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MUNI

Deep Learning for Protein Structure

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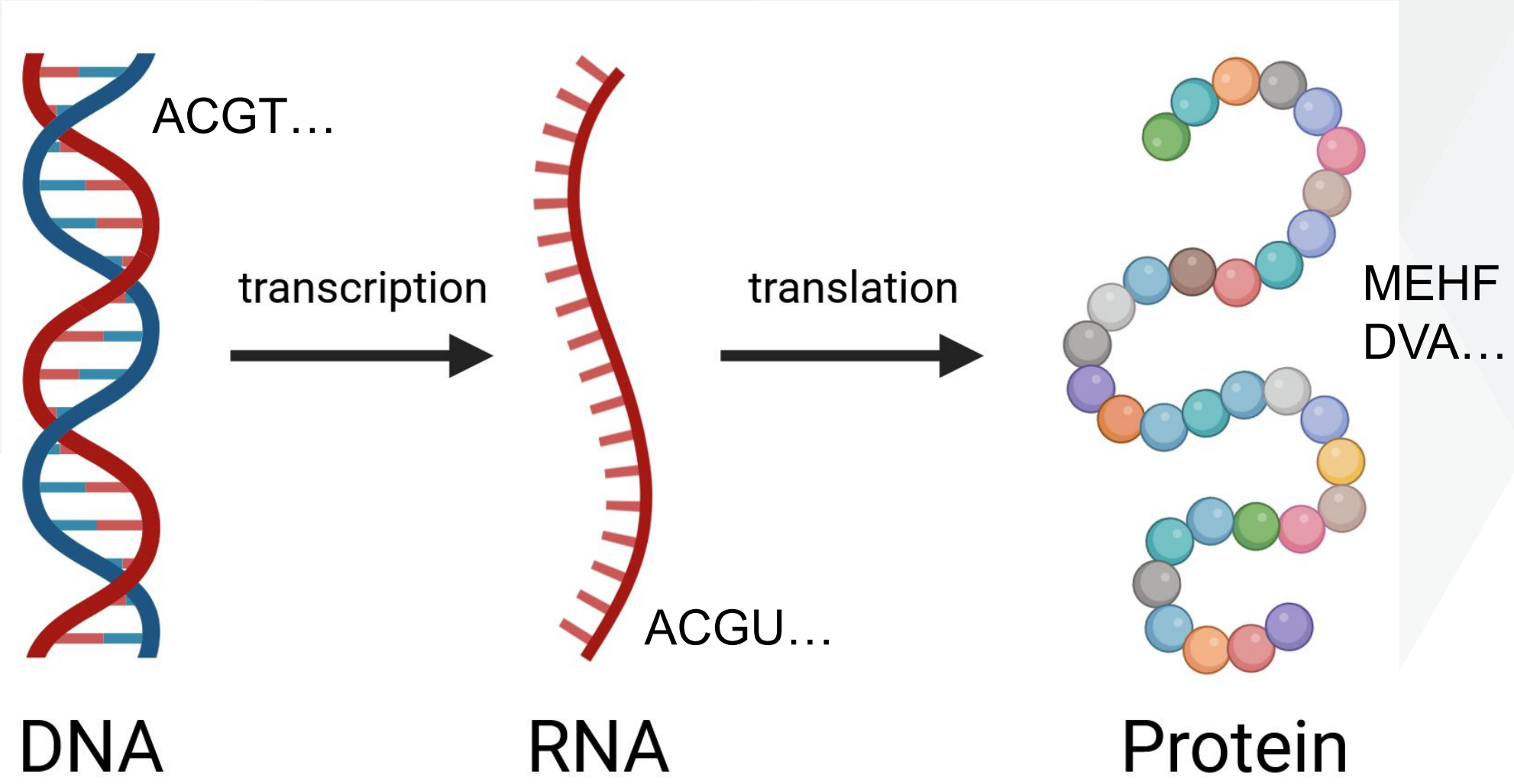
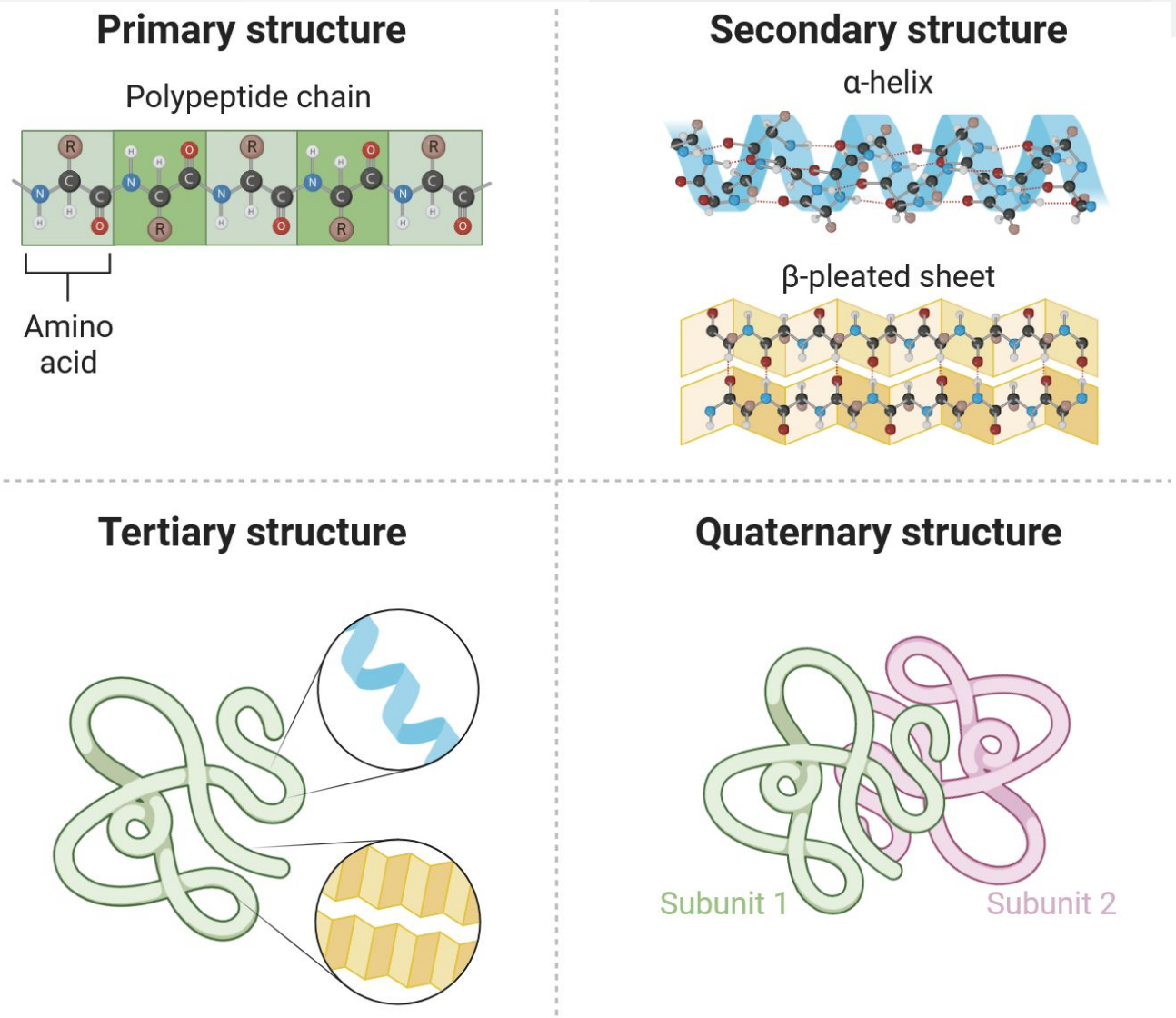
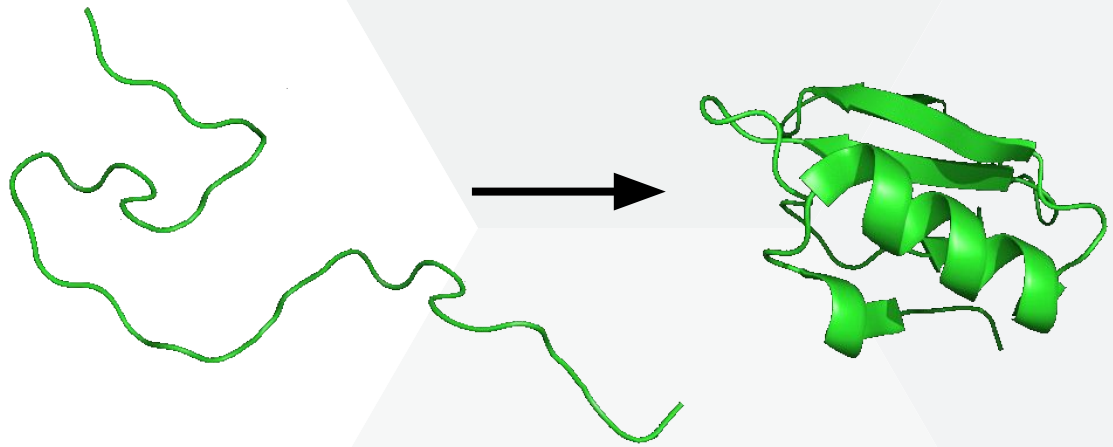
Central dogma of biology



Protein folding problem

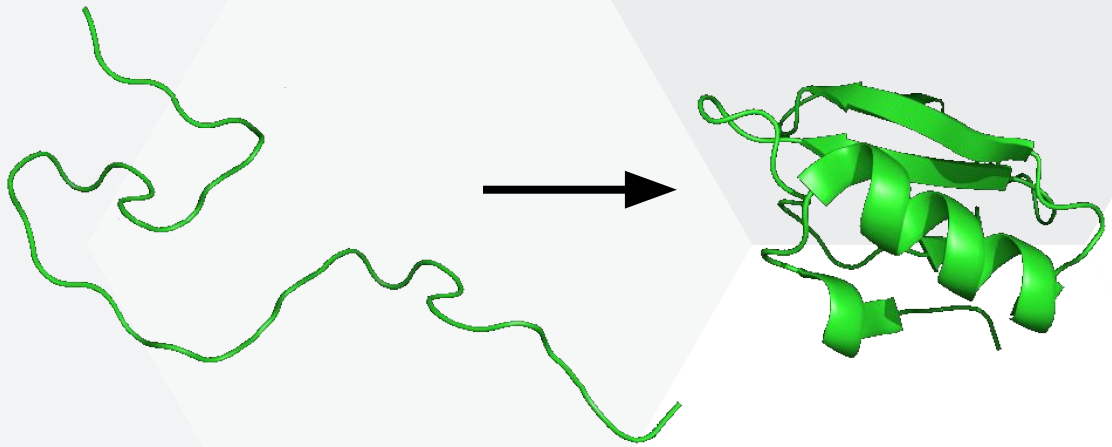




protein before and after folding

https://en.wikipedia.org/wiki/Protein_folding

Protein folding problem



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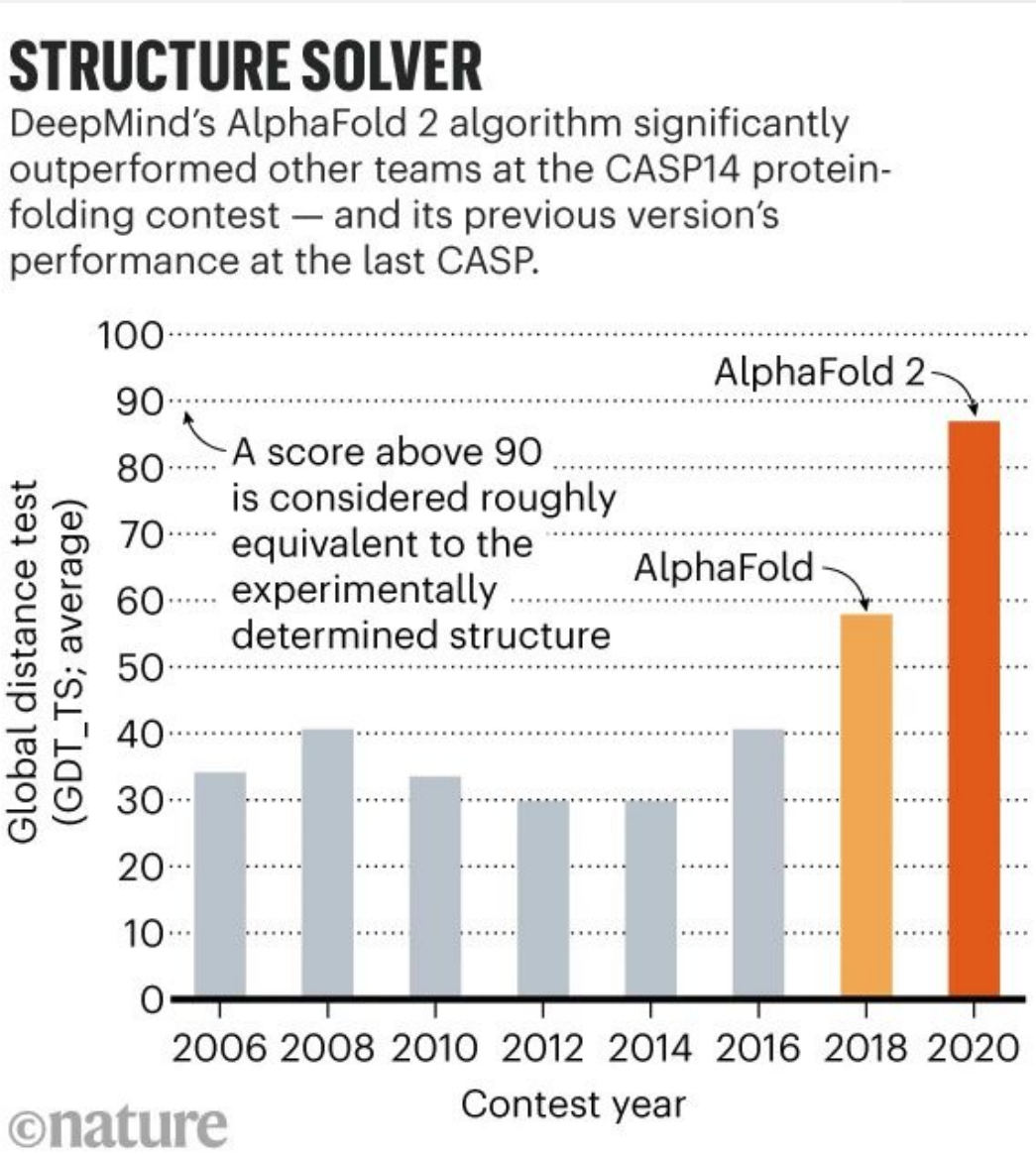


https://elearning.vib.be/courses/alphafold/lessons/introduction-to-alphafold/topic/critical-assessment-for-structure-prediction-casp/

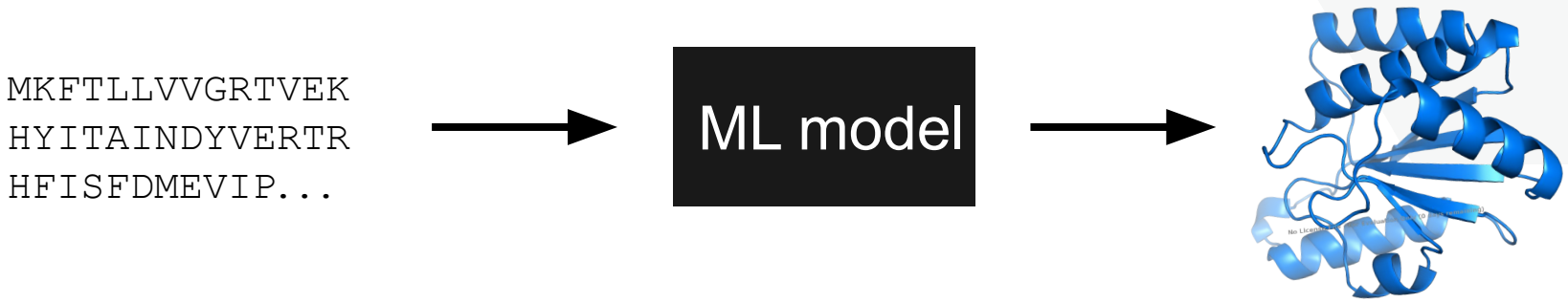
Anfisen's dogma ("thermodynamics hypothesis")

"at least for a small globular protein in its standard physiological environment, ***the native structure is determined only by the protein's amino acid sequence****"* - Christian B. Anfinsen

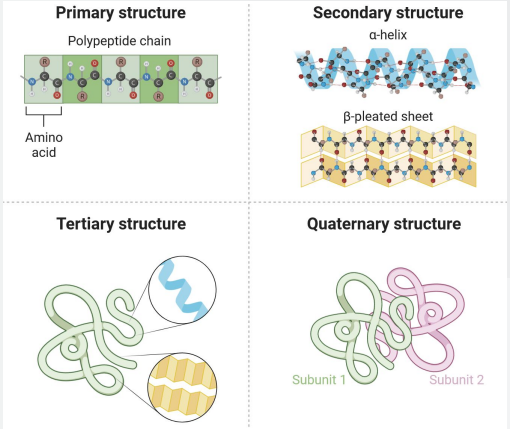
=> we can treat proteins as their amino acid sequences

=> we can use other methods that have been widely used on text (NLP)

=> deep learning models, Transformers, …



Protein (data format) from NLP point of view



- protein == string of amino acids
- alphabet usually consists of 20 common amino acids + X that stands for an arbitrary amino acid (less frequent amino acids (UZOB) are replaced by X during preprocessing)

Protein (data format) from NLP point of view

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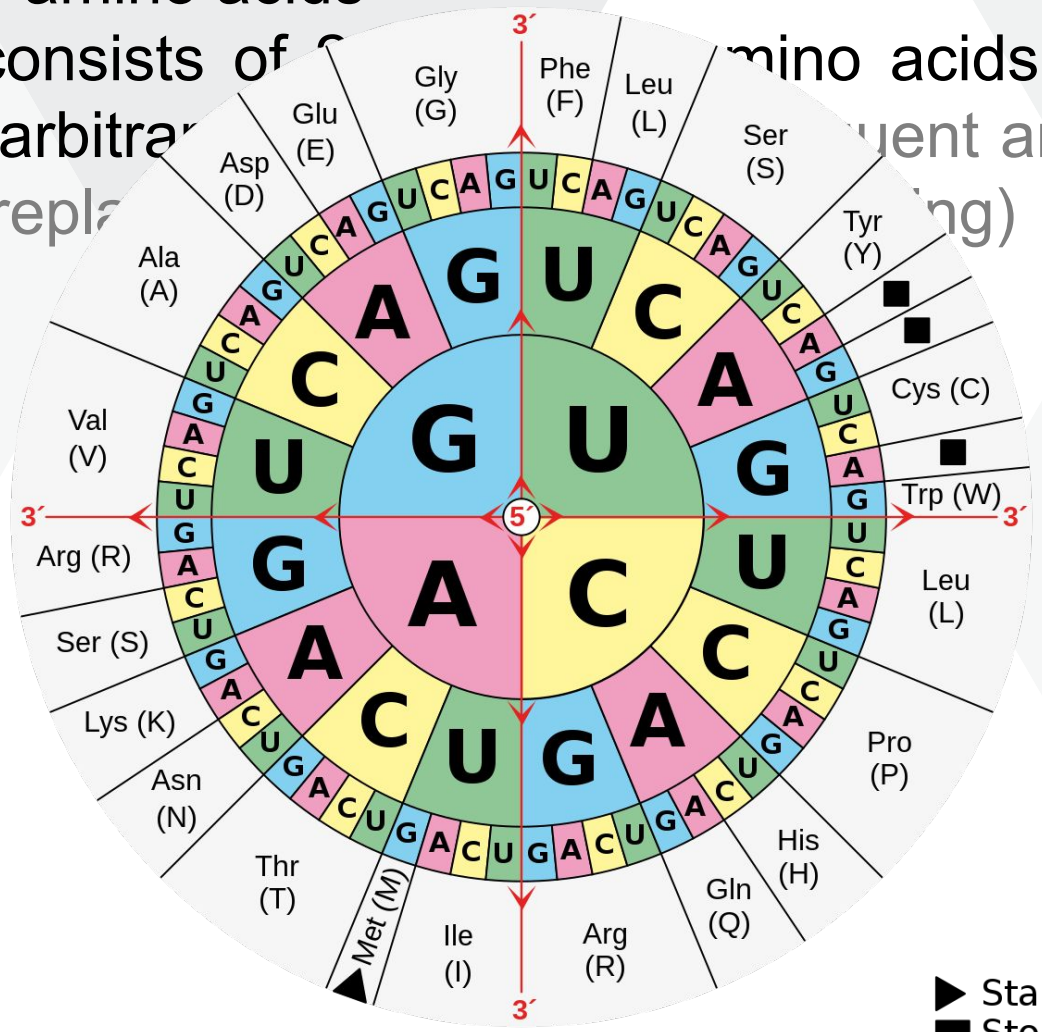

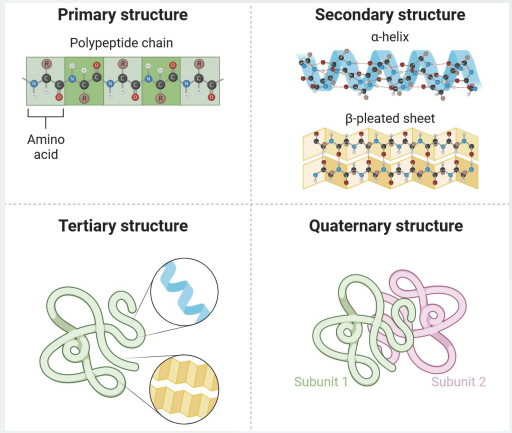

https://en.wikipedia.org/wiki/DNA_and_RNA_codon_tables

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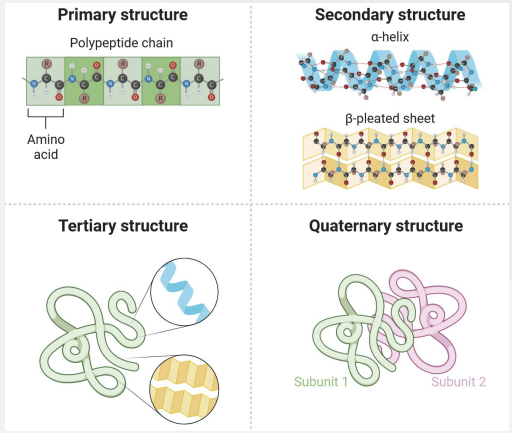
Protein (data format) from NLP point of view



- protein == string of amino acids
- alphabet usually consists of 20 common amino acids + X that stands for an arbitrary amino acid (less frequent amino acids (UZOB) are replaced by X during preprocessing)

M	Met	Methionine	F	Phe	Phenylalanine
I	Ile	Isoleucine	W	Trp	Tryptophan
L	Leu	Leucine	Y	Tyr	Tyrosine
V	Val	Valine	G	Gly	Glycine
A	Ala	Alanine	P	Pro	Proline
C	Cys	Cysteine	S	Ser	Serine
D	Asp	Aspartic acid	T	Thr	Threonine
E	Glu	Glutamic acid	H	His	Histidine
N	Asn	Asparagine	K	Lys	Lysine
Q	Gln	Glutamine	R	Arg	Arginine
O	Pyl	Pyrrolysine	U	Sec	Selenocysteine
B	Asx	Asparagine or Aspartic acid	Z	Glx	Glutamine or Glutamic acid
J	Xle	Leucine or Isoleucine	X	Xaa	Any amino acid

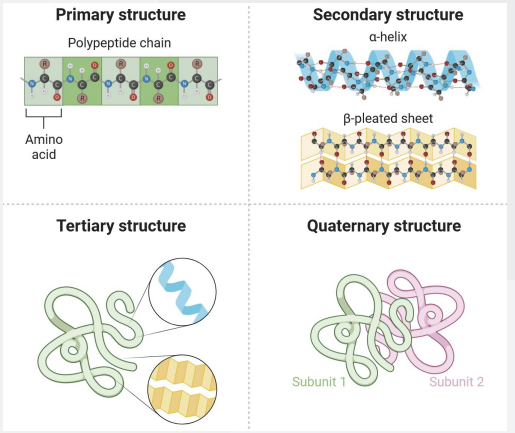
http://www.h-invitational.jp/csmview/aa_table.html

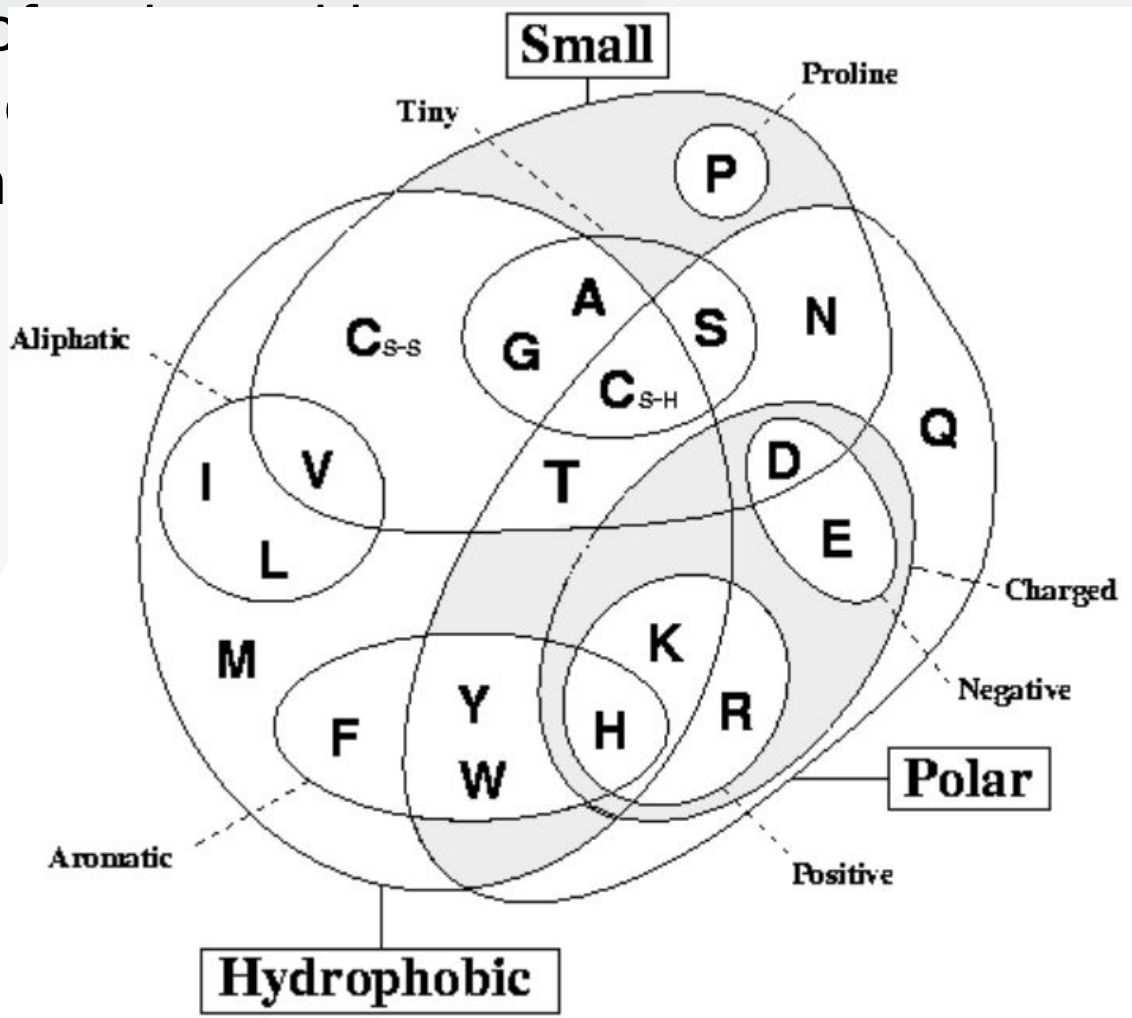
Protein (data format) from NLP point of view

- protein == string o
- alphabet usually
  that stands for an
  acids (UZOB) are

X

no





Overview: http://www.russelllab.org/aas/

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.PDB file format

1. header with information about the protein
2. amino acid sequence
3. structure coordination

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HEADER                                                  01-JUN-22
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TITLE    2 SUPERFAMILY PROTEIN (K1SW45)
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COMPND   2 MOLECULE: SPOUT METHYLTRANSFERASE SUPERFAMILY PROTEIN;
COMPND   3 CHAIN: A
SOURCE    MOL_ID: 1;
SOURCE   2 ORGANISM_SCIENTIFIC: HUMAN GUT METAGENOME;
SOURCE   3 ORGANISM_TAXID: 408170
REMARK   1
REMARK   1 REFERENCE 1
REMARK   1  AUTH   JOHN JUMPER, RICHARD EVANS, ALEXANDER PRITZEL, TIM GREEN,
                                    ...
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SEQRES   2 A  147  LYS HIS TYR ILE THR ALA ILE ASN ASP TYR VAL GLU ARG
SEQRES   3 A  147  THR ARG HIS PHE ILE SER PHE ASP MET GLU VAL ILE PRO
SEQRES   4 A  147  GLU LEU LYS ASN THR LYS ASN LEU SER MET GLU GLN GLN
SEQRES   5 A  147  LYS GLU LYS GLU GLY GLU LEU ILE LEU LYS ALA LEU LEU
SEQRES   6 A  147  PRO GLY ASP VAL VAL VAL LEU LEU ASP GLU HIS GLY LYS
SEQRES   7 A  147  GLU PHE ARG SER VAL GLU PHE ALA ASN TRP ILE GLU ARG
SEQRES   8 A  147  LYS MET HIS THR VAL ASN LYS ARG LEU VAL PHE ILE ILE
SEQRES   9 A  147  GLY GLY PRO TYR GLY PHE ALA PRO LYS ILE TYR ASP ALA
SEQRES  10 A  147  ALA GLN GLU LYS ILE SER LEU SER LYS MET THR PHE SER
SEQRES  11 A  147  HIS GLN MET ILE ARG LEU ILE PHE VAL GLU GLN LEU TYR
SEQRES  12 A  147  ARG ALA MET THR
                                    ...
MODEL        1
ATOM      1  N   MET A   1       6.248   6.075 -15.215  1.00 92.75           N
ATOM      2  CA  MET A   1       5.220   5.606 -14.264  1.00 92.75           C
ATOM      3  C   MET A   1       5.642   5.969 -12.845  1.00 92.75           C
ATOM      4  CB  MET A   1       5.038   4.093 -14.419  1.00 92.75           C
ATOM      5  O   MET A   1       6.834   5.932 -12.565  1.00 92.75           O
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alpha-N atom of the first residue (MET) of peptide chain A

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SOURCE    MOL_ID: 1;
SOURCE   2 ORGANISM_SCIENTIFIC: HUMAN GUT METAGENOME;
SOURCE   3 ORGANISM_TAXID: 408170
REMARK   1
REMARK   1 REFERENCE 1
REMARK   1  AUTH   JOHN JUMPER, RICHARD EVANS, ALEXANDER PRITZEL, TIM GREEN,
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SEQRES   4 A  147  GLU LEU LYS ASN THR LYS ASN LEU SER MET GLU GLN GLN
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.PDB file format

x, y, and z coordinates
(Angstrom units == 10^{-10} m)

…

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```

alpha-N atom of the first residue (MET) of peptide chain A

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element name

alpha-N atom of the first residue (MET) of peptide chain A

.PDB file format

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(Angstrom units == 10^{-10} m)

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element name

alpha-N atom of the first residue (MET) of peptide chain A

temperature
== a measure of confidence in the location of atom

.PDB file format

x, y, and z coordinates
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…

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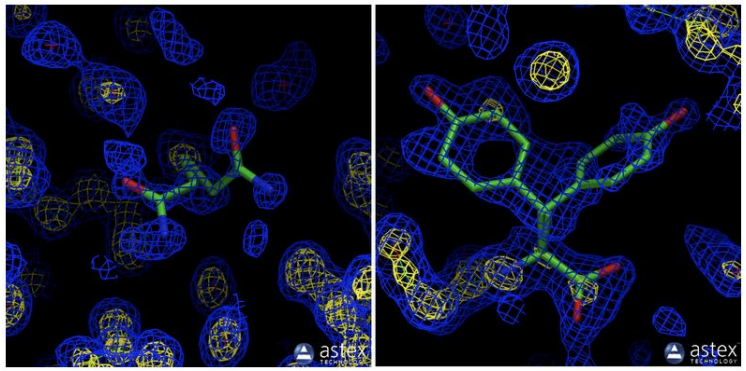
element name

alpha-N atom of the first residue (MET) of peptide chain A

occupancy
== 1 if atom is found in the same place in the crystal in all molecules

temperature
== a measure of confidence in the location of atom



alternate conformations
in myoglobin

https://pdb101.rcsb.org/learn/guide-to-understanding-pdb-data/dealing-with-coordinates

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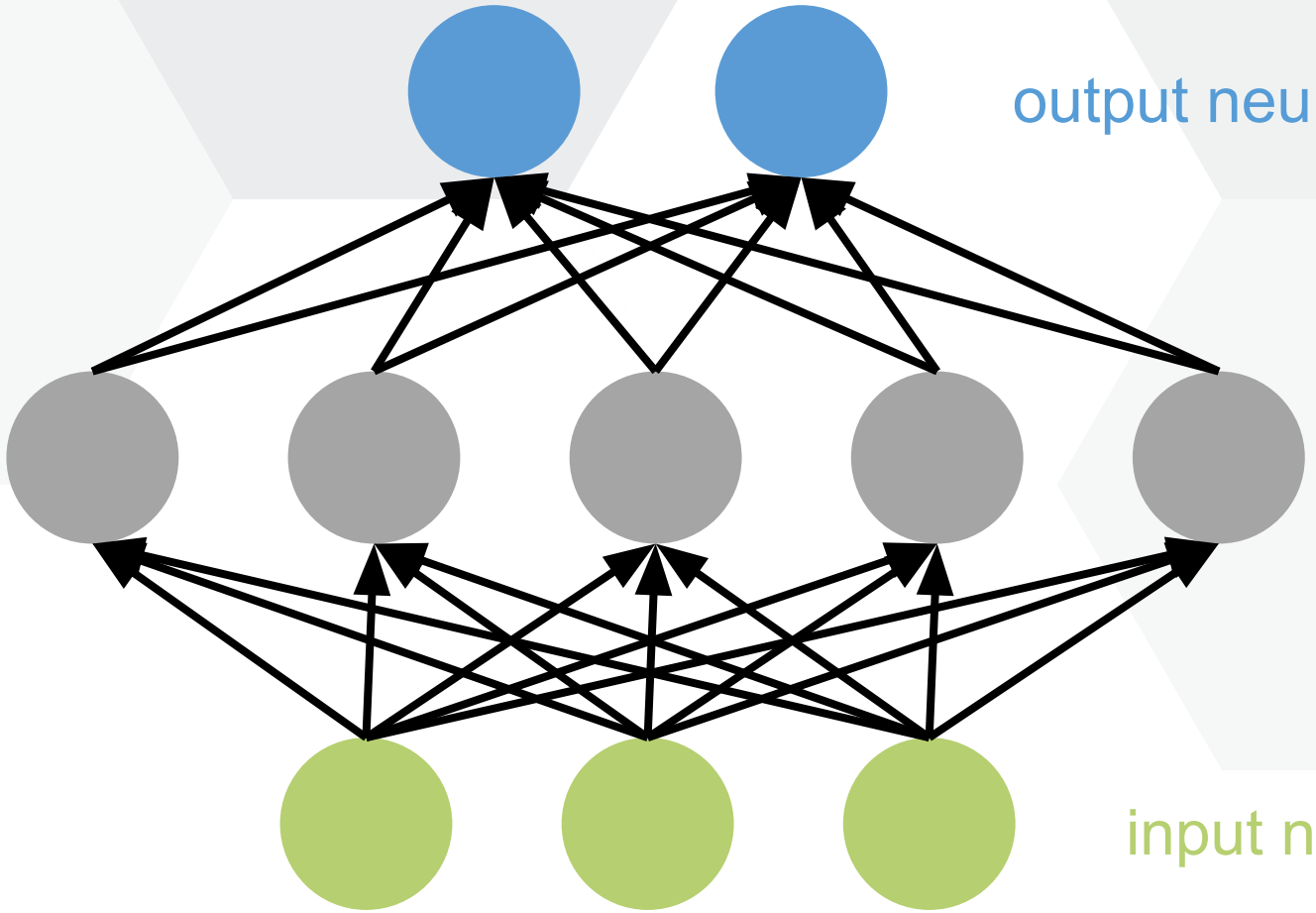
Models for solving the protein folding problem

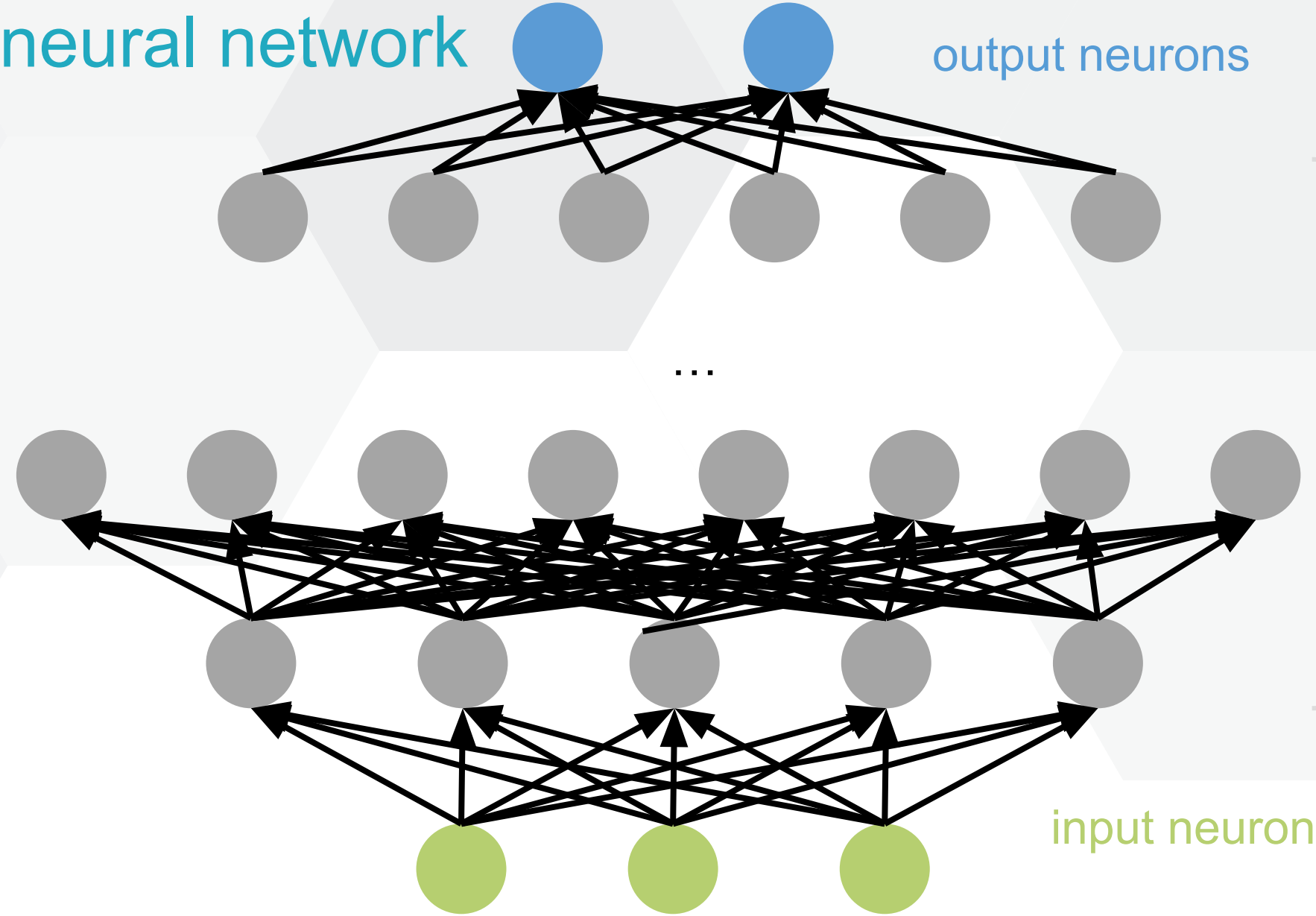
Model

== a machine learning approach that has been trained to solve some specific task

Multi-layer Perceptron

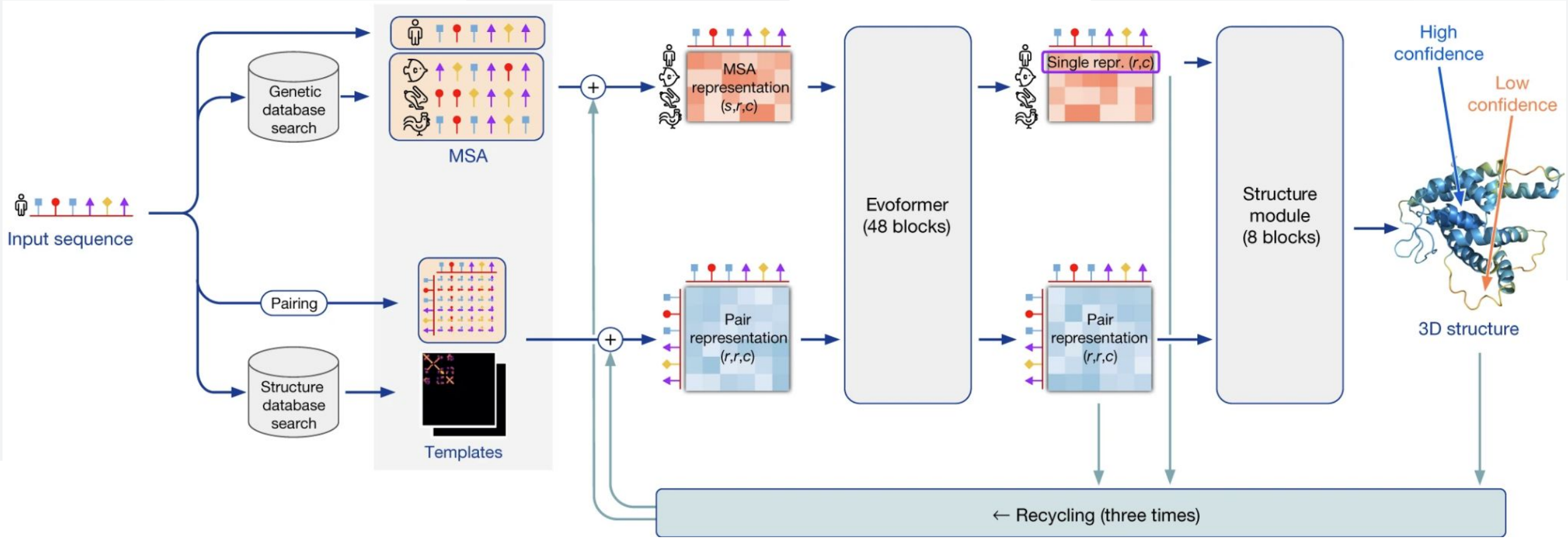


Deep neural network



AlphaFold2 [1]

- orphan proteins



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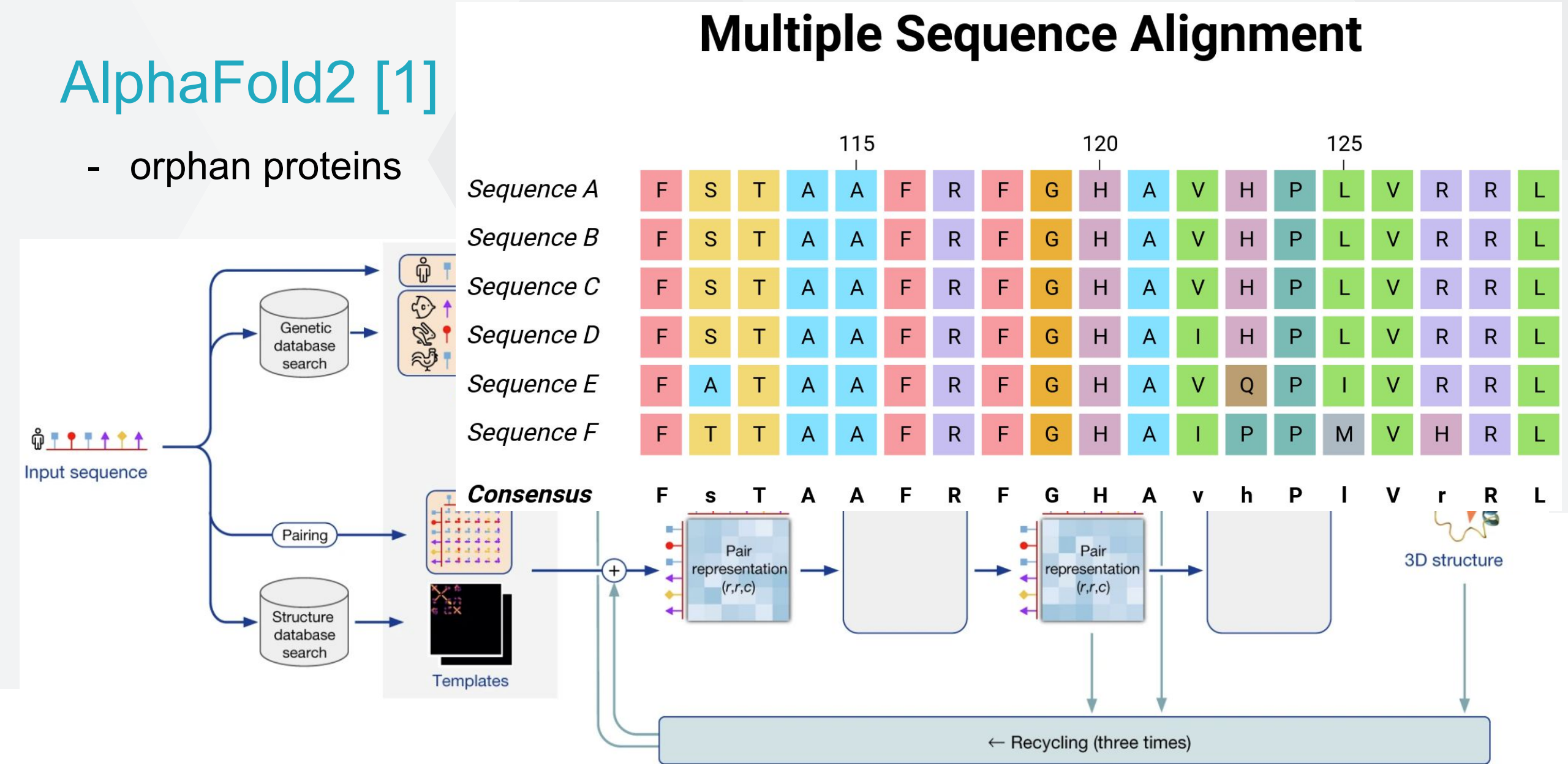

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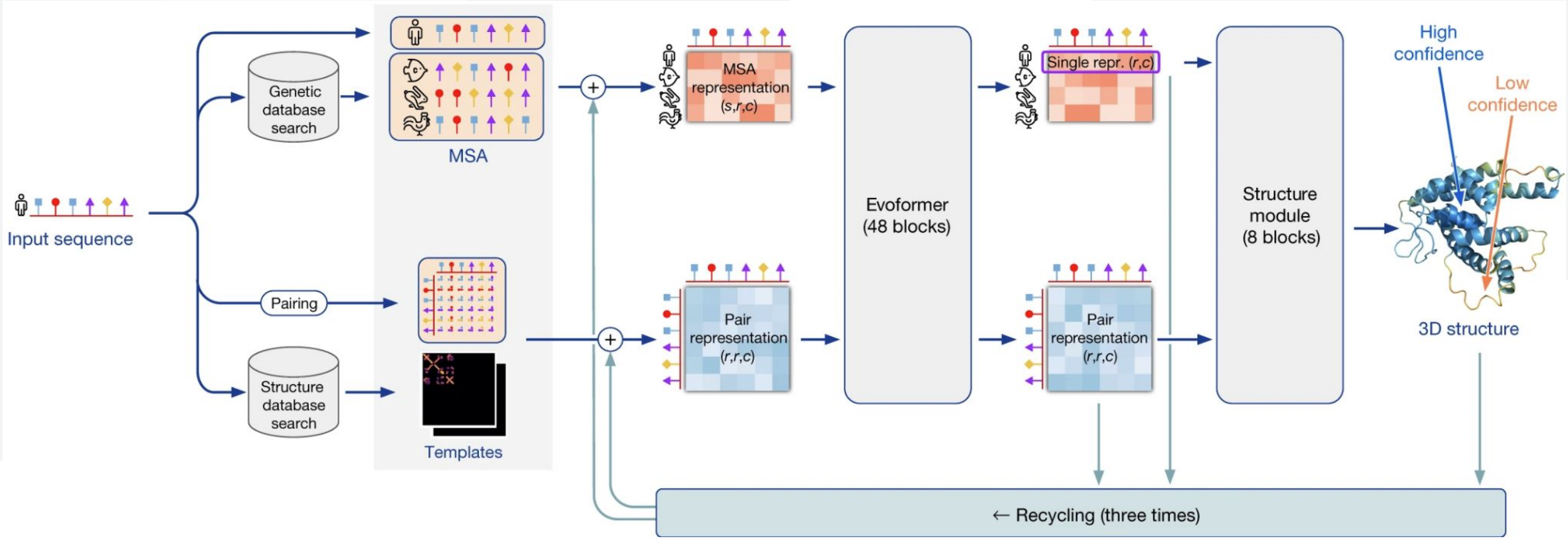
AlphaFold2 [1]

- orphan proteins



AlphaFold2 [1]

- orphan proteins

AlphaFold2 fails to predict protein fold switching

Devlina Chakravarty [1], Lauren L Porter [1 2]

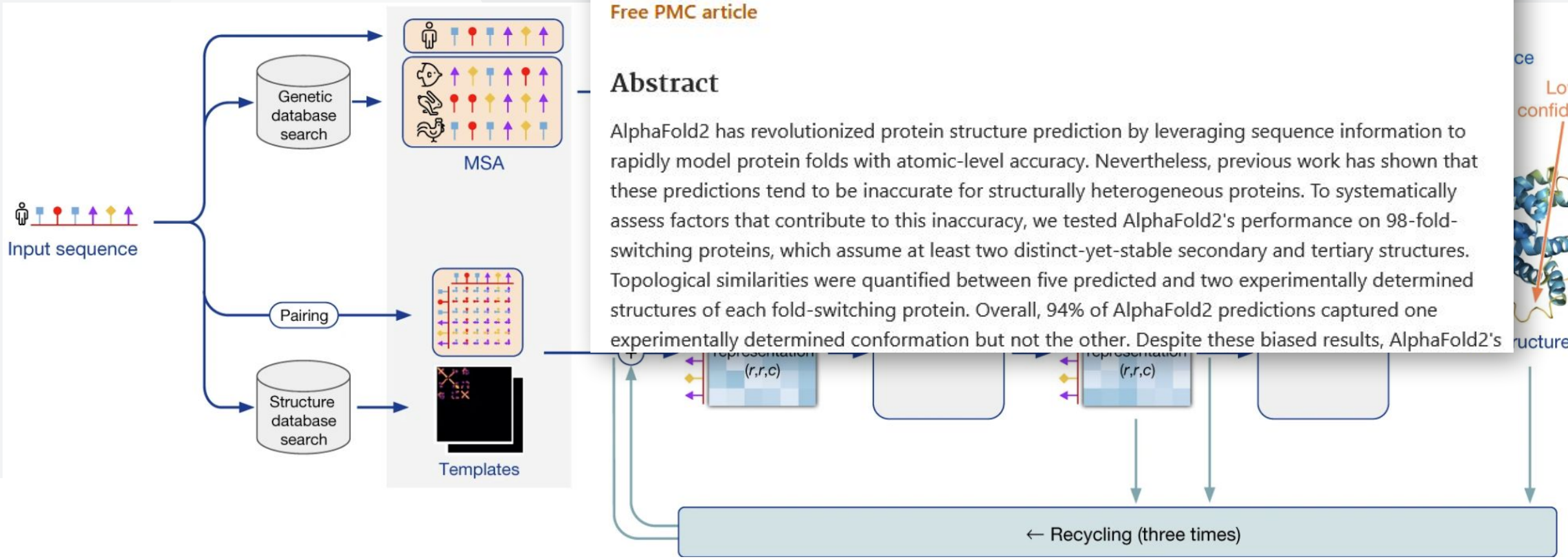
Affiliations + expand

PMID: 35634782 PMCID: PMC9134877 DOI: 10.1002/pro.4353

Free PMC article

Abstract

AlphaFold2 has revolutionized protein structure prediction by leveraging sequence information to rapidly model protein folds with atomic-level accuracy. Nevertheless, previous work has shown that these predictions tend to be inaccurate for structurally heterogeneous proteins. To systematically assess factors that contribute to this inaccuracy, we tested AlphaFold2's performance on 98-fold-switching proteins, which assume at least two distinct-yet-stable secondary and tertiary structures. Topological similarities were quantified between five predicted and two experimentally determined structures of each fold-switching protein. Overall, 94% of AlphaFold2 predictions captured one experimentally determined conformation but not the other. Despite these biased results, AlphaFold2's



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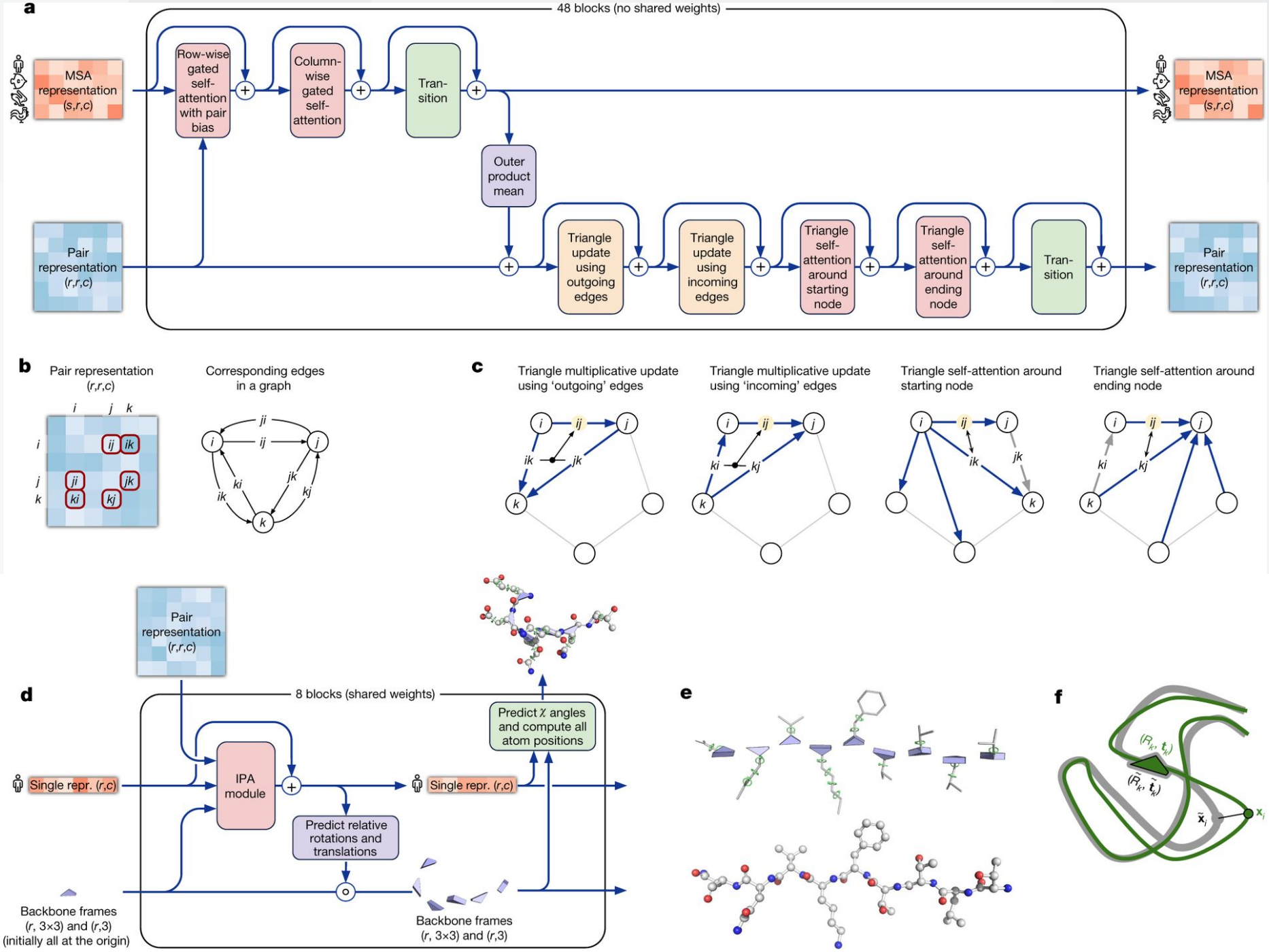
AlphaFold2



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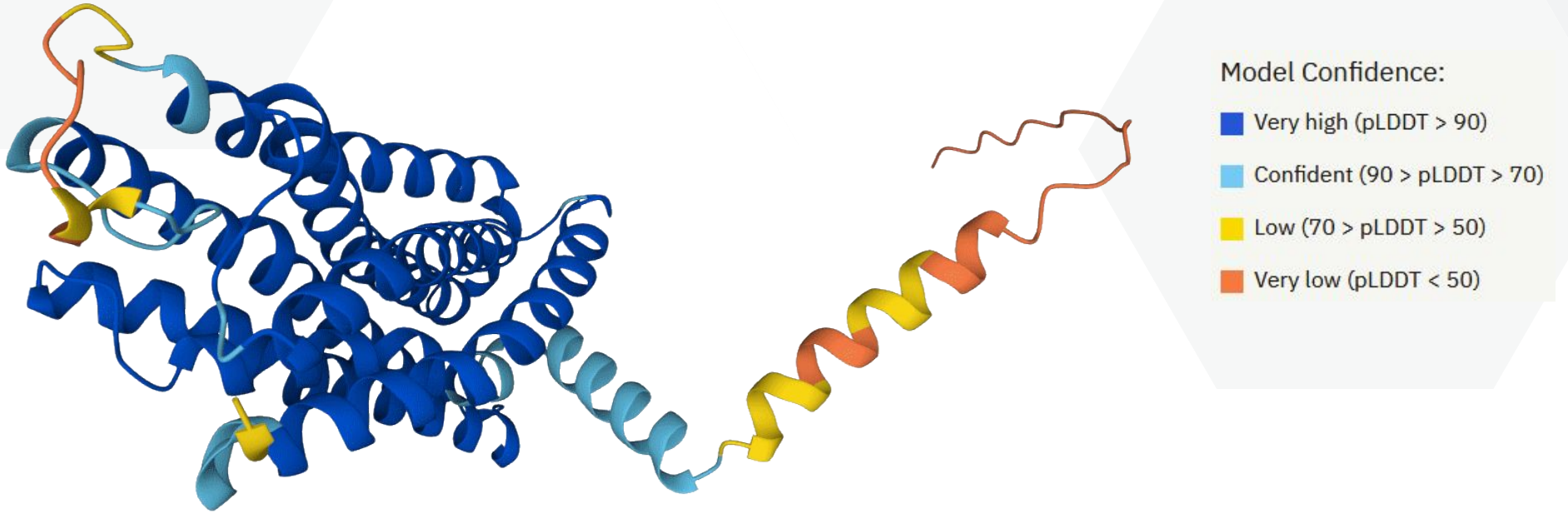
Prediction confidence [1]

pLDDT == per-residue estimate of its confidence on a scale from 0 - 100

- pLDDT > 90 is considered to be modelled to high accuracy
- pLDDT < 50 often have a ribbon-like appearance and should not be interpreted
  - suggests that such region is either unstructured in physiological conditions or only structured as a part of a complex (analysed on well-studied proteins)



https://alphafold.ebi.ac.uk/entry/Q8VCK6

Prediction confidence

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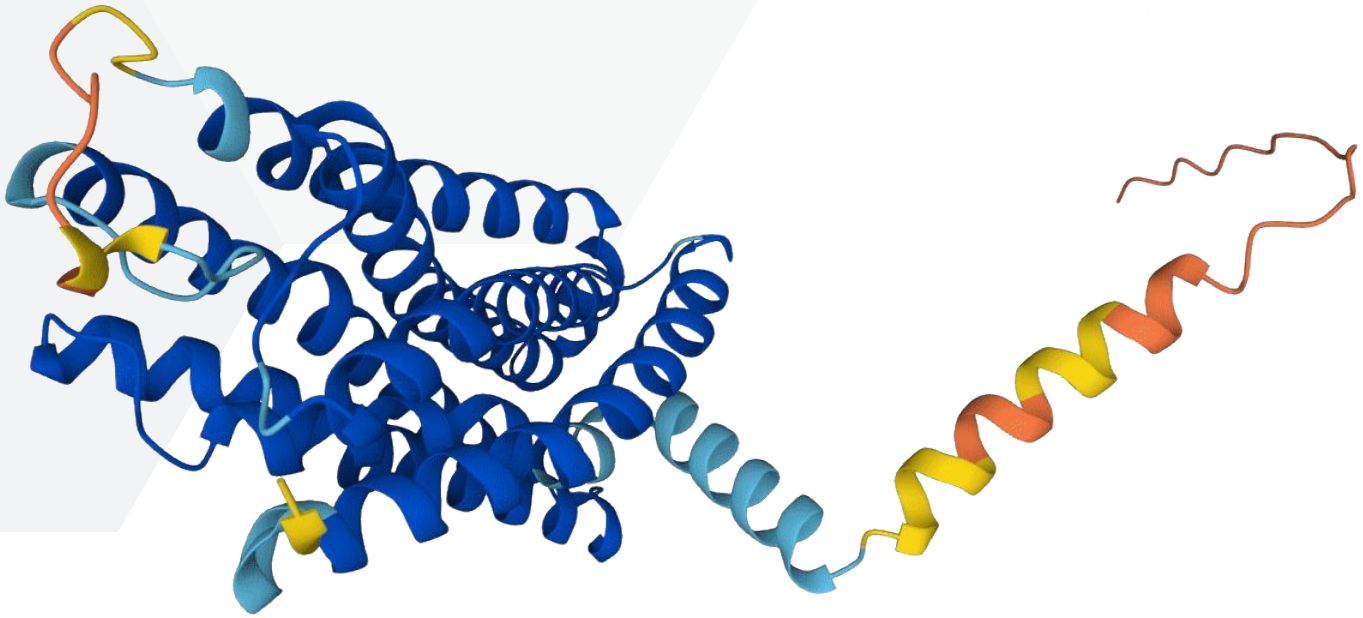
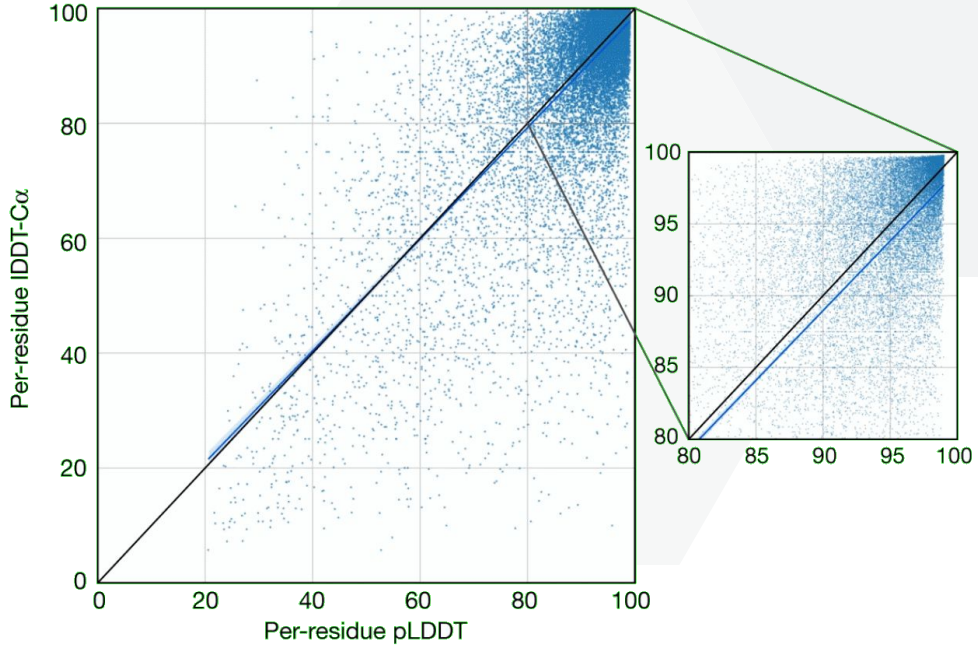
- how well the prediction would agree with an experimental structure based on the local distance difference test Cα (lDDT-Cα)

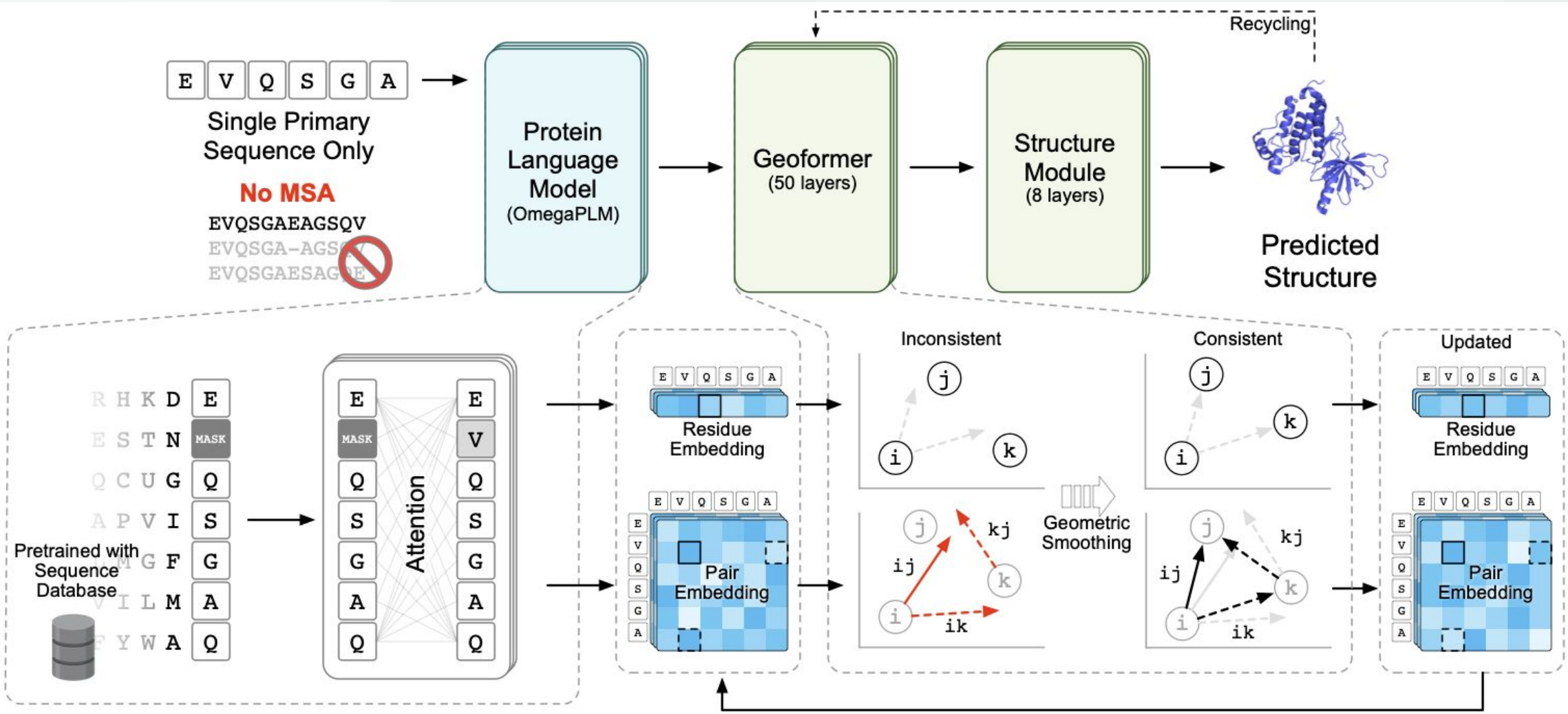


https://alphafold.ebi.ac.uk/entry/Q8VCK6

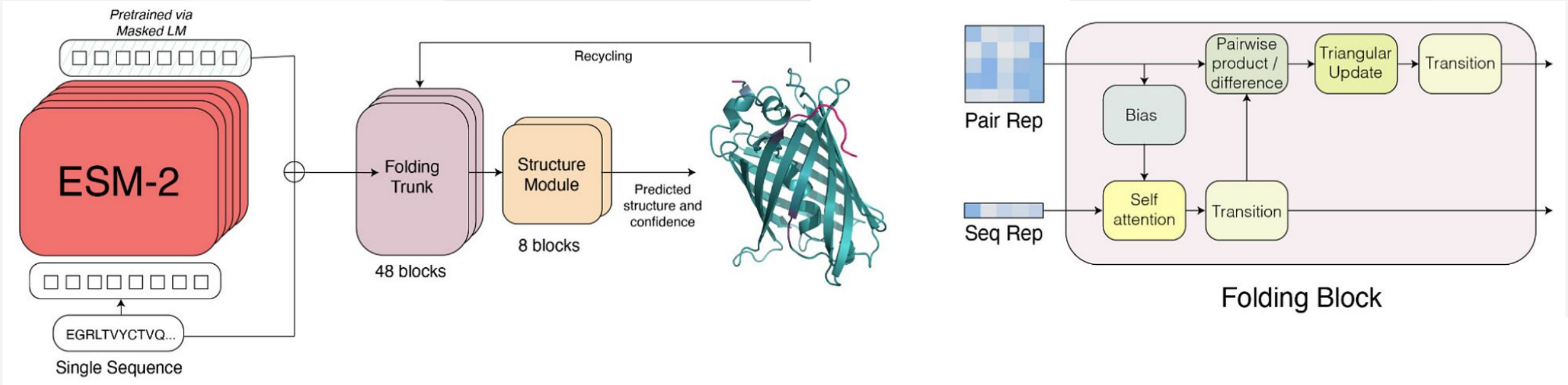
correlation between per-residue pLDDT and lDDT-Cα:



OmegaFold [2]

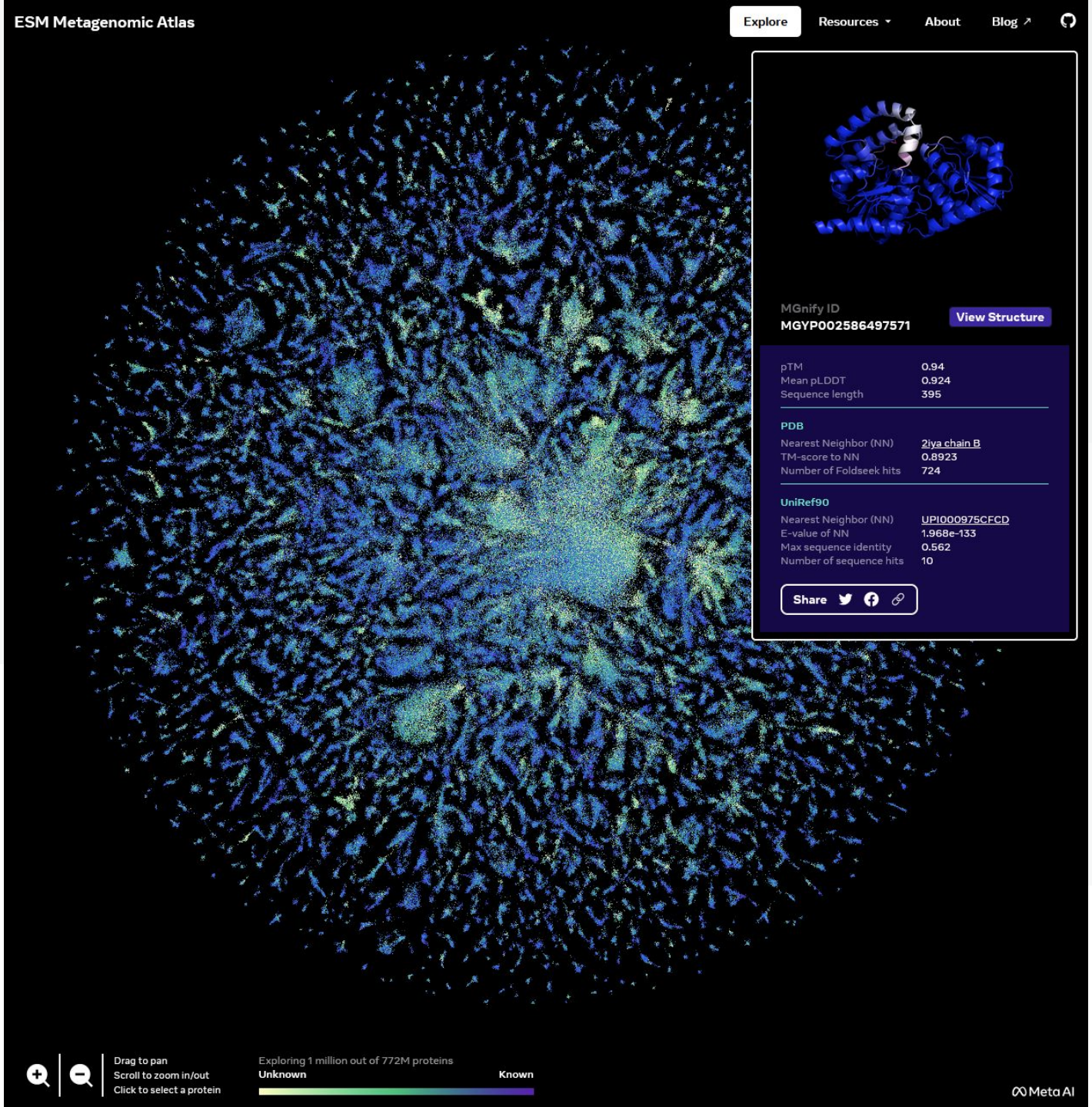

Recycling
E V Q S G A
Single Primary Sequence Only
No MSA
EVQSGAEAGSQV
Protein Language Model (OmegaPLM)
Geoformer (50 layers)
Structure Module (8 layers)
Predicted Structure
Pretrained with Sequence Database
Attention
Residue Embedding
Pair Embedding
Inconsistent
Consistent
Geometric Smoothing
Updated

ESMFold [3]


Pretrained via Masked LM
ESM-2
EGRLTVYCTVQ...
Single Sequence
Recycling
Folding Trunk
48 blocks
Structure Module
8 blocks
Predicted structure and confidence
Pair Rep
Seq Rep
Pairwise product / difference
Triangular Update
Transition
Bias
Self attention
Transition
Folding Block

ESMFold

https://esmatlas.com/



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Comparison of the models [1,2,3,4]

- benchmark results:

AlphaFold (ColabFold)

Length	Running time	pLDDT	CPU memory	GPU memory
50	45	0.89	10 GB	10 GB
100	55	0.38	10 GB	10 GB
200	91	0.55	10 GB	10 GB
400	210	0.82	10 GB	10 GB
800	810	0.54	10 GB	10 GB
1600	2800	0.41	10 GB	10 GB

OmegaFold

Length	Running time	pLDDT	CPU memory	GPU memory
50	3.66	0.86	10 GB	6 GB
100	7.42	0.39	10 GB	7 GB
200	34.07	0.65	10 GB	8.5 GB
400	110	0.76	10 GB	10 GB
800	1425	0.53	10 GB	11 GB
1600	FAILED	-	-	17 GB

ESMFold

Length	Running time	pLDDT	CPU memory	GPU memory
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- since AlphaFold utilizes MSA, it is not accurate on orphan proteins, since ESMFold leverages the power of transformer models, it effectively addresses the “twilight zone” problem

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Other folding tools

https://github.com/biolists/folding_tools

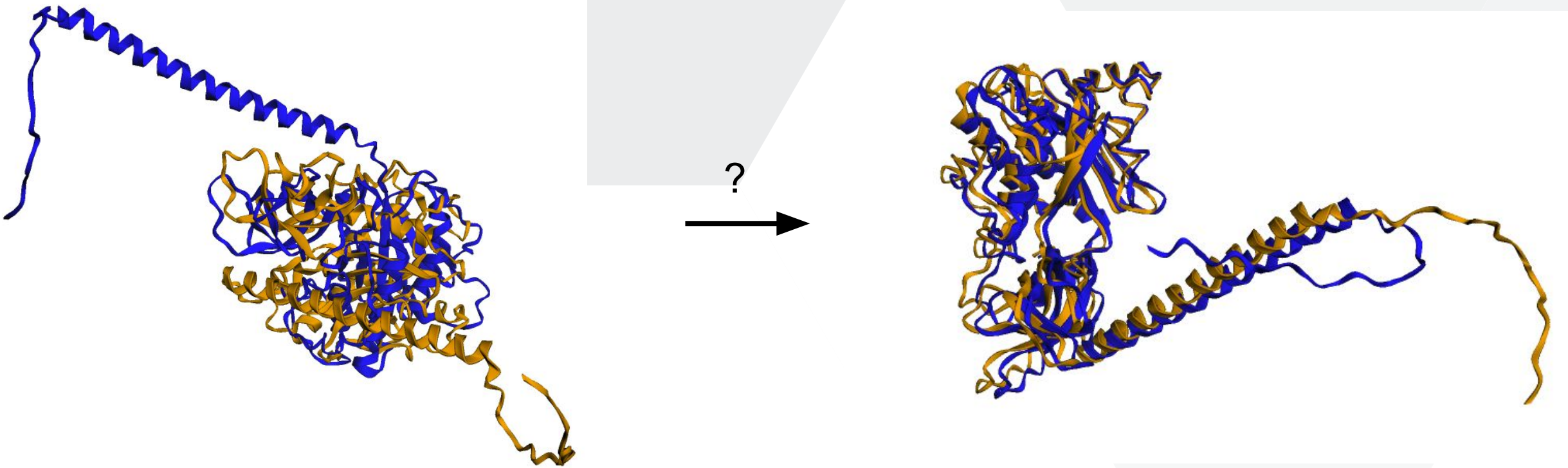
Predictors

[*in alphabetical order*]

- **MSA-based** (uses Multiple Sequence Alignments (MSAs) as input)
  - AlphaFold2 repo JAX DOI 10.1038/s41586-021-03819-2
    - The original AlphaFold 2 method
    - Features: monomer, multimer
    - Other: Colab Notebook
  - ColabFold repo JAX DOI 10.1038/s41592-022-01488-1
    - Faster AF2 compiling and MSA generations
    - Features: monomer, multimer
    - Other: localcolabfold
  - FastFold repo PyTorch arxiv 2203.00854
    - Runtime improvements to OpenFold (see below)
    - Features: monomer
  - HelixFold repo PaddlePaddle arxiv 2207.05477
    - Reimplementation of AF2 in PaddlePaddle
    - Features: monomer

- **pLM-based** (using embeddings from protein Language Models (pLMs) as input)
  - ESM-Fold repo PyTorch DOI 10.1101/2022.07.20.500902
    - Features: monomer
    - Other: Unofficial Colab notebook,API
  - EMBER3D repo PyTorch
    - Features: monomer
  - HelixFold-single repo PaddlePaddle arxiv 2207.13921
    - Features: monomer
    - Resource: https://paddlehelix.baidu.com/app/drug/protein-single/forecast
  - IgFold repo PyTorch DOI 10.1101/2022.04.20.488972
    - pLM focused on antibody sequences
    - Features: monomer
    - Other: Colab Notebook
  - OmegaFold repo PyTorch DOI 10.1101/2022.07.21.500999
    - Features: monomer
    - Other: Unofficial Colab Notebook, [tweet] Martin comparing structures, [tweet] Sergey's positional encoding observation
  - RGN2 Github
    - Uses AlphaFold's structure module (AF2Rank's template protocol) for final structure refinement.

How can we compare two 3D structures?



RMSD (root-mean-square deviation)

== measure of the average distance between the atoms (usually the backbone atoms) of superimposed proteins

$$RMSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\delta_i^2}$$

where δ_i is the distance between atom *i* and either a reference structure or the mean position of the *N* equivalent atoms *(often calculated for the backbone heavy atoms C, N, O, and* C_α *or sometimes just the* C_α *atoms)*

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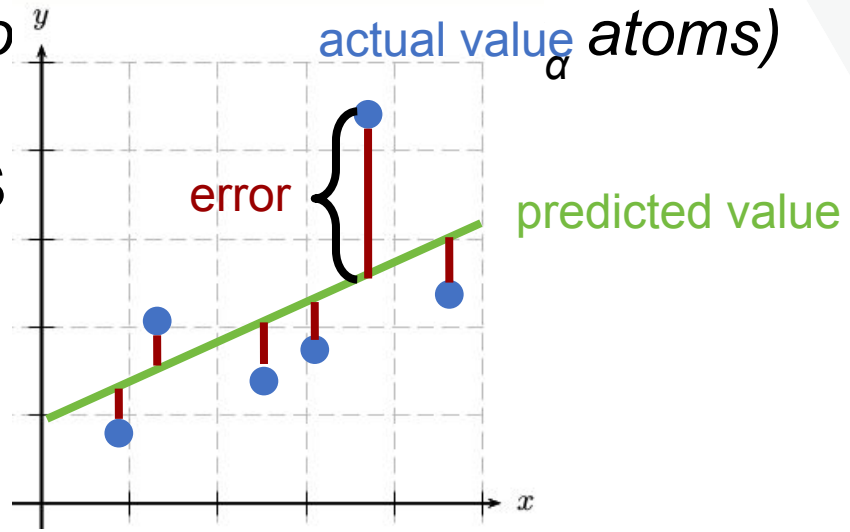
like RMS

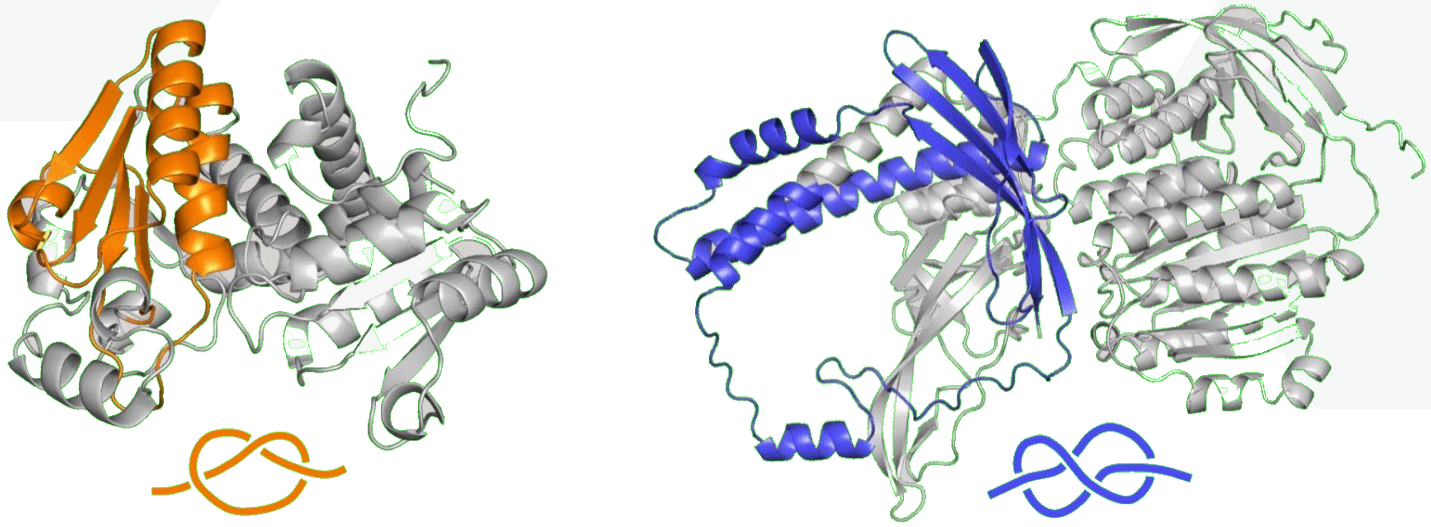


Exercises

AlphaFold2 - `maltaomics_ex0a_alphafold.ipynb`
OmegaFold - `maltaomics_ex0b_omegafold.ipynb`
ESM - `maltaomics_ex0c_esmfold.ipynb`

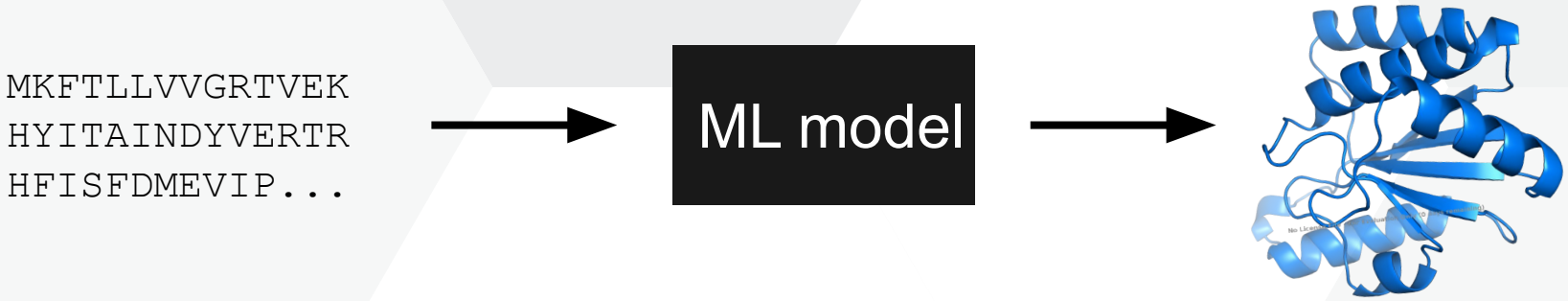
Other protein structure problems

- structure property
  - predict from amino acid sequence whether it's folded structure possesses the property
  - interpret what motif is responsible for the property occurrence
- ideally in future: flip the problem and design new proteins -> get amino acid sequence from a structure that has some wanted property



Do we have to work with the 3D structures?

- since protein is determined by its amino acid sequence => it should be enough to work directly with the sequence



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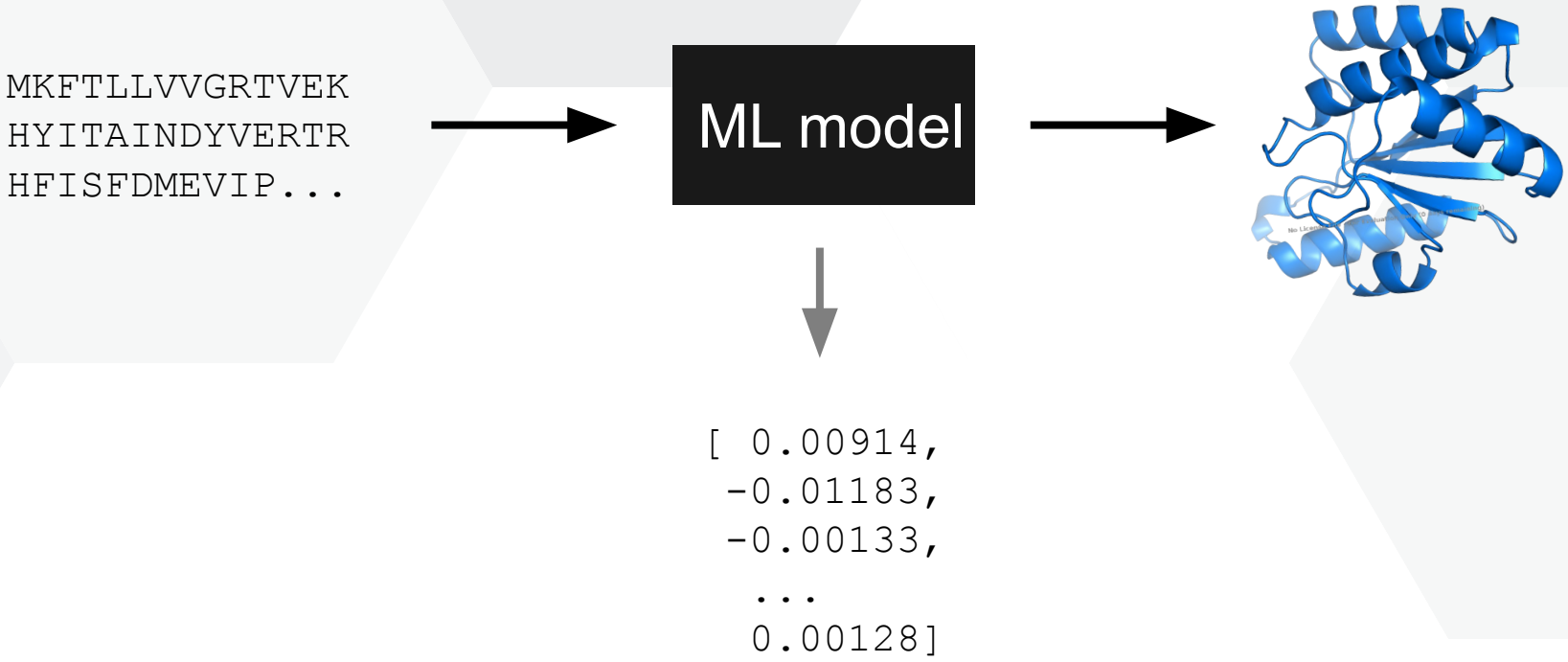
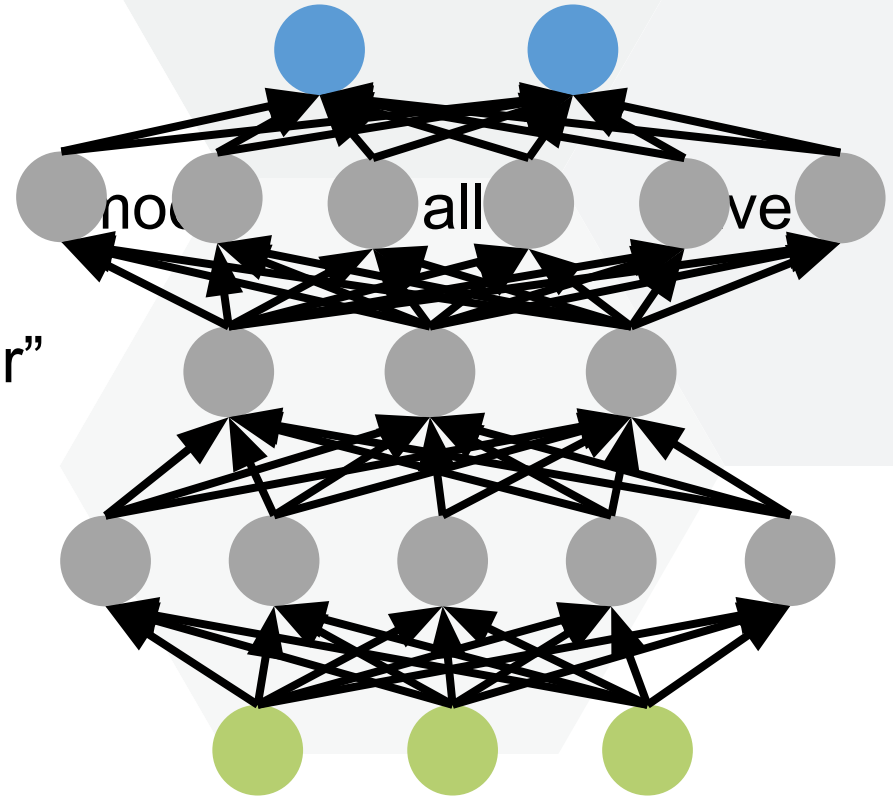


What is an embedding and why you should care

- a relatively low-dimensional numerical representation of some input expressed as a vector

Advantages:

- embeddings from some trained mo all ve the same size (unlike the original inputs)
- embeddings of similar inputs will be “close together”



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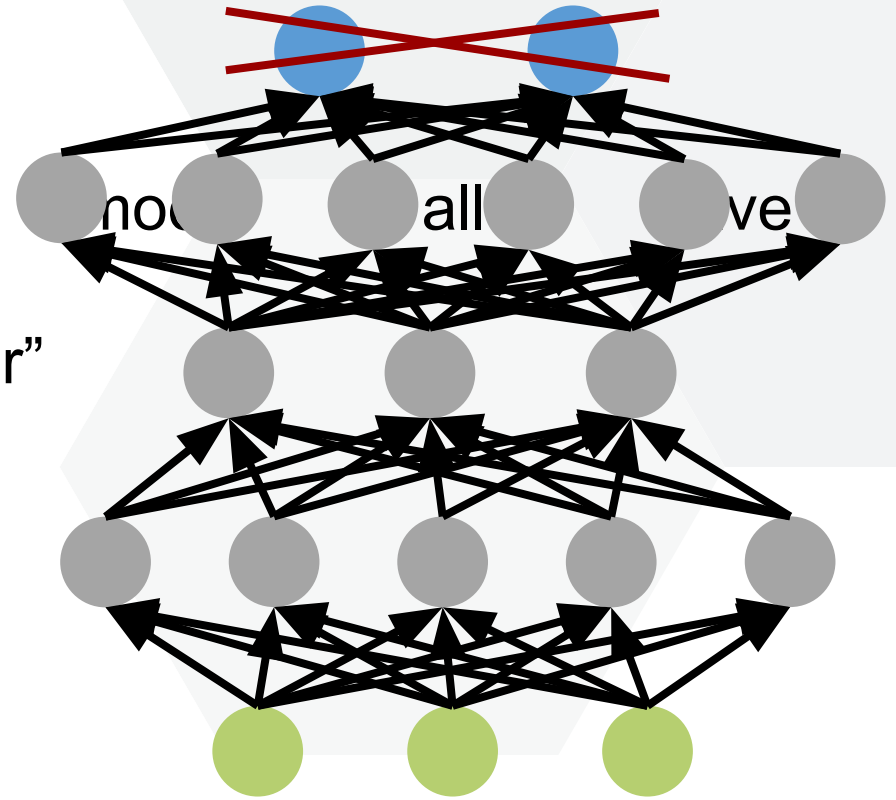

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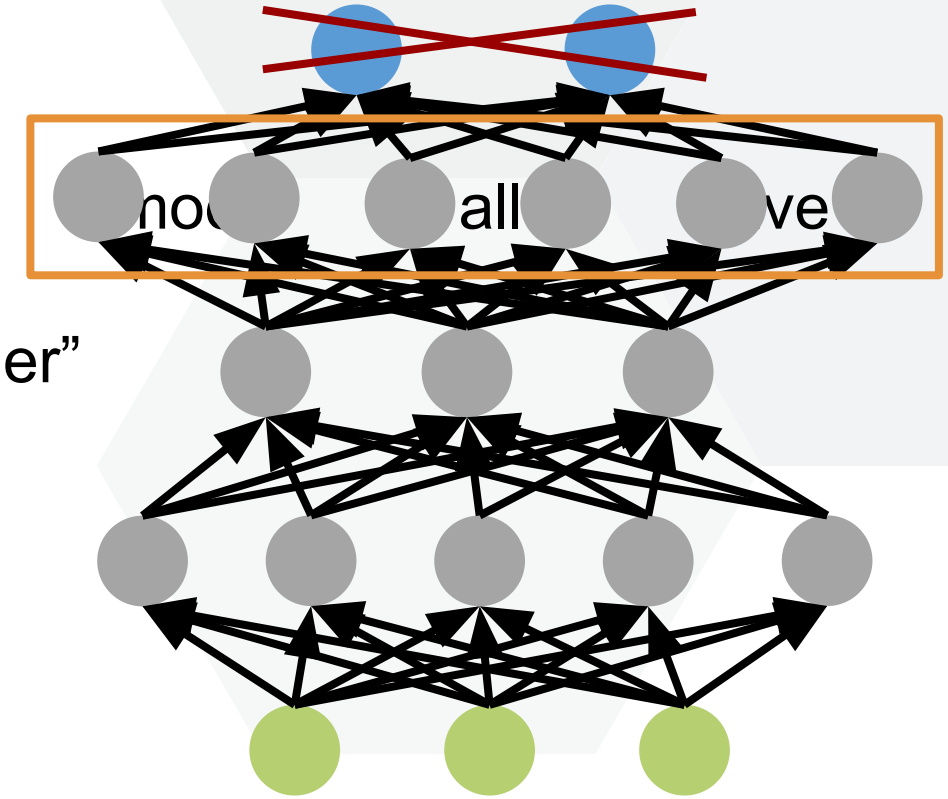

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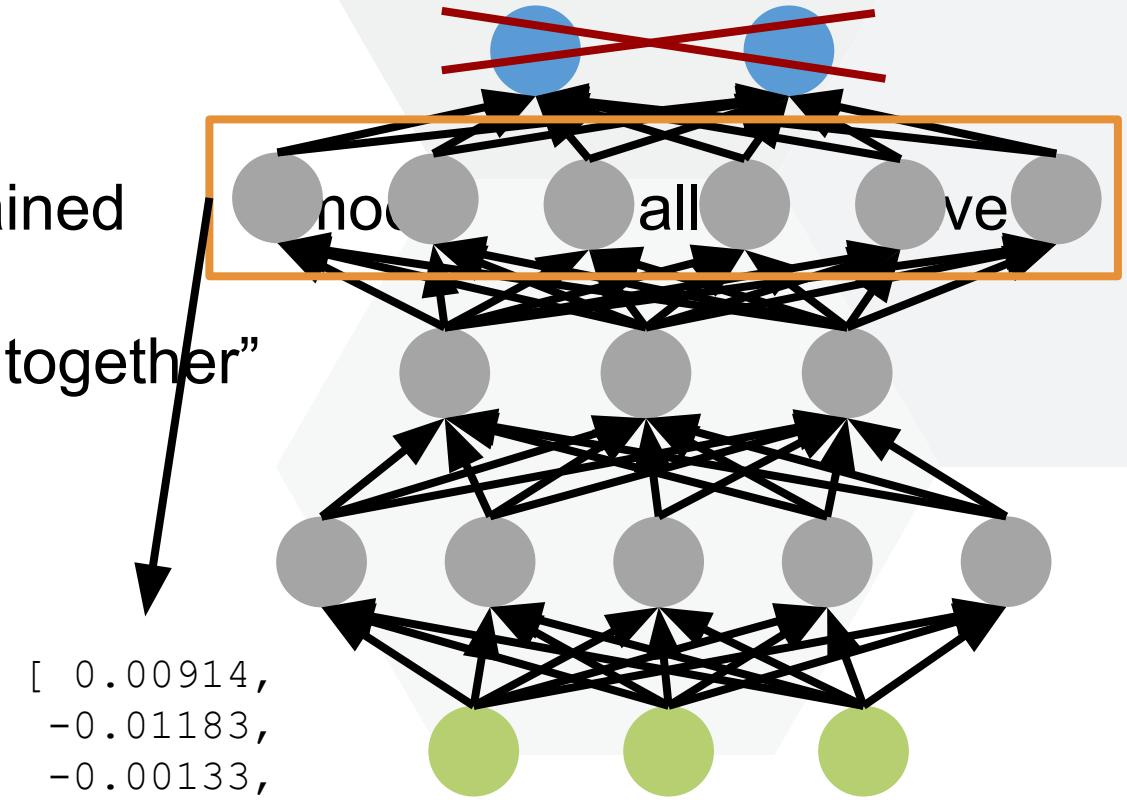

```
[ 0.00914,
 -0.01183,
 -0.00133,
  ...
  0.00128]
```

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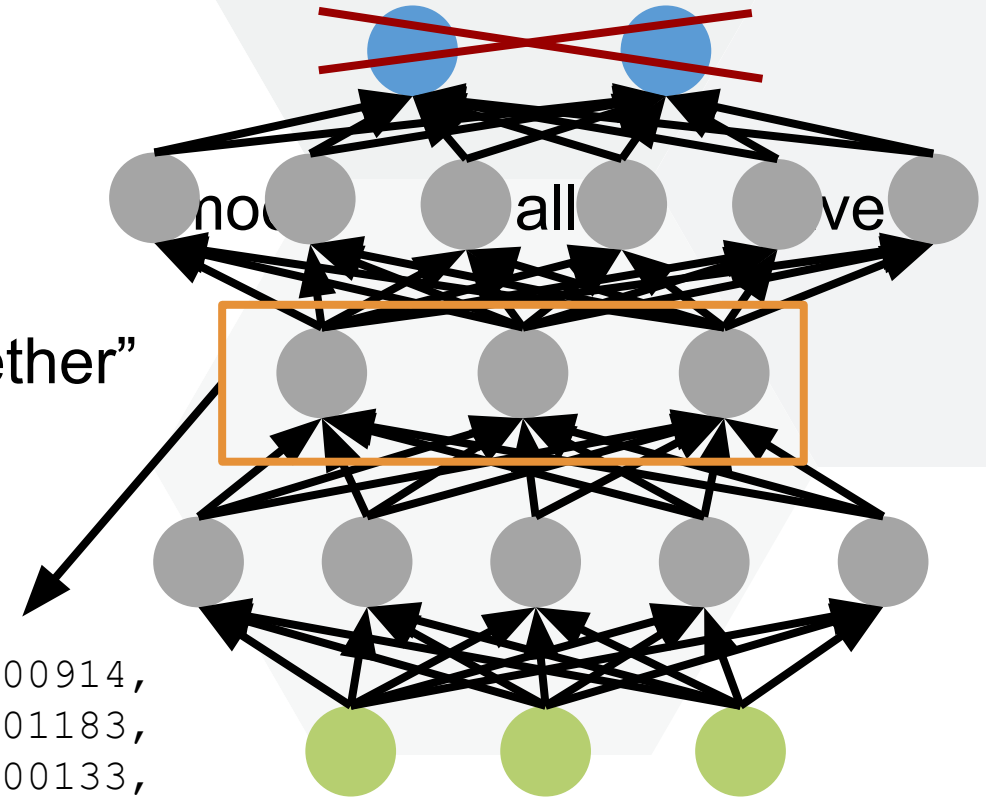

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The Nucleotide Transformer: Building and Evaluating Robust Foundation Models for Human Genomics

Hugo Dalla-Torre[1], Liam Gonzalez[1], Javier Mendoza Revilla[1], Nicolas Lopez Carranza[1], Adam Henryk Grzywaczewski[2], Francesco Oteri[1], Christian Dallago[2 3], Evan Trop[1], Hassan Sirelkhatim[2], Guillaume Richard[1], Marcin Skwark[1], Karim Beguir[1], Marie Lopez*† [1], Thomas Pierrot*† [1]

[1]InstaDeep [2]Nvidia [3]TUM

Abstract

Closing the gap between measurable genetic information and observable traits is a longstanding challenge in genomics. Yet, the prediction of molecular phenotypes from DNA sequences alone remains limited and inaccurate, often driven by the scarcity of annotated data and the inability to transfer learnings between prediction tasks. Here, we present an extensive study of foundation models pre-trained on DNA sequences, named the Nucleotide Transformer, integrating information from 3 202 diverse human genomes, as well as 850 genomes from a wide range of species, including

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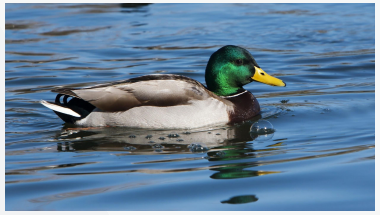

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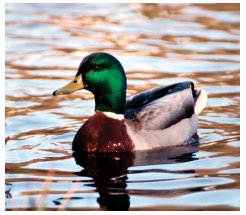

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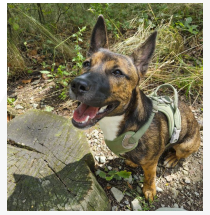
   ...
  0.00129]
```



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  0.42666]
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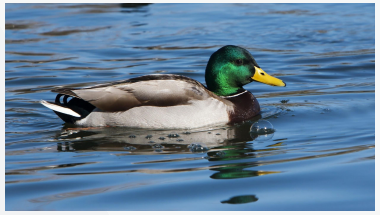

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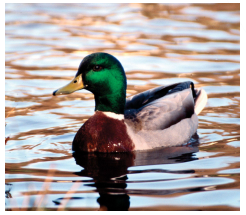

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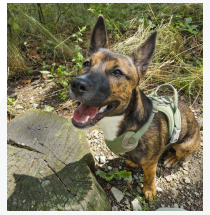

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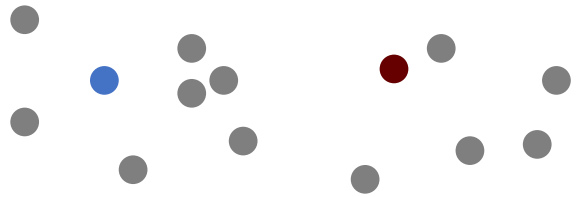

(projection of the embeddings to 2D)

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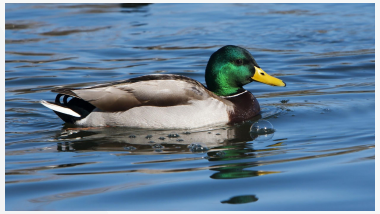

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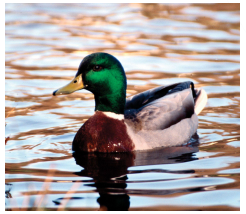
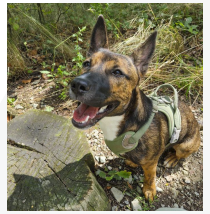
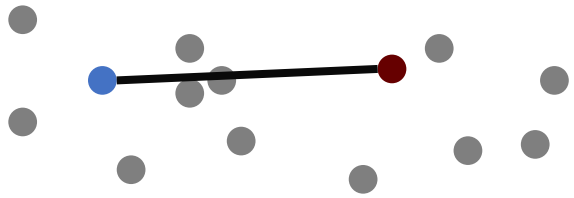
  0.00128]
```



```
[ 0.00926,
 -0.01097,
 -0.00301,
  ...
  0.00129]
```



```
[ 0.04111,
  0.00873,
 -0.0986,
  ...
 -0.42666]
```

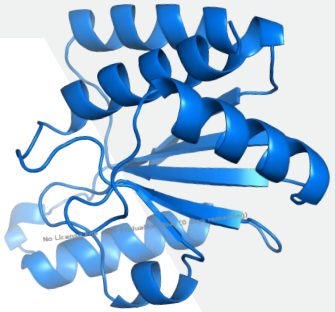


Euclidean distance: $d(p,q) = \sqrt{(p-q)^2}$

Extracting embeddings

```
MKFTLLVVGRTVEK
HYITAINDYVERTR
HFISFDMEVIP...
```

ML model



```
[ 0.00914,
 -0.01183,
 -0.00133,
  ...
  0.00128]
```

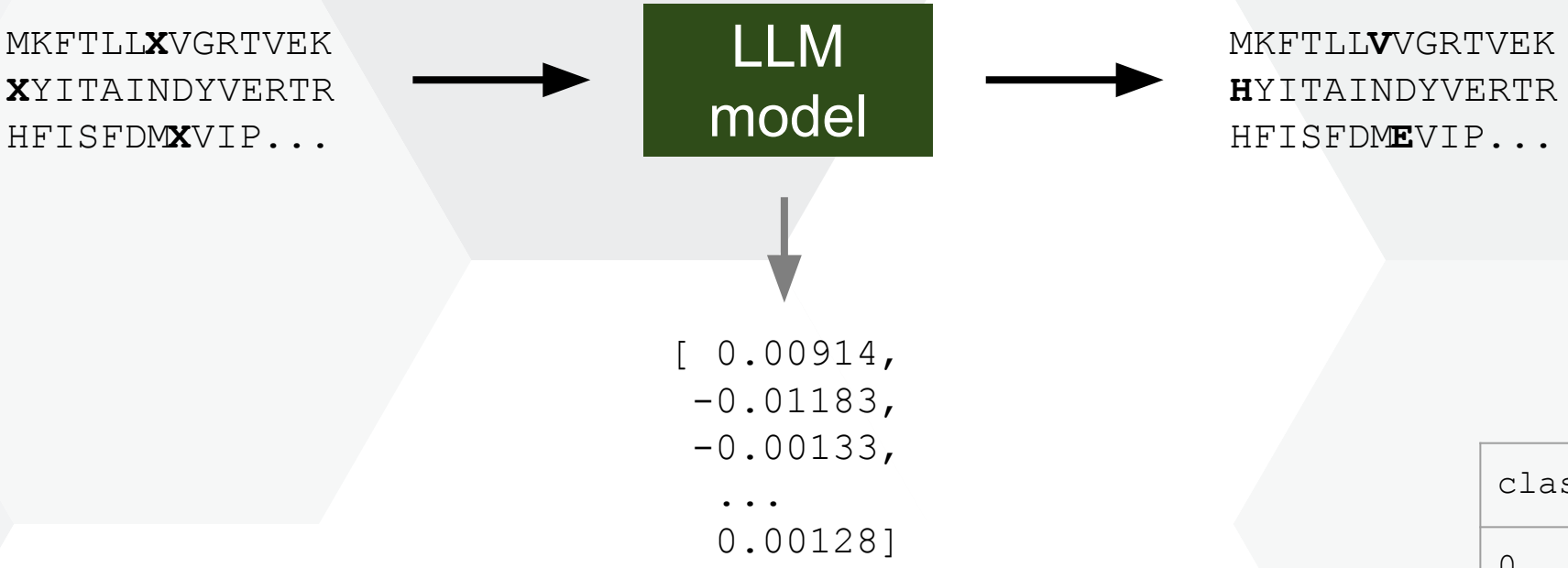
class	probability
0	0.02749
1	0.98361

Next: We can train a simple model on these embeddings.

simple ML model

linear regression, decision tree, CNN, …

Extracting embeddings



class	probability
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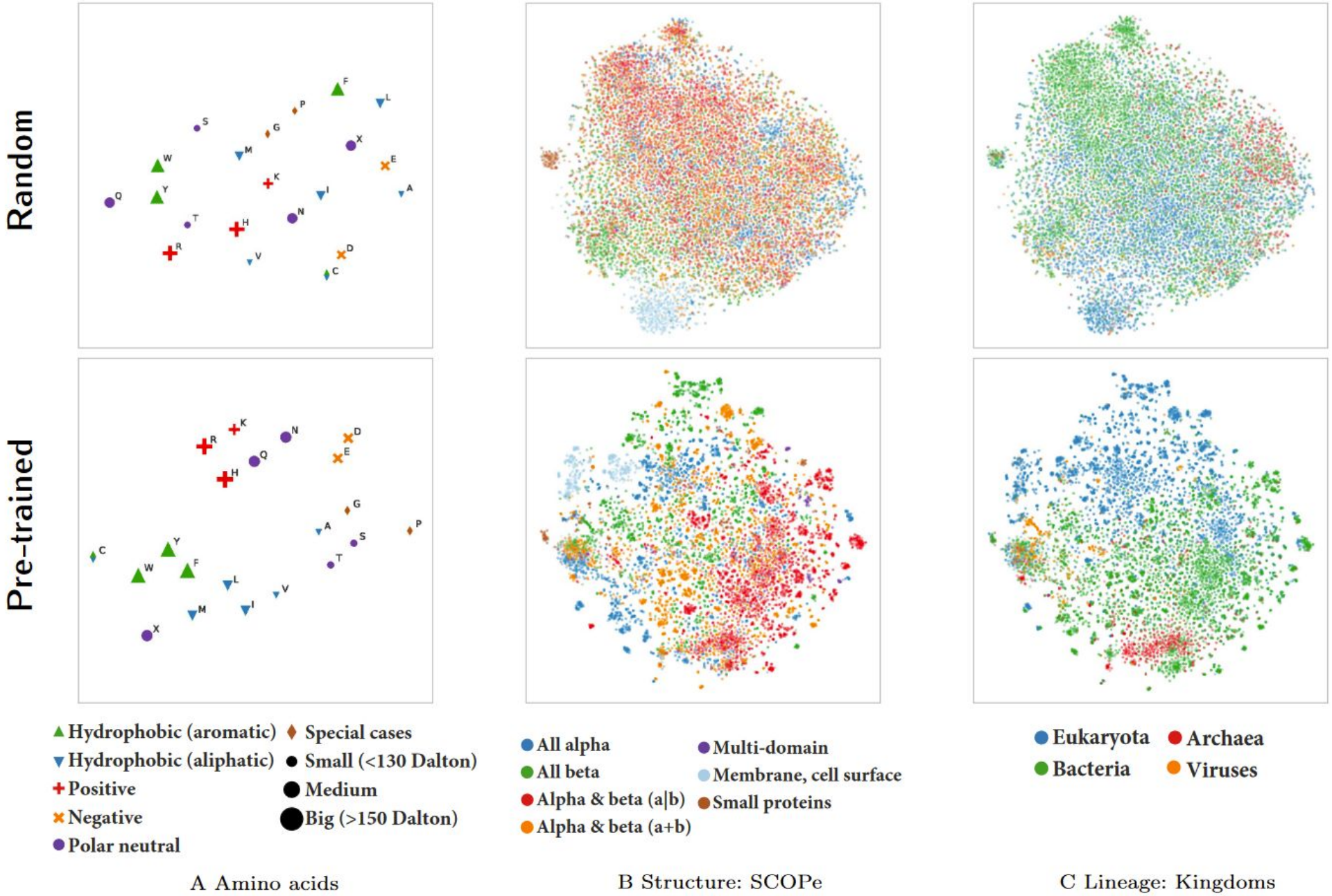
Next: We can train a simple model on these embeddings.

simple ML model

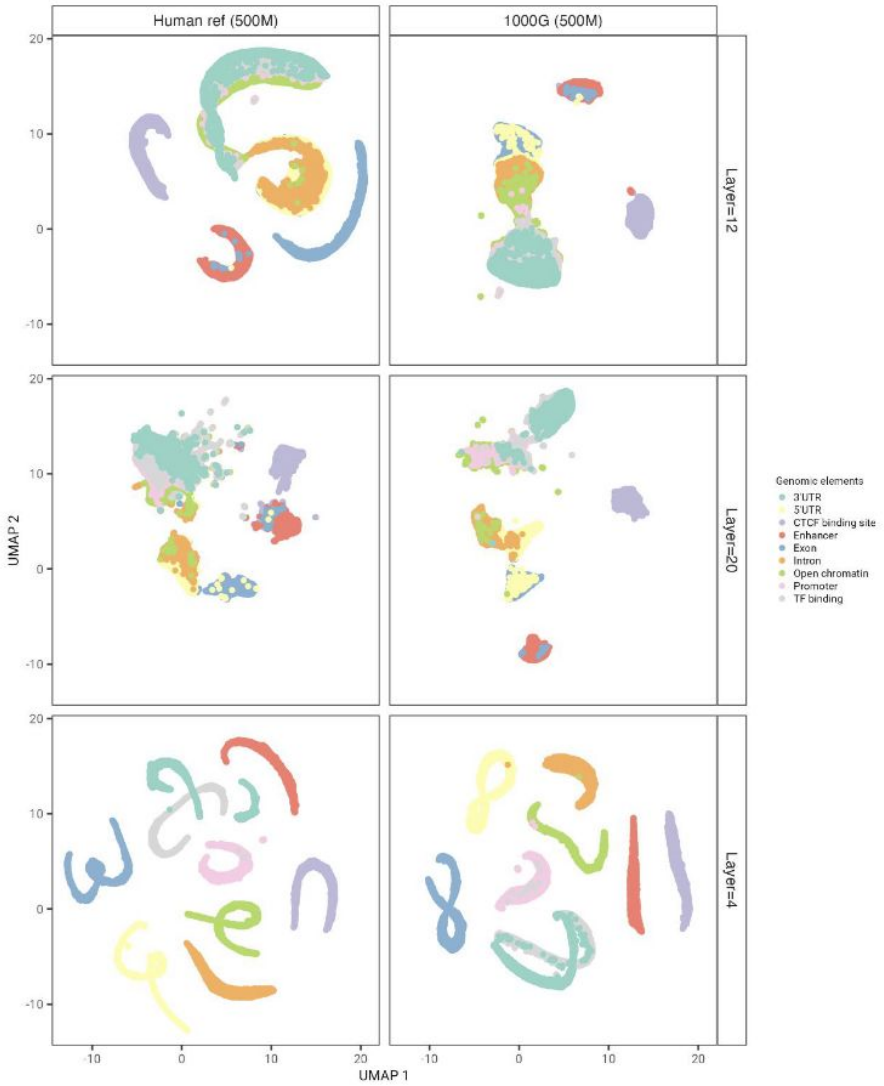
linear regression, decision tree, CNN, …



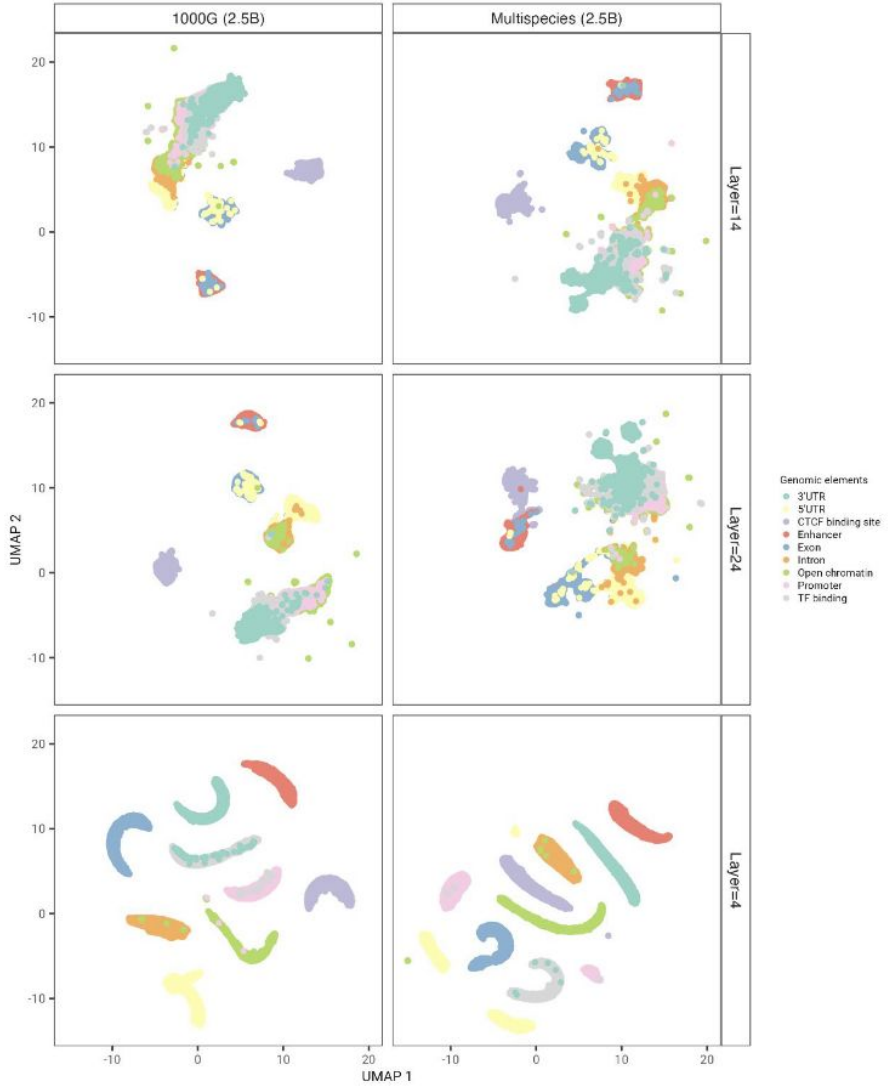
https://arxiv.org/ftp/arxiv/papers/2007/2007.06225.pdf

CEITEC The LLM is able to learn some biological+chemical properties of the amino acids [5]

Do the embeddings encode representations of the different genomic sequence features? [6]



Supplementary Figure 14: U-MAP projections of embeddings of nine regulatory elements from layers 4, 14 and 24 for the two Nucleotide Transformer 500M parameters models.

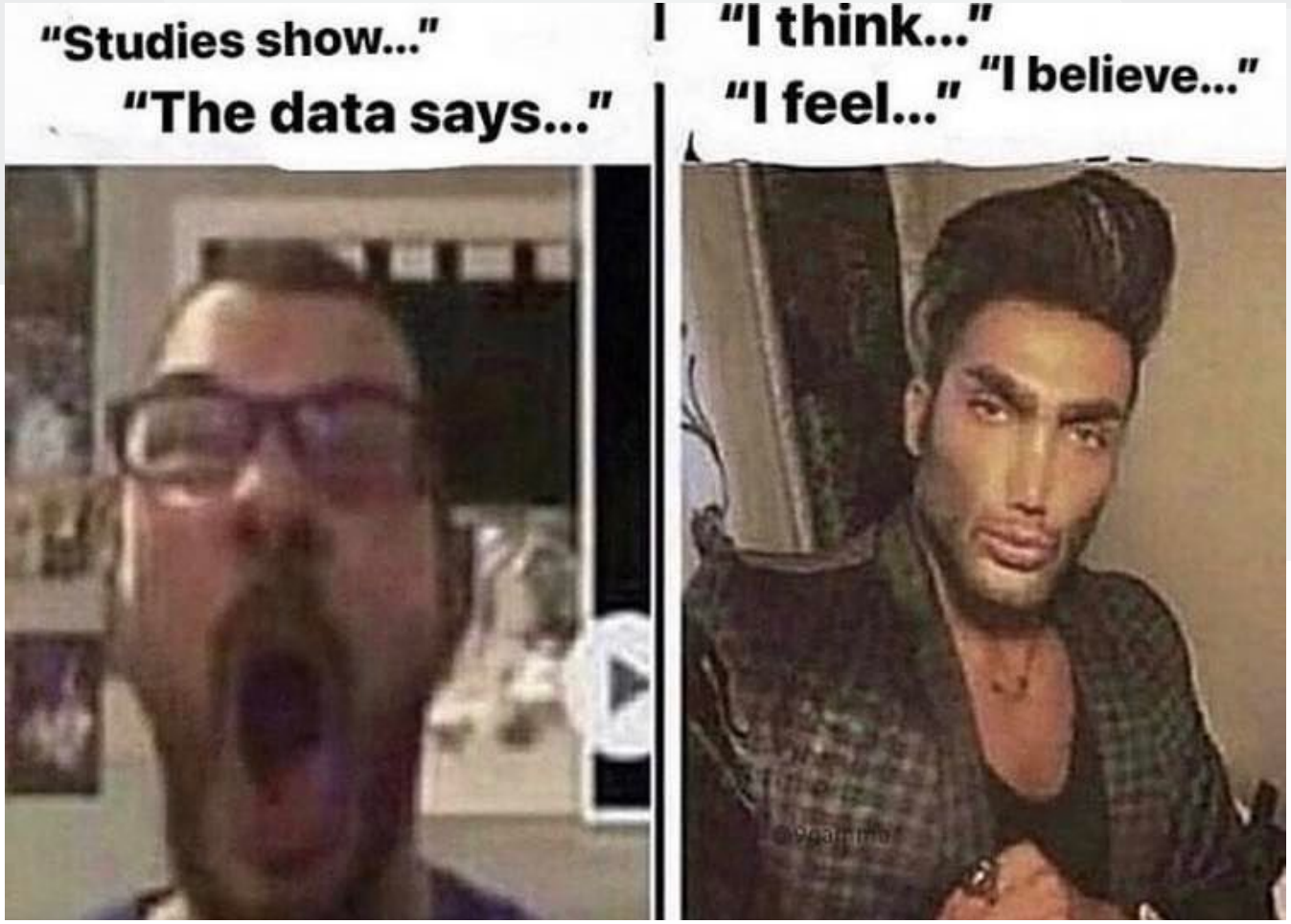


Supplementary Figure 13: U-MAP projections of embeddings of nine regulatory elements from layers 4, 14 and 24 for the two Nucleotide Transformer 2.5B parameters models.

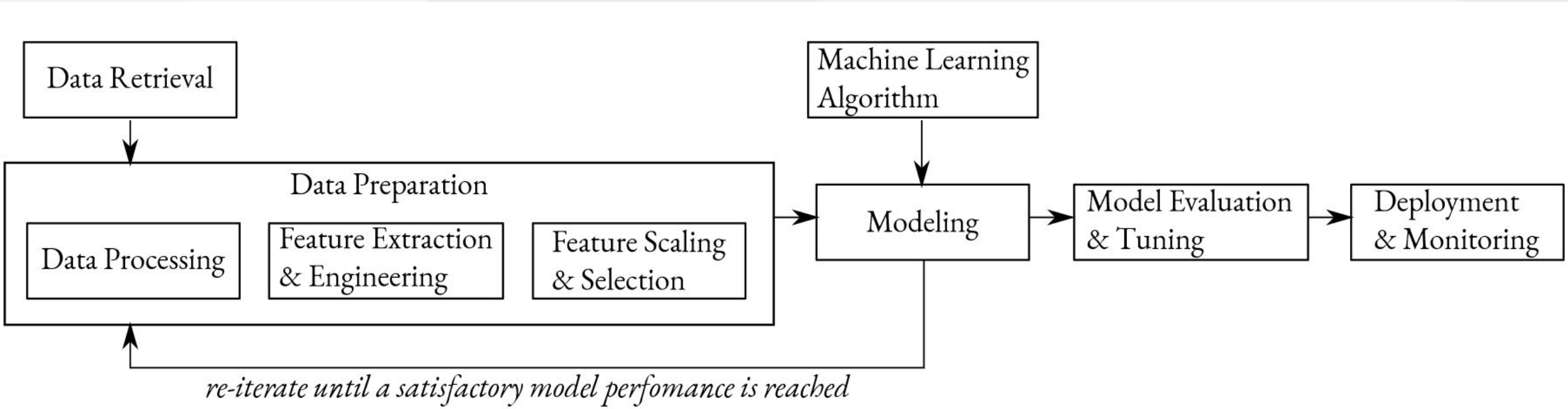
CEITEC

-> confirms layer specialization

30 minutes coffee break



Machine Learning pipeline



How can we preprocess sequence data?
What are the properties of ideal dataset?

Tokenizer

- divides text into smaller units (“tokens”)

1. Tokenization in NLP:

Tokenizer

- divides text into smaller units (“tokens”)

1. Tokenization in NLP:
   - word-level: “This sentence means nothing.” -> “This”, “sentence”, “means”, “nothing”

Tokenizer

- divides text into smaller units (“tokens”)

1. Tokenization in NLP:
- word-level: “This sentence means nothing.” -> “This”, “sentence”, “means”, “nothing”
- character-level: -> “T”, “h”, “i”, “s”, “s”, “e”, “n”, “t”, “e”, “n”, “c”, “e”, “m”, “e”, …

Tokenizer

- divides text into smaller units (“tokens”)

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- word-level: “This sentence means nothing.” -> “This”, “sentence”, “means”, “nothing”
- character-level: -> “T”, “h”, “i”, “s”, “s”, “e”, “n”, “t”, “e”, “n”, “c”, “e”, “m”, “e”, …
- subword-level: -> “This”, “sentence”, “mean”, “s”, “nothing”

Tokenizer

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   - subword-level: -> “This”, “sentence”, “mean”, “s”, “nothing”
2. Mapping tokens to integers:
   - dictionary (unique value for each token)

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   - character-level: -> “T”, “h”, “i”, “s”, “s”, “e”, “n”, “t”, “e”, “n”, “c”, “e”, “m”, “e”, …
   - subword-level: -> “This”, “sentence”, “mean”, “s”, “nothing”
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3. Dealing with different input lengths:
   - padding: adding special `[PAD]` token to the end of short sentences
   - truncation: cutting off ends of too long sentences

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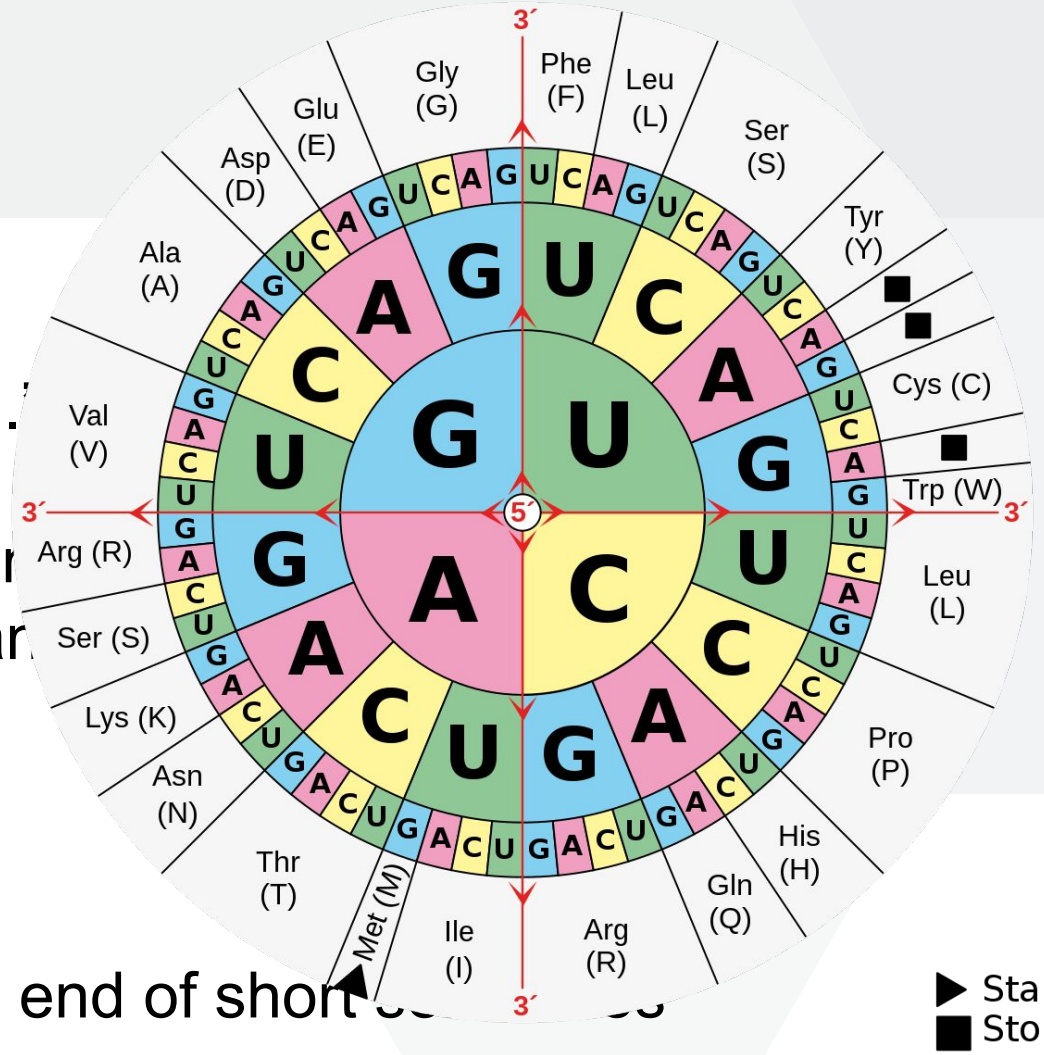
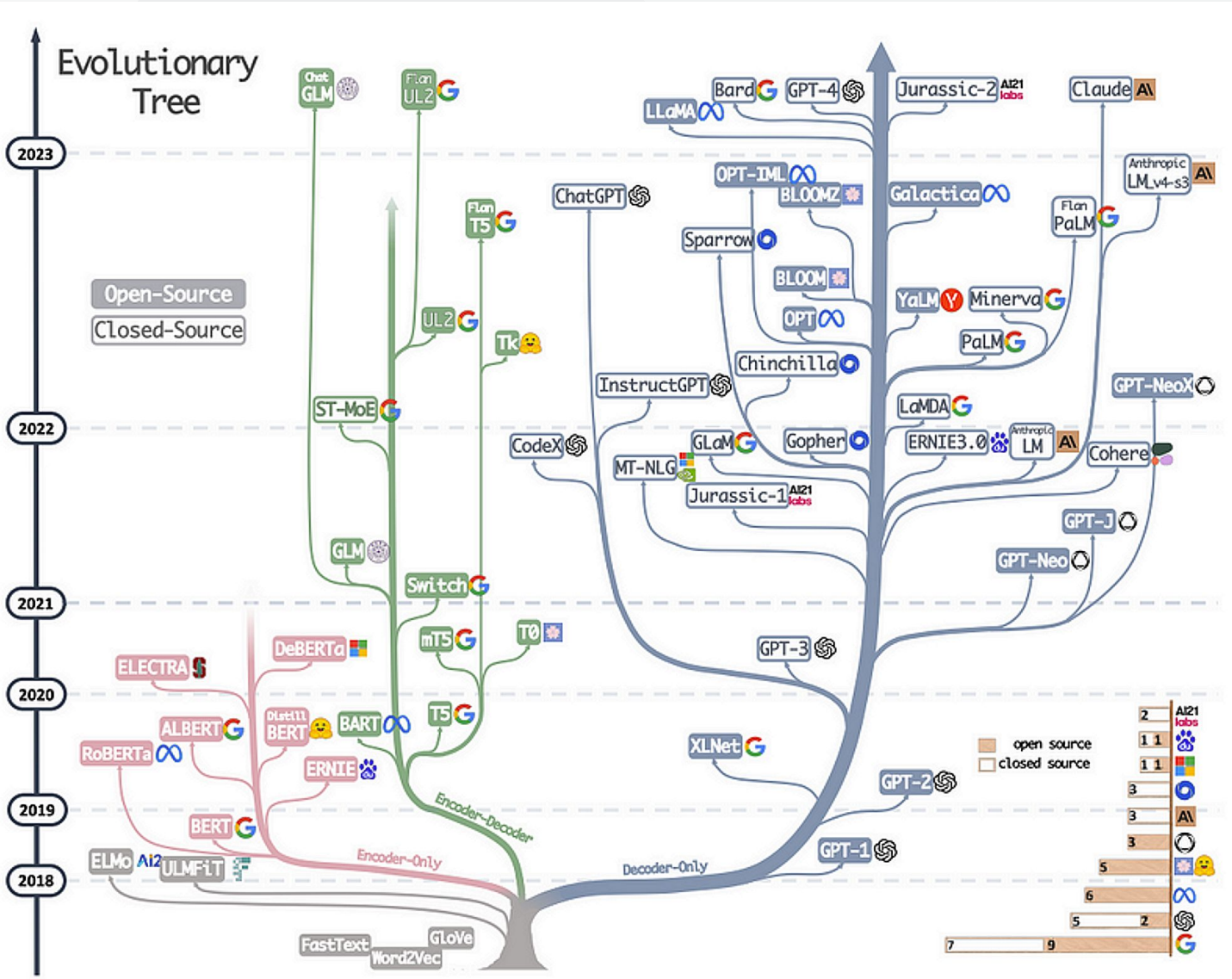
- divides text into smaller units (“tokens”)

1. Tokenization in NLP:
   - word-level: “This sentence means nothing.” -> “This”, “sentence”, “means”, “nothing”
   - character-level: -> “T”, “h”, “i”, “s”, “s”, “e”, “n”, “t”, “e”, “n”, “c”, “e”, “m”, “e”, “a”, “n”, “s”, “n”, “o”, “t”, “h”, “i”, “n”, “g”, “.”
   - subword-level: -> “This”, “sentence”, “mean”, “s”, “nothing”, “.”
2. Mapping tokens to integers:
   - dictionary (unique value for each token)
3. Dealing with different input lengths:
   - padding: adding special `[PAD]` token to the end of short sequences
   - truncation: cutting off ends of too long sentences



Large Language Models (LLMs)

Large Language Models

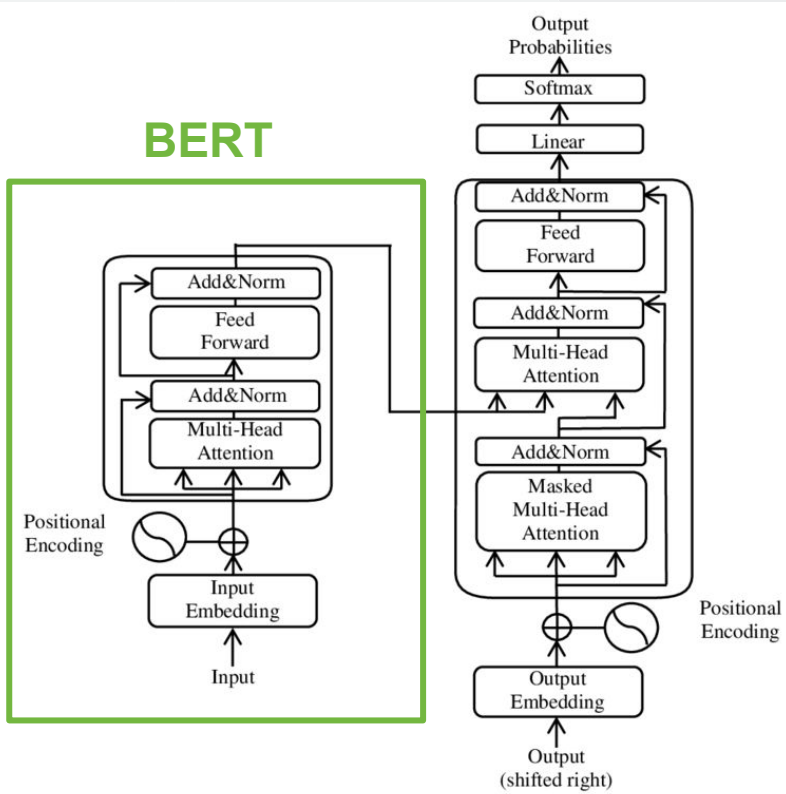


https://abiaryan.com/posts/intro-llms/

Transformer architecture [7]

- originally used in NLP (goal: understand not only single words, but also the context of those words)
- NLP tasks: translation, sentence classification, word classification, text generation, text summarization, extracting answers from text, …
- Encoder-Decoder architecture:
  Encoder: converts input to some numerical representation
  Decoder:optimized to generating outputs
  (originally designed for translation)

The most important mechanism: **Attention** == how important is each word in the input sequence.

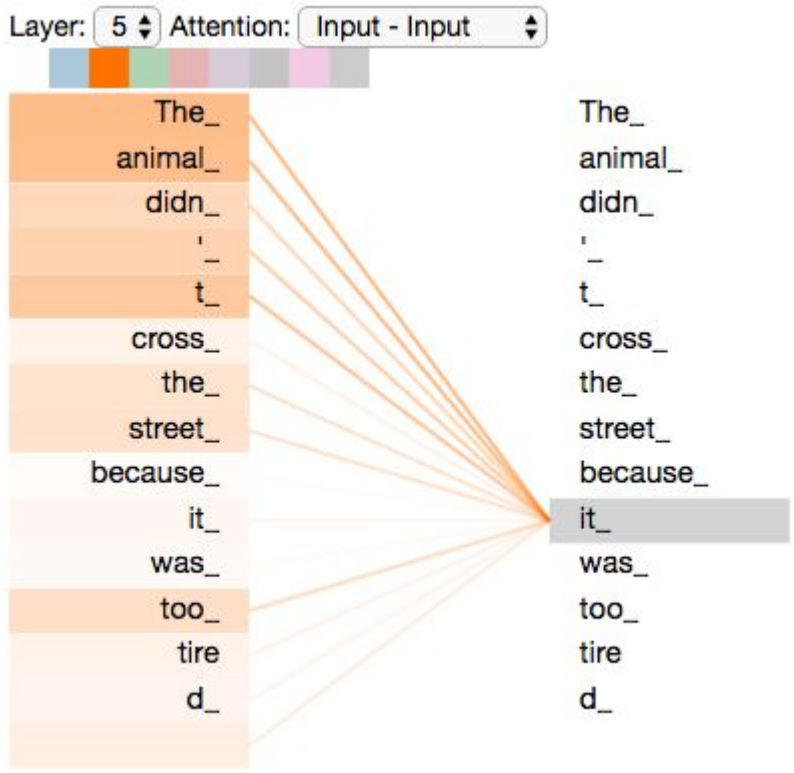


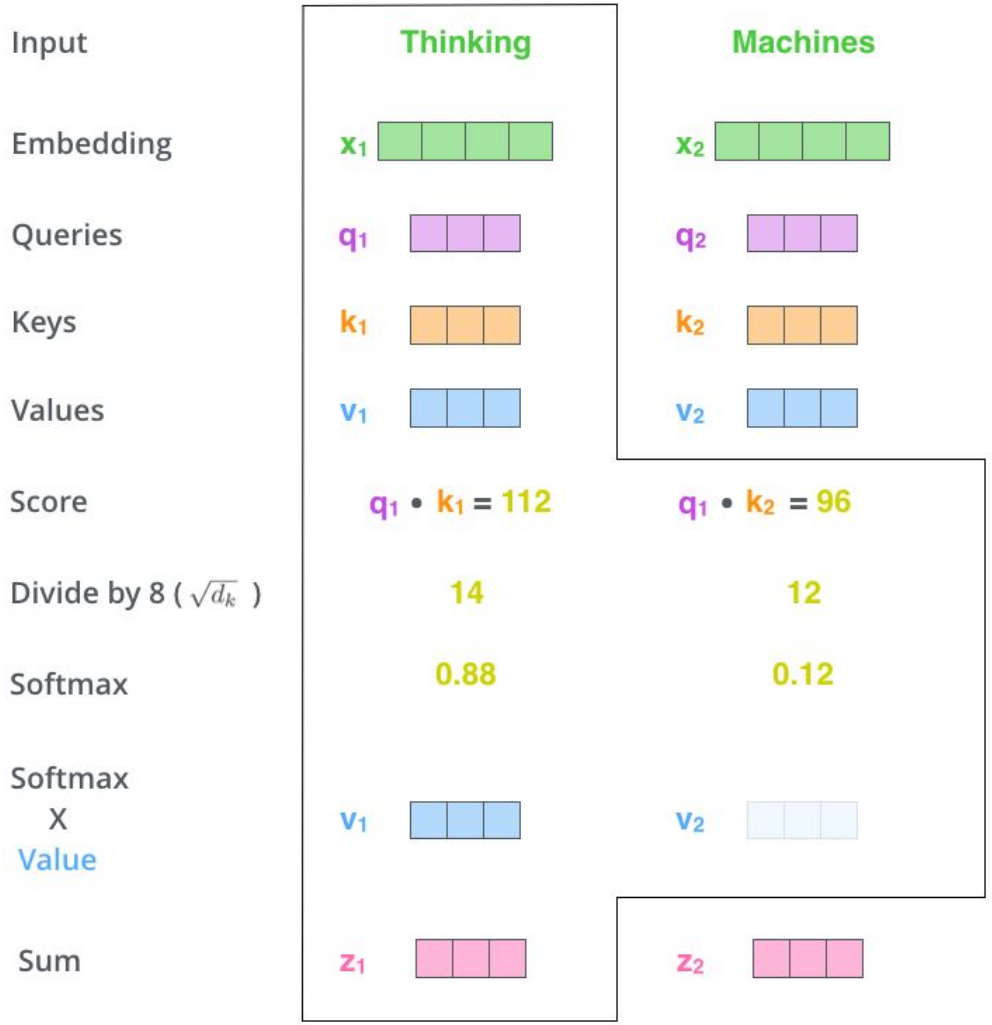
Attention Is All You Need

Ashish Vaswani* Google Brain avaswani@google.com
Noam Shazeer* Google Brain noam@google.com
Niki Parmar* Google Research nikip@google.com
Jakob Uszkoreit* Google Research usz@google.com
Llion Jones* Google Research llion@google.com
Aidan N. Gomez* † University of Toronto aidan@cs.toronto.edu
Łukasz Kaiser* Google Brain lukaszkaiser@google.com
Illia Polosukhin* ‡ illia.polosukhin@gmail.com

Transformers: Attention (http://jalammar.github.io/illustrated-transformer/)

$$\text{Attention}(Q, K, V) = \text{softmax}(\frac{QK^T}{\sqrt{d_k}})V$$





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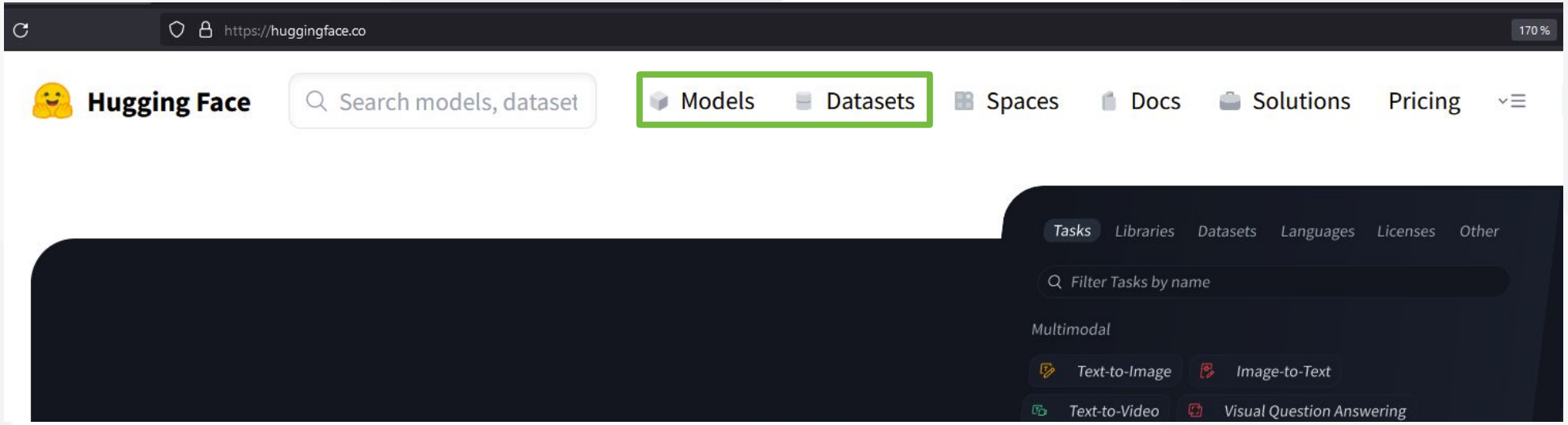
HuggingFace 🤗 (https://huggingface.co/)

- data science platform that provides tools to build, train and deploy ML models
- repository of models and datasets



HuggingFace 🤗 (https://huggingface.co/)

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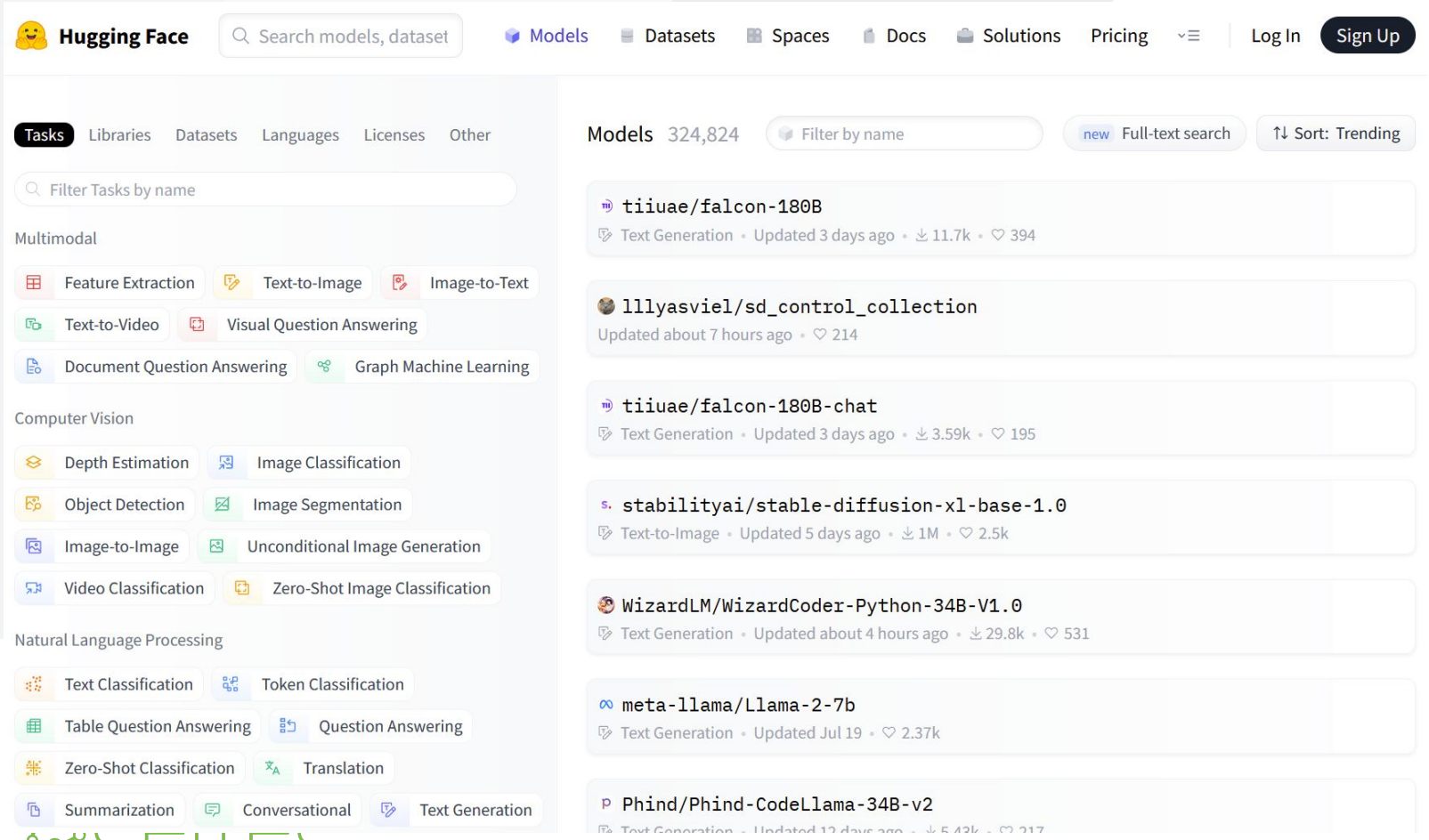

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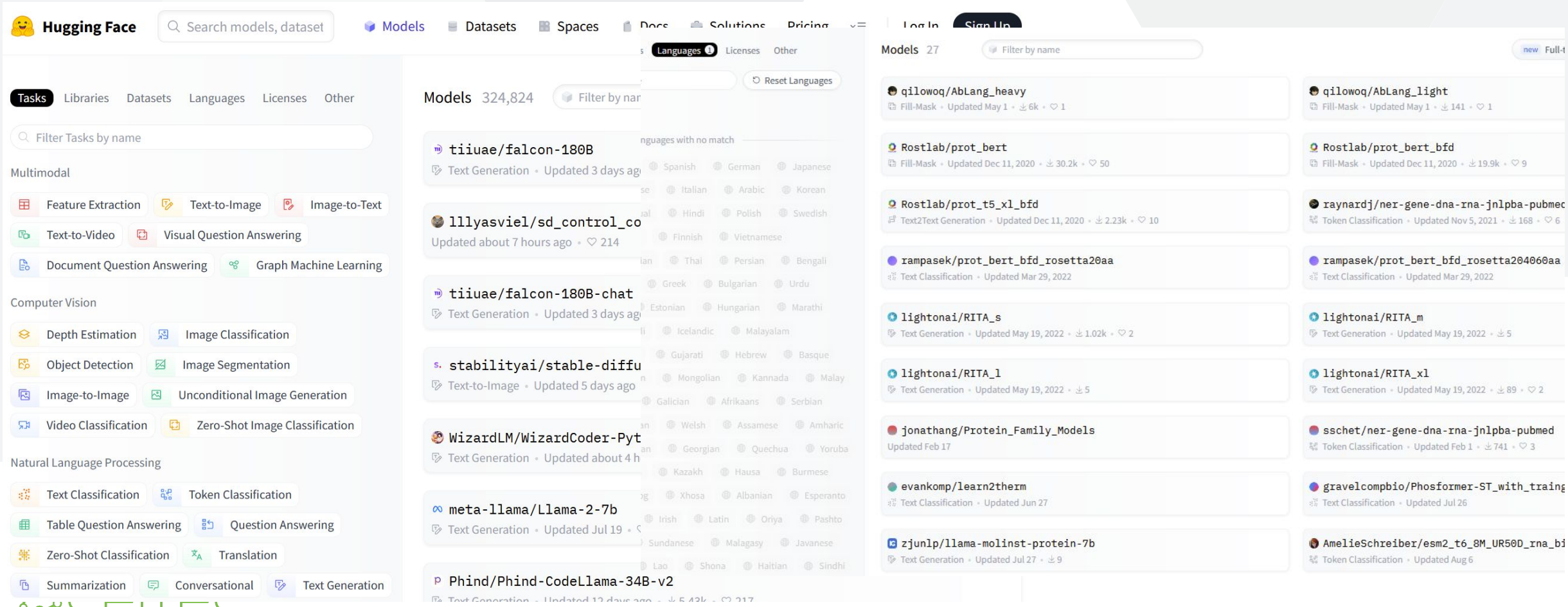

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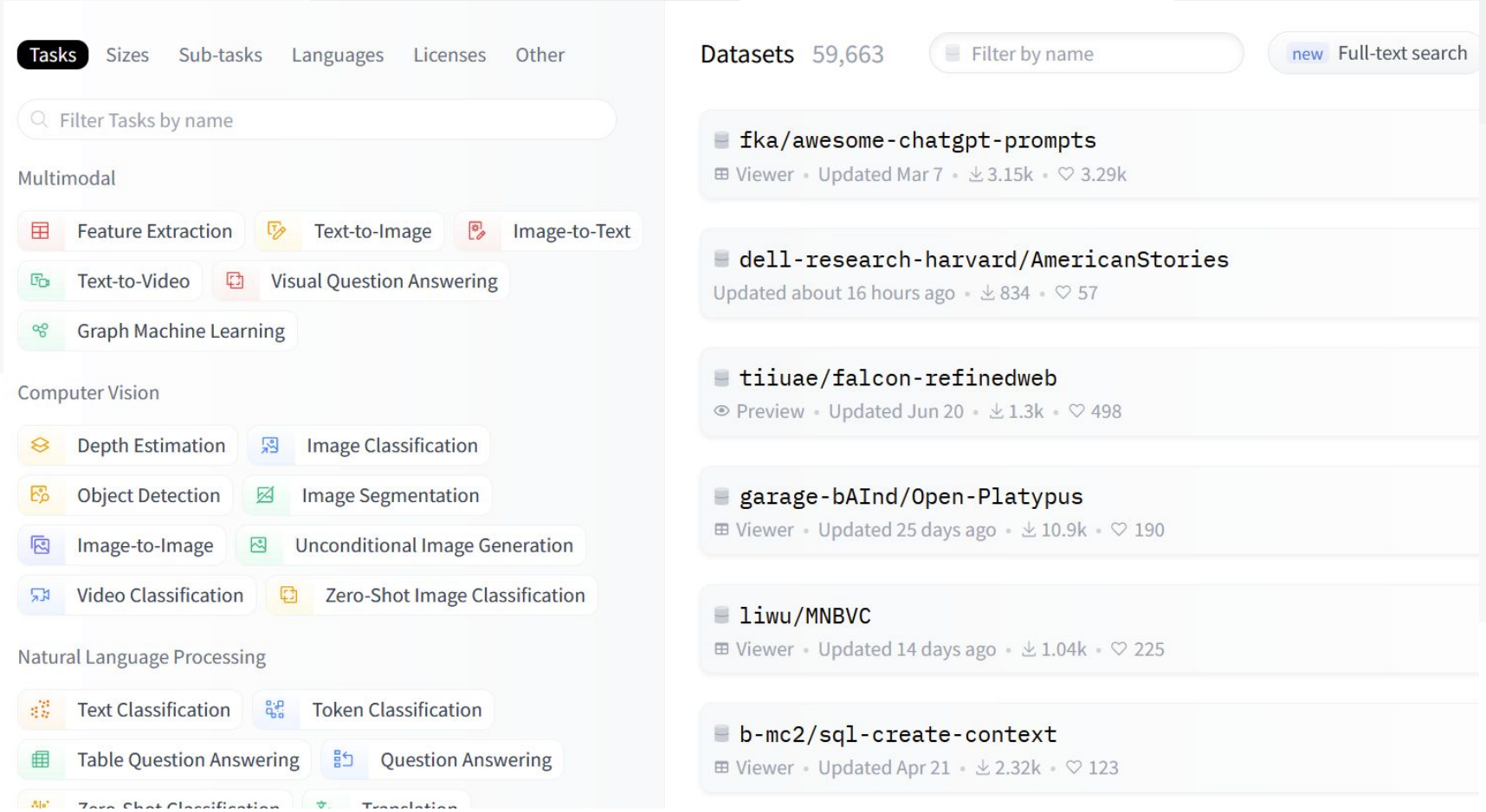
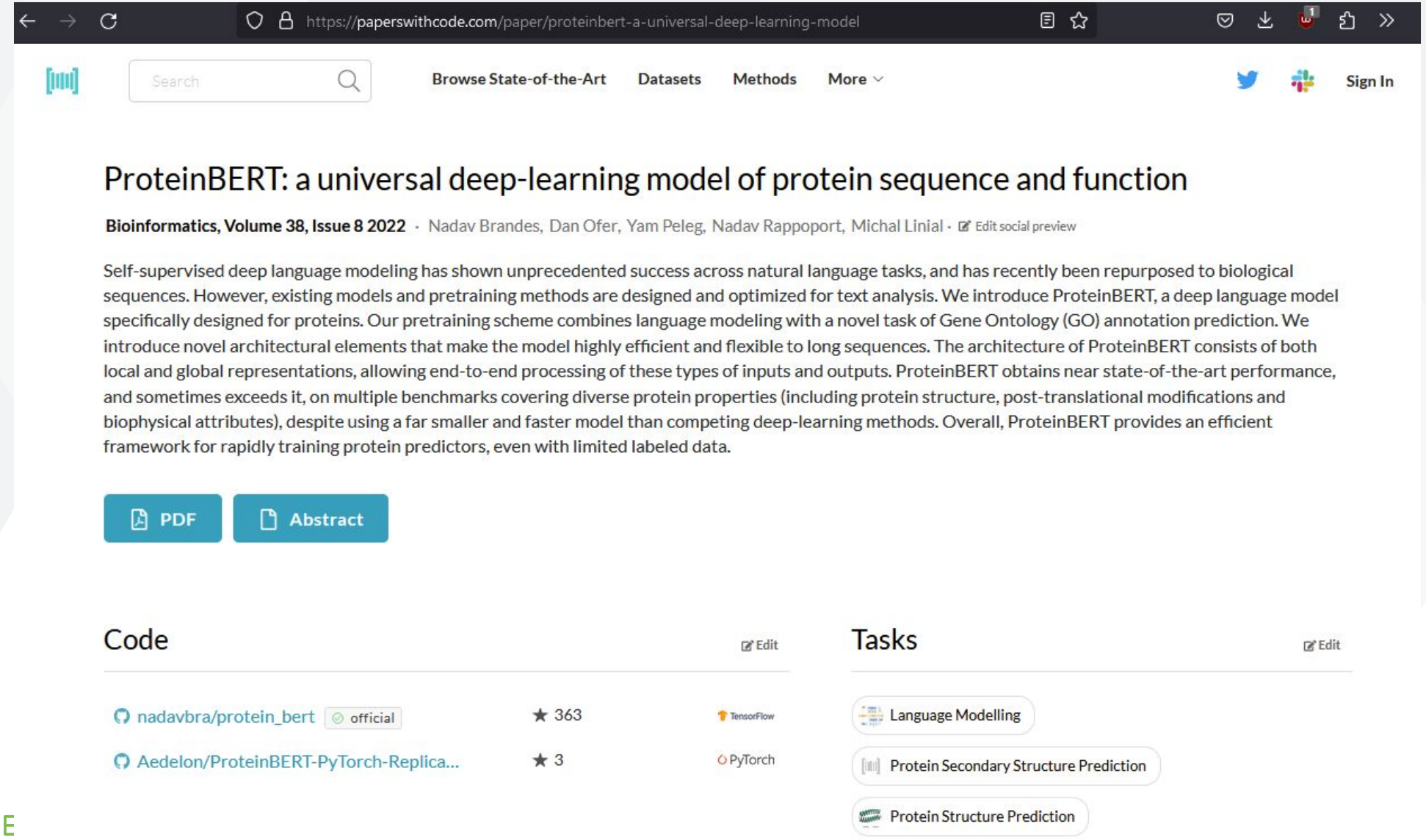


CEITEC

Reproducibility (https://paperswithcode.com/)



HuggingFace 🤗 (https://huggingface.co/)

Loading a Dataset:

```
from datasets import Dataset, load_dataset

dss = load_dataset('<USER_NAME>/<DATASET_NAME>')
dss
```

code cell

```
DatasetDict({
    test: Dataset({
        features: ['identifier', 'aa_sequence', 'length', 'label', 'family_name'],
        num_rows: 39412
    })
    train: Dataset({
        features: ['identifier', 'aa_sequence', 'length', 'label', 'family_name'],
        num_rows: 157644
    })
})
```

code cell output

HuggingFace 🤗 (https://huggingface.co

Pipelines

- objects that abstract complex code from the library

Parameters

- **task** (`str`) — The task defining which pipeline will be returned. Currently accepted tasks are:
  - `"audio-classification"`: will return a AudioClassificationPipeline.
  - `"automatic-speech-recognition"`: will return a AutomaticSpeechRecognitionPipeline.
  - `"conversational"`: will return a ConversationalPipeline.
  - `"depth-estimation"`: will return a DepthEstimationPipeline.
  - `"document-question-answering"`: will return a DocumentQuestionAnsweringPipeline.
  - `"feature-extraction"`: will return a FeatureExtractionPipeline.
  - `"fill-mask"`: will return a FillMaskPipeline:.
  - `"image-classification"`: will return a ImageClassificationPipeline.
  - `"image-segmentation"`: will return a ImageSegmentationPipeline.
  - `"image-to-text"`: will return a ImageToTextPipeline.
  - `"mask-generation"`: will return a `MaskGenerationPipeline`.
  - `"object-detection"`: will return a ObjectDetectionPipeline.
  - `"question-answering"`: will return a QuestionAnsweringPipeline.
  - `"summarization"`: will return a SummarizationPipeline.
  - `"table-question-answering"`: will return a TableQuestionAnsweringPipeline.
  - `"text2text-generation"`: will return a Text2TextGenerationPipeline.
  - `"text-classification"` (alias `"sentiment-analysis"` available): will return a TextClassificationPipeline.
  - `"text-generation"`: will return a TextGenerationPipeline:.
  - `"text-to-audio"` (alias `"text-to-speech"` available): will return a TextToAudioPipeline:.
  - `"token-classification"` (alias `"ner"` available): will return a TokenClassificationPipeline.
  - `"translation"`: will return a TranslationPipeline.
  - `"translation_xx_to_yy"`: will return a TranslationPipeline.
  - `"video-classification"`: will return a VideoClassificationPipeline.
  - `"visual-question-answering"`: will return a VisualQuestionAnsweringPipeline.
  - `"zero-shot-classification"`: will return a ZeroShotClassificationPipeline.
  - `"zero-shot-image-classification"`: will return a ZeroShotImageClassificationPipeline.
  - `"zero-shot-audio-classification"`: will return a ZeroShotAudioClassificationPipeline.
  - `"zero-shot-object-detection"`: will return a ZeroShotObjectDetectionPipeline.
- **model** (`str` or PreTrainedModel or TFPreTrainedModel, *optional*) — The model that will be used by the pipeline to make predictions. This can be a model identifier or an actual instance of a pretrained model inheriting from PreTrainedModel (for PyTorch) or TFPreTrainedModel (for TensorFlow).

HuggingFace 🤗 (https://huggingface.co/)

Using a Model (+ Tokenizer in a Pipeline) for prediction:

```
from transformers import AutoTokenizer, AutoModelForSequenceClassification, TextClassificationPipeline

tokenizer = AutoTokenizer.from_pretrained(MODEL_NAME, do_lower_case=False)
model = AutoModel.from_pretrained(MODEL_NAME, num_labels=2)
pipe = TextClassificationPipeline(model=model, tokenizer=tokenizer, return_all_scores=True)
```

On 1 sequence:

```
pipe('DENCADENCA')
```

```
[[{'label': 'LABEL_0', 'score': 0.5323733687400818},
  {'label': 'LABEL_1', 'score': 0.4676266014575958}]]
```

Or on the whole Dataset:

```
def tokenize_function(examples):
    return tokenizer(' '.join(list(examples['seq'])))
tokenized_dss = dss.map(tokenize_function, num_proc=4)
results = pipe(tokenized_dss['test']['seq'])
```

Case study: Protein knots

(https://topoly.cent.uw.edu.pl/)

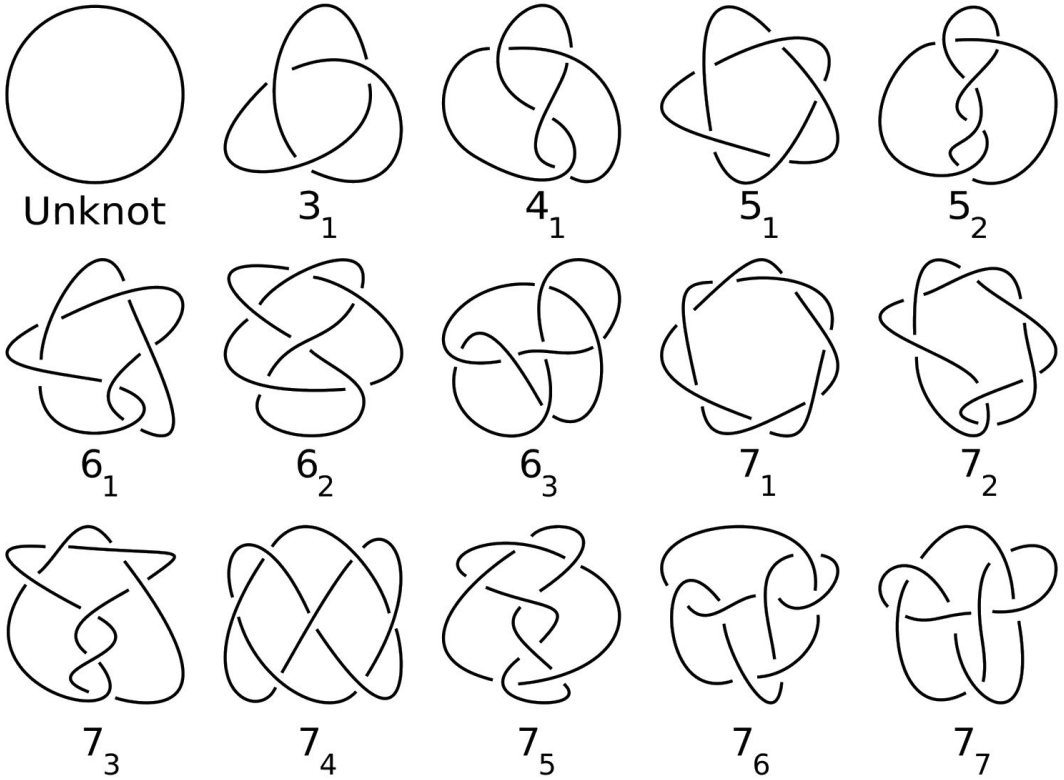
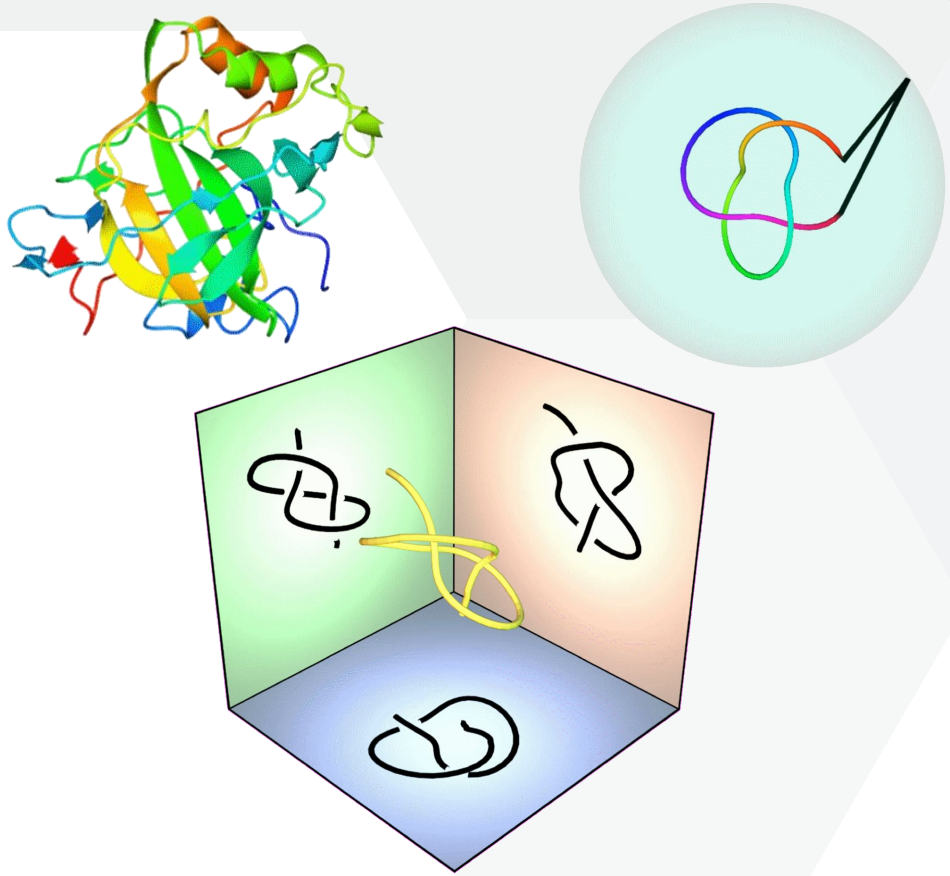


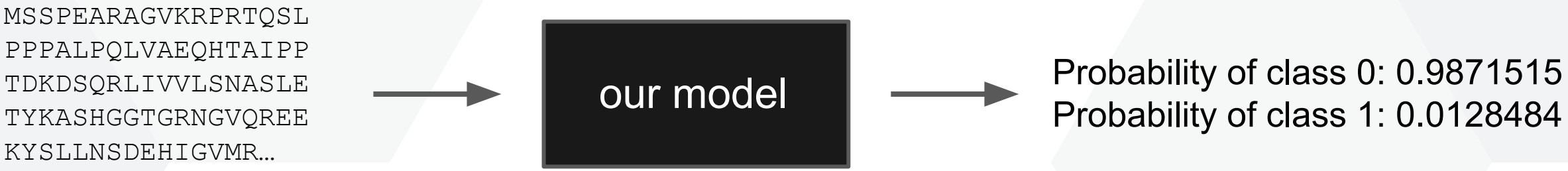
Figure "Prime Knots with seven or less crossings" source: https://en.wikipedia.org/wiki/File:Knot_table.svg (accessed: 12.12.2022)



https://www.nature.com/articles/srep42300

Our Approach

The simplified problem we are trying to solve: **for a given protein sequence*** (string of amino acids) **decide whether it is knotted or unknotted** *(== binary classification)*.



*no additional information (MSA, tertiary or quaternary structure) is provided to the model!

Our Approach

The simplified problem we are trying to solve: **for a given protein sequence*** (string of amino **otted** *(== binary classification)*.

```
MSSPEARAGVKRPRTQSL
PPPALPQLVAEQHTAIPP
TDKDSQRLIVVLSNASLE
TYKASHGGTGRNGVQREE
KYSLLNSDEHIGVMR...
```

of class 0: 0.9871515
of class 1: 0.0128484

Knot or Not? Sequence-Based Identification of Knotted Proteins With Machine Learning

Denisa Šrámková*,[†,‡] Maciej Sikora*,[¶,§] Dawid Uchal,[¶,‖] Eva Klimentová,[‡,†] Agata P. Perlinska,[¶] Mai Lan Nguyen,[¶] Marta Korpacz,[¶,§] Roksana Malinowska,[¶,§] Pawel Rubach,[¶,⊥] Petr Šimeček,[‡] and Joanna I. Sulkowska*,[¶]

†*National Centre for Biomolecular Research, Faculty of Science, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic*

‡*Central European Institute of Technology, Masaryk University, Brno, 62500, Czech Republic*

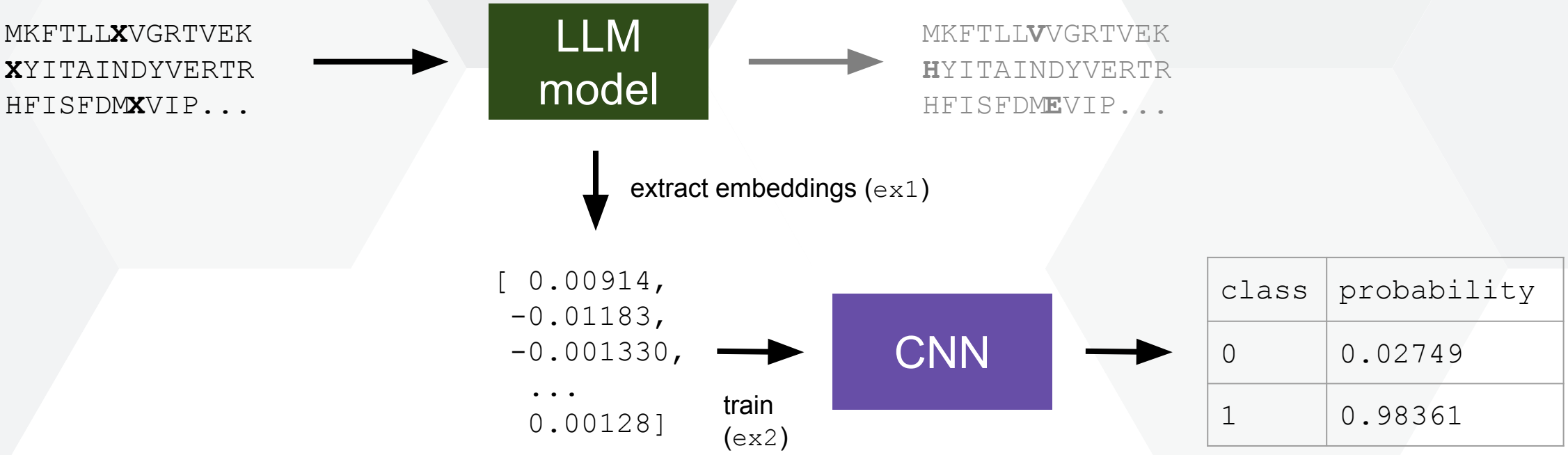
**no additional information (MSA, tertiary or quaternary structure) is provided to the model!*

Exercise

HuggingFace basics - `maltaomics_ex0_huggingface.ipynb`

Exercises

Extracting ProtBert-BFD embeddings - `maltaomics_ex1_embedding_extraction.ipynb`
Training a CNN classifier on top of the embeddings - `maltaomics_ex2_embedding_training.ipynb`



Drawbacks of using embeddings

```
[ 0.00914,
 -0.01183,
 -0.001330,
   ...
  0.00128]
```

simple ML model

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But why?

Drawbacks of using embeddings

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   ...
  0.00128]
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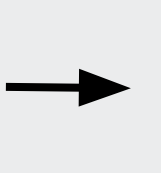

simple ML model

class	probability
0	0.02749
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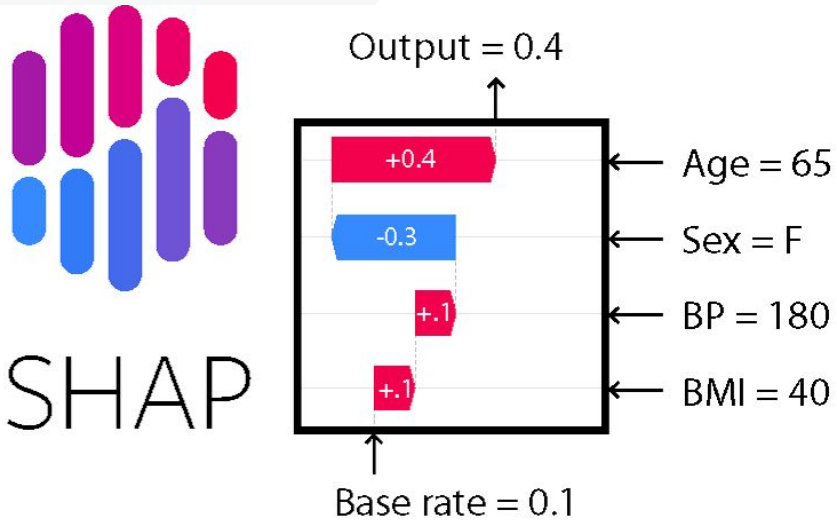
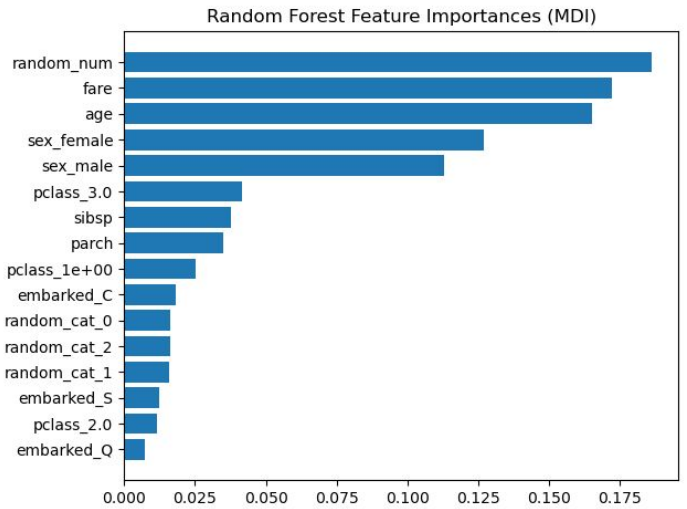
very good

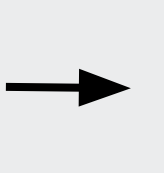
But why?





Drawbacks of using embeddings

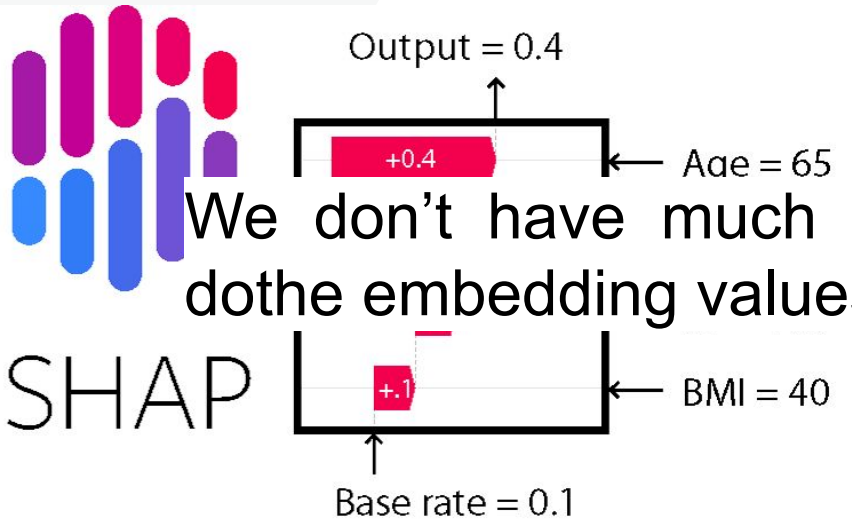
```
[ 0.00914,
 -0.01183,
 -0.001330,
  ...
  0.00128]
```



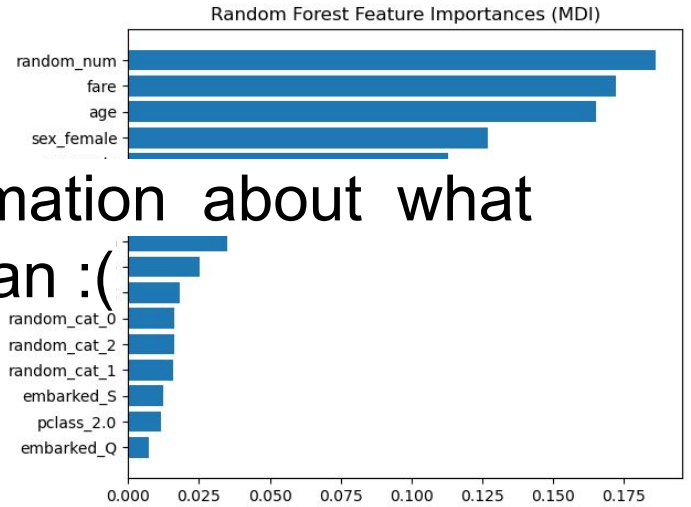
class	probability
0	0.02749
1	0.98361

very good

But why?



We don't have much information about what dothe embedding values mean :(



HuggingFace 🤗 (https://huggingface.co/)

Finetuning a Model:

```
from transformers import AutoTokenizer, AutoModelForSequenceClassification, Trainer,
TrainingArguments

tokenizer = AutoTokenizer.from_pretrained(MODEL_NAME, do_lower_case=False)
model = AutoModel.from_pretrained(MODEL_NAME)

trainer = Trainer(
    model,
    training_args,
    train_dataset=tokenized_dss['train'],
    eval_dataset=tokenized_dss['test'],
    tokenizer=tokenizer,
    compute_metrics=compute_metrics
)
trainer.train()
```

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    tokenizer=tokenizer,
    compute_metrics=compute_metrics
)
trainer.train()
```

```
training_args = TrainingArguments(
    output_dir='<OUTPUT_DIR_PATH>',
    learning_rate=1e-5,
    num_train_epochs=1,
    weight_decay=0.01,
    optim='adafactor'
    ...)
```

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HuggingFace 🤗 (https://huggingface.co/)

Finetuning a Model:

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from transformers import AutoTokenizer, AutoModelForSequenceClassification, Trainer,
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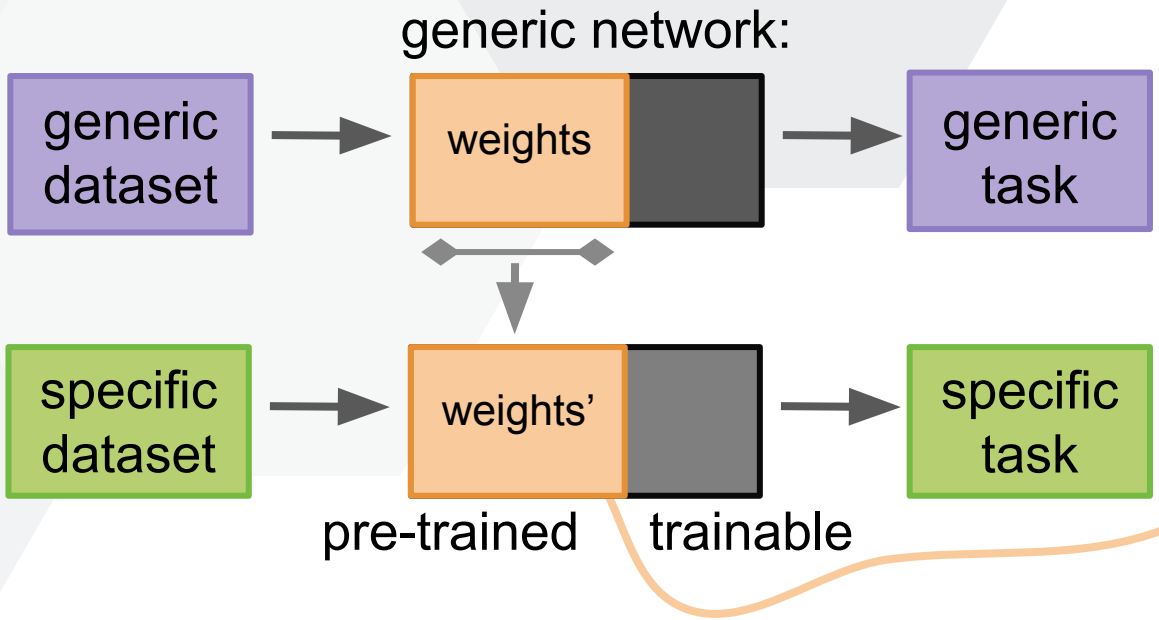
    tokenizer=tokenizer,
    compute_metrics=compute_metrics
)
trainer.train()
```

```
from sklearn.metrics import accuracy_score


def compute_metrics(eval_preds):
  metric = evaluate.load('precision')
  logits, labels = eval_preds
  predictions = np.argmax(logits, axis=-1)
  return {'accuracy': accuracy_score(labels,
                                     preds)
          }
```

Exercise

Finetuning a ProtBert-BFD model - `maltaomics_ex3_finetuning.ipynb`



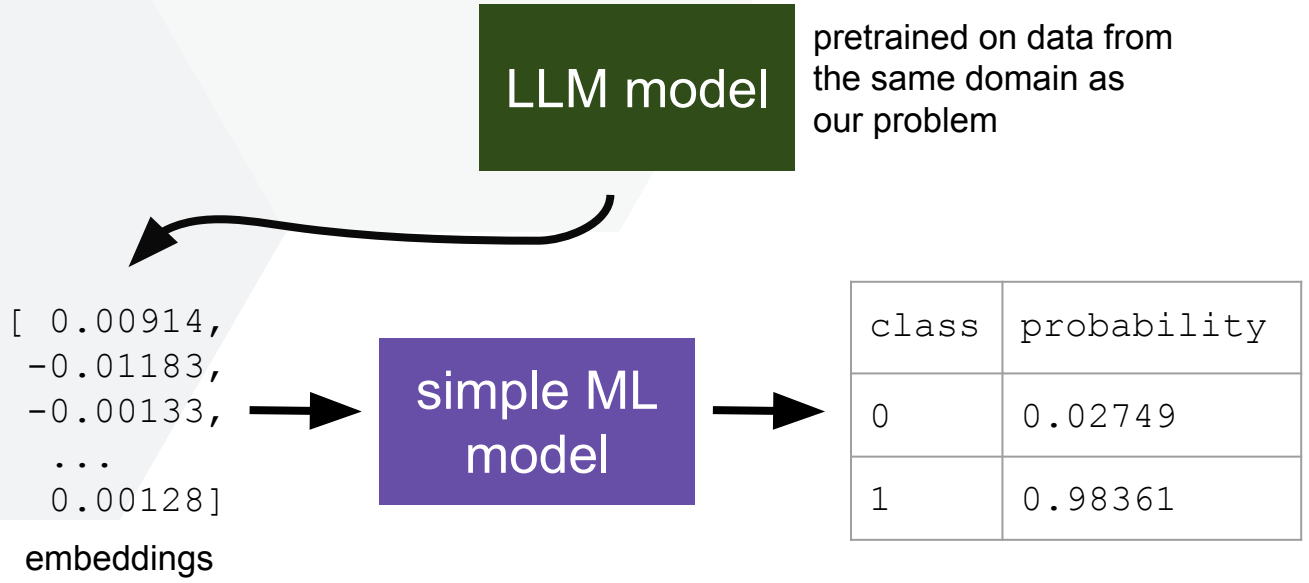
DistilProtBERT originally trained for distinguishing between real proteins and their randomly shuffled counterparts.
ProtBert-BFD on masked language modelling

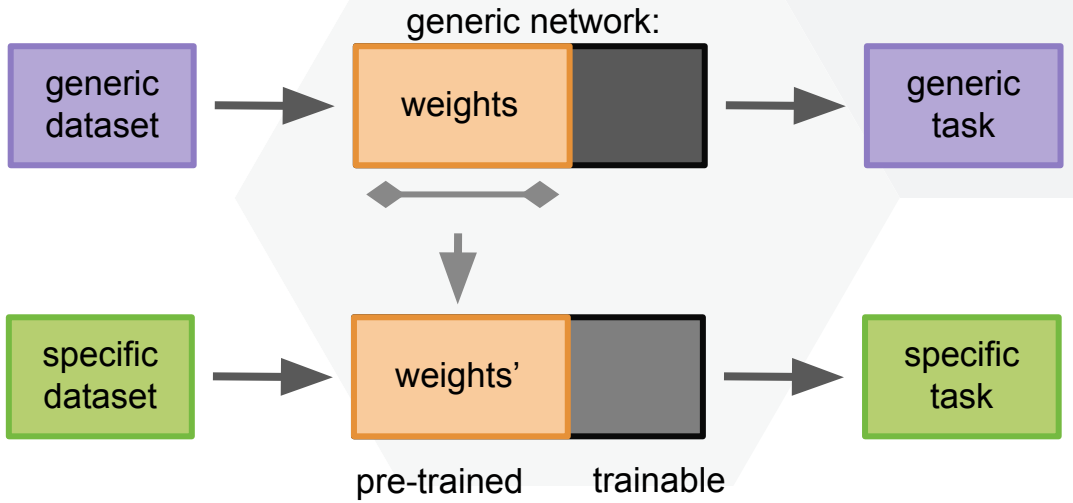
Finetuning == approach to transfer learning in which weights of pre-trained model are trained on new data

- can be done on entire neural network, or on subset of its layers (other layers are “frozen”)

Summary

- we should get as much from already existing solutions as possible
- when we are solving protein structure problems it is possible to work only with amino acid sequences
- **2 approaches:**





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