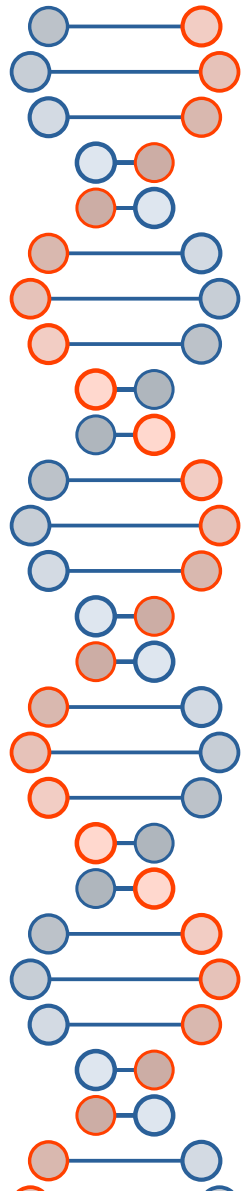Workflow summary

Workflow

- The workflow is based on the assumption that perturbation of valid targets influcences tumor cells while at most small effects on normal cells are observed

- The workflow allows simulating two different types of gene perturbations: downregulation and upregulation of a single gene:

    - Downregulation is implemented by setting expression of the gene to 0 in all cells

    - Upregulation is implemented by setting expression of the gene to the maximum value observed in the dataset

- Steps:

    - Baseline embedding of tumor and normal cells

    - Embedding of perturbed gene expression data

    - Analysis of differences in baseline and perturbed embedding

Example: ENSG00000118655

- Due to computational constraints, the example is run on a small subset of the data

    - Only the first 1000 lines of the scRNA dataset are read

    - The first 100 Tumor_KC_Basal and the first 100 normal cells are included

- Simulated is upregulation of ENSG00000118655 (DCLRE1B)

    - This gene encodes for DNA Cross-Link Repair 1B, which is involved in repair of interstrand cross-links during DNA repair
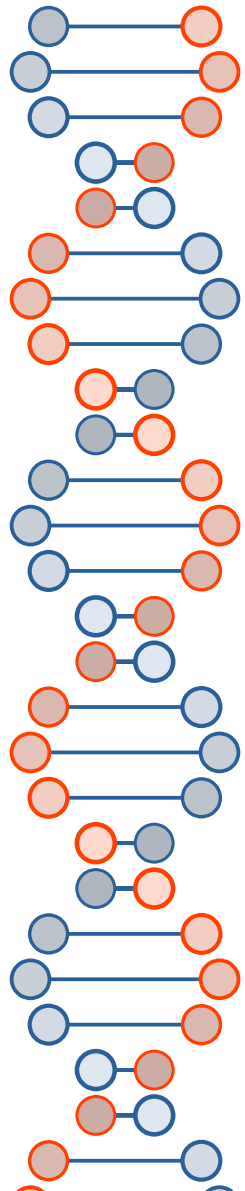
Evaluation

- Three criteria are used to evaluate the perturbation effect:

1) Median change in embedding
   The median change of embedding is higher
   for normal cells than tumor, which suggests a
   higher impact on normal cells

Cell type	Median change
Normal	3.458
Tumor	2.623

2) Cell type predicted by 5 nearest neighbors:
   The confusion matrix shows that neither normal
   nor tumor cells are shifting to a different
   neighborhood to a large extend.

	Normal Predicted	Tumor Predicted
Normal Original	85	15
Tumor Original	13	87

Evaluation (2)

3) Classification metrics
   Predicting the cell type based on the perturbed gene expression shows that there is not much different between original and perturbed expression datasets

	Precision	Recall
Normal	0.87	0.85
Tumor	0.85	0.87

Overall, higher expression and thereby the activity of ENSG00000118655 is not a promising treatment strategy for squamous cell carcinoma