Machine Learning and its application to Protein Engineering

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https://github.com/MohsenSadeghi/ml_course

"There's method in the madness"

This quote, from *Hamlet*, suggests that there is a logical reason or purpose behind seemingly irrational or chaotic behavior. In the context of protein engineering using machine learning, this could be interpreted as meaning that although the process of designing and optimizing proteins may seem complex and unpredictable, there is a underlying structure and organization to the data and algorithms involved. Machine learning algorithms can help to uncover these patterns and relationships, enabling the design of proteins with specific properties and functions. The use of machine learning in protein engineering can therefore provide a systematic and rational approach to a field that might otherwise seem chaotic or unpredictable.

ChatGPT, OpenAI

Introduction

Proteins

- Macromolecules formed from single strands of amino acids

Protein Engineering

- Implies designing, changing proteins
- Why mess with proteins?

Living systems use proteins for a wide range of functions

- Digesting food and metabolism, muscle movement, vision
- Its interesting that all this function stems from rather simple chemistry
  - ~20 building blocks (amino acids), 1D polymers

Maybe we can design proteins for our own set of purposes

- drugs, antibodies, carbon capture (RuBisCO), plastic recycling (PETase)
- Evolution did it, probably there is something to it
- We can use readily available protein factories, i.e. living cells

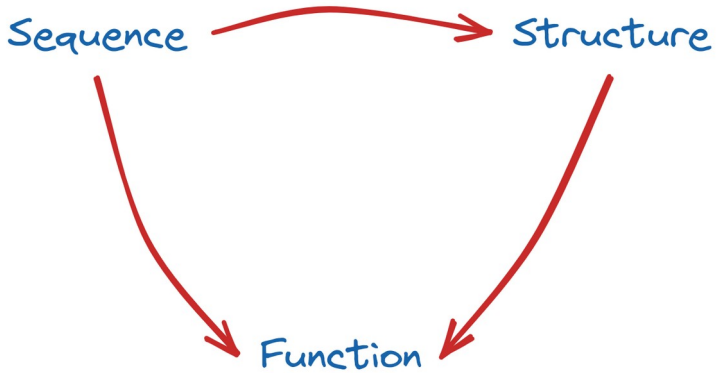
Introduction

Why do we need the help of computers? i.e. machine learning

- Consider the combinatorial possibilities in the sequence space (20^N)
  - Every written text in English belongs to a set of 26^N possibilities
- How are we going to come up with proteins that
  - Pass some structural criterion: maybe fold in the first place
  - Evolutionary fitness
  - Have a certain function, without unwanted effects
  - Are top-performers

The art of using data to come up with new data

- "Modeling" data
- Making sense of large amounts of data
  - Picking up patterns, generating new data



Machine learning (ML)

Automatically find representations of large amounts of data

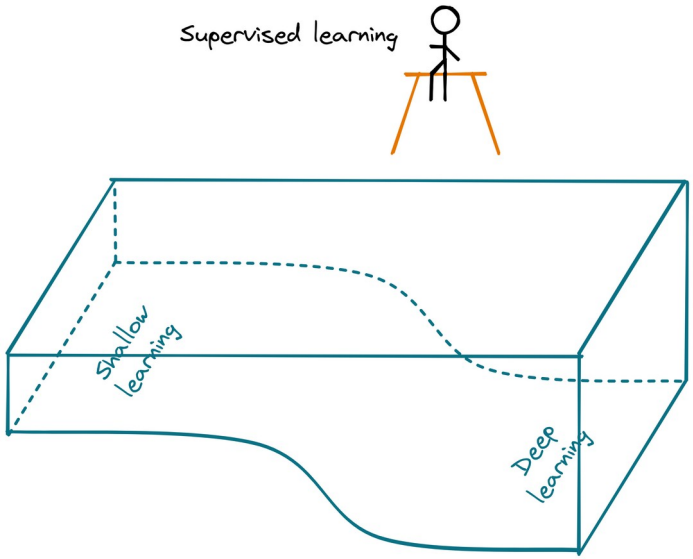
- For protein: encoding function, structure, and evolutionary role

Different ways of categorizing ML models

- Shallow vs. deep learning
- Supervised vs. unsupervised (self-supervised) learning

GPUs have helped a lot with the recent advances in ML

- Well-established software frameworks for harnessing their computational power
  - PyTorch
  - TensorFlow, JAX



Case 1: regression

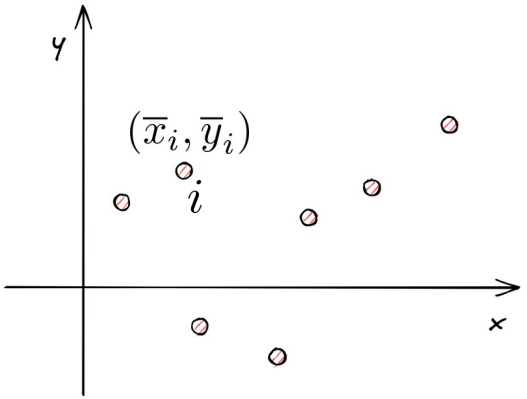
Given some data points, which inherently include noise, find a best-fitting function

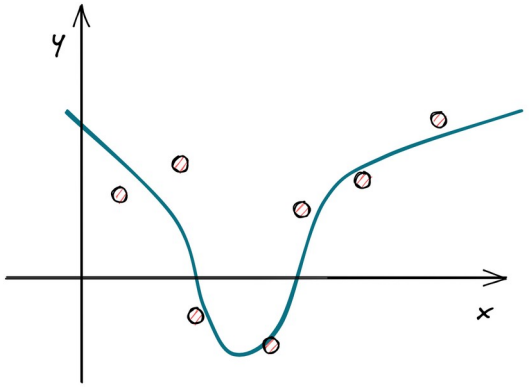
- Learning functions in a supervised manner
- Translate the learning problem into an optimization in parameter-space

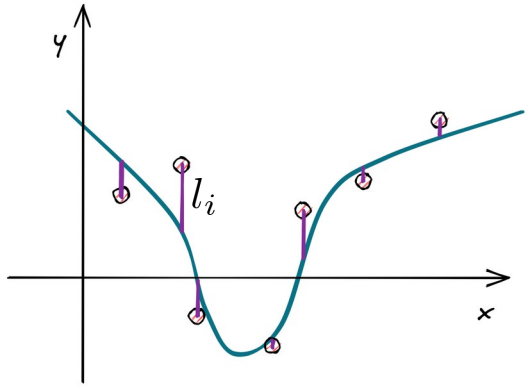
$$f\left(x;\{w_j\}\right) = w_0 + w_1 x + w_2 x^2 + \dots$$

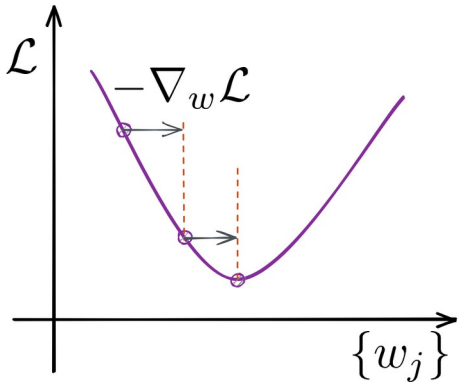
Training dataset

$$D = \{(\overline{x}_1, \overline{y}_1), (\overline{x}_1, \overline{y}_1), \dots\}$$

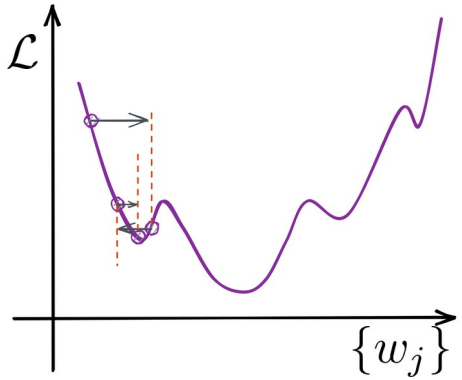








Gradient descent



Stochastic gradient descent

$$\mathcal{L} = \frac{1}{N}\sum_{i=1}^{N} l_i^2 = \frac{1}{N}\sum_{i} \left(f\left(\overline{x}_i\right) - \overline{y}_i\right)^2$$

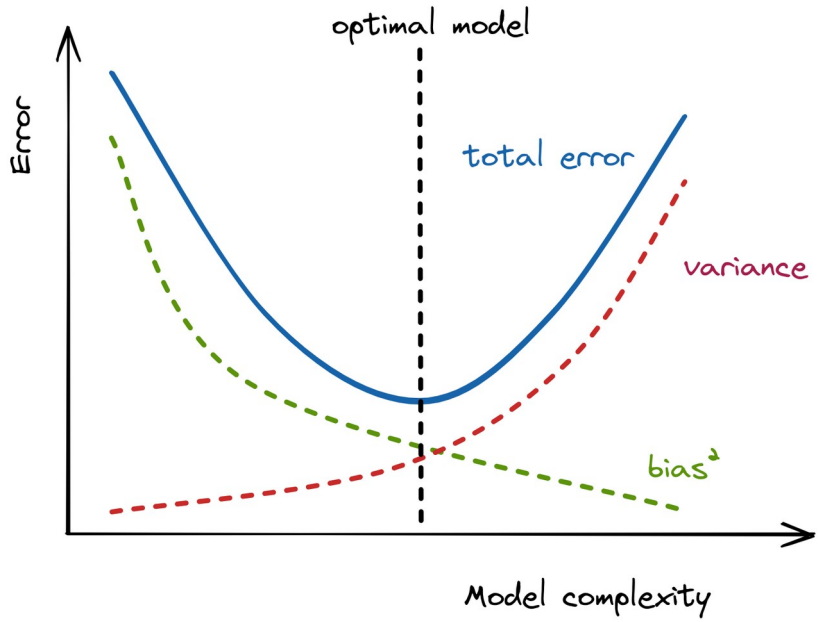
The loss function
Mean Squared Error

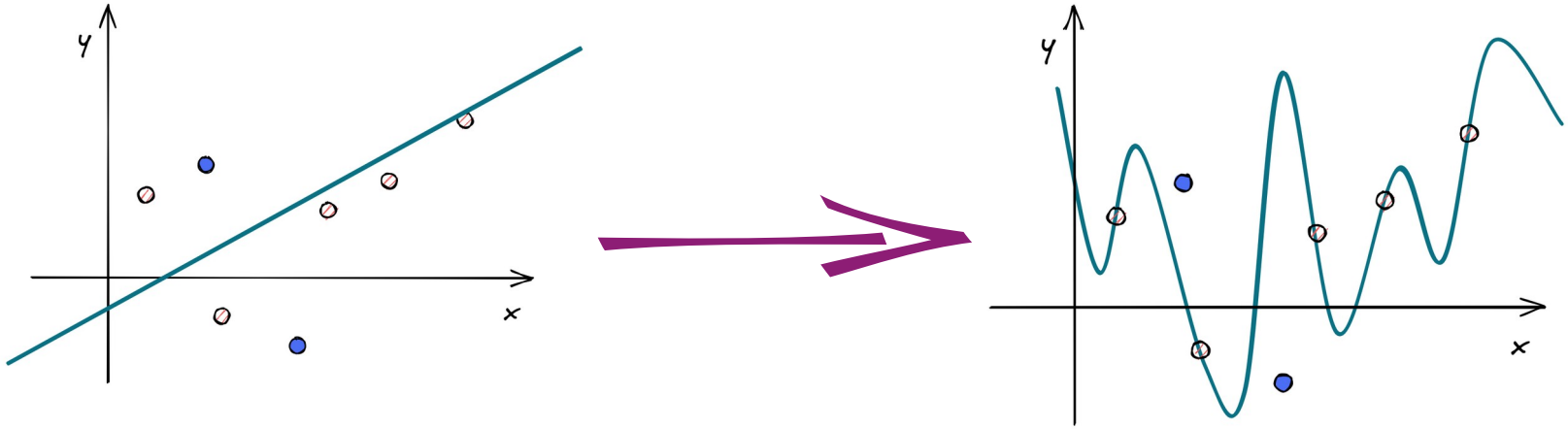
Case 1: regression

The question of how complex the model needs to be

How to check if the model learned anything or memorized everything?

- ↳ The concept of overfitting
- ↳ Cross-validation
  - Leave some data points out
  - Check the performance on them
  - train/validation split





Case 1: regression

Code time

Task:

fitting a polynomial to a bunch of random data points, using stochastic gradient-descent

Case 2: classification

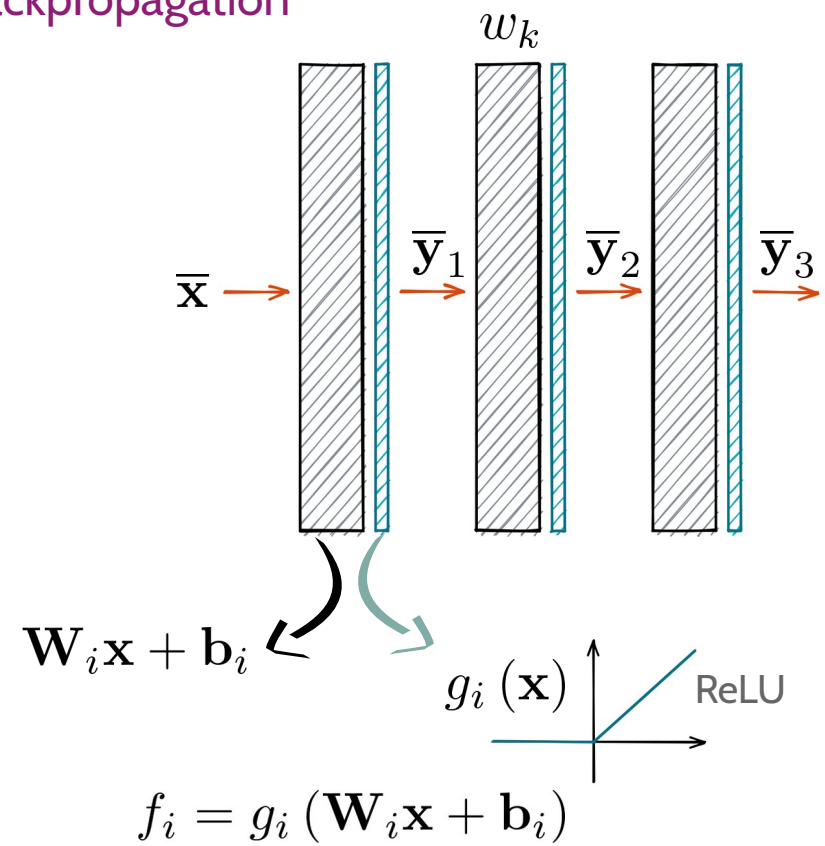
Let's make "learning the function" a bit more generic and interesting.

Stacking up "layers" in a feed-forward network

↳ Moving from a shallow model with a hand-crafted parametric function to a deep model

We just need the gradients to train similarly

↳ Backpropagation



$$f(\overline{\mathbf{x}}) = f_N(f_{N-1}(\dots(f_1(\overline{\mathbf{x}}))\dots))$$

$$\mathcal{L} \equiv \mathcal{L}(\overline{\mathbf{y}}_3)$$

$$\frac{\partial \mathcal{L}}{\partial w_k} = \frac{\partial \mathcal{L}}{\partial \overline{\mathbf{y}}_3} \cdot \frac{\partial \overline{\mathbf{y}}_3}{\partial \overline{\mathbf{y}}_2} \cdot \frac{\partial \overline{\mathbf{y}}_2}{\partial w_k}$$

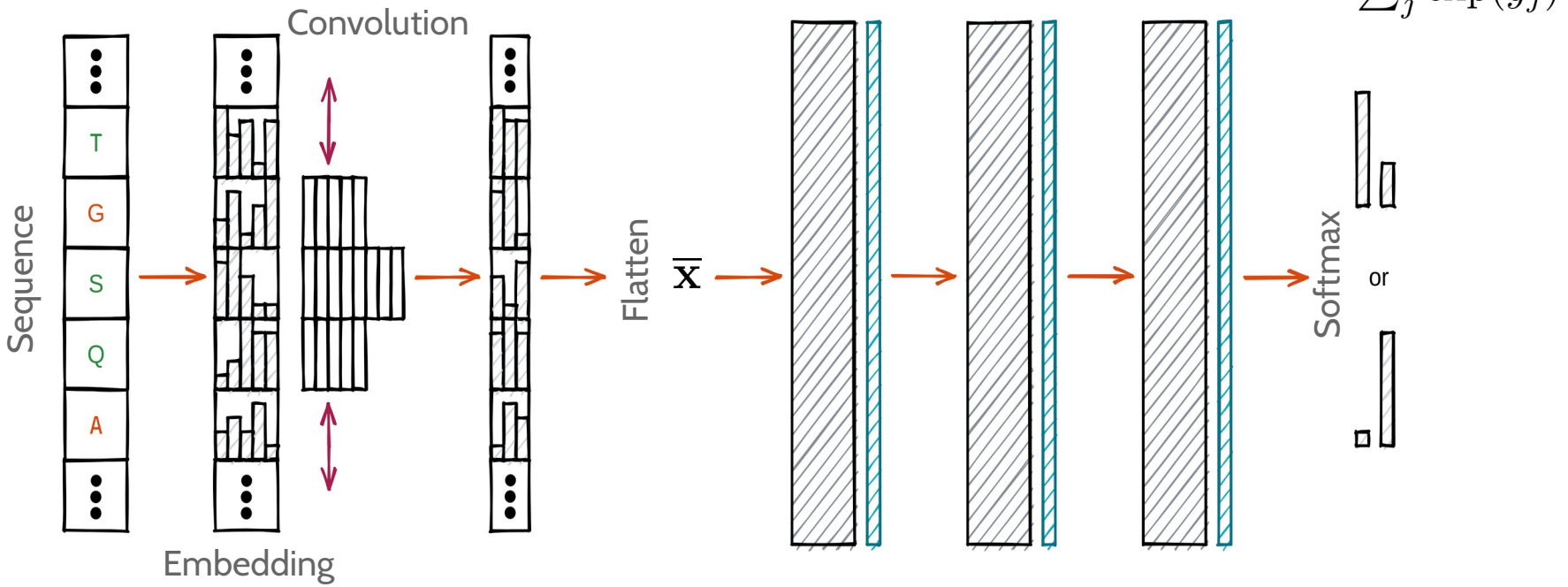
Case 2: classification

In silico screening: training the model to decide on the family, function, etc. based on the sequence

- Turning the alphabet of protein sequence into numerical tokens
- Use a combination of convolutional and dense layers
- Make predictions on class probabilities
- Cross-entropy loss function

$$\mathcal{L} = -\sum_i \overline{p}_i \log p_i$$

$$p_i = \text{softmax}\,(\mathbf{y})_j = \frac{\exp(y_j)}{\sum_j \exp(y_j)}$$



Case 2: classification

Code time

Task:

Train a deep network to distinguish between two protein classes based on sequence data

(Apolipoprotein or not)

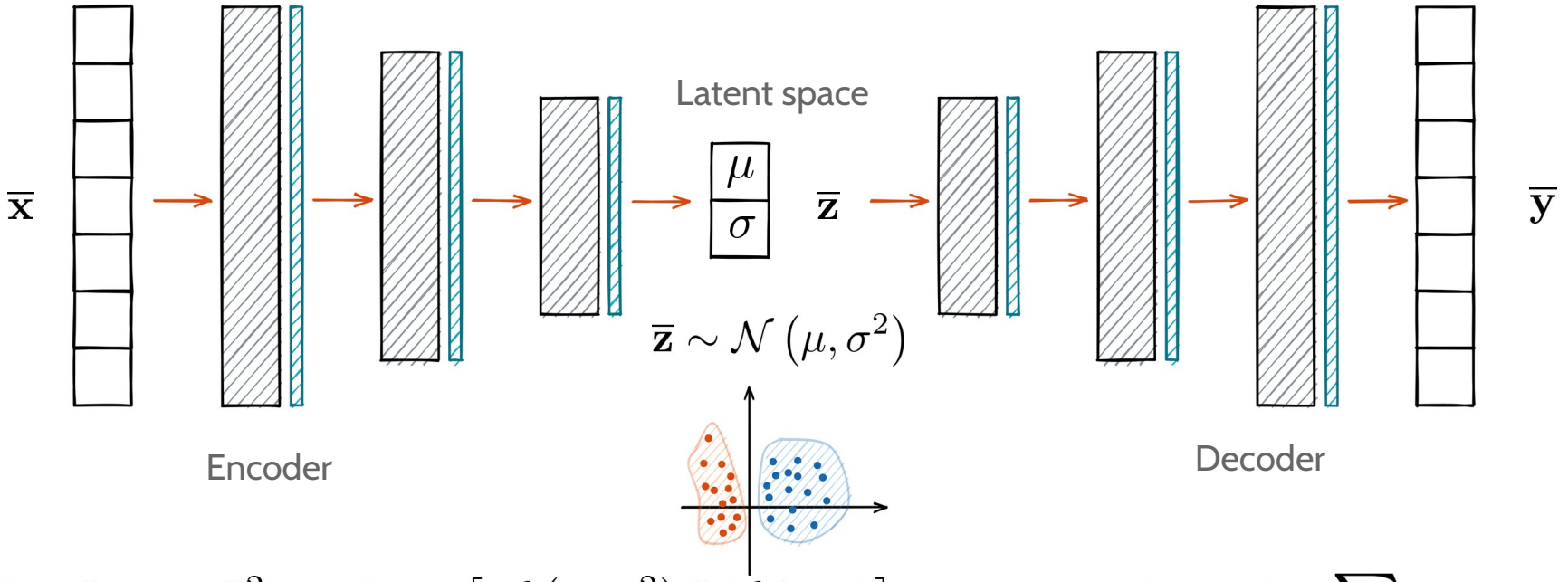
Tang, H., et al. (2016). Identification of apolipoprotein using feature selection technique. *Scientific Reports*, **6**(1), 1–6.

Case 3: representation

Learning distributions versus learning functions

- Can the computer pick on similarities in the data on its own (i.e. without labels)?
  - Self-supervised learning
- Moving from learning the function to learning from which distribution the data points come from.
  - The exciting possibility of generating new and unseen samples (Generative learning).

Behold, the Variational Autoencoder (VAE)



$$\mathcal{L} = \|\overline{\mathbf{y}} - \overline{\mathbf{x}}\|^2 + \lambda D_{KL}\left[\mathcal{N}(\mu, \sigma^2) \,\|\mathcal{N}(0,1)\right]$$

$$D_{KL}[P\|Q] = \sum_x P(x) \log \frac{P(x)}{Q(x)}$$

Code time

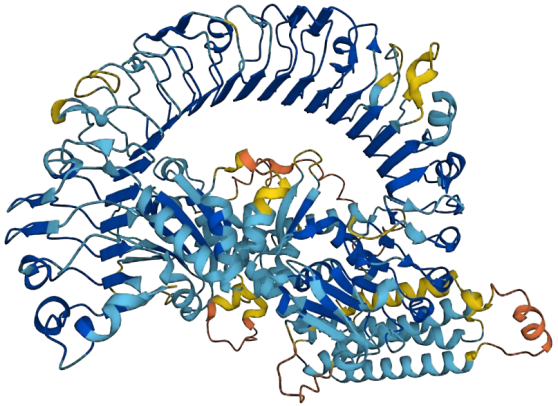
Task:

Train a variational autoencoder to learn the distinction between cis and trans conformations of random molecules from the position of their 4 atoms

State-of-the-art

AlphaFold2

- Google's DeepMind
- sequence → structure
- Blew the competition out of the water at CASP14 (Critical Assessment of Structure Prediction)
- Multiple sequence alignment (MSA) + residue-residue pairwise distance prediction



https://alphafold.ebi.ac.uk/entry/Q8W3K0

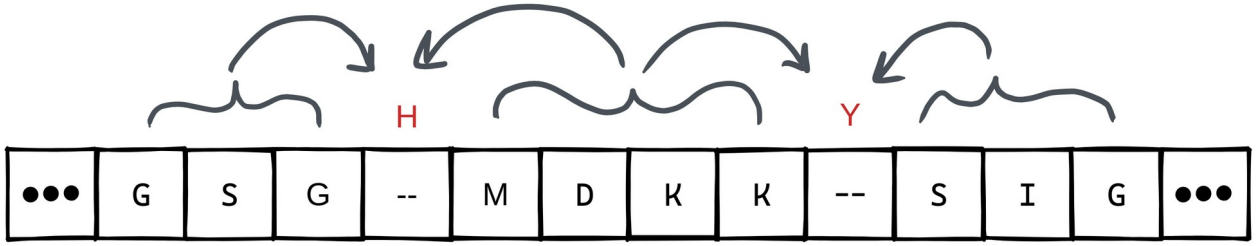
Pereira, J., et al. (2021). High-accuracy protein structure prediction in CASP14. *Proteins: Structure, Function and Bioinformatics*, **89**(12), 1687–1699.

Jumper, J., et al. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, **596**(7873), 583–589.

State-of-the-art

Using language models to process sequence data

- Shallow learning: Hidden Markov Models
- Deep Language Models
  - Using Recurrent Neural Networks with attention-based memory (transformers)
- MetaAI Evolutionary Scale Modeling (ESM) Atlas https://esmatlas.com/explore
  - 617 million proteins in one representation map
  - Structural information has been internally learned by the network!



Callaway, E. (2022). AlphaFold's new rival? Meta AI predicts shape of 600 million proteins. *Nature*, **611**(7935), 211–212.

Conclusion

You have (hopefully) learned

- The importance of protein design and engineering and the main challenge involved
- How machine learning can help make sense out of the universe of possibilities
- The wide range of ML models
  - Learning functions
  - Classification in a supervised manner
  - Learning representations and probability distributions
- State-of-the-art in ML for protein engineering
  - Structure prediction
  - Large language models trained on sequences

References and further reading

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