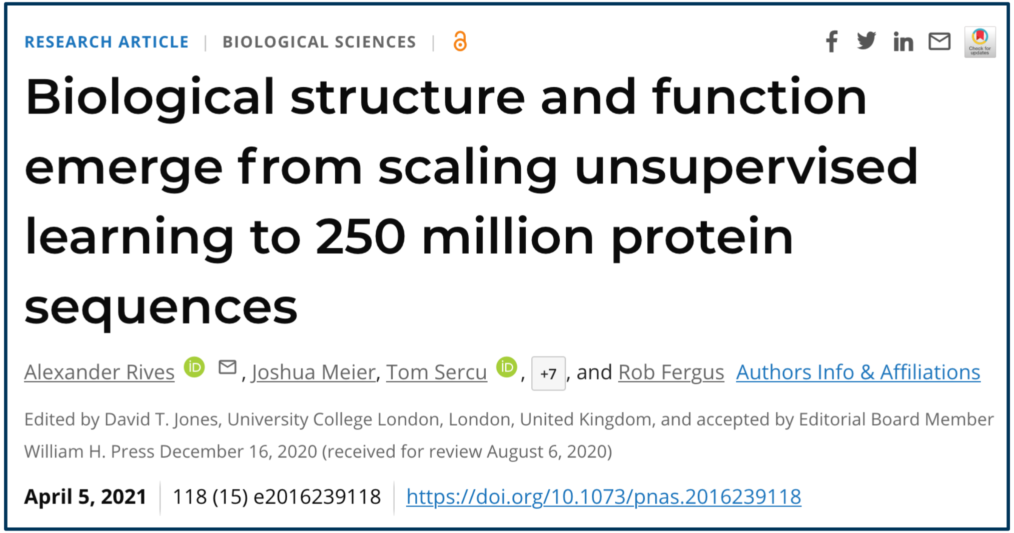
The ESM-1b Transformer Network

What is the ESM-1b Transformer Network?



RESEARCH ARTICLE | BIOLOGICAL SCIENCES |

Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences

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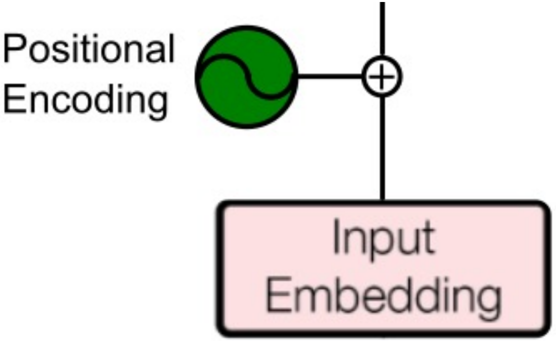
- Open-Source protein language model by the Facebook AI research team
- Architecture: Transformer Network Encoder
- Training for Masked Language Modeling (MLM)

Rives, A., Meier, J., Sercu, T., Goyal, S., Lin, Z., Liu, J., ... & Fergus, R. (2021). *PNAS*, *118*(15), e2016239118.

ESM-1b Architecture – Input Embeddings

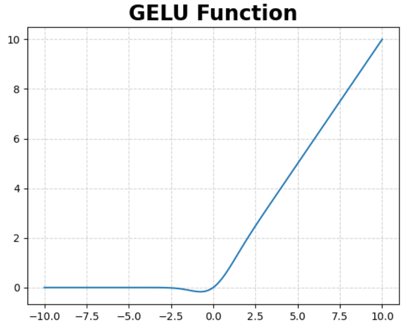
- Token embeddings are learned with a dimension of $d = 1280$
- Sinusoidal positional encodings were compared to learned positional encodings:
  - Learned positional embeddings led to better results
- How can we learn token (and positional) embeddings?

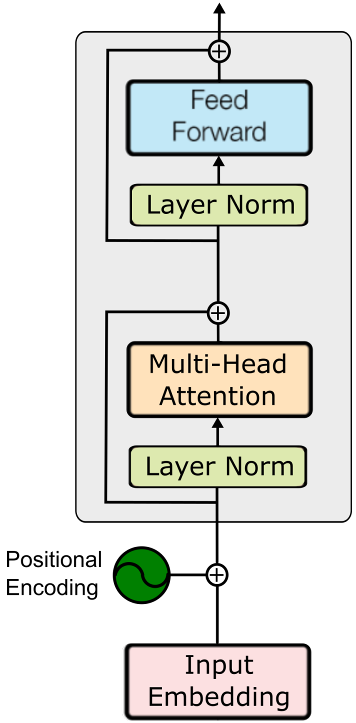
$$\begin{pmatrix} w_{1,1} & \cdots & w_{1,1280} \\ \vdots & \ddots & \vdots \\ w_{23,1} & \cdots & w_{23,1280} \end{pmatrix} \begin{pmatrix} 0 \\ 1 \\ \vdots \\ 0 \end{pmatrix} = \begin{pmatrix} w_{2,1} \\ w_{2,2} \\ \vdots \\ w_{2,1280} \end{pmatrix}$$



ESM-1b Architecture – Encoder

- Each encoder layer
  - Dimension of representations $d = 1280$
  - Number of attention heads $h = 20$
  - Maximum sequence length: 1024
  - Hidden dimension of FFN: $5120\ (4 \cdot d)$
- 33 encoder layers: $652.4\ M$ learnable parameters
- Layer Normalization before Attention and FFN block
- Activation of Feed Forward Neural Network:
  GELU instead of ReLU





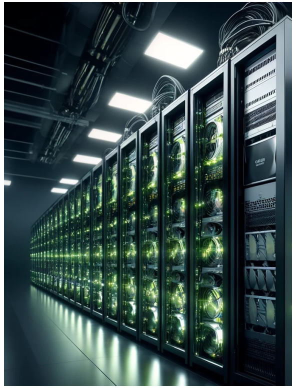
GELU: medium.com/@gauravnair :“The Spark Your Neural Network Needs“; Modified figure from: Vaswani, A., et al. (2017). Attention is all you need.

ESM-1b Training

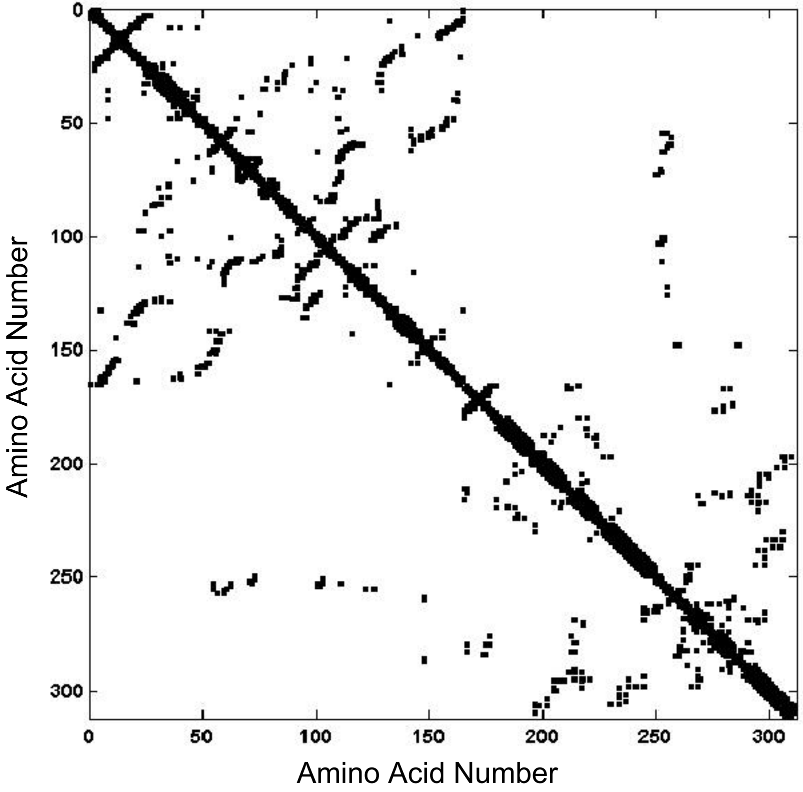
- Training task: Masked Language Modeling (MLM)

A	L	?	A	…	A

  - Randomly select 15% of the input tokens that shall be predicted: Of these:
    - 80% are replaced with the mask token
    - 10% are placed with a random amino acid
    - 10% are not changed
- Training dataset: UniRef50 dataset with $\sim 30M$ protein sequences
- Training time: ~20 days of 64 NVIDIA V100 GPUs
  - Each epoch took 8.5 hours
  - 56 epochs in total



Applications – Contact Map Prediction



- Protein contact maps
  - Black dots indicate which amino acids are close to each other in the protein 3D structure
- Predicting Contact Maps using amino acid representations shows learned structural information
  - Binary prediction problem:
    - Let h_i and h_j be the representations of amino acids i and j
    - $f(h_i, hj) = sigmoid(< P \cdot h_i, Q \cdot h_j > \ +b) \in [0,1]$

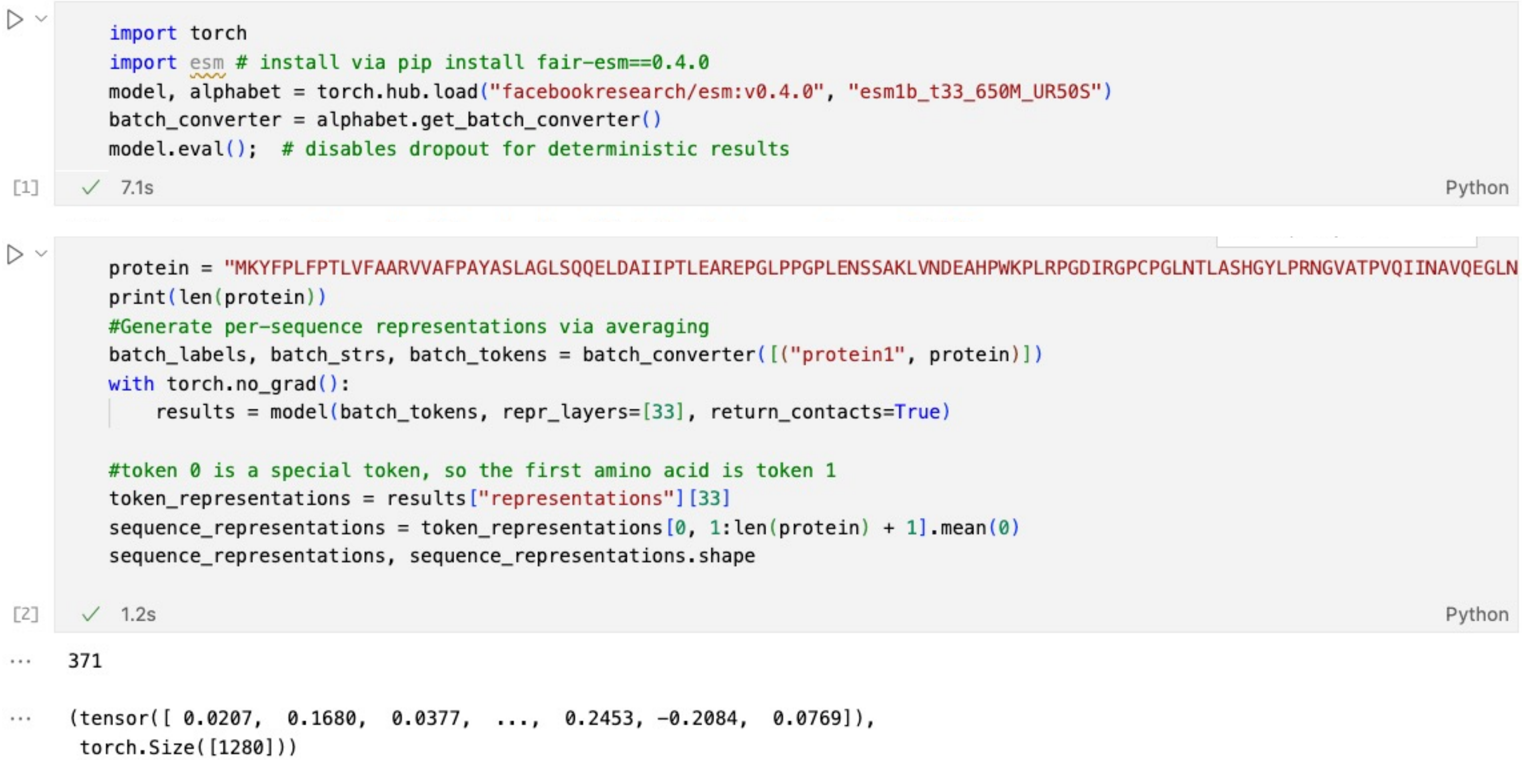
Image source: Ramanathan, A et al. (2008). *Using tensor analysis to characterize contact-map dynamics of proteins* (PhD thesis)

Applications – Function Prediction

- ESM-1b vectors (whole protein representations) have been successfully used for all kinds of protein function predictions:
  - Enzyme functions
  - Substrates for transport proteins
  - Protein-Protein interactions
  - Drugs inhibiting proteins
  - …
- To solve these prediction tasks, the ESM-1b vectors $\vec{e}$ (element-wise mean of all amino acid representations) are used as the input of new prediction models

$$f(\vec{e}) = y$$

How to use the model



```
import torch
import esm # install via pip install fair-esm==0.4.0
model, alphabet = torch.hub.load("facebookresearch/esm:v0.4.0", "esm1b_t33_650M_UR50S")
batch_converter = alphabet.get_batch_converter()
model.eval();  # disables dropout for deterministic results
```

```
protein = "MKYFPLFPTLVFAARVVAFPAYASLAGLSQQELDAIIPTLEAREPGLPPGPLENSSAKLVNDEAHPWKPLRPGDIRGPCPGLNTLASHGYLPRNGVATPVQIINAVQEGLN
print(len(protein))
#Generate per-sequence representations via averaging
batch_labels, batch_strs, batch_tokens = batch_converter([("protein1", protein)])
with torch.no_grad():
    results = model(batch_tokens, repr_layers=[33], return_contacts=True)

#token 0 is a special token, so the first amino acid is token 1
token_representations = results["representations"][33]
sequence_representations = token_representations[0, 1:len(protein) + 1].mean(0)
sequence_representations, sequence_representations.shape
```

```
371
```

```
(tensor([ 0.0207,  0.1680,  0.0377,  ...,  0.2453, -0.2084,  0.0769]),
 torch.Size([1280]))
```

Code copied from https://github.com/facebookresearch/esm

Other Protein Language Models

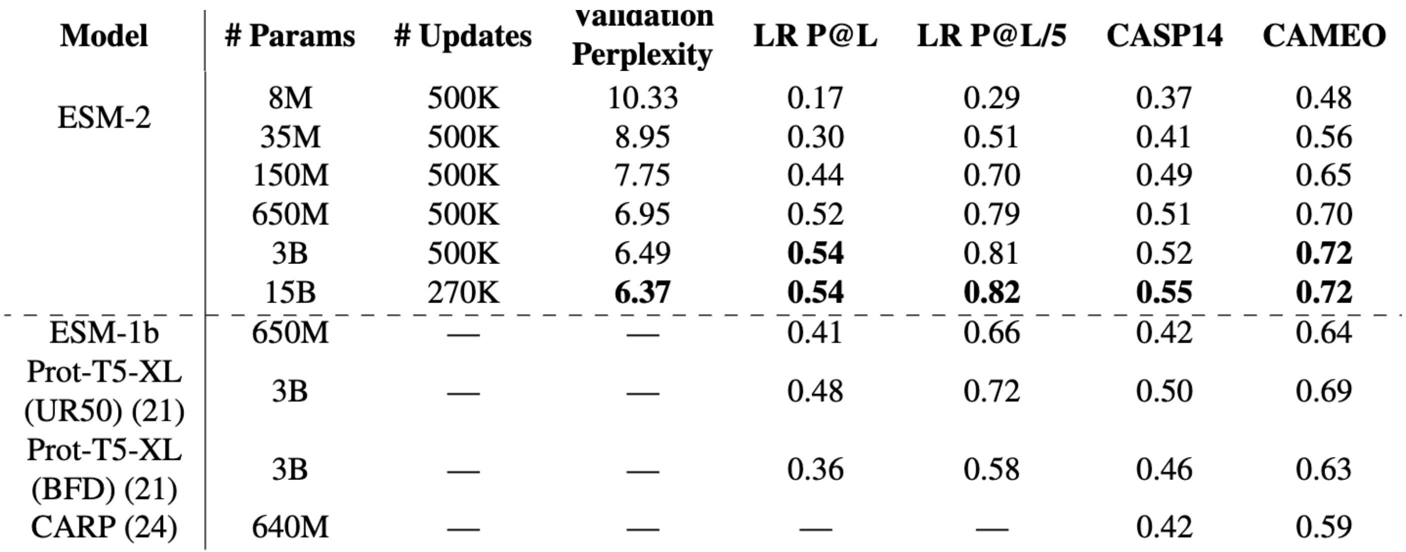
- ESM-2 (successor of ESM-1b)
  - Family of protein language models with different sizes: 8M to 15B
  - ESM-2 are Transformer Network encoder trained for masked language modeling (such as ESM-1b)
  - Improvements:
    - Data: ~65M unique protein sequences
    - Architecture: Different positional encodings (RoPE)
    - Training: Removed dropout
    - Computational resources

ESM-2 paper: DOI: 10.1126/science.ade2574

Other Protein Language Models (2)

- ProtT5 (ProtT5-XL-U50)
  - Training task:
    - Masked language modeling with masking probability of 15%
  - Training data:
    - UniRef50: ~45M unique protein sequences
  - Model architecture:
    - T5 Transformer Network consisting of encoder and decoder (for training)
    - Only uses the encoder for generating protein representations
    - 3B learnable parameters

Comparison between protein language models



Model	# Params	# Updates	Validation Perplexity	LR P@L	LR P@L/5	CASP14	CAMEO
ESM-2	8M	500K	10.33	0.17	0.29	0.37	0.48
	35M	500K	8.95	0.30	0.51	0.41	0.56
	150M	500K	7.75	0.44	0.70	0.49	0.65
	650M	500K	6.95	0.52	0.79	0.51	0.70
	3B	500K	6.49	**0.54**	0.81	0.52	**0.72**
	15B	270K	**6.37**	**0.54**	**0.82**	**0.55**	**0.72**
ESM-1b	650M	—	—	0.41	0.66	0.42	0.64
Prot-T5-XL (UR50) (21)	3B	—	—	0.48	0.72	0.50	0.69
Prot-T5-XL (BFD) (21)	3B	—	—	0.36	0.58	0.46	0.63
CARP (24)	640M	—	—	—	—	0.42	0.59

Modified table from: https://doi.org/10.1101/2022.07.20.500902