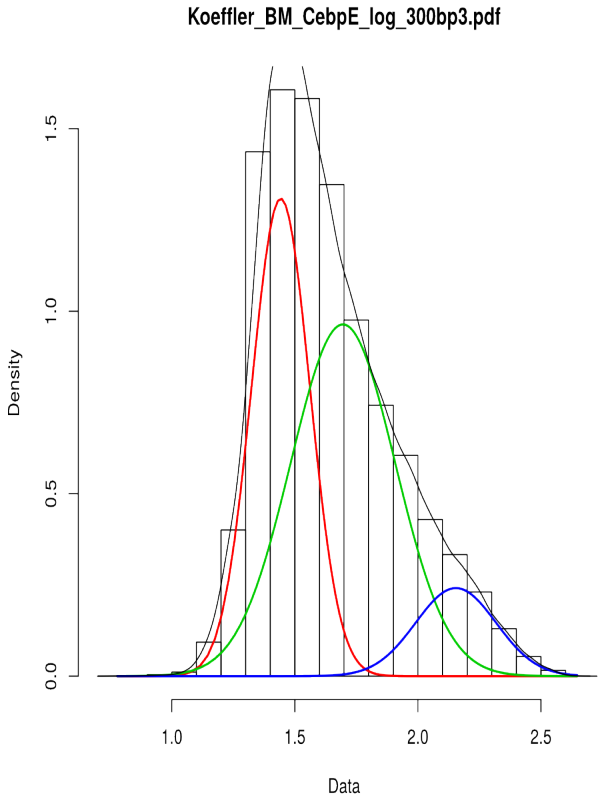
MIN1



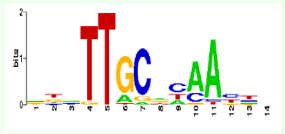


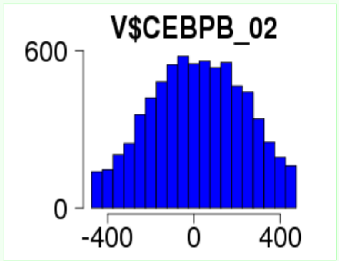
3.53e-8

Component 2: intermediate peak score (28851 peaks)



CEBP





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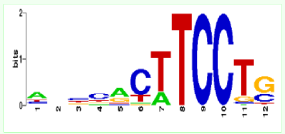
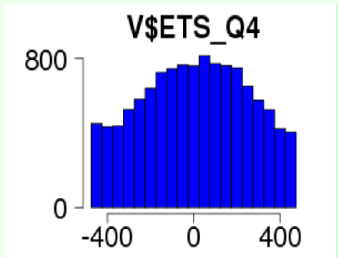
ETS





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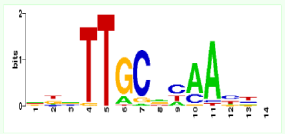
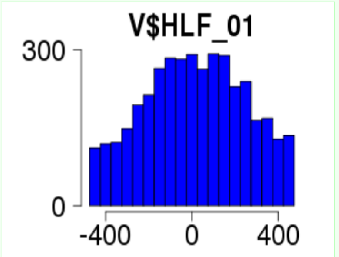
CREB





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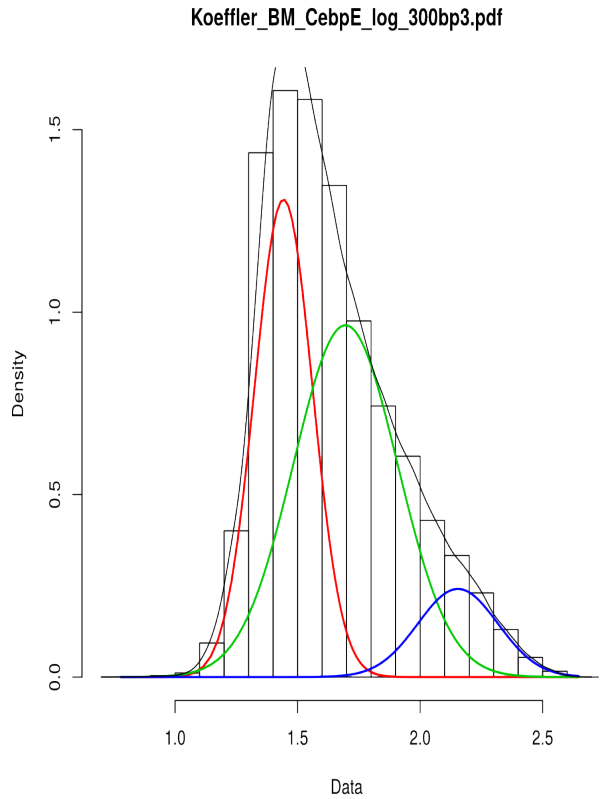
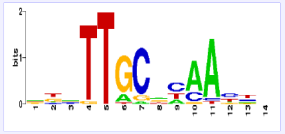
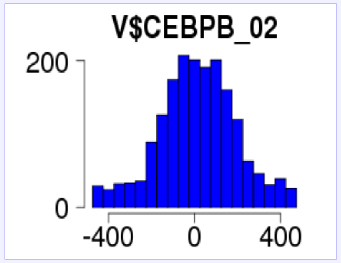
Component 3: high peak score (5741 peaks)



CEBP





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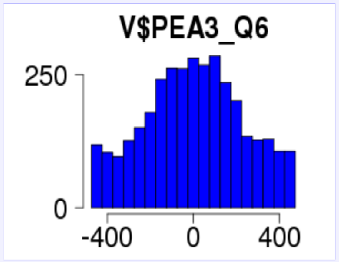
ETS



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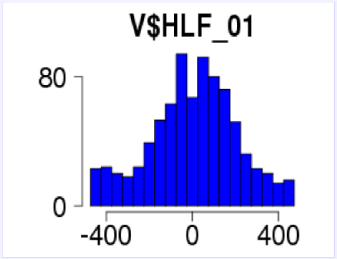
CREB



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Summary: Motif Calls

- Cebp motif is found in group 2 and 3 in 3-component GMMS using centdist

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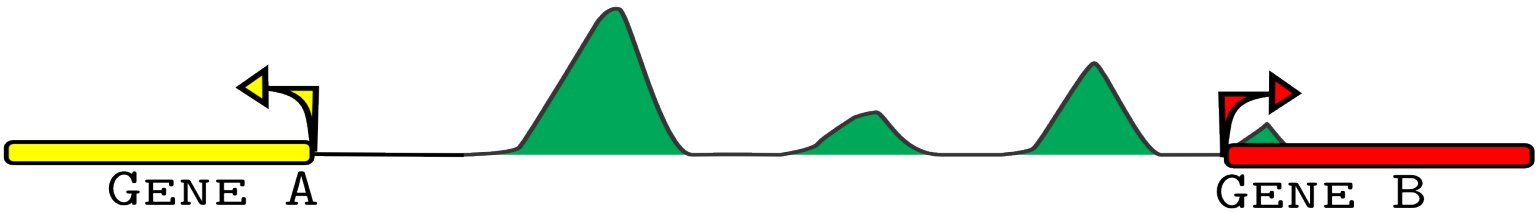
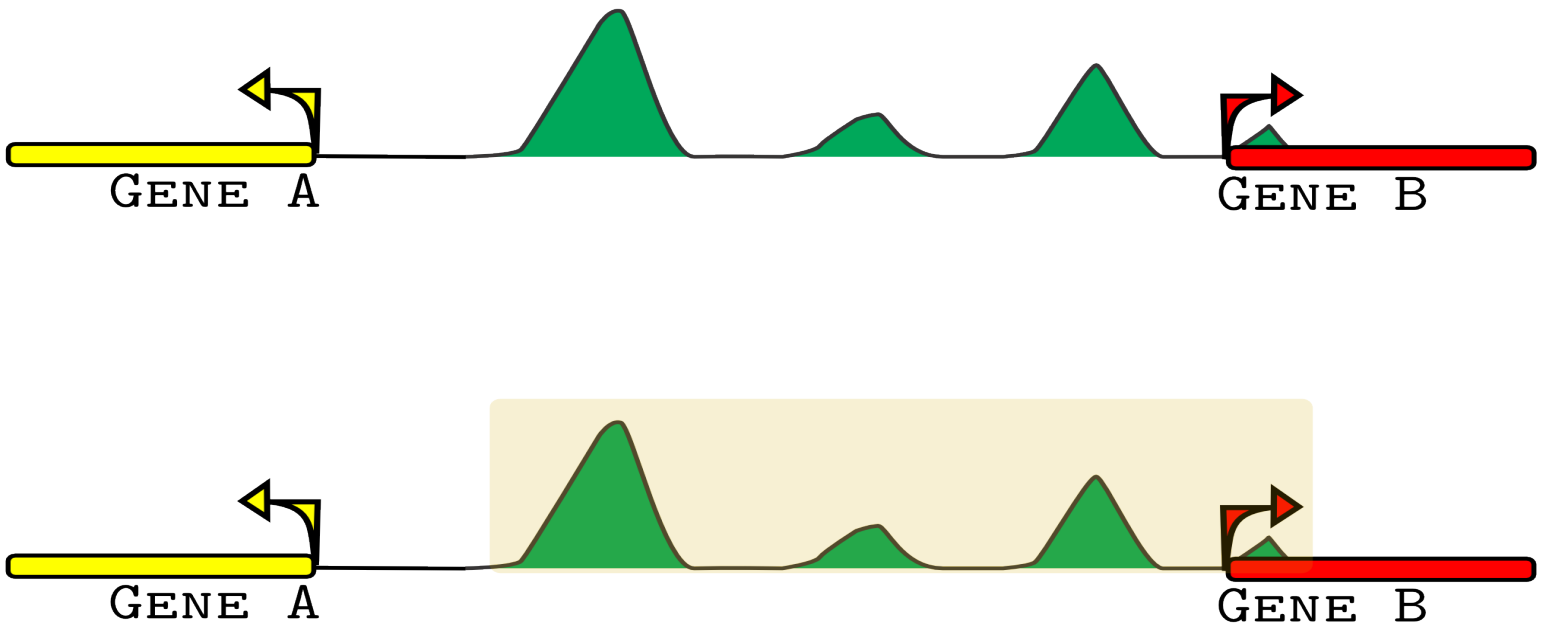
- Cebp motif is found in group 2 and 3 in 3-component GMMS using centdist
- Next, can we further segregate these groups into direct and indirect bindings?

Peak Annotation

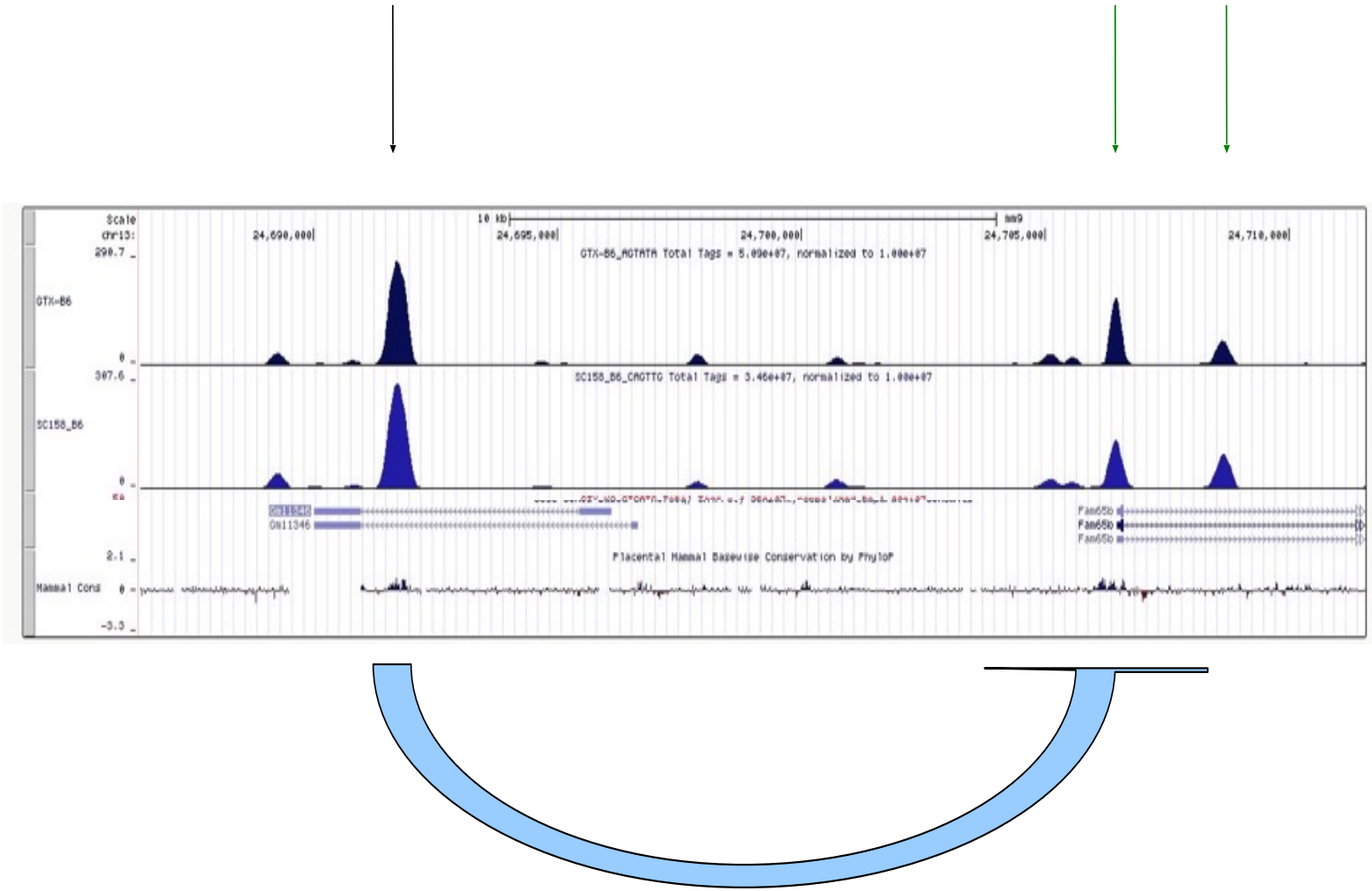


Peak Annotation: Clustering



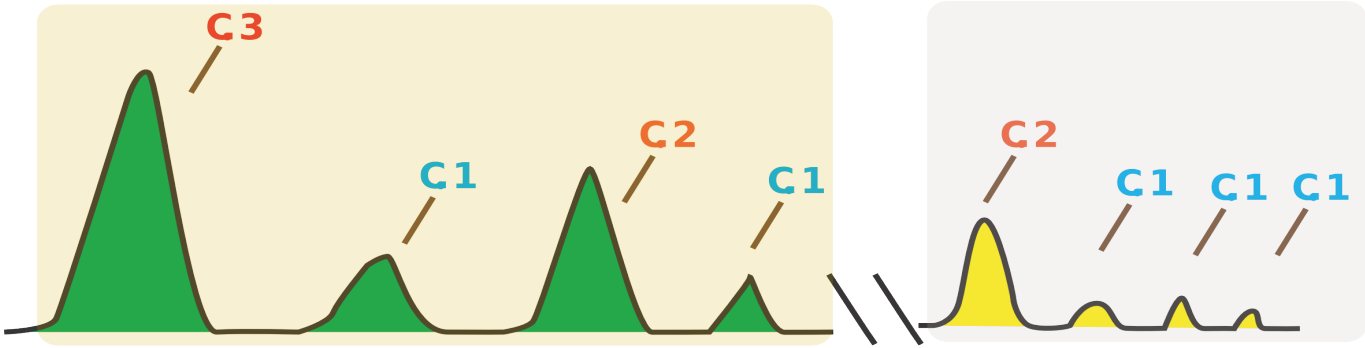
What problems the invention solves and advantages over existing methods?

An Example:

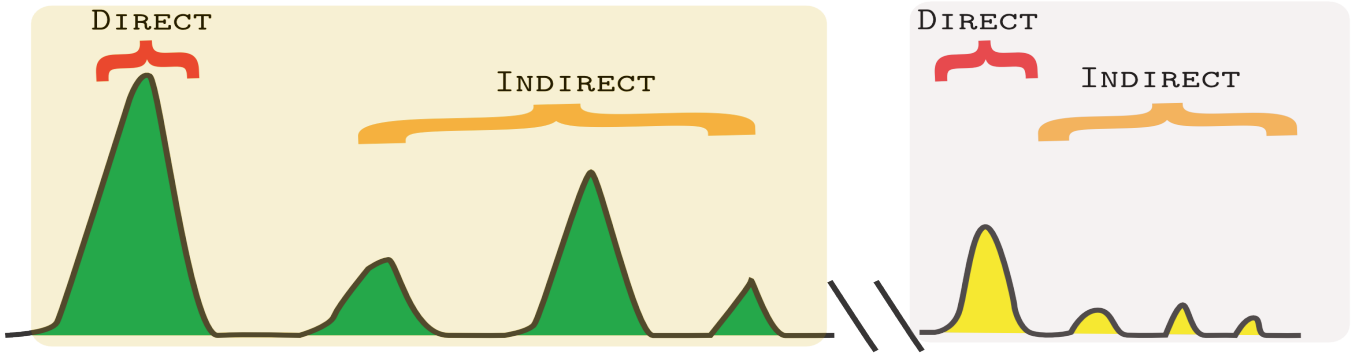


Peak Clustering

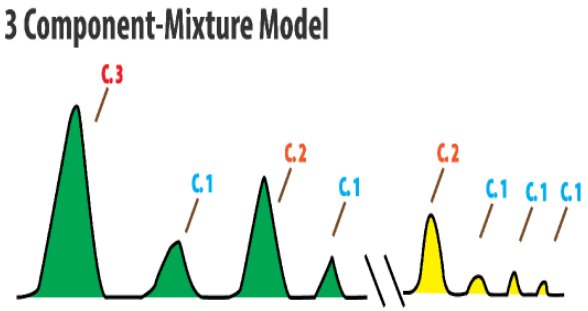
Component Clustering



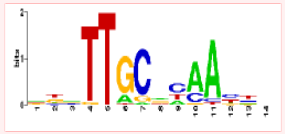
Local Clustering

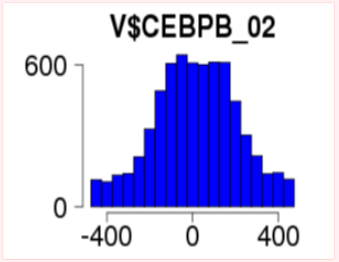


Direct: 24948 peaks



CEBP





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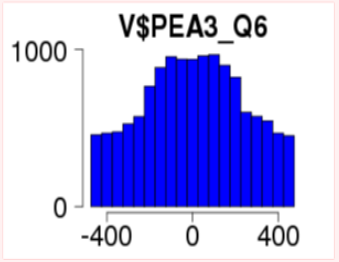
ETS



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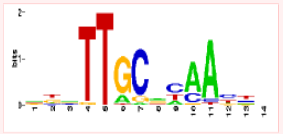
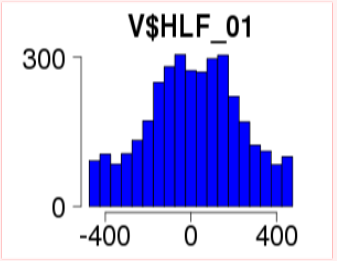
CREB





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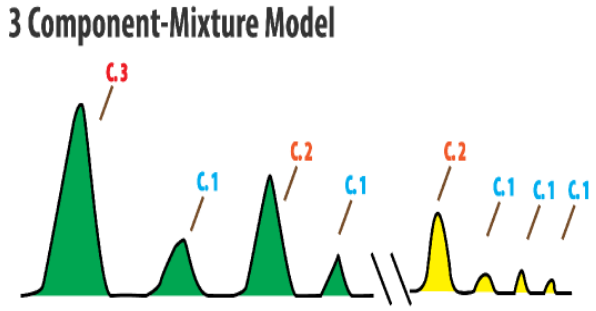
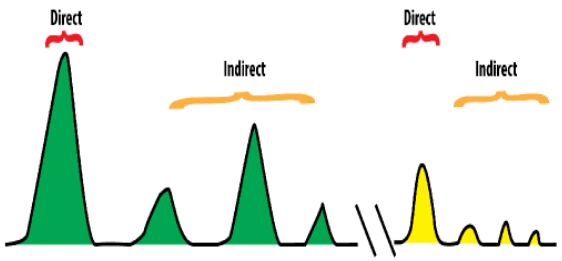
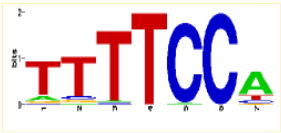
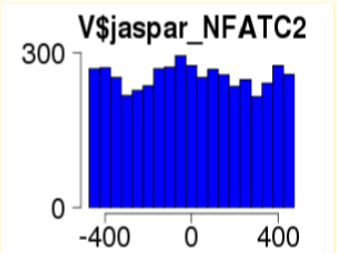
Indirect: 26547 peaks





REL





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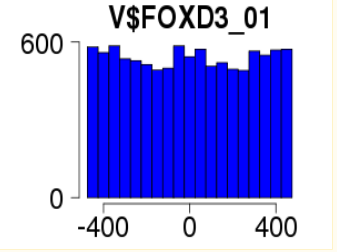
FOX



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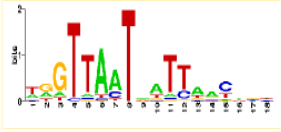
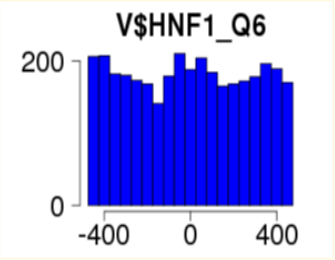
HNF1





0.00266

- Our current method could separate direct and indirect bindings

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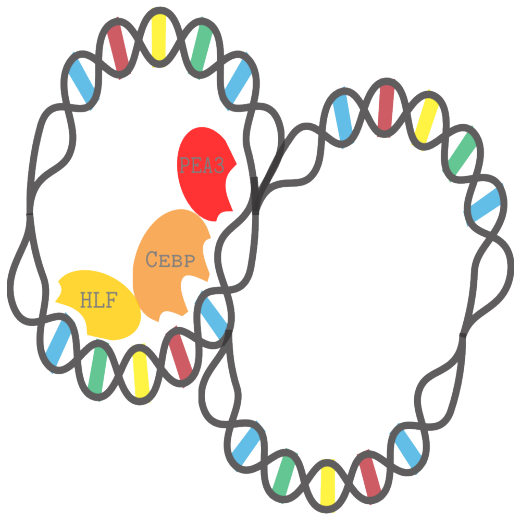

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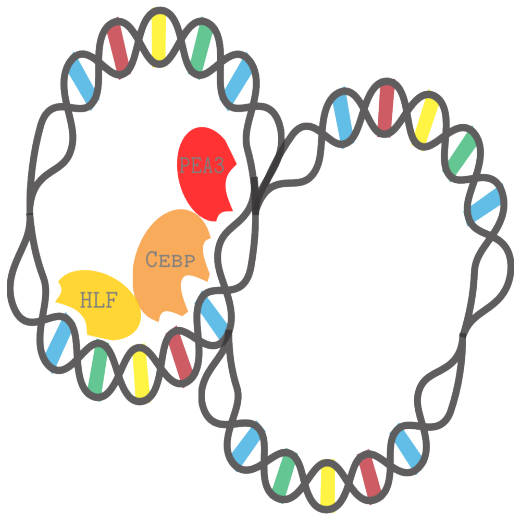

- Next, how this chromatin conformation functions?

Acknowledgement

- Touati Benoukraf (CSI-NUS)
- Samuel Collombet (Ecole Normale Superieur)
- Agus Salim (La Trobe University)
- Tong Yin (CEDARS SINAI Hospital)
- Phillip Koeffler (CSI-NUS)