McGill UNIVERSITY

RAPPPID: Towards Generalisable Protein Interaction Prediction with AWD-LSTM Twin Networks

Joseph **Szymborski**[1,2] and Amin **Emad**[1,2,3,*]

[1]Department of Electrical and Computer Engineering, McGill University, Montréal, QC, Canada
[2]Mila, Quebec AI Institute, Montréal, QC, Canada
[3]The Rosalind and Morris Goodman Cancer Institute, Montréal, QC, Canada
*amin.emad@mcgill.ca

Emad's COMBINE Lab

1. Introduction

1.1 Motivation

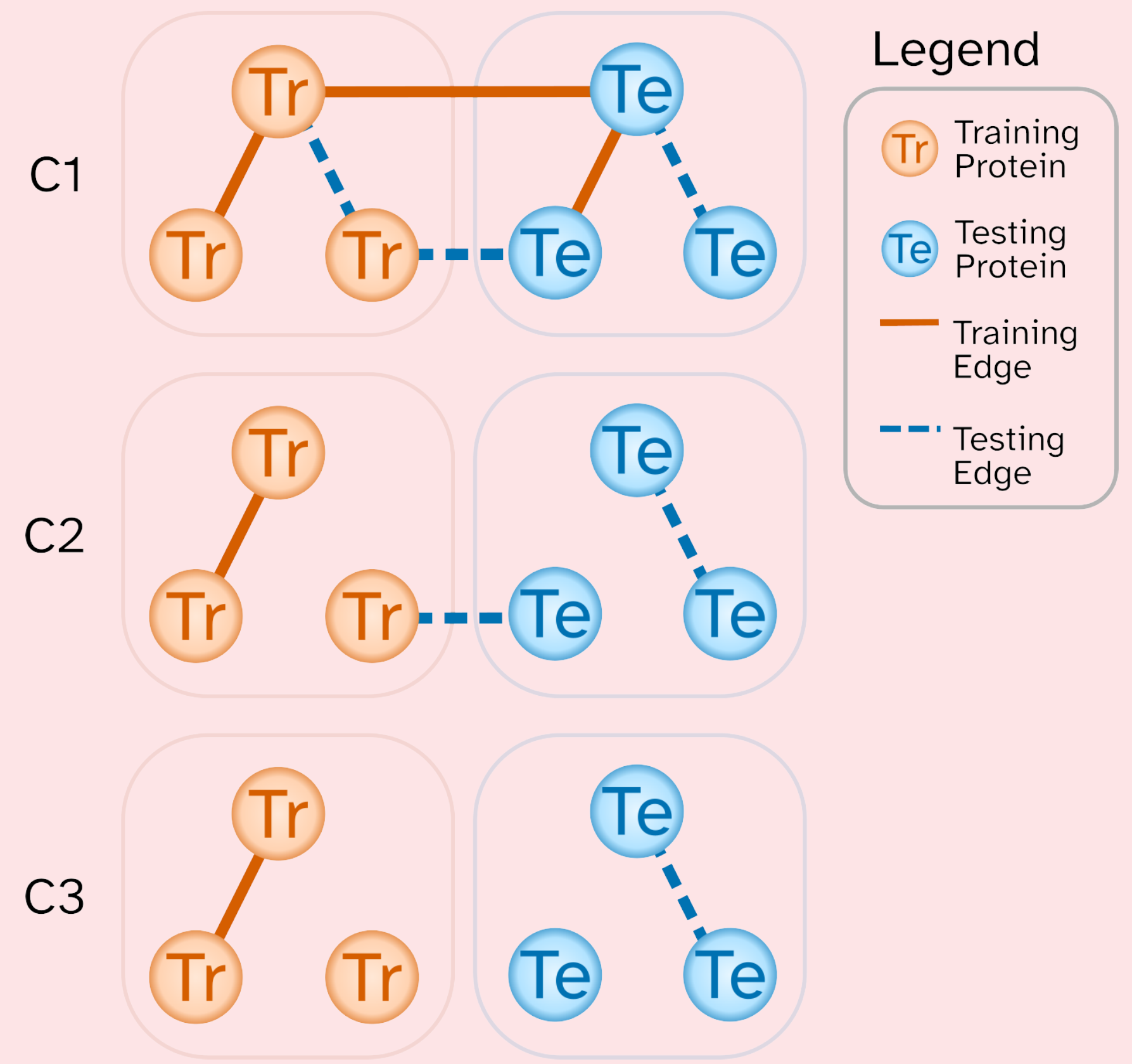
- Uncovering protein-protein interactions (PPIs) is very important for understanding most biological processes.
- Interactions can be **validated by a number of experiments**, however **they are costly** in terms of time, labour, and materials [1].
- **Computational approaches** to predict protein-protein interactions (PPIs) are therefore useful to help towards **reducing the number of costly experiments** researchers are required to perform.

1.2 Information Leakage in PPI Datasets

- The nature of PPI networks makes it easy to create datasets with **testing/training splits which leak information** [2].
- This results in **inflated performance metrics** that cannot properly assess the generalisability of these methods.

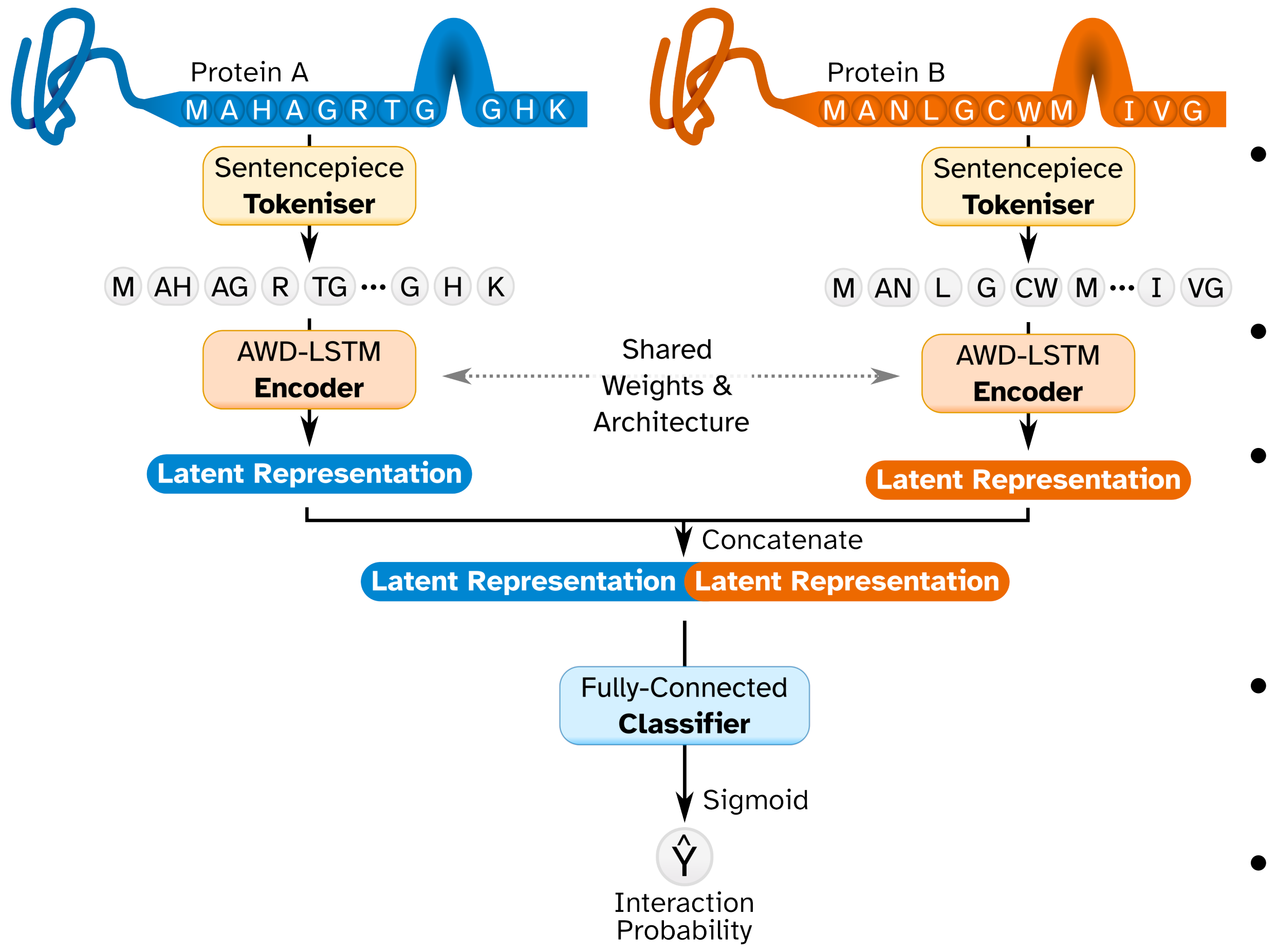
2. Methodology

2.1 Special Considerations for Validation & Testing Dataset Construction



- Park & Marcotte identified an information leakage problem with PPI prediction validation techniques [2].
- They described three types of validation sets (C1, C2, and C3).
- **C3** assures no proteins in the testing or validation set are in the training set.
- **C2** assures no more than one protein in training interaction pairs are in the testing or validation set.
- **C1** training pairs may contain one or two proteins found in the testing or validation set.

2.2 Overview of the RAPPPID Architecture

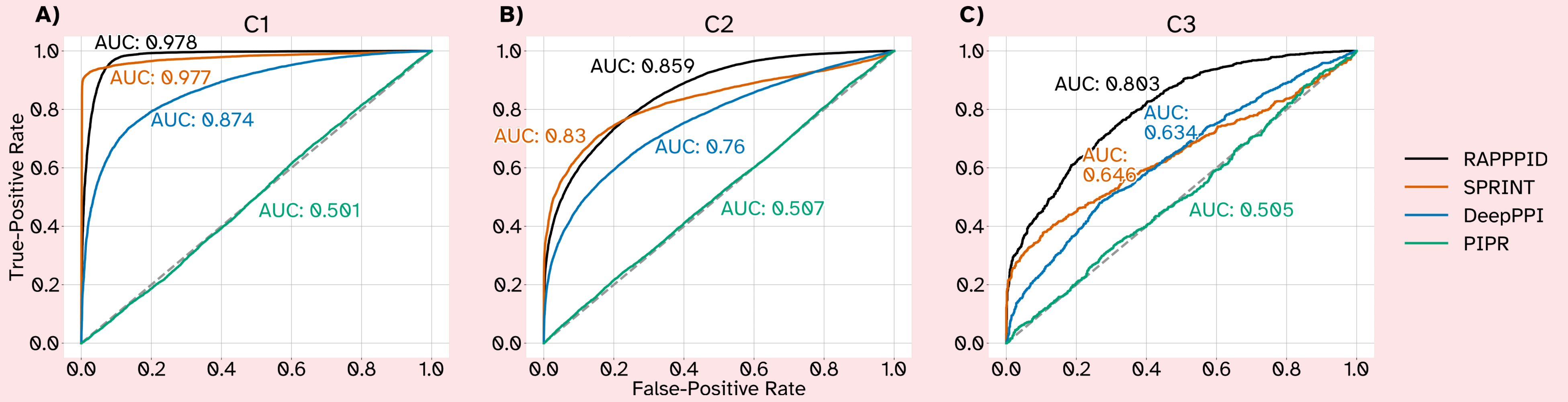


- RAPPPID is a regularised twin neural network that adopts a modified AWD-LSTM [3].
- RAPPPID considers pairs of amino acid (AA) sequences with an interaction label.
- AA sequences are first tokenised with the Sentencepiece algorithm [4].
- Fixed-length latent vector representations are computed for each sequence using bi-directional AWD-LSTMs.
- Latent vectors are concatenated and are inputted into a two-layer fully-connected classification head.
- Output of the classifier is the interaction probability

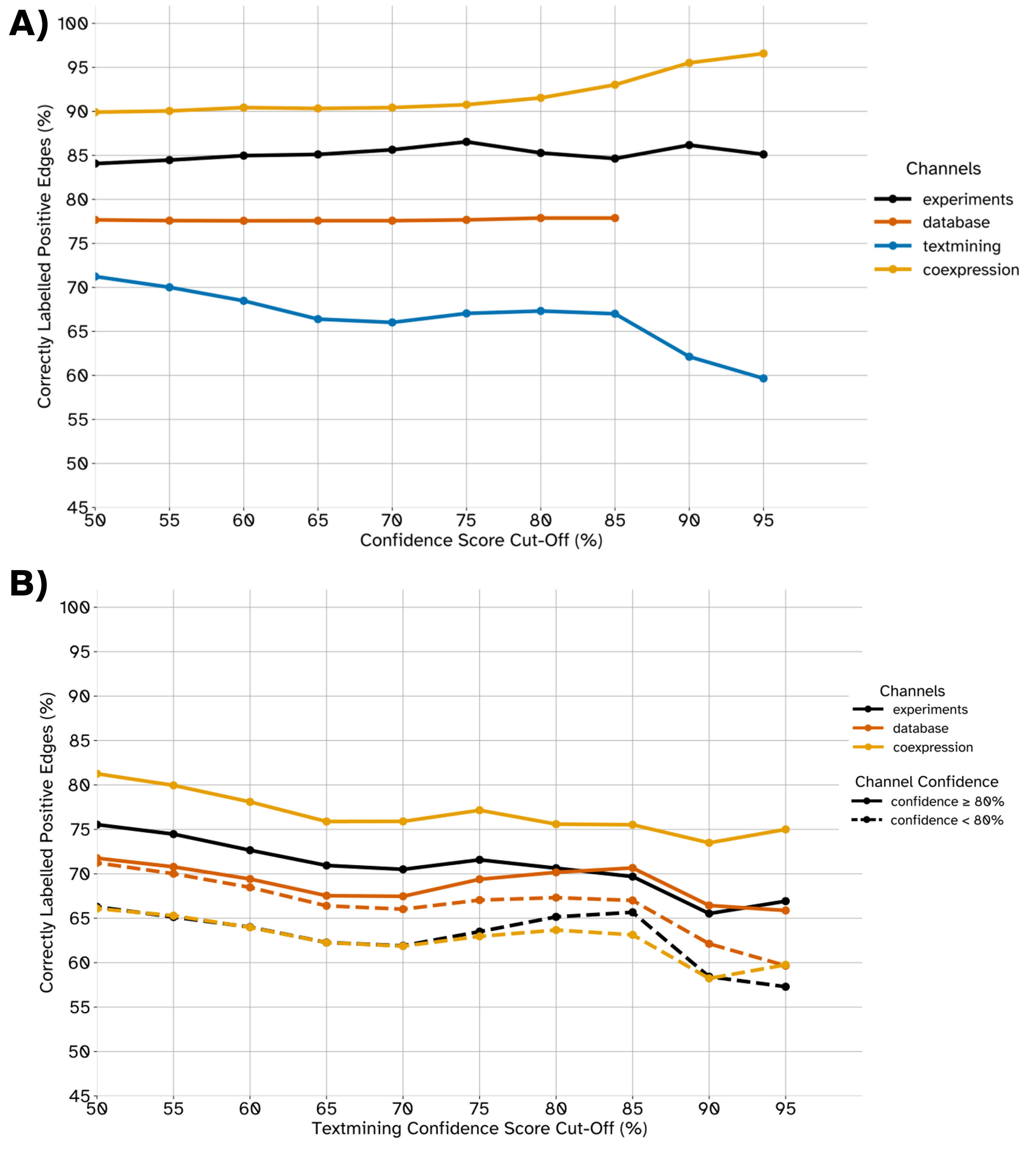
3. Results

3.1 Performance evaluation of RAPPPID and other algorithms

- Across C1, C2, and C3 testing datasets, **RAPPPID achieved higher AUROC than all other methods tested**.
- The margin between RAPPPID and the second highest performing method (SPRINT in all cases) was **highest when performed on the stricter C3 dataset**, resulting in approximately a **24.3% improvement**.
- The improvement obtained by RAPPPID compared to SPRINT was **lower on the C2 dataset (approximately 3.4%)**, and finally **nearly equivalent on the least strict C1 dataset**.
- Experiments were also conducted to establish the independence of RAPPPIDs accuracy and the similarity between the sequences evaluated.
- To further isolate any effects on model performance from the dataset, **we repeated the experiment on multiple random training, testing, and validation splits** as well as stratifying model performance by PPI evidence.
- All experiments indicated that model performance was not unduly influenced by our treatment of the dataset.



3.2 Channel-specific performance of RAPPPID



- The STRING database, integrates and annotates protein association data from a wide range of sources termed "channels".
- The "database", "text-mining", "experiments", and "coexpression" channels make-up over 98% of the edges in our datasets
- We sought to identify source of the testing edges RAPPPID correctly and incorrectly identified.
- The figure to the right (A) illustrates that RAPPPID accurately predicts the testing set edges that have a high confidence score in biologically supported channels of co-expression, experiments, and database.
- Further experiments (B) suggest that the inferior performance of RAPPPID on the text-mining channel is indeed due to the edges that are supported only by text-mining and not by other biologically identified channels.

4. Conclusion

- RAPPPID succesfully addresses the challenges of creating generalisable PPI prediction models posed by inherent characteristics of PPI datasets.
- By adopting a modified AWD-LSTM training routine, RAPPPID was able to surpass state-of-the-art models under testing conditions that carefully controlled for information leakage and other sources of prediction accuracy inflation.
- RAPPPID's ability to predict interactions warrants further study into relevant tasks that might benefit from a similar approach.

5. Acknowledgments

Mila
compute canada | calcul canada
Calcul Québec
MiCM McGill initiative in Computational Medicine
INNOVATION.CA
CANADA FOUNDATION FOR INNOVATION
FONDATION CANADIENNE POUR L'INNOVATION
VADASZ SCHOLARS

6. References

More information including references can be found at **https://jszym.com/meetings/2021_mlcb**