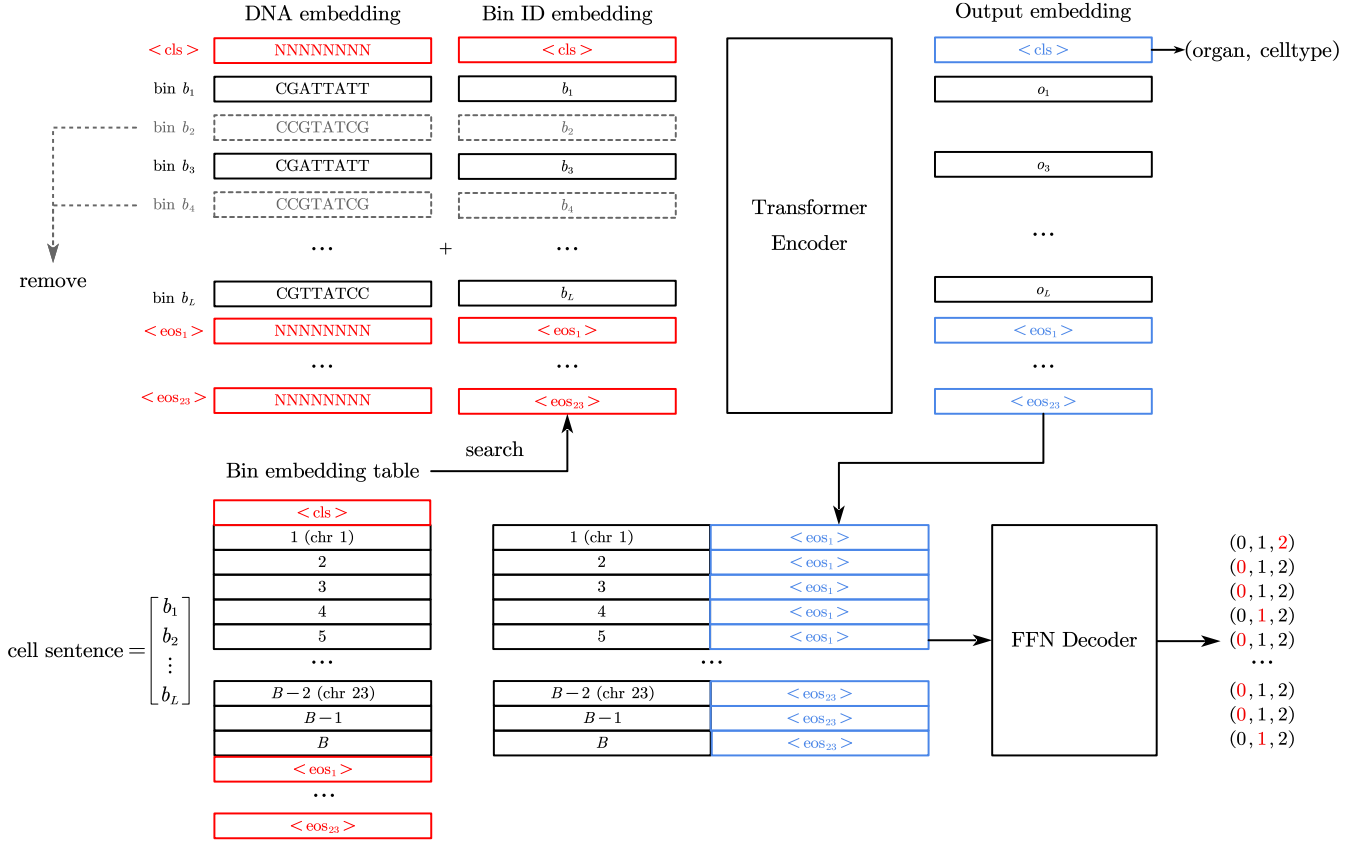


atacFormer Summary

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1 Current Framework



Suppose that we have B different ATAC bins in total. Each bin corresponds to a DNA sequence with length 5000, as in SnapATAC. In each cell, suppose that ATAC bins b_1, b_2, \dots, b_L are open. The cell sentence is formulated as (b_1, b_2, \dots, b_L) . As the input to the model, some open bins will be removed from the sentence (as masked tokens in BERT).

Bin ID embedding

Since the vocabulary size is very large, to reduce the number of parameters, we use **embedding factorization**: The embedding matrix E (of size $V \times d$, where V is the vocabulary size and d is the embedding dimension) is factorized into:

- E_1 : A smaller embedding matrix of size $V \times k$ (where $k \ll d$);
- E_2 : A projection matrix of size $k \times d$, which maps the reduced k -dimensional embeddings to the final d -dimensional space.

In our case, we take $V = B + 25$, where 25 is for the embeddings of $\langle cls \rangle$, $\langle pad \rangle$ and $\langle eos_1 \rangle, \dots, \langle eos_{23} \rangle$ for 23 chromosomes. We take $k = 64$ and $d = 512$.

DNA embedding

We plan to use **Nucleotide Transformer** to build DNA embedding table for all 5000-bp DNA sequence of each bin. For special tokens, the DNA embedding can be fixed to zero vector.

Transformer encoder

12 transformer encoder layers built by Flash Attention 1. The maximum sequence length (of cell sentence) is fixed to 5000.

Deocder and MLM loss

The output embeddings of $\langle eos_1 \rangle, \dots, \langle eos_{23} \rangle$ (512 dimensional) are first compressed to 64 dimensional, and then concatenated with bin ID embeddings on the corresponding chromosome (e.g. $\langle eos_1 \rangle$ is concatenated with all bins on chromosome 1) into 128-dimensional feature vectors. These feature vectors are feed into a feed-forward network (FFN) decoder to output the probability of 3 states: 0 (not in the cell sentence), 1 (in the cell sentence) and 2 (in the cell sentence but be removed).

Supervised loss

The output embedding corresponding to $\langle cls \rangle$ is used to predict the organ and the celltype of the cell using FFN.

2 Future Perspective

Decoder by genomic regions

The $\langle eos \rangle$ can be designed for different genomic regions instead of chromosomes. The following are possible annotated regions for ATAC bins.

1. Gene-related Regions

- **Promoter**: Located in the gene promoter region (typically 2 kb upstream to 0.5 kb downstream of the transcription start site).
- **Exon**: Located in the exon region of a gene.
- **Intron**: Located in the intron region of a gene.
- **5' UTR**: Located in the 5' untranslated region of a gene.
- **3' UTR**: Located in the 3' untranslated region of a gene.
- **TTS (Transcription Termination Site)**: Located near the transcription termination site of a gene.

2. Non-gene-related Regions

- **Intergenic**: Located in intergenic regions, far from any known genes.
- **Non-coding RNA (ncRNA)**: Located in non-coding RNA gene regions.

3. Regulatory Elements

- **Enhancer**: Located in known or predicted enhancer regions.
- **Insulator**: Located in insulator regions.
- **CTCF Binding Site**: Located in CTCF binding site regions.

4. Other Features

- **Repeat**: Located in repeat regions (e.g., LINE, SINE, LTR).
- **Conserved**: Located in evolutionarily conserved regions.

We can use **HOMER** to annotate ATAC bins. For each class c of bins, we use one $\langle eos_c \rangle$ to predict the open/closed state of ATAC bins in this class.

Decoder by attention

The decoder can be replaced by attention calculation. In this setting we let $\langle eos_k^{(l)} \rangle$ denote the l -th embedding for capturing state k ($l = 1, \dots, 8; k = 0, 1, 2$). Then we use B bin ID embedding as queries ($\mathbb{R}^{B \times 64}$), $\langle eos_k^{(l)} \rangle_{k=0,1,2}$ as keys ($\mathbb{R}^{3 \times 64}$) and identity matrix I ($\mathbb{R}^{3 \times 3}$) as values to obtain 8 attention matrices. These 8 attention matrices are integrated together as final prediction.

$\langle eos_k^{(l)} \rangle_{l=1, \dots, 8}$ can also be from different linear transformations of the same output embedding $\langle eos_k \rangle$, i.e., $E_{\langle eos_k^{(l)} \rangle} = W_l \cdot E_{\langle eos_k \rangle}$. In this way there only needs three $\langle eos_k \rangle$ in the cell sentence.

