

Chromatin Conformation Prediction from ChIPseq Signal



Ricky Lim

Cancer Science Institute of Singapore - NUS
Touati Benoukraf's Lab

CSI-Meeting
<mailto:csilr@nus.edu.sg>

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Chromatin Conformation Prediction

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

Inferring direct DNA binding from ChIP-seq

Timothy L. Bailey^{1,*} and Philip Machanick²

¹Institute for Molecular Bioscience, The University of Queensland, Brisbane 4072, Queensland, Australia and

²Department of Computer Science, Rhodes University, Grahamstown 6140, South Africa

Received November 10, 2011; Revised April 2, 2012; Accepted April 23, 2012

Chromatin Conformation Prediction

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- **Strategy:** Model ChIPseq signal using Mixture Models to cluster the direct and indirect bindings.

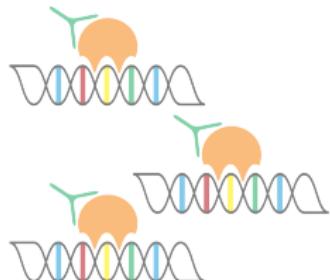
What is ChIPseq?

CHIP-SEQ



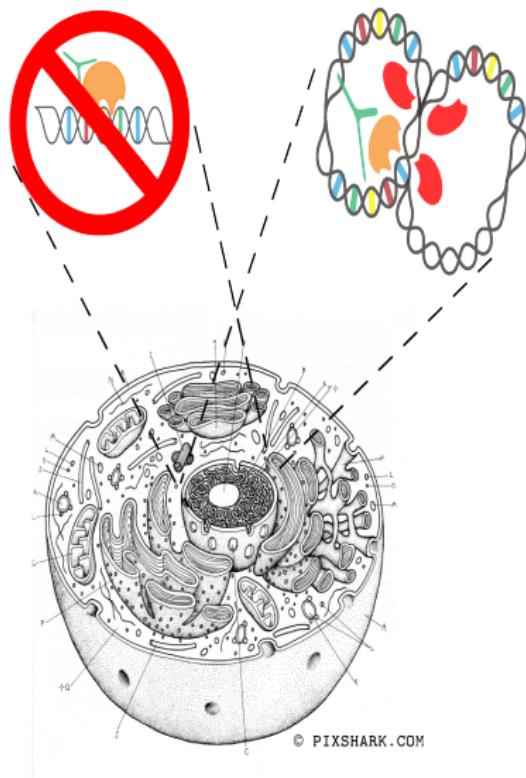
CHROMATIN
IMMUNOPRECIPITATION

SEQUENCING
CAGTTACGGCTAAGGCCA

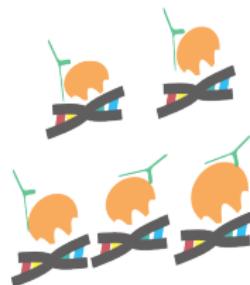


GENE
REFERENCE GENOME

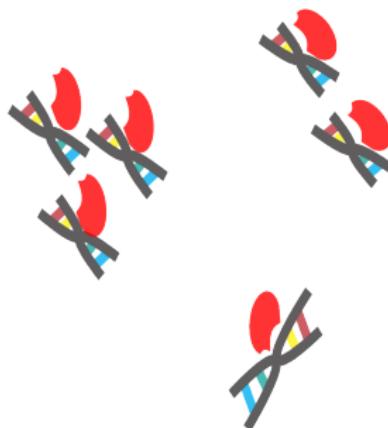
CHROMATIN CONFORMATION



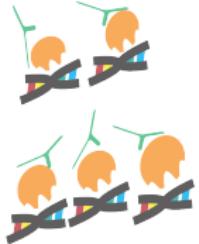
DIRECT BINDING SITES



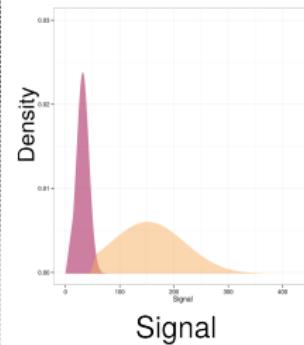
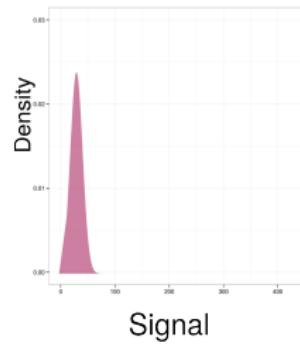
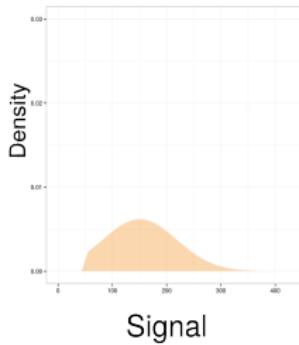
INDIRECT BINDING SITES



DIRECT BINDING SITES



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

Types of clustering methods:

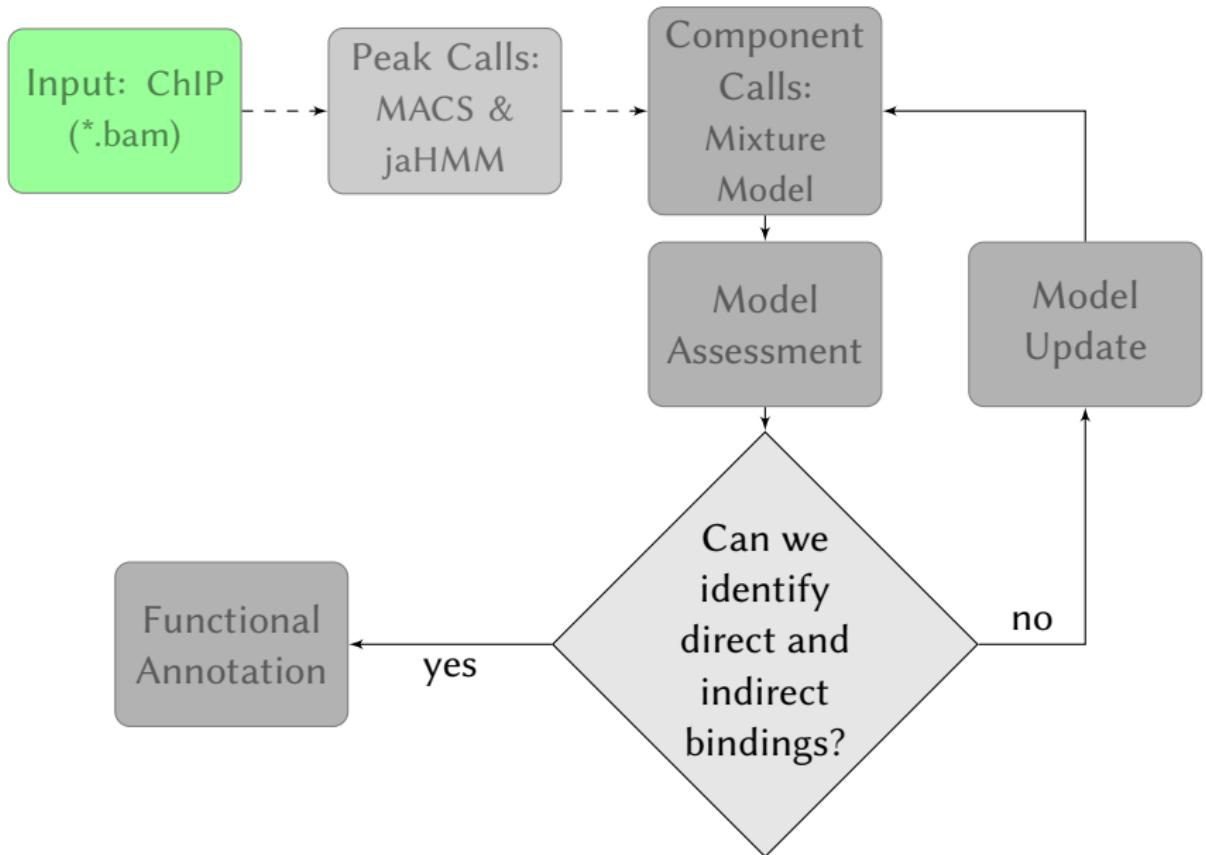
- Hard clustering: non-overlapping clusters
- Soft clustering: overlapping clusters

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-seq of Cebpe 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

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

²Filion 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 calls¹

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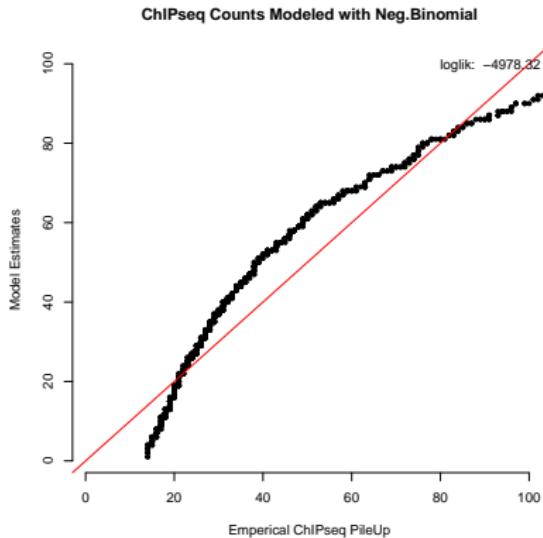
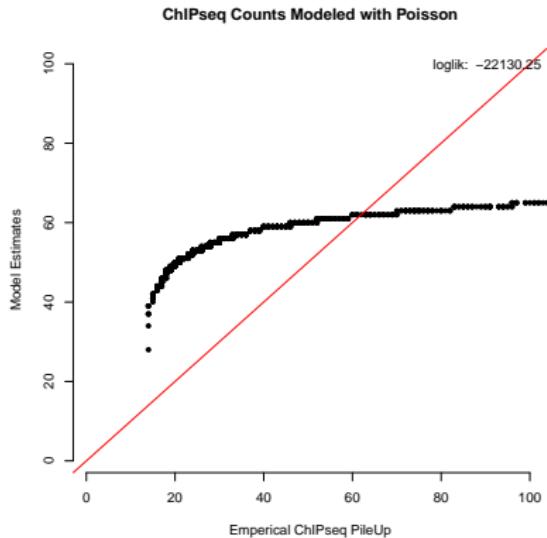
Peak Calls: MACS2 vs jaHMM

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

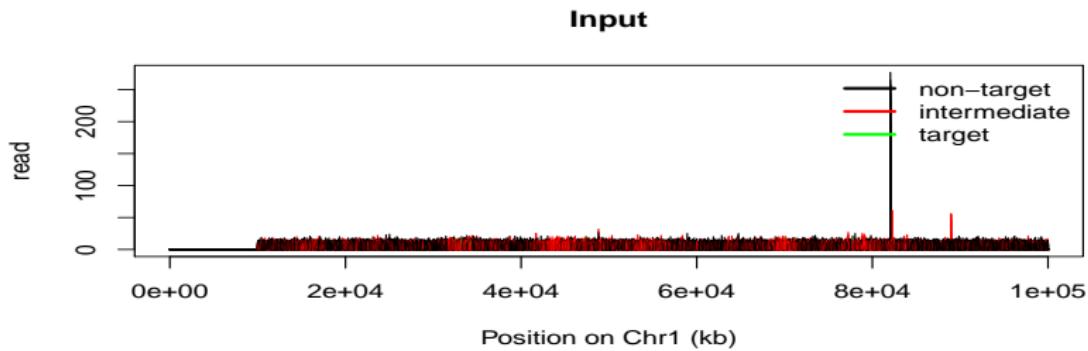
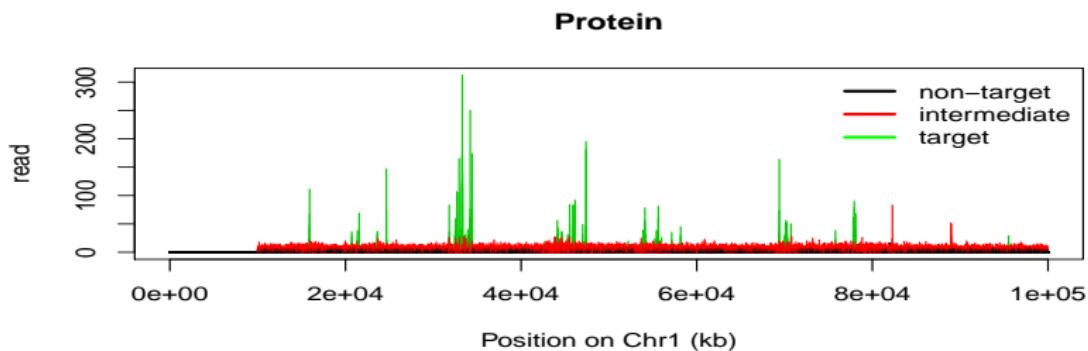
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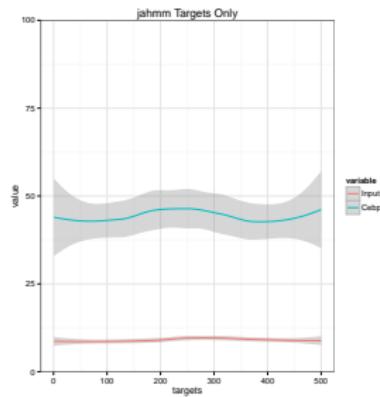
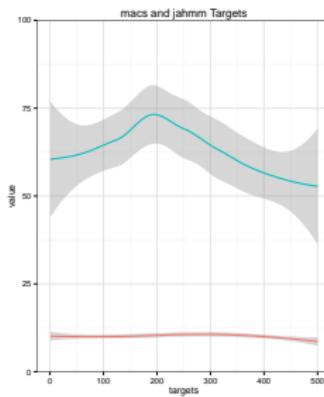
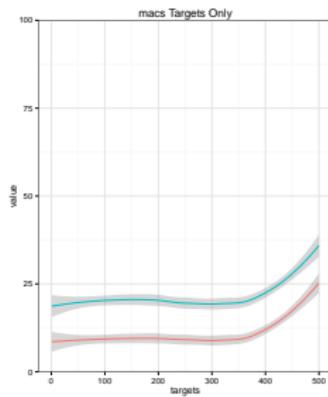
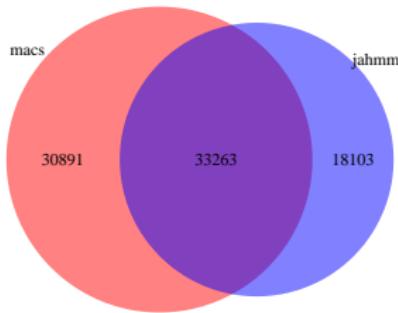
jaHMM fits ChIPseq Signals better than MACS2



Peaks Called by jahmm



Peaks Called by MACS2 vs jahmm



Summary: Peak Calls

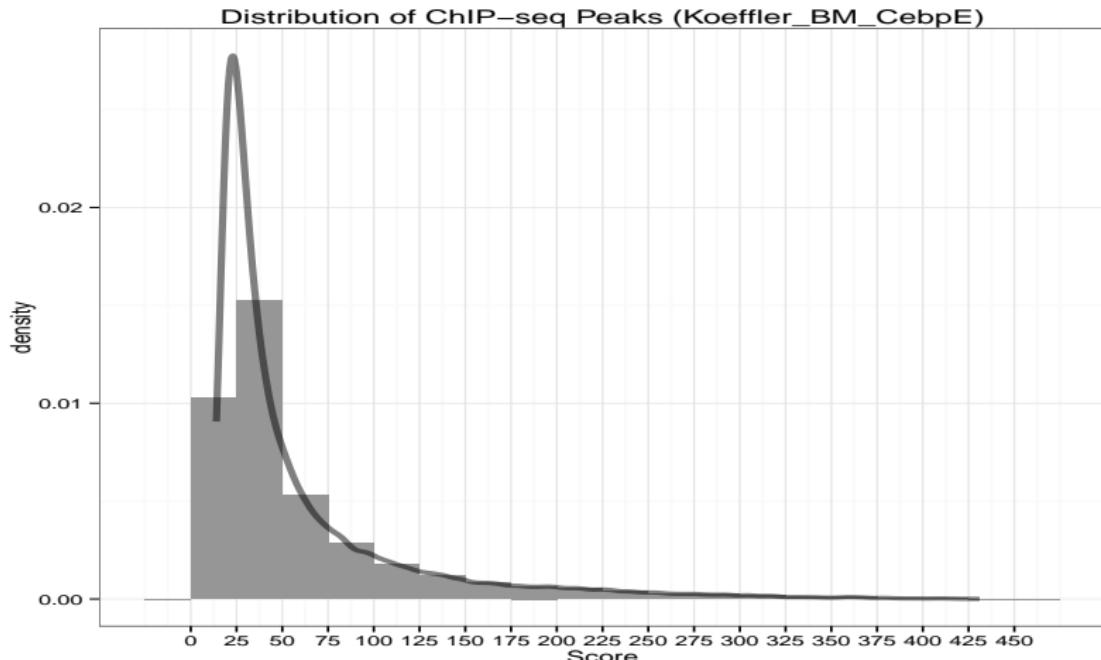
- Given our dataset, MACS2 is able to call peaks however, the estimated scores are less fit than JAHMM

Summary: Peak Calls

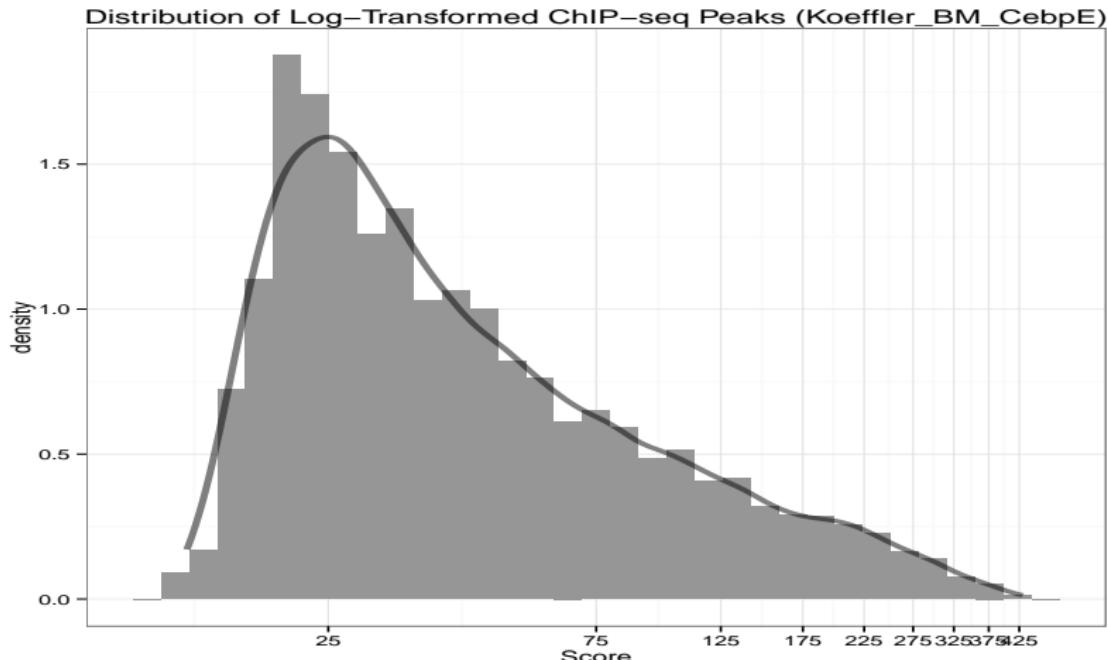
- Given our dataset, MACS2 is able to call peaks however, the estimated scores are less fit than JAHMM
- Peaks identified solely by jaHMM have scores higher with respect to their input (higher ratio) than solely by MACS2

Can we model ChIPseq using components of MMs?

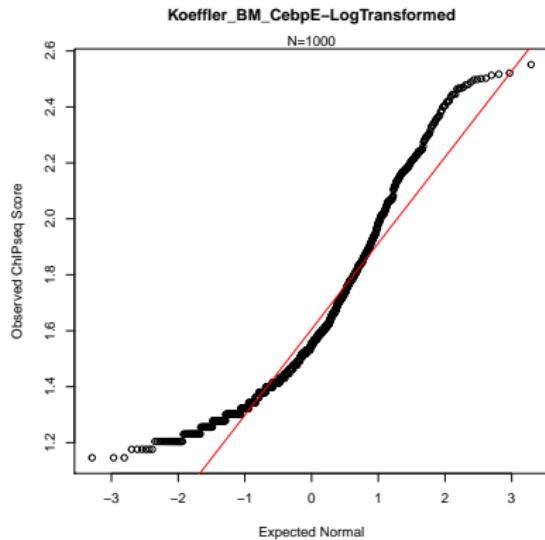
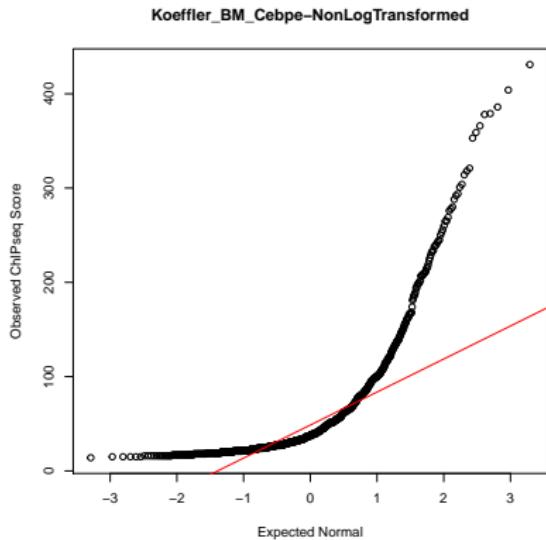
Input: ChIP-seq of Cebp ϵ from Koeffler-BM



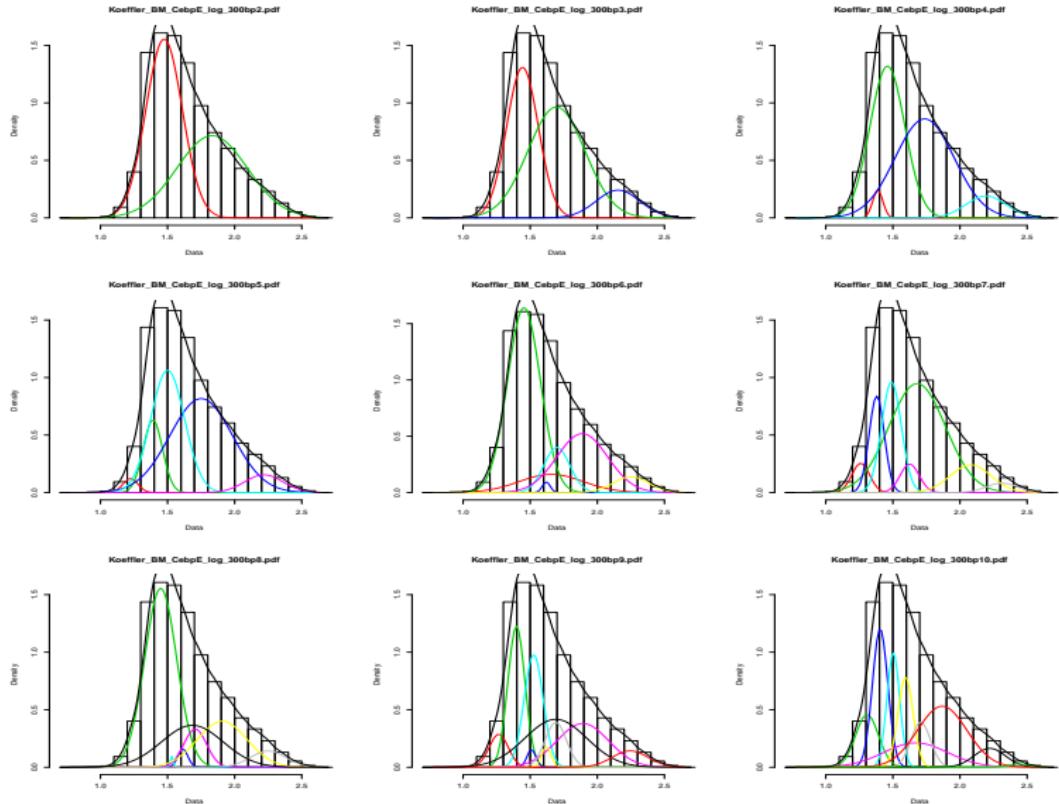
Log Transformation of ChIP-seq Input



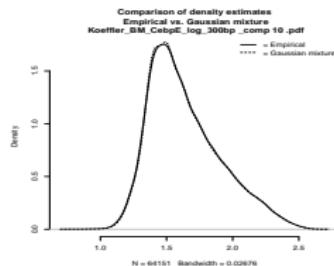
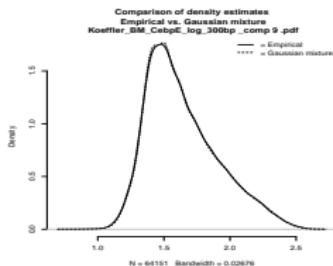
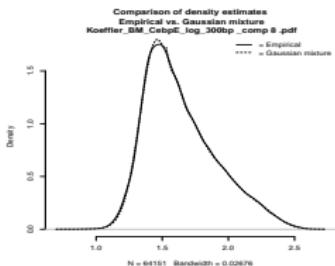
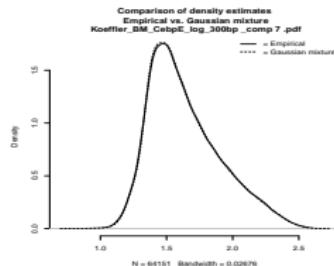
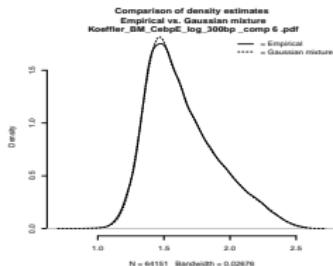
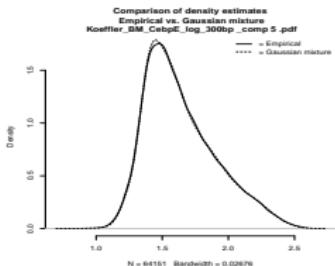
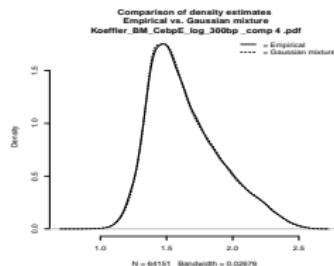
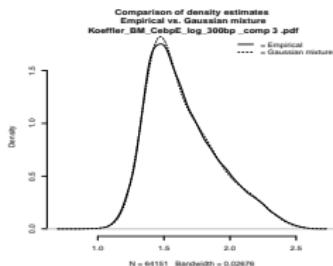
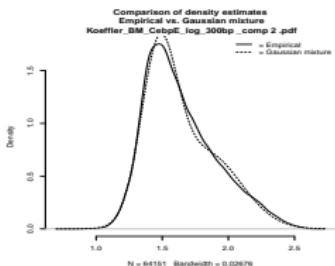
Check the Gaussian Normality



ComponentCalls: Fit ChIPseq Peaks with GMMs



GMM-ModelAssessment: Overfit



Model Assessment: BIC-AIC

AIC¹ and BIC² is based on Occam's razor principle, i.e, the simplest the better.

$$\text{AIC} = -2 \times \log L + 2 * P$$

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

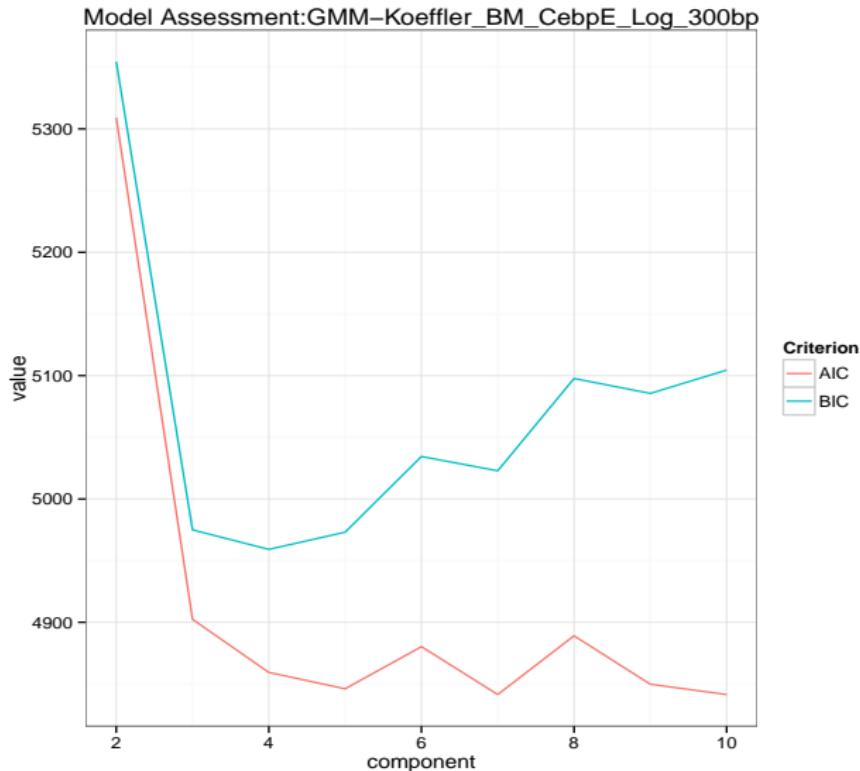
L is likelihood

P is the number of parameters

¹Akaike information criterion

²Bayesian 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.

Summary: Gaussian Mixture Models (GMMs)

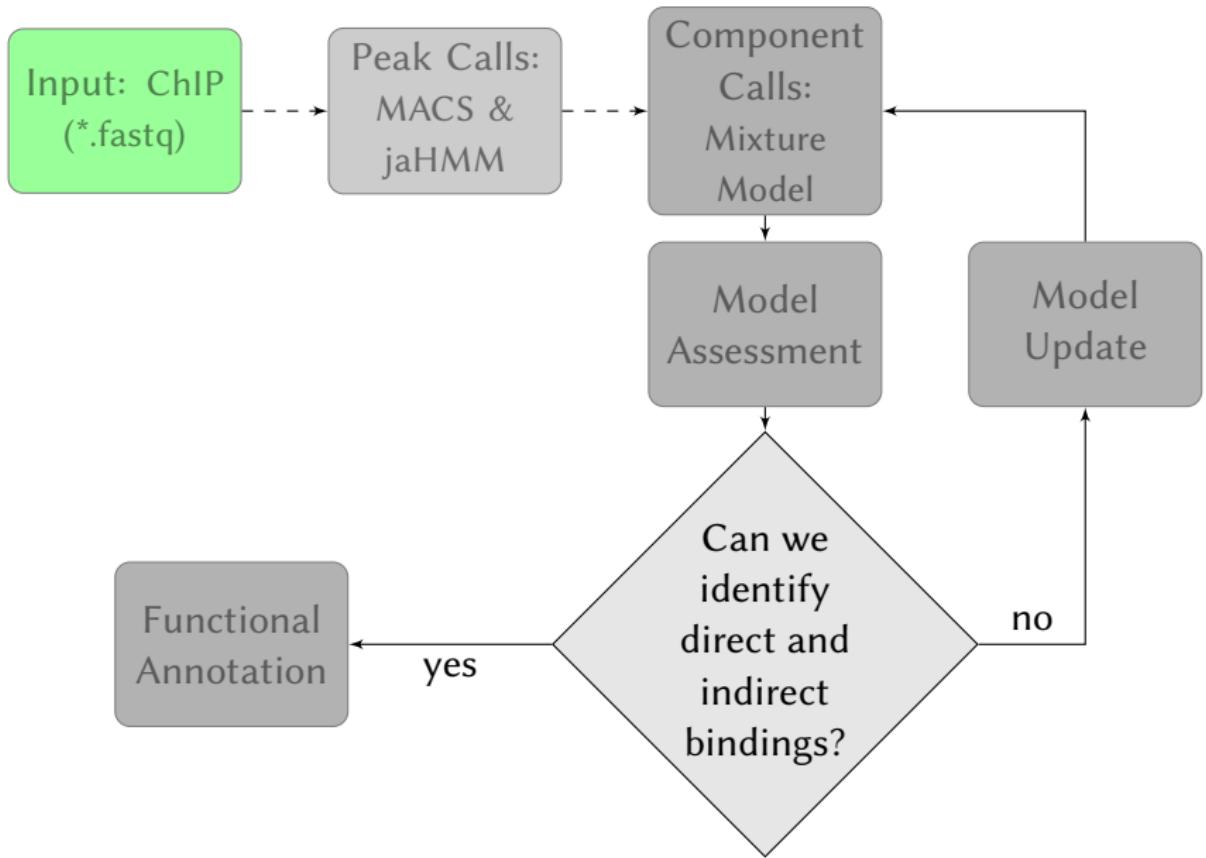
- **Can we model ChIPseq using several components of MMs?**

Yes, our ChIPseq Peaks identified by jaHMM can be fit with GMMs.

- **How many components are required?**

From AIC-BIC model assessment, 3 components are sufficient to fit ChIPseq signals.

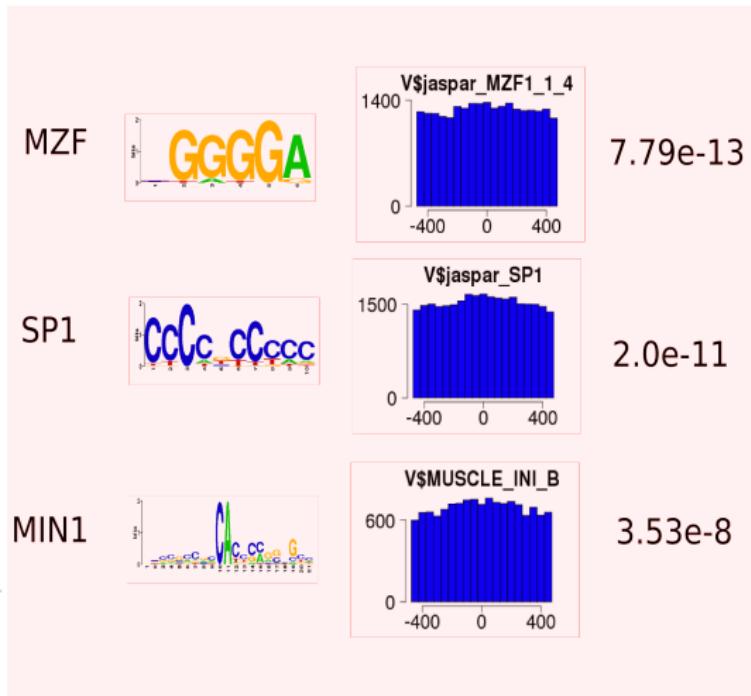
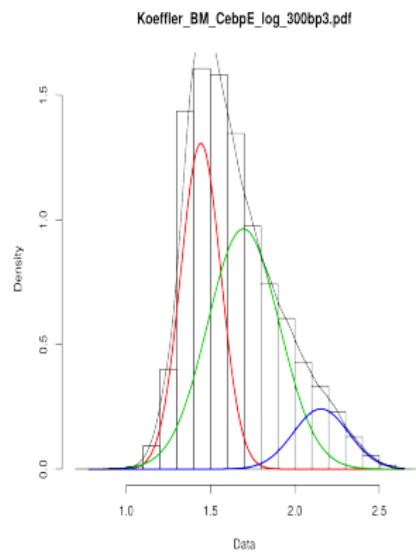
Note: the lower the AIC and BIC values, the better the fitting.



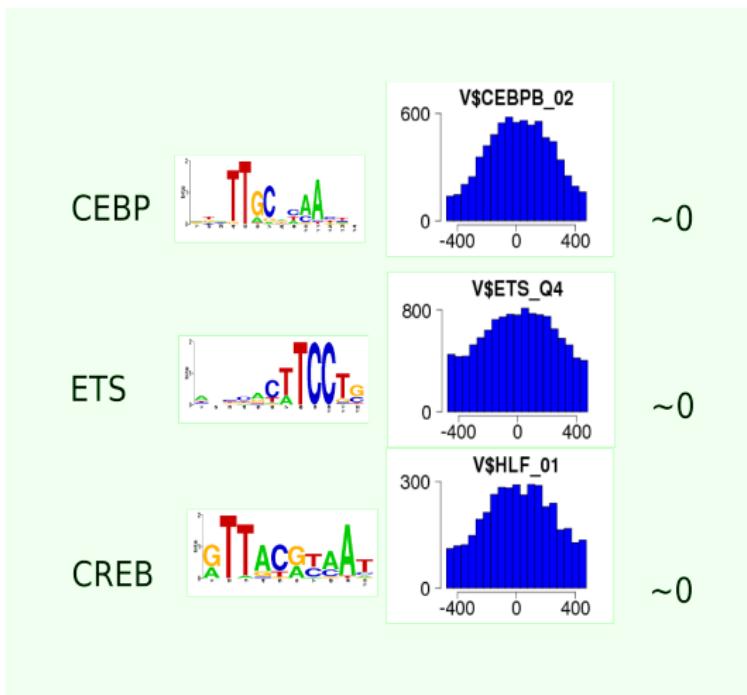
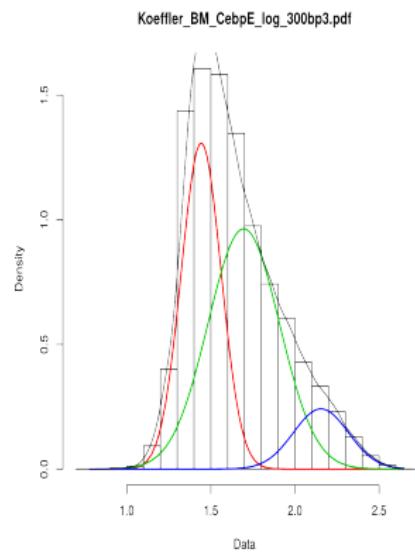
Motif Calls using Centdist ¹

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

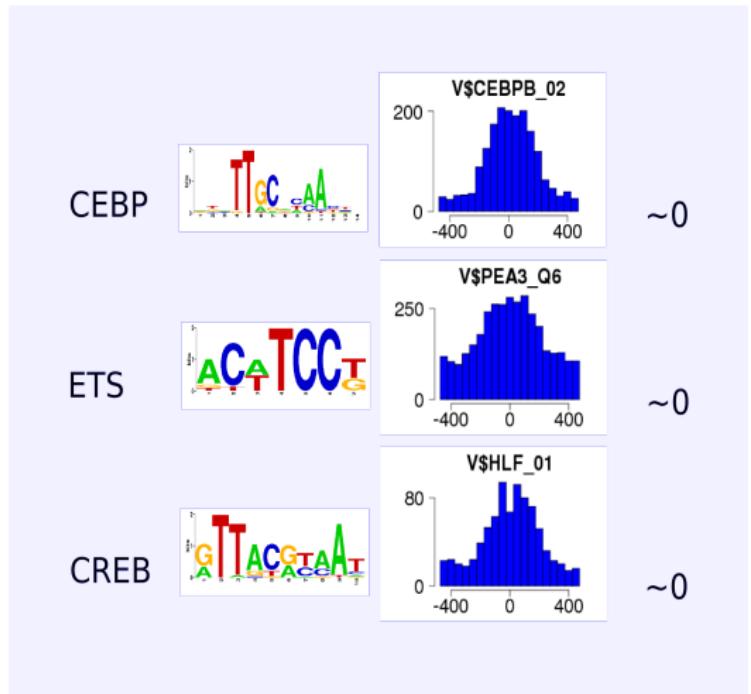
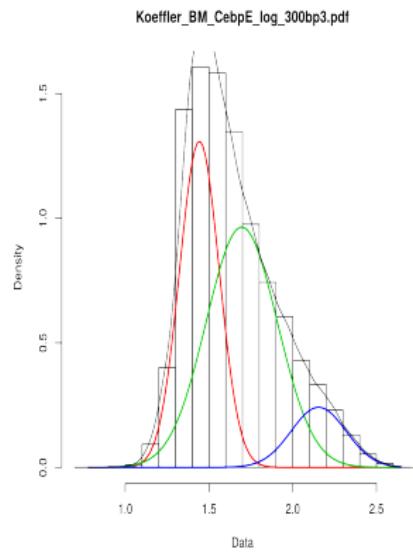
Component 1: low peak score (29559 peaks)



Component 2: intermediate peak score (28851 peaks)



Component 3: high peak score (5741 peaks)



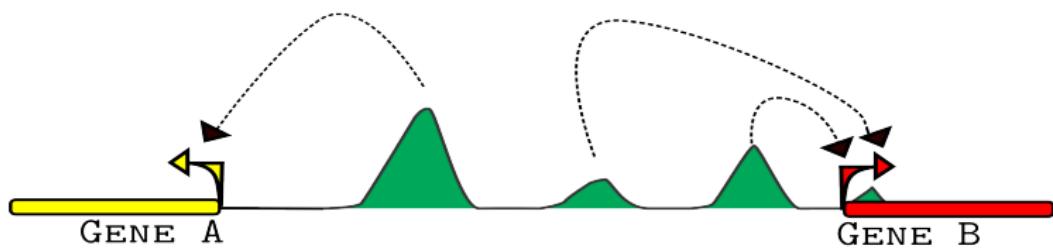
Summary: Motif Calls

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

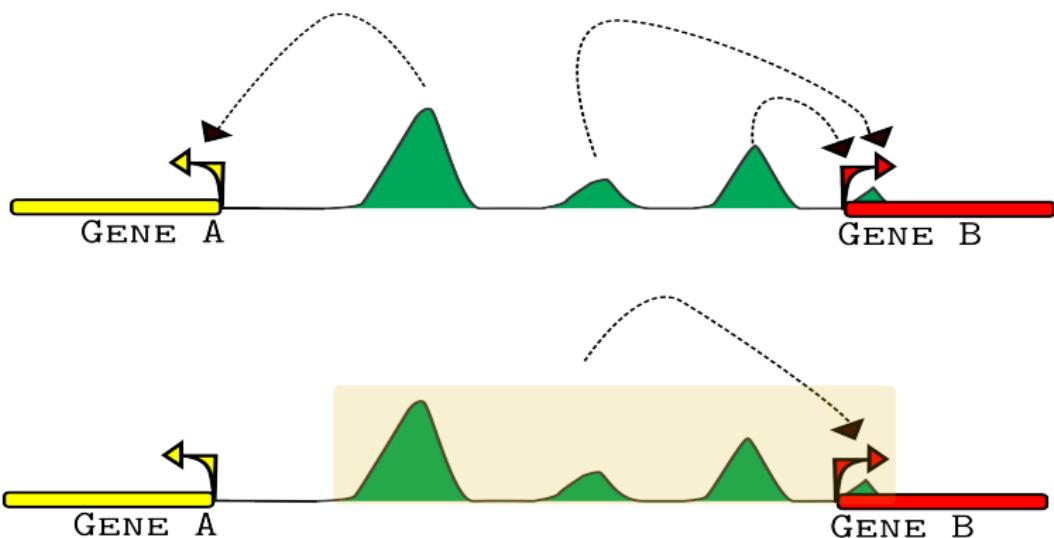
Summary: Motif Calls

- 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

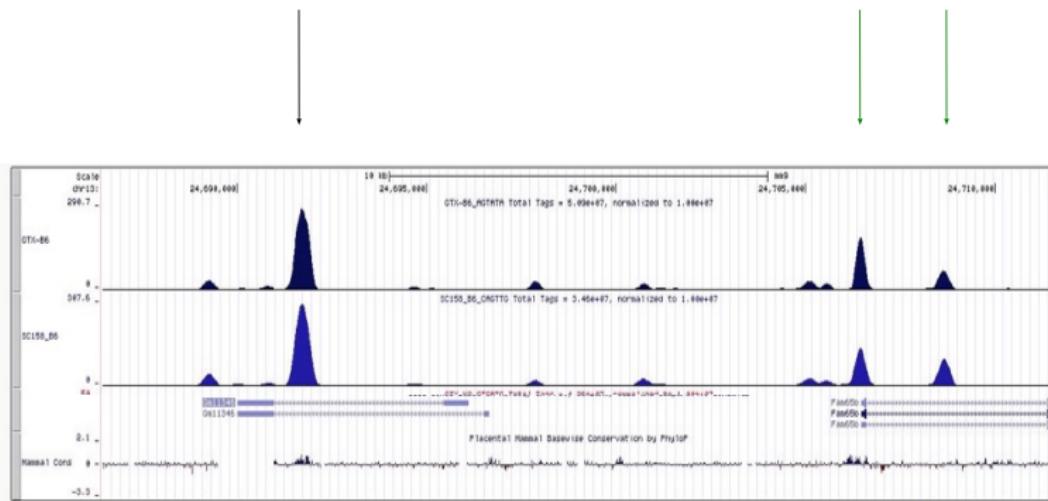


Peak Annotation: Clustering



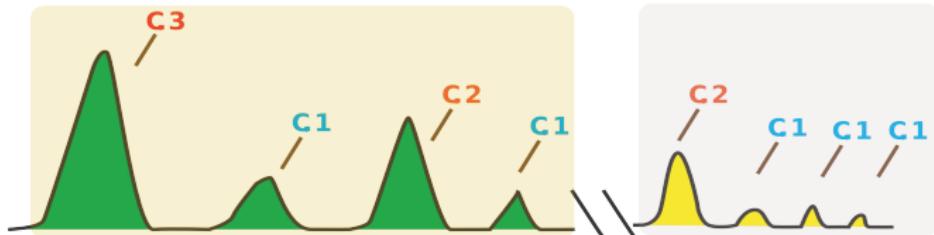
What problems the invention solves and advantages over existing methods?

An Example:

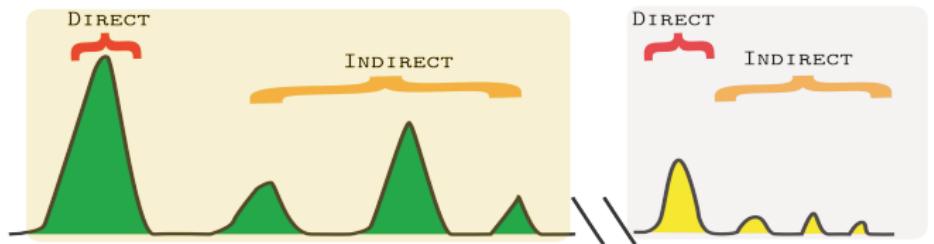


Peak Clustering

COMPONENT CLUSTERING

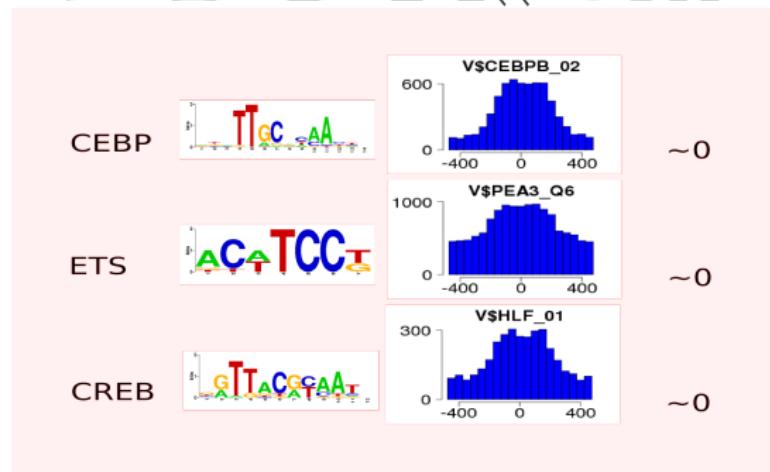


LOCAL CLUSTERING



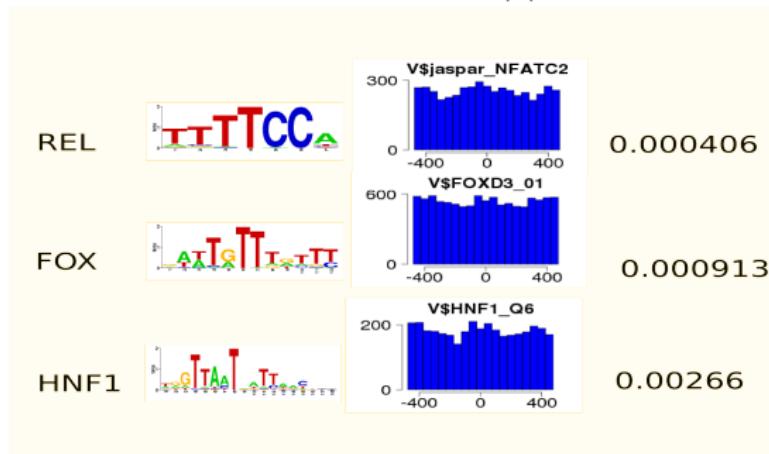
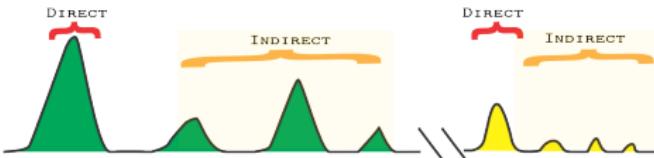
Direct: 24948 peaks

LOCAL CLUSTERING



Indirect: 26547 peaks

LOCAL CLUSTERING



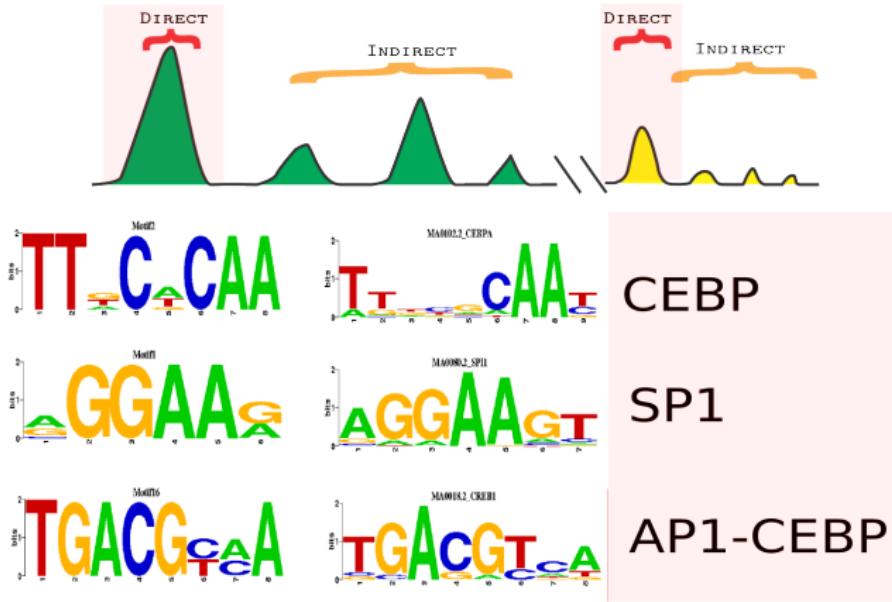
Motif Discovery using MEME-ChIP¹ and STAMP²

¹Machanick, P and Bailey, T. MEME-ChIP: motif analysis of large DNA datasets. Nucleic Acids (2011)

²Mahony, S and Benos, P. STAMP: a web tool for exploring DNA-binding motif similarities. Nucleic Acids (2007)

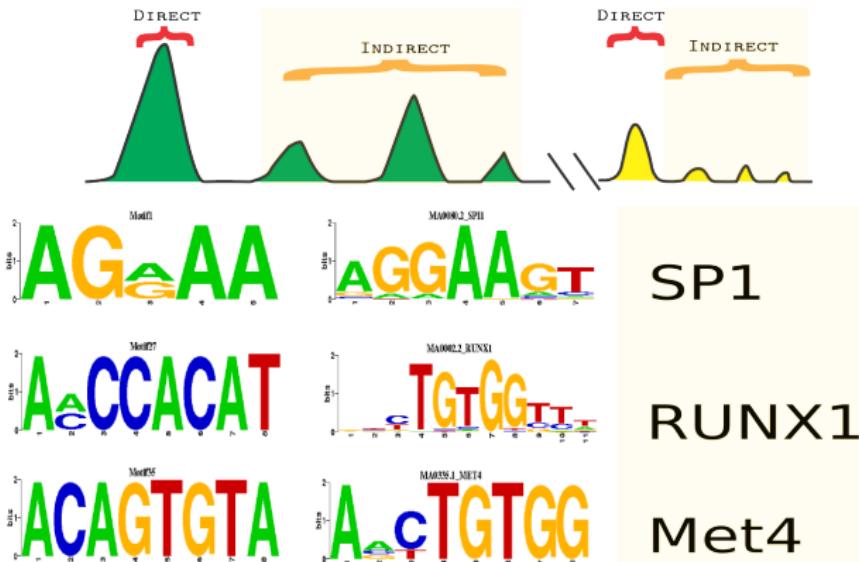
Direct: 24948 peaks

LOCAL CLUSTERING



Indirect: 26547 peaks

LOCAL CLUSTERING

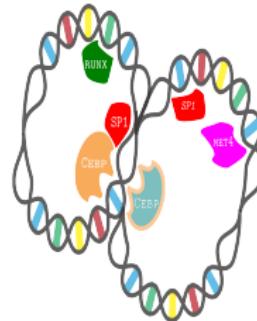


Summary: Chromatin Conformation Prediction from ChIPseq Signal

- Our current method could separate direct and indirect bindings

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- Our current method could separate direct and indirect bindings
- Given Cebpe ChIPseq, we could predict the chromatin conformation of Cebp



Future Directions

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- Wet-lab work
 - Peak clusters validation by 3C and ChIP

Acknowledgement

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