Deep learning on single-cell ATAC-seq data to decipher enhancer logic

Deep Learning together with cisTopic on single-cell and bulk ATAC-seq on melanoma lines reveals melanoma enhancer logic.

Melanoma is a type of skin cancer and malignant melanoma development is characterized by a bistable switch between different states called "phenotype switching." Melanocyte-like state is regulated by MITF and SOX10, while Mesenchymal-like state is regulated by AP-1 and TEAD as the major transcription factors.

In this project, we study the enhancer logic of this state transition by using both bulk and single-cell ATAC-seq.

First layer of the model identifies Core Regulatory Complex

By applying this approach to a cohort of melanoma patient samples, we show that key melanoma transcription factors can be identified from the convolutional filters.

The code of disease related enhancers is revealed by the model and validated by MPRAs

To validate our models, we tested synthetic cell state specific enhancers using publicly available and in-house massively parallel enhancer reporter assays.

The model uses DNA sequence of the enhancers as input

Our method outperformed other methods in terms of predicting the effect of a single nucleotide change on IFH4 enhancer.

Variants identified from Personalized Cancer Genomes are exploited by the model

We furthermore exploit network explaining methods to predict the impact of personal variants, using patient matched whole genome sequencing.

Cross-species analysis validates the model and uncovers conserved enhancer code

We use a cohort of in-house generated ATAC-seq on melanoma cells from different species including human, mouse, pig, horse, dog, and zebrafish. Network explaining method applied on our model identifies conserved core elements of the same enhancer in different species.

Personal melanoma genomes reveal the existence of differential accessibility for the same enhancer. Mutations that cause accessibility gain/loss are identified from personal cancer genomes and it is validated by the model trained on personal melanoma ATAC profiles.