

# Integrating Transformer-Based Pathway Reconstruction with Virtual RNA Interference for Enhanced Spatial Gene Expression Prediction

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## ABSTRACT

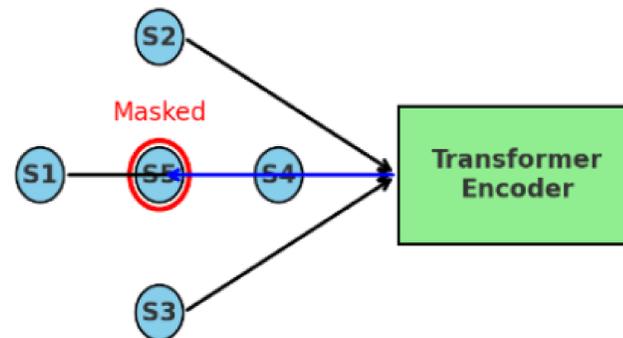
We present two transformer-based strategies for enhancing Virtual RNA Interference (VRI) predictions by integrating spatial context at the pathway level. Method 1 pretrains a transformer and penalizes VRI predictions that deviate from these transformer inferences. Method 2 jointly trains a transformer and VRI model to directly predict pathway expression. Method 1 yielded a 7.3% reduction in MSE relative to baseline, while Method 2 achieved a 9.1% reduction, particularly benefiting low-expression regions. These results highlight the utility of transformer-based spatial priors for improving spatial transcriptomic inference.

## INTRODUCTION

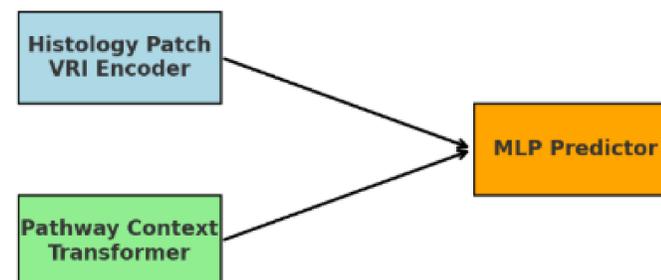
- Virtual RNA Interference (VRI) is a deep learning approach that predicts pathway-level expression from histological image patches.
- While effective, VRI primarily relies on morphological features and lacks explicit modeling of spatial dependencies.
- We hypothesize that integrating transformer-based spatial reasoning into VRI will improve the accuracy and smoothness of predicted expression maps.

## Methodology

- Method 1: Pretrained a transformer to reconstruct masked pathway values from surrounding spatial context, later integrated into VRI.



- Method 2: Jointly trained VRI image encoder and transformer spatial encoder, merging features for pathway inference.

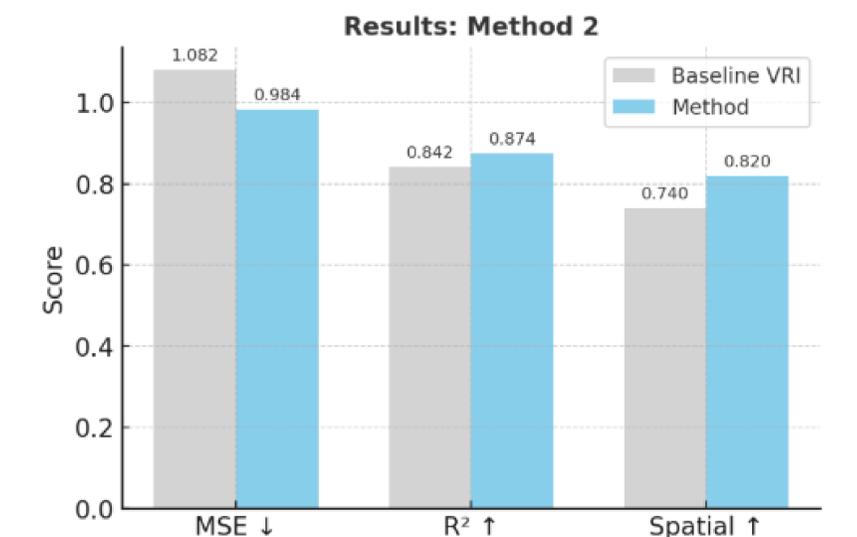
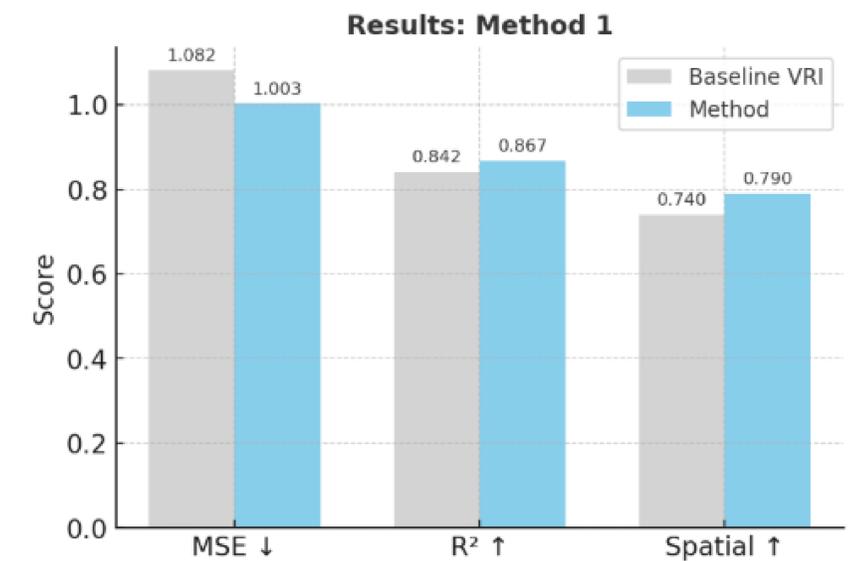


## Results

Baseline: MSE: 1.082,  $R^2$ : 0.842, Spatial: 0.74.

Method 1: MSE: 1.003,  $R^2$ : 0.867, Spatial: 0.79.  
(7.3% reduction of MSE)

Method 2: MSE: 0.984,  $R^2$ : 0.874, Spatial: 0.82.  
(9.1% reduction of MSE)



These results highlight the value of transformers as spatial priors in computational genomics.