Improving Ames prediction with graph transformer neural networks

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An Introduction to the Ames test and computational modelling

The Ames Test 🧪

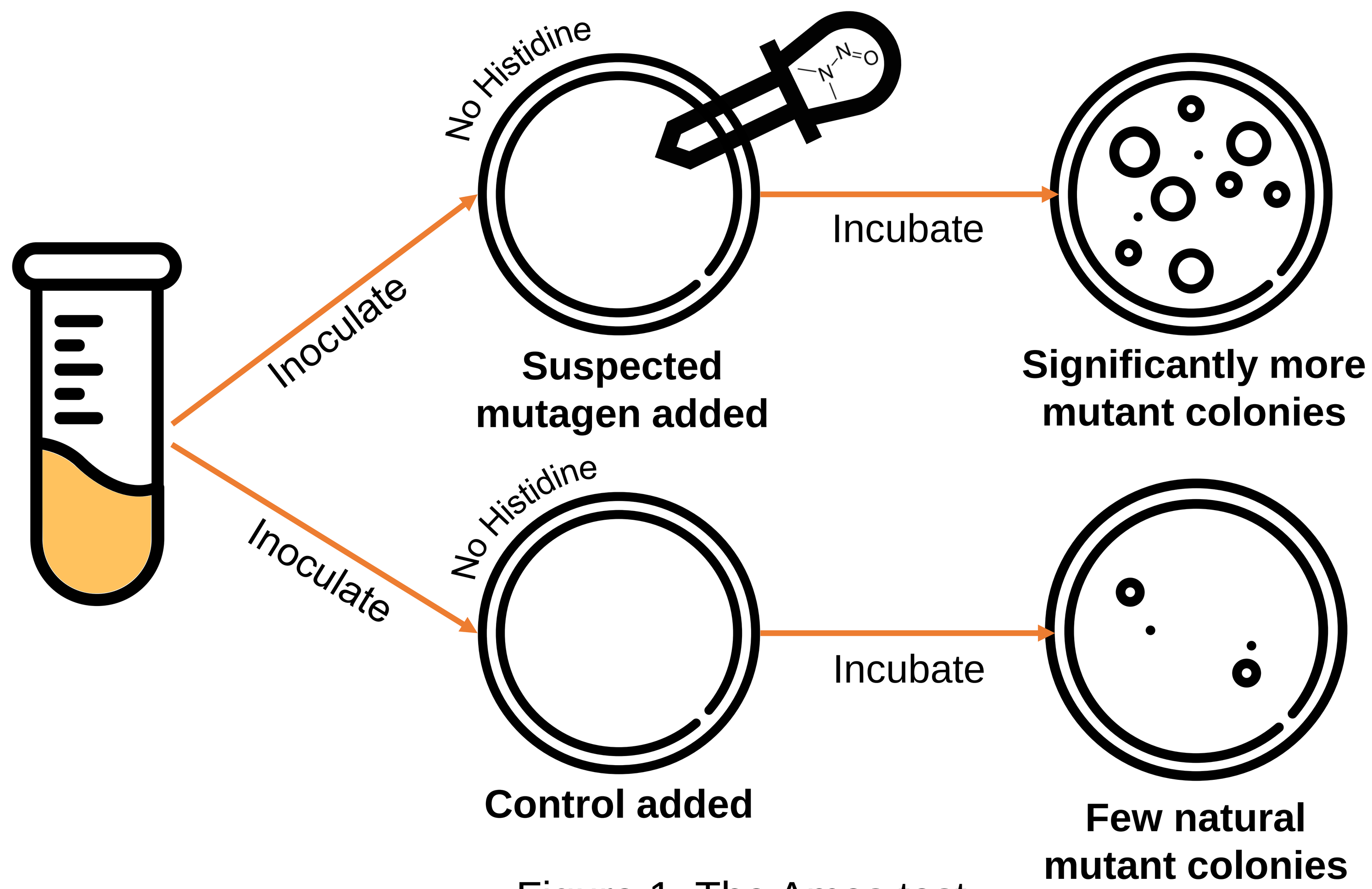


Figure 1. The Ames test

How does the Ames test work? [1]

1. Inoculate an empty plate with histidine-dependent Salmonella
2. Add a control to one plate, and the suspected mutagen to another
3. **If the plate shows more, a mutagen's for sure; if it's scant and bare, no mutagen there.**

Why *In silico*? 🤔

The Ames test is great…
But it's *expensive at scale*
15 000 new molecules daily * $2000 each = **Too expensive to test everything** [3]

However, we can't just take Ames *in silico*. It's too ***unreliable:***

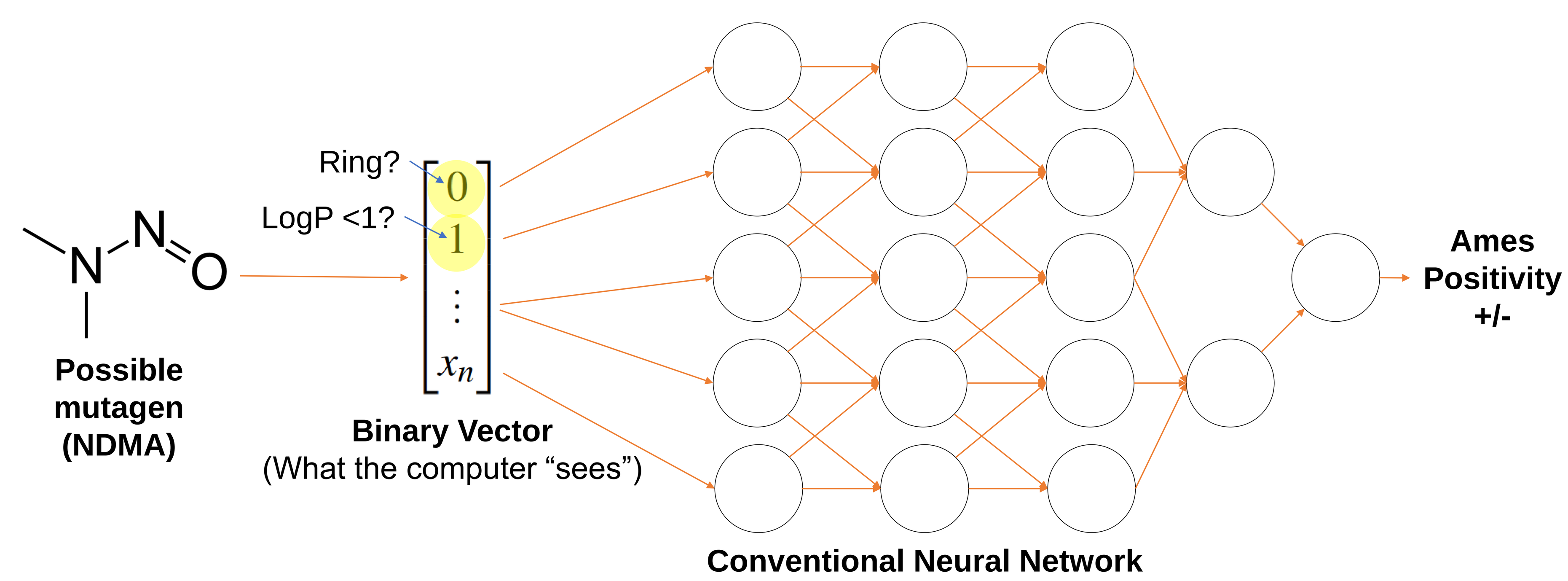


Figure 2. Classical neural network for predicting Ames mutagenicity

Classical methods poorly capture chemical structures [2]. We lose:
Structural info – The molecule is just a vector
Quantity info – The vector is binary, we don't know the quantity of each atom

How can we solve these problems? – *Graph Transformers*

We aim to:

1. **Improve Ames models by incorporating chemical structure into the network**
2. Leverage a cutting-edge graph transformer approach

We hypothesise that:

1. **Our graph transformer will achieve near-state-of-the-art performance**
2. A working model is trainable with current hardware & Ames data availability

So, our approach is:

- Give the network extra positional information via new encodings
- Make the network "pay attention" to each atom's local neighbourhood

All enabled by the transformer!

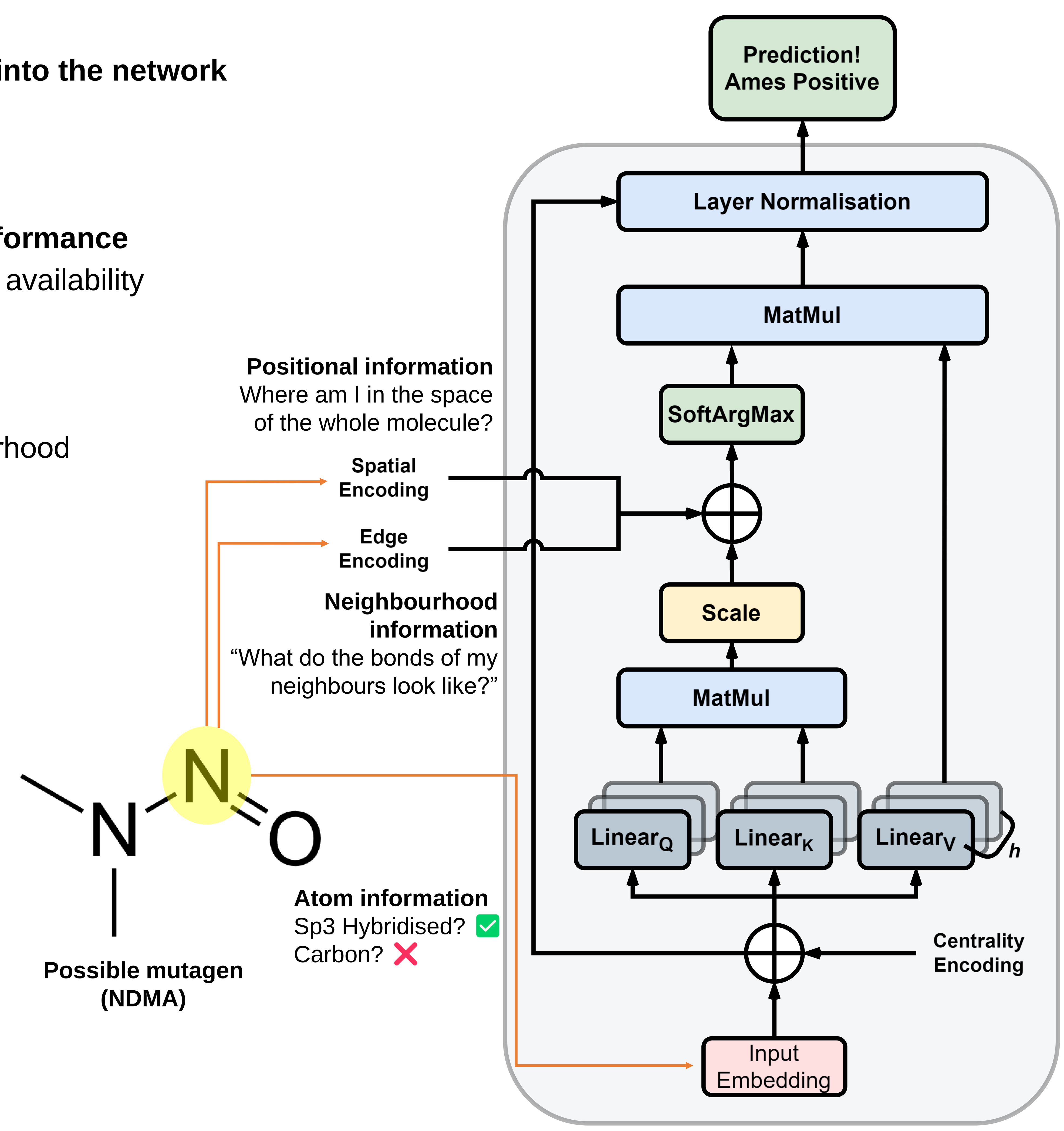
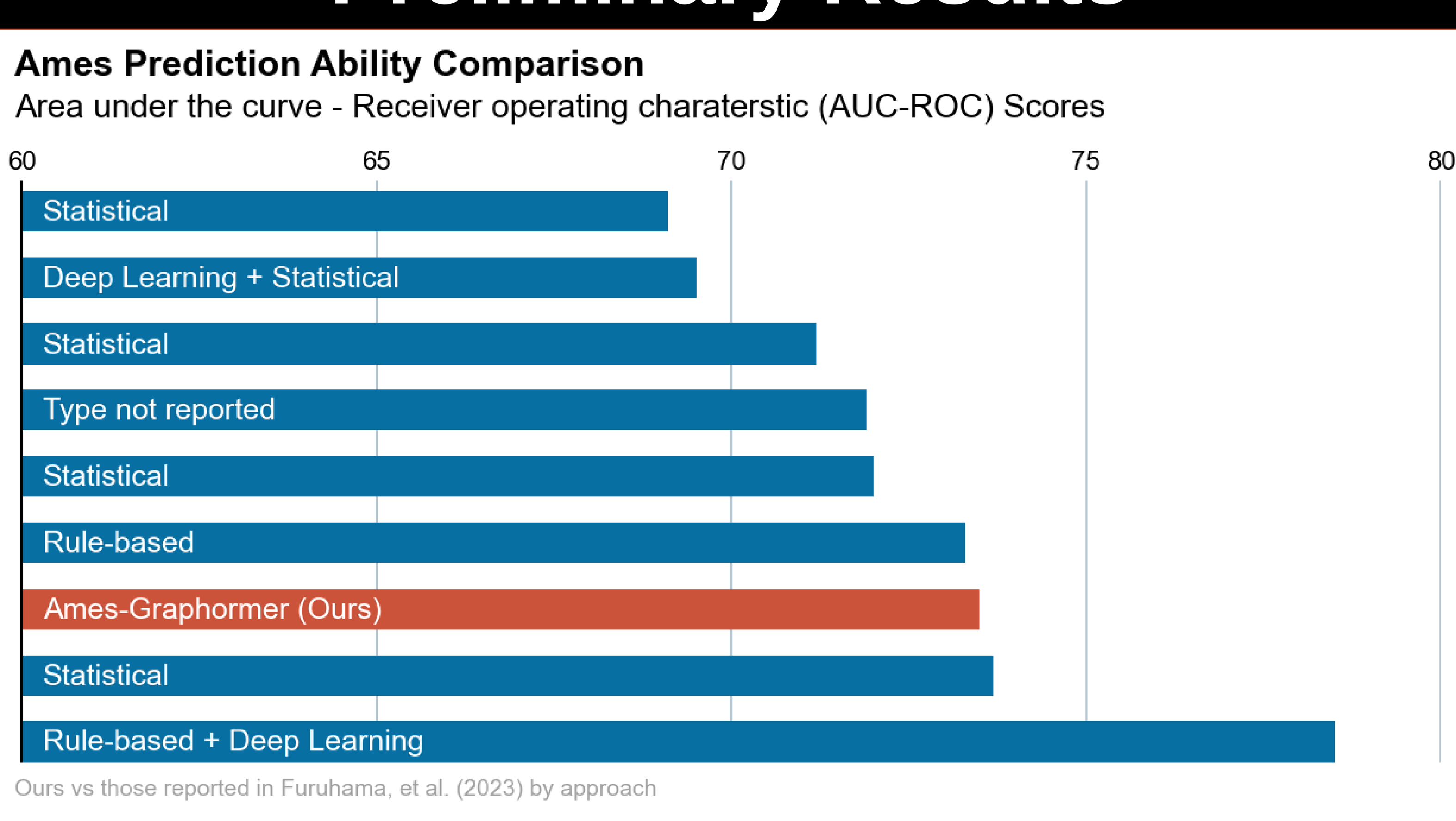


Figure 3. The input and architecture of our model – The Ames graph transformer

Preliminary Results



$$\text{AUC} = \int_0^1 \text{TPR}(x)\,dx$$

Equation 1. The ROC-AUC formula

Conclusions & Future Directions

We explore the cutting edge of neural network architectures for Ames prediction

We show that transformer-based graph neural networks *achieve near-state-of-the-art performance* for Ames mutagenicity prediction

Our method is *extensible* - The Python code is written in a modular form allowing future architectural developments, such as FlashAttention2, to be incorporated and improve performance without the need to re-write the whole code-base.

With the addition of uncertainty estimation, our model has direct regulatory application and fulfills OECD requirements

References: [1] Ames, et al. (1973) Procedures of the National Academy of Sciences. 70, DOI: 10.1073/pnas.70.3.782 [2] Boldini, et al. (2023), Chemrxiv, DOI: 10.26434/chemrxiv-2023-0m355 [3] Honma, et al. (2019), Mutagenesis, 34, DOI: 10.1093/mutage/gey031