Using positional information for predicting transcription factor binding sites

Raphaël Romero, Christophe Menichelli, Jean-Michel Marin, Sophie Lèbre, Charles-Henri Lecellier, Laurent Brehelin

Using positional information for predicting transcription factor binding sites

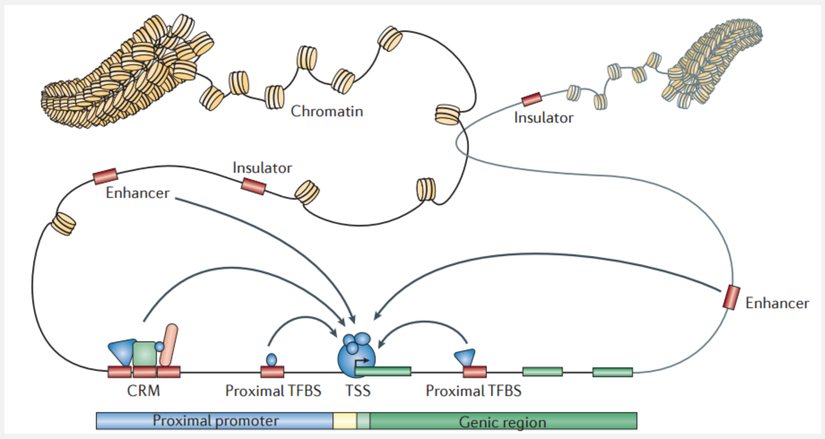
Raphaël Romero, Christophe Menichelli, Jean-Michel Marin, Sophie Lèbre*, Charles-Henri Lecellier*, Laurent Bréhélin*

IMAG, LIRMM, IBC, IGMM, Univ. Montpellier, CNRS

* These authors contributed equally to this work

Introduction

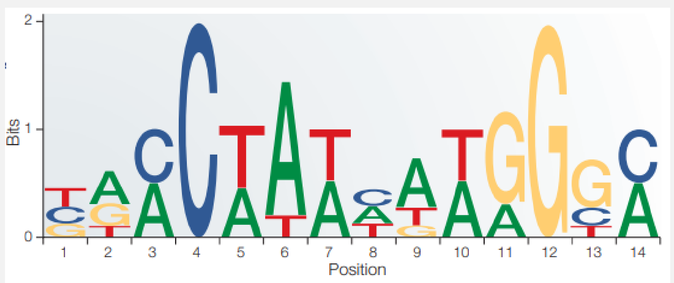
Transcription factors (TF) are proteins that play a central role in the mechanism of transcription. **Those proteins bind DNA in promoters** (the region around the Transcription Start Sites -TSSs- of each gene) **or in enhancers** (a region distant from TSS but also associated with gene regulation). Each TF usually recognises and binds a specific set of k-mers. TFs often bind together with other TFs and **cooperate to regulate the transcription.**



Adapted from Lenhard *et al.*[1].

Scoring TF binding affinity

The set of k-mers recognised by a TF are usually slight variations of a common motif that can be resumed in a probabilistic model known as a binding motif or **Position Weight Matrix (PWM)**. PWMs of many TFs are available in dedicated database (JASPAR [2]).



TF: MEF2, image adapted from Wasserman and Sandelin April 2004[3]

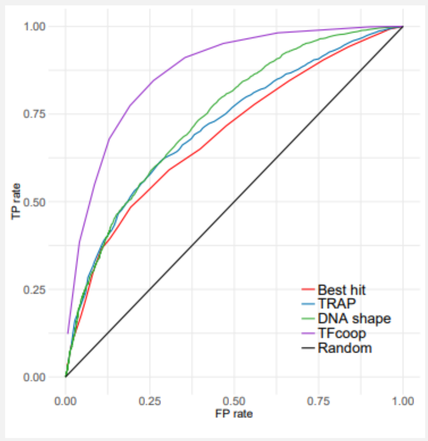
Such motif can be used to scan a DNA sequence and to identify potential binding sites of the associated TF. At each position, a score is computed on the basis of the probability to generate the k-mer that starts at this position with PWM. The affinity of the TF for a given DNA sequence is estimated by the maximal score computed at any position of the sequences (Best-hit approach). This approach is known to suffer from low accuracy, with lot of false positives.

TFcoop

- TFcoop [4] is a recent statistical approach which considers PWM scores of all TFs possibly cooperating with the target TF.
- 22.000 sequences (promoters) centred around the TSS (size = 1kbp).
- Predictive variables: binding affinities of JASPAR PWMs (S_i, $i \in \{1, \dots, p\}$ $p = 662$) and dinucleotide rates of the sequences (R_i, $i \in \{1, \dots, q\}$ $q = 12$).
- Predicted variable Y: Promoters bound or not bound by the TF.
- Logistic regression with L1 penalisation - **LASSO**

$$\ln \frac{\mathbb{P}(Y = 1 \mid X)}{1 - \mathbb{P}(Y = 1 \mid X)} = \beta_0 + \sum_{i=1}^{p} \beta_i S_i + \sum_{j=1}^{q} \gamma_j R_j + \epsilon$$

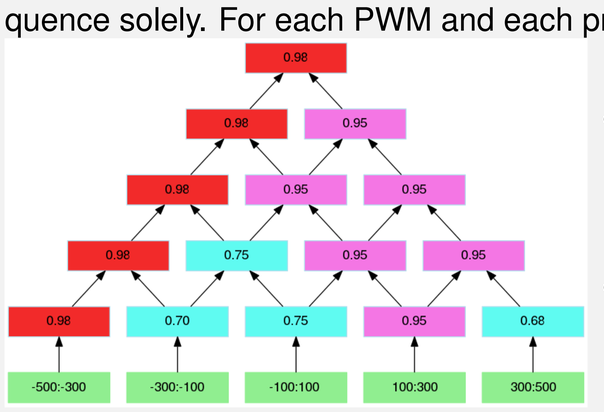
Where $X = (S_1, \dots, S_p, R_1, \dots, R_q)$ and $\epsilon \sim N(0, \sigma^2)$



- TFcoop outperforms the single PWM method (Best-Hit) in term of prediction accuracy
- Additional information may help to improve the accuracy of this approach. **We propose to use positional information of TFs occurrences**

Principle of our approach

Computing binding affinities in various sub-sequences rather than in the entire sequence solely. For each PWM and each promoter sequence a lattice is computed:



- Each node of the lattice contains the binding affinity of PWM for the associated sub-sequence.
- Allows to quickly explore many different sub-sequences.

Methods

- For each PWM, compute the lattices associated with each sequence
- We have two sets of lattices: bound or not bound sequences

- Each lattice position is assessed to identify the sub-sequence allowing the best discrimination between bound and unbound sequences.

New model

The most discriminative position of each PWM is used to create a new variable (positional variable P_k, $k \in \{1, \dots, p\}$) that is added to the TFcoop model:

$$\ln \frac{\mathbb{P}(Y = 1 \mid X)}{1 - \mathbb{P}(Y = 1 \mid X)} = \beta_0 + \sum_{i=1}^{p} \beta_i S_i + \sum_{j=1}^{q} \gamma_j R_j + \sum_{k=1}^{p} \alpha_k P_k + \epsilon$$

Simulations

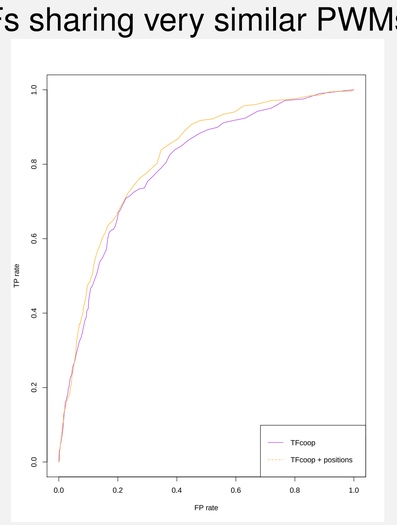
- Take one ChIP-seq experiment.
- Add some false positives occurrences in %FP of sequences, position follows a $U[0, 1000]$
- Add some true positives occurrences in %TP of sequences, position follows a $N(\mu, \sigma)$
- Run the approach and compare the identified sub-sequence R_1 to the region $R_2 = [\mu - 1,96\sigma; \mu + 1,96\sigma]$
- Compare both regions with Jaccard index : $J = \frac{|R_1 \cap R_2|}{|R_1 \cup R_2|}$

	TP=1%	TP=7%	TP=30%
FP=1%	0.24	0.64	0.97
FP=7%	0.24	0.75	0.97
FP=30%	0.25	0.68	0.89

Means of Jaccard indexes

Experiments

We apply our approach for discriminating the sequences bound by two different TFs sharing very similar PWMs



- A set of sequences bound by Fra1 (FOSL1) and a set of sequences bound by Fra2 (FOSL2).
- Slightly better accuracy than the TF-coop approach (AUC = 0.80 vs 0.82)

Perspectives

1. Use this method to discriminate other TF pairs with very similar motifs.
2. Improve the approach by including relative position information between TFs.
   - binary variable: the TF is upstream/downstream of another TF.
   - distance (bp) between two TF binding sites.

Huge increase of the number of variables: adequate strategies are needed.

References

[1] B. Lenhard, A. Sandelin, and P. Carninci. Metazoan promoters: emerging characteristics and insights into transcriptional regulation. 13(4):233–245.

[2] A. Sandelin, W. Alkema, P. Engstrm, W. W. Wasserman, and B. Lenhard. JASPAR: an open-access database for eukaryotic transcription factor binding profiles. 32:D91–94.

[3] W. W. Wasserman and A. Sandelin. Applied bioinformatics for the identification of regulatory elements. *Nature Reviews Genetics*, 5(4):276–287, April 2004.

[4] J. Vandel, O. Cassan, S. Lebre, C. Lecellier, and L. Brehelin. Probing transcription factor combinatorics in different promoter classes and in enhancers. *BMC Genomics - In press 2019*, March 2018.

Acknowledgements

Thanks to **Fabienne Bejjani** and **Isabelle Jariel-Encontre** from **IGMM** for providing us Fra1/Fra2 data.