Review of NLP Applications to Protein Science

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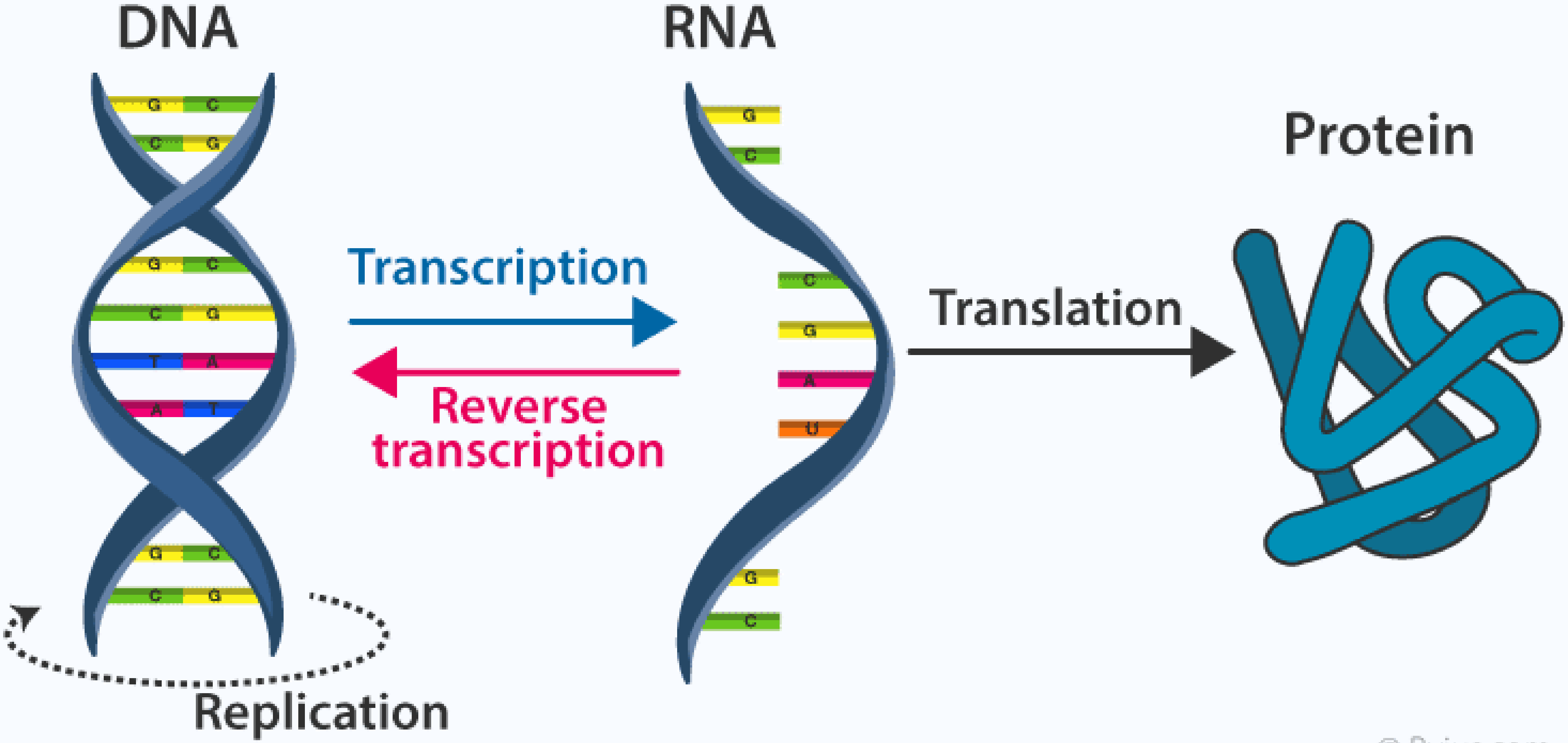
Why Proteins?

- Responsible for almost all biological processes critical to life.
  - Hemoglobin: carries oxygen to your cells,
  - Insulin: regulates blood glucose level
  - Rhodopsin: required for vision in dim light
- Useful in industrial settings
  - Enzymes (e.g.: Proteases, Amylases, Lipases, Cellulase) break down stains into smaller pieces to make stains easier to remove.

CENTRAL DOGMA : DNA TO RNA TO PROTEIN

BYJU'S
The Learning App



DNA

RNA

Protein

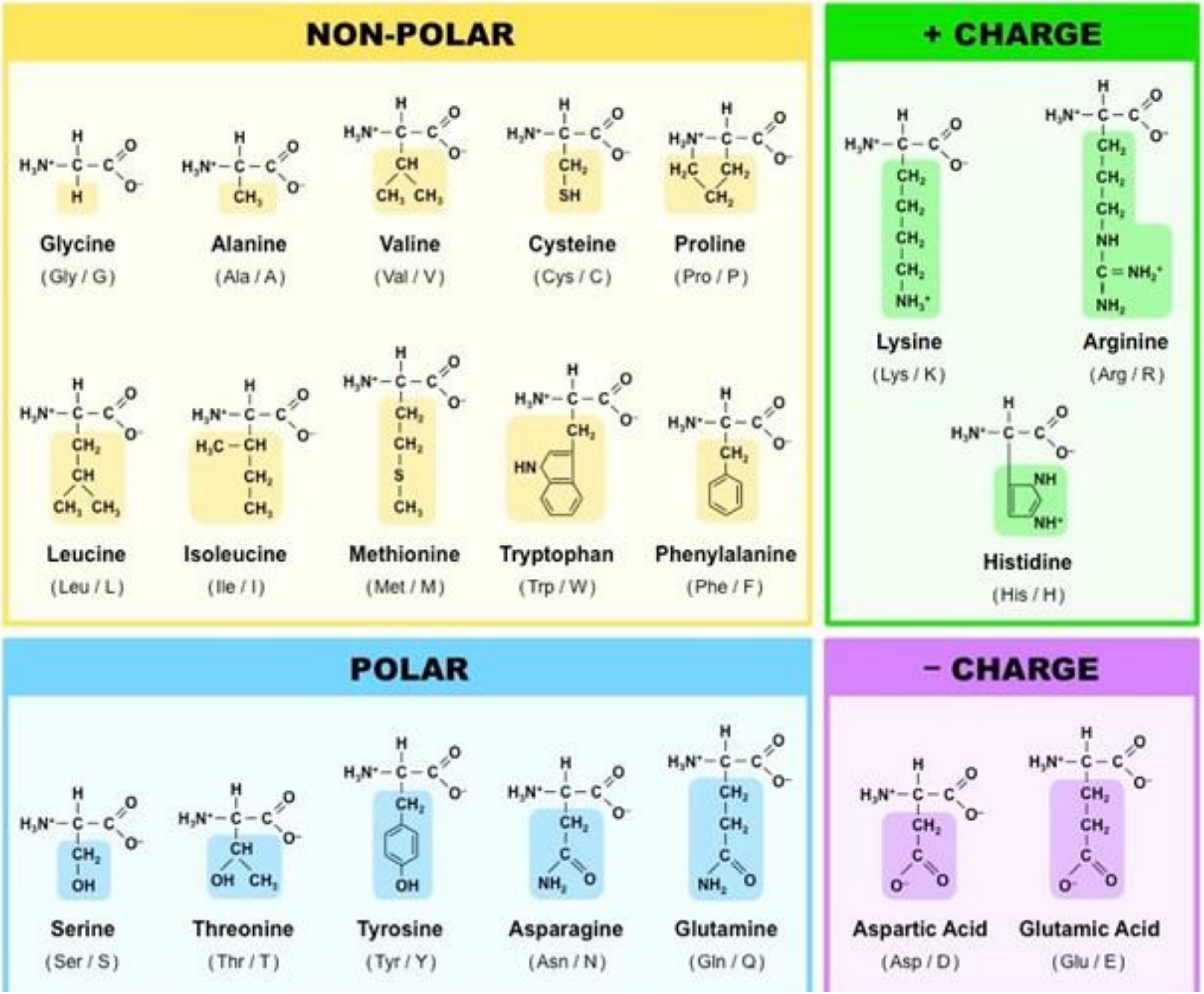
Transcription

Reverse transcription

Translation

Replication

Amino Acids are the building blocks of proteins

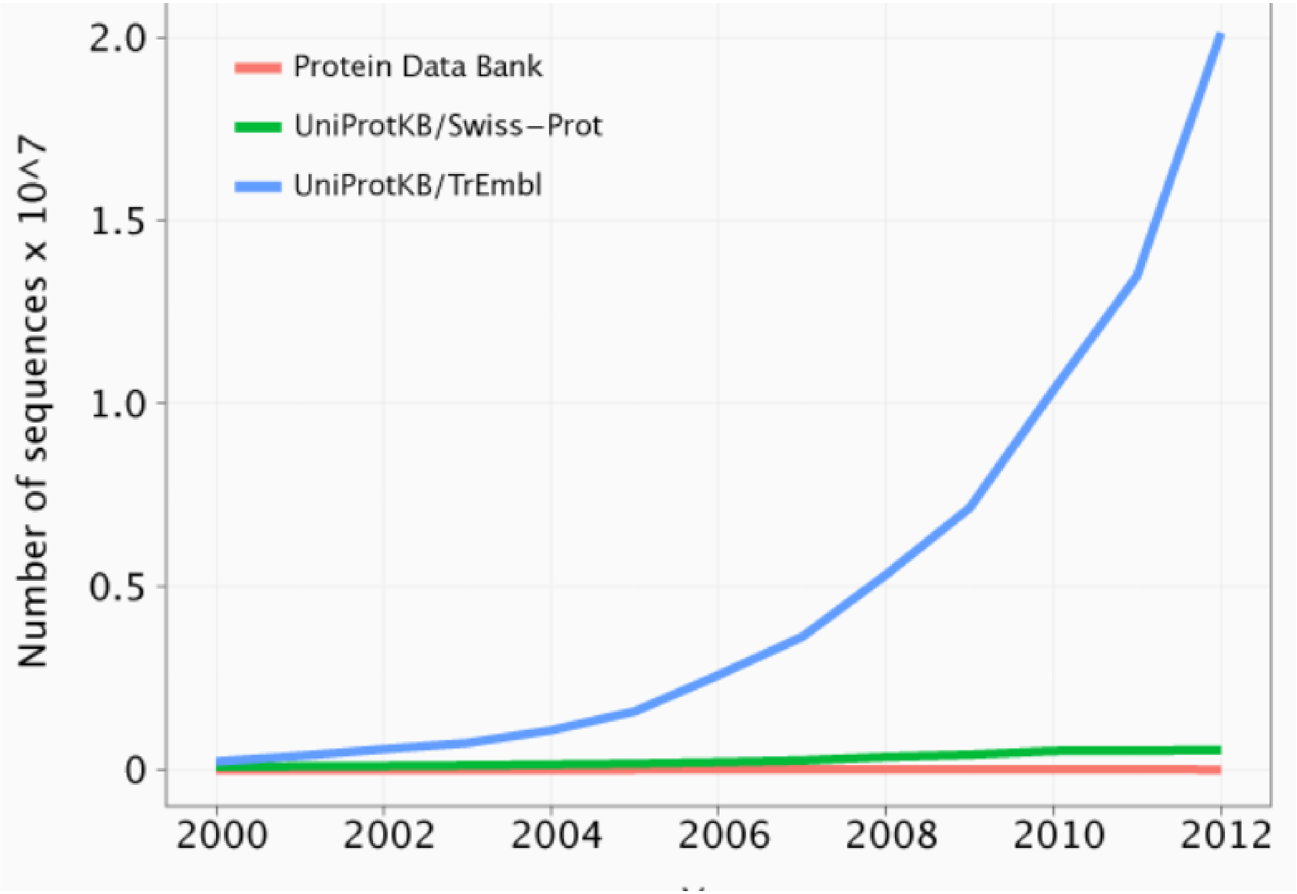


Protein As A Language

- Represented as a sequence of characters
- 25 letters for its “alphabet”
    - 20 characters for the standard (essential) amino acids,
    - 2 for the non-standard amino acids selenocysteine and pyrrolysine,
    - 2 for ambiguous amino acids, and
    - 1 for when the amino acid is unknown
- …But no concept of “words”, “sentences”, “paragraph” in the way we know it. Just letters.

Why NLP is great for protein studies

- Sequence – Structure gap



Observe how the green line (the protein sequences associated with a known or predicted function) is very close to the red line (the number of known protein structures). However, there is a growing gap between the red and the blue line (the number of protein sequences).

Protein-Based NLP Models

- ProtTrans (Elnaggar, 2020 (published this Summer))
  - Trained on data containing up to 393 billion amino acids (words) from 2.1 billion protein sequences (22- and 112-times the entire English Wikipedia)
  - Demos on HuggingFace:
    - Uniref100: https://huggingface.co/Rostlab/prot_bert
    - BFD: https://huggingface.co/Rostlab/prot_bert_bfd
    - BFD (T5, XL): https://huggingface.co/Rostlab/prot_t5_xl_bfd

Protein Datasets

- ProteinNet (AlQuraishi, 2019)
  - Standardized data set for machine learning of protein structure.
  - Provides protein sequences, structures (secondary and tertiary), multiple sequence alignments (MSAs), position-specific scoring matrices (PSSMs), and standardized training / validation / test splits.
  - Publicly available
- Protein Data Bank (PDB)
- UniProt
- Pfam
- Uniref100

Performance Evaluation: TAPE

- TAPE: **T**asks **A**ssessing **P**rotein **E**mbeddings (Roshan et al, NeurIPS 2019)
- Includes five (5) biologically relevant supervised tasks that evaluate the performance of learned protein embeddings.
  - Task 1: Secondary Structure (SS) Prediction (Structure Prediction Task)
  - Task 2: Contact Prediction (Structure Prediction Task)
  - Task 3: Remote Homology Detection (Evolutionary Understanding Task)
  - Task 4: Fluorescence Landscape Prediction (Protein Engineering Task)
  - Task 5: Stability Landscape Prediction (Protein Engineering Task)

Performance Evaluation: TAPE

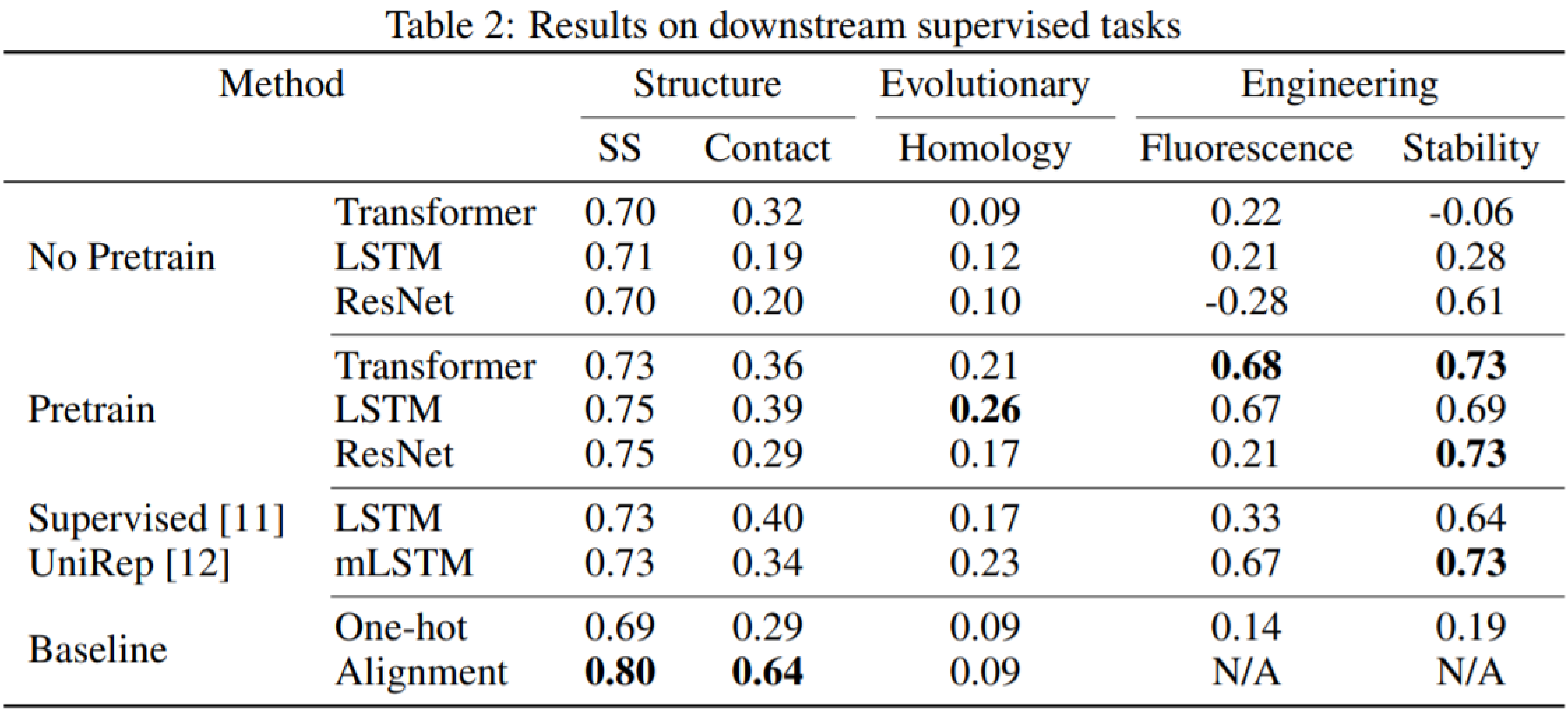


Table 2: Results on downstream supervised tasks

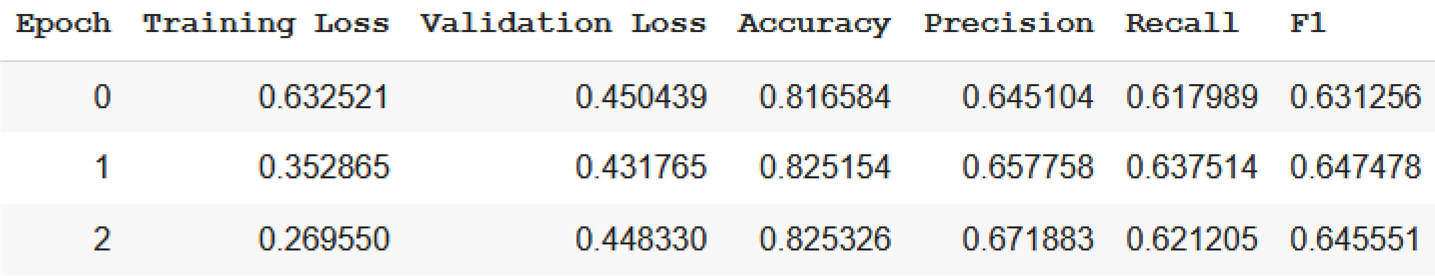
Method		Structure		Evolutionary	Engineering	
		SS	Contact	Homology	Fluorescence	Stability
No Pretrain	Transformer	0.70	0.32	0.09	0.22	-0.06
	LSTM	0.71	0.19	0.12	0.21	0.28
	ResNet	0.70	0.20	0.10	-0.28	0.61
Pretrain	Transformer	0.73	0.36	0.21	**0.68**	**0.73**
	LSTM	0.75	0.39	**0.26**	0.67	0.69
	ResNet	0.75	0.29	0.17	0.21	**0.73**
Supervised [11]	LSTM	0.73	0.40	0.17	0.33	0.64
UniRep [12]	mLSTM	0.73	0.34	0.23	0.67	**0.73**
Baseline	One-hot	0.69	0.29	0.09	0.14	0.19
	Alignment	**0.80**	**0.64**	0.09	N/A	N/A

My Experiments

- Task
  - Predicting masked amino acids
- Dataset:
  - ProteinNet
- Model
  - ProtTrans: fine-tuning vs feature extraction approaches.

SS3: 3-class secondary structure prediction

- Model: Prot-Bert model from Prot-Trans
- Approach: Fine-tuning
- Training data: netsurfp 2 (Klausen et al, 2019)



Epoch	Training Loss	Validation Loss	Accuracy	Precision	Recall	F1
0	0.632521	0.450439	0.816584	0.645104	0.617989	0.631256
1	0.352865	0.431765	0.825154	0.657758	0.637514	0.647478
2	0.269550	0.448330	0.825326	0.671883	0.621205	0.645551

Comparing Result on CB513 Dataset
Task: Secondary Structure Prediction (Q8)

Model	Parameters	Accuracy (%)
UniRef (Alley et al, 2019)	18M	58.4
SeqVec (Heinzinger et al, 2019)	93M	62.1
TAPE (Rao et al, 2019)	38M	58.0
ProtBert (from ProtTrans)	420M	66.0
ProtBert-BFD (from ProtTrans)	420M	70.0
Prot-Bert (ours; on NetSurf2; MAX_LEN = 512)	420M	30.9
Prot-Bert-BFD (ours; on NetSurf2; MAX_LEN = 512)	420M	40.0

Comparing Result on CASP12 Dataset
Task: Secondary Structure Prediction (Q8)

Model	Parameters	Accuracy (%)
UniRef (Alley et al, 2019)	18M	
SeqVec (Heinzinger et al, 2019)	93M	
TAPE (Rao et al, 2019)	38M	58.0
ProtBert (from ProtTrans)	420M	63.0
ProtBert-BFD (from ProtTrans)	420M	65.0
Prot-Bert (ours; on NetSurf2; MAX_LEN = 512)	420M	32.2
Prot-Bert-BFD (ours; on NetSurf2; MAX_LEN = 512)	420M	40.9

Comparing Result on TS115 Dataset
Task: Secondary Structure Prediction (Q8)

Model	Parameters	Accuracy (%)
UniRef (Alley et al, 2019)	18M	
SeqVec (Heinzinger et al, 2019)	93M	
TAPE (Rao et al, 2019)	38M	58.0
ProtBert (from ProtTrans)	420M	72.0
ProtBert-BFD (from ProtTrans)	420M	73.0
Prot-Bert (ours; on NetSurf2; MAX_LEN = 512)	420M	26.8
Prot-Bert-BFD (ours; on NetSurf2; MAX_LEN = 512)	420M	36.0

So, why are my results so poor, comparatively?

- Default hyperparameters used
  - These defaults were set based on LM training; not on the specific task of secondary structure prediction
- Max sequence length cut to 512
  - Recommended max length is 1024
- Underfitting
  - Training was done for 3 epochs only.

These suboptimal choice were just to enable me run the model on my machine and get results in reasonable time.

References

- Roshan Rao, Nicholas Bhattacharya, Neil Thomas, Yan Duan, Xi Chen, John Canny, Pieter Abbeel, and Yun S Song. Evaluating protein transfer learning with TAPE. In Advances in Neural Information Processing Systems, 2019.
- Neil C. Jones and Pavel A. Pevzner. An introduction to bioinformatics algorithms. MIT Press, 2004.
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