Predicting enhancer-promoter interaction using genomic sequence features

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Introduction

In the human genome, a large number of distal enhancers regulate target genes through proximal promoters by forming enhancer-promoter interactions (EPIs). Recent high-throughput chromatin interaction mapping methods allow us to recognize potential EPIs, but it is largely unknown if the sequence level features are sufficient to build a predictive model for EPIs.

Research Questions

- Are there sequence-level EPI determinants?
- If so...
  - What are they?
  - Are they sufficient to be used to predict EPIs?
  - How consistent are they across cell lines?

Data

1. Active enhancers and promoters identified from ENCODE [1] and Roadmap Epigenomics [3] annotations, in each of 6 cell lines.
2. As in [2], EP pairs were annotated as positive (interacting) or negative (non-interacting) using cell-line-specific genome-wide chromatin contact measurements based on Hi-C [4].
3. 20 negative pairs sampled per positive pair
   - positive/negative pairs were constrained to have similar distributions of enhancer-promoter distance
4. Thus, data are heavily imbalanced ($> 95\%$ negative), in accordance with the fact that most enhancer/promoter pairs do not interact.

References

[1] ENCODE Project Consortium. *Nature*, 489(7414):57-74, 2012.

[2] Whalen et al. *Nature Genetics*, 48(5):488-496, 2016.

[3] Roadmap Epigenomics Consortium. *Nature*, 518(7539):317-330, 2014.

[4] Rao et al. *Cell*, 159(7):1665-1680, 2014.

[5] Chen and Guestrin. *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. 2016.

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Motif/Embedding Model (PEP)

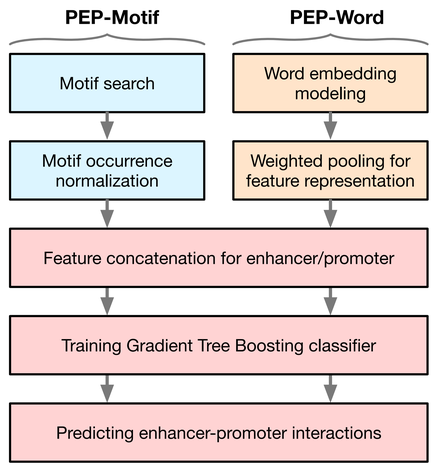


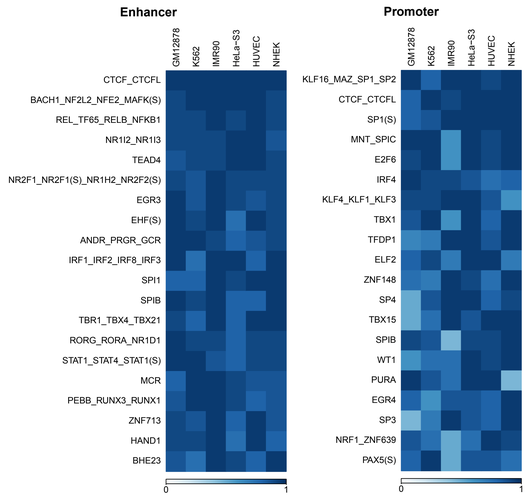
Figure 1: Diagram of PEP pipeline.

PEP learns a gradient tree boosting model [5] using two sets of features:

- PEP-Motif finds known transcription factor binding site (TFBS) patterns.
- PEP-Word learns a word embedding model to obtain continuous distributed feature representation of sequences.

Sequence Features from PEP

We ranked clustered TF features from PEP-Motif based on feature importance estimated using XGBoost.



Deep Learning Model (SPEID)

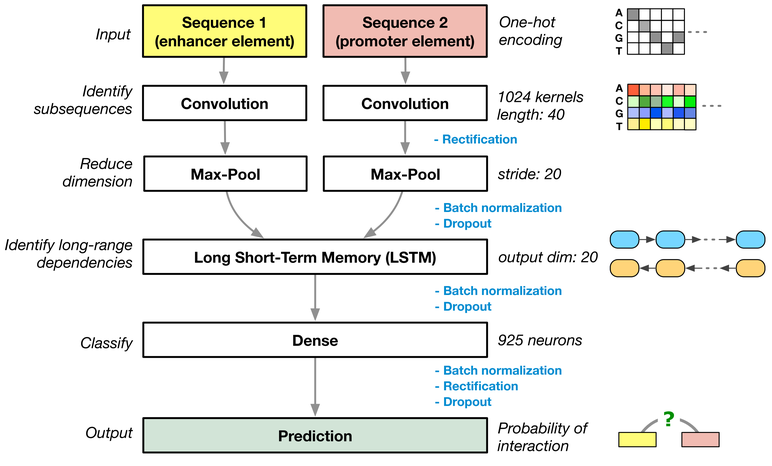


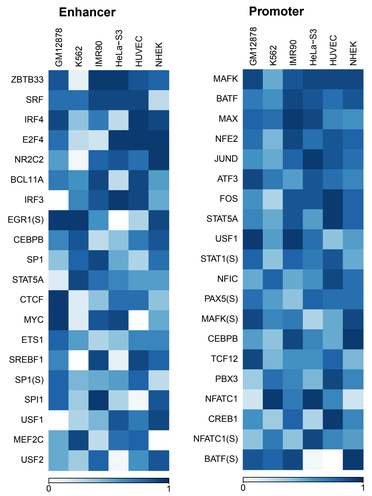
Figure 2: Diagram of SPEID network.

SPEID has three main sequential layers:

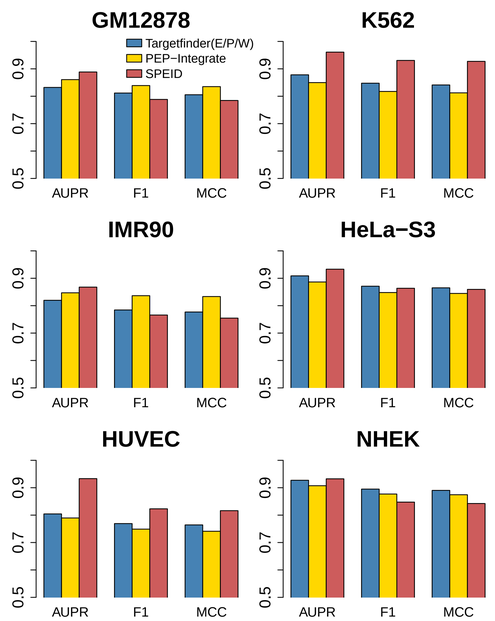
- Parallel convolution/pooling layers learn to extract short (40bp) sequence features from both inputs.
- LSTM layer learns to identify interactions between sequence features and between inputs.
- Dense layer predicts EPI from these high-level features.

Sequence Features from SPEID

We ranked importance of TF's in SPEID using *in silico mutagenesis* (replacing TFBS with noise and measuring impact on prediction performance).



Prediction Results



Conclusions

Main Result

Proposed methods achieve state-of-the-art EPIs prediction performance using only DNA sequence-based features. Thus, sequences encode the vital mechanisms mediating EPIs.

- Recent machine learning models and representations for complex features, such as deep networks and word embeddings, can help extract crucial predictive information directly from genetic sequences.
- Sequence-based prediction models can identify sequence features predictive of EPI.

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