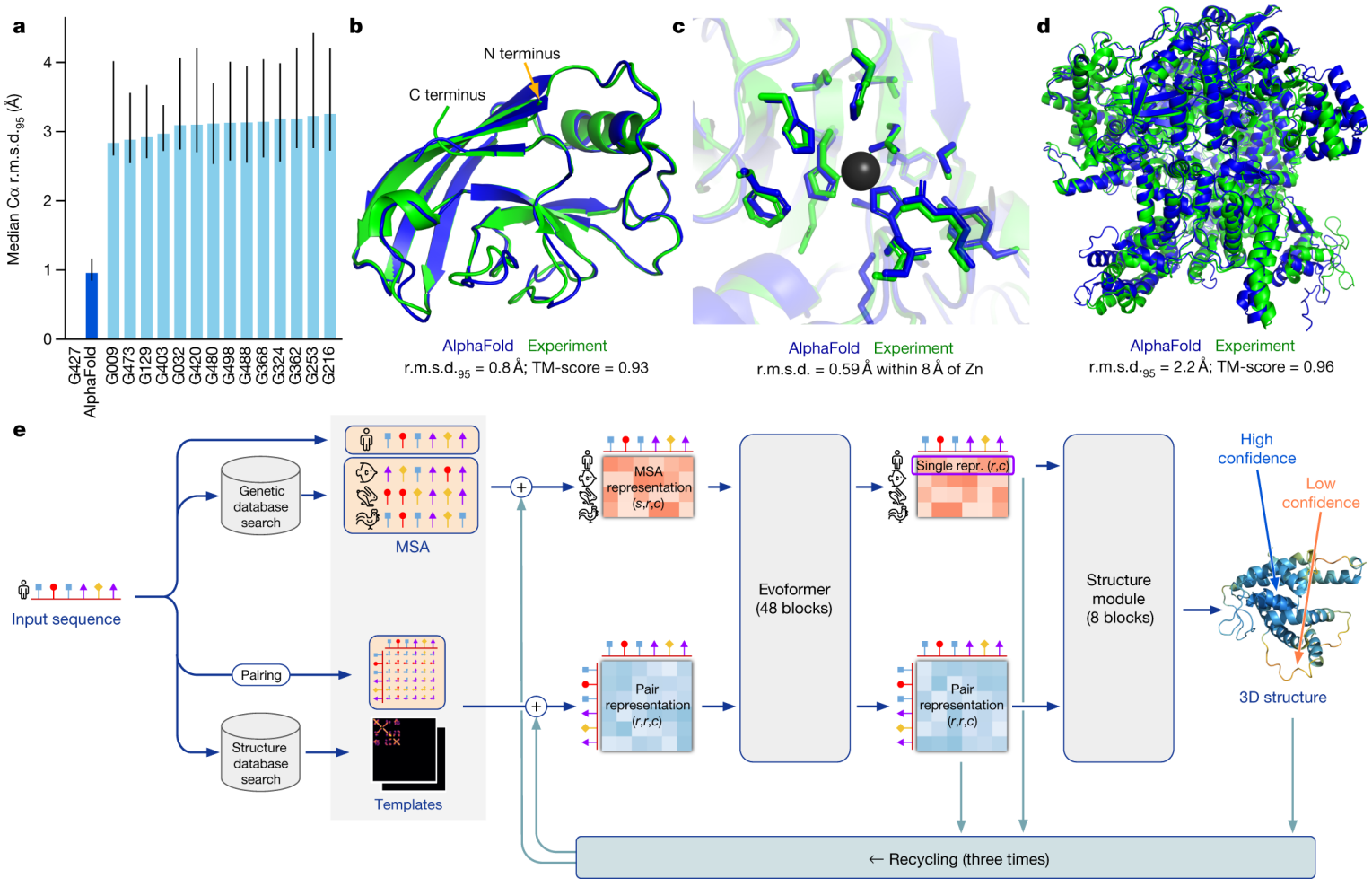
Why Deep Learning?

- Complexity: DL excels with complex data (images).
- Data Size: Takes advantage of big data (Uniprot 10^8 sequences).
- Automatic Features: No manual feature crafting needed.
- Superiority: Outperforms ML in image and text generation.
- End-to-End: Direct input-output, e.g., AlphaFold for protein folding.

(generated with midjourney)

AlphaFold, AI to predict the fold of globular proteins at the experimental accuracy

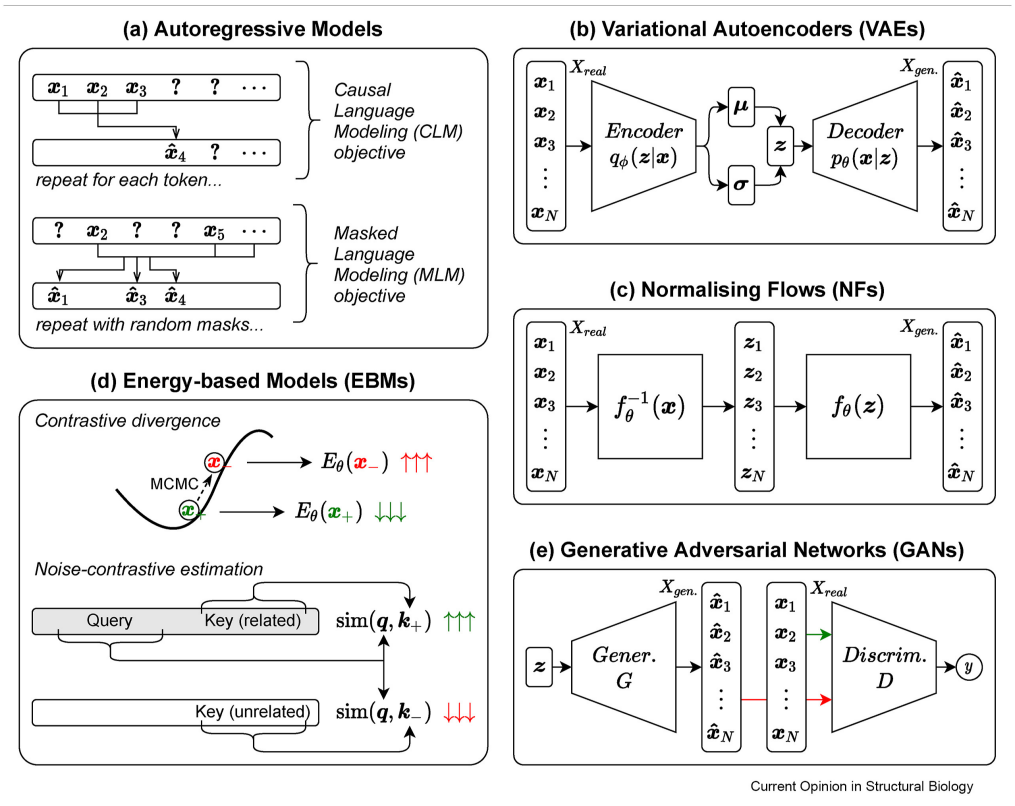


J. Jumper *et al*, 2020, Nature (And > 50 years of data collection)

Generative models to sample sequences

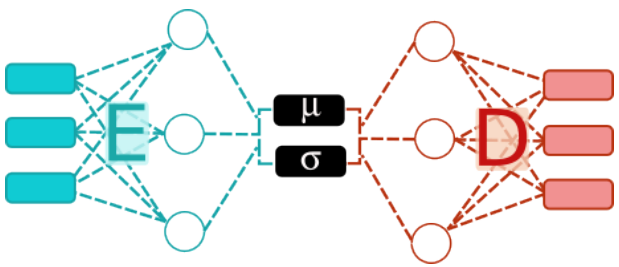
Deep Generative Models

- VAEs: Probabilistic; encoder-decoder structure.
- GANs: Generator vs. discriminator competition.
- RBMs: Energy-based with visible/hidden layers.
- Normalizing Flows: Complex distribution transformations.
- Autoregressive: Sequence prediction.
- Energy-Based Models (EBMs): Learn energy functions.

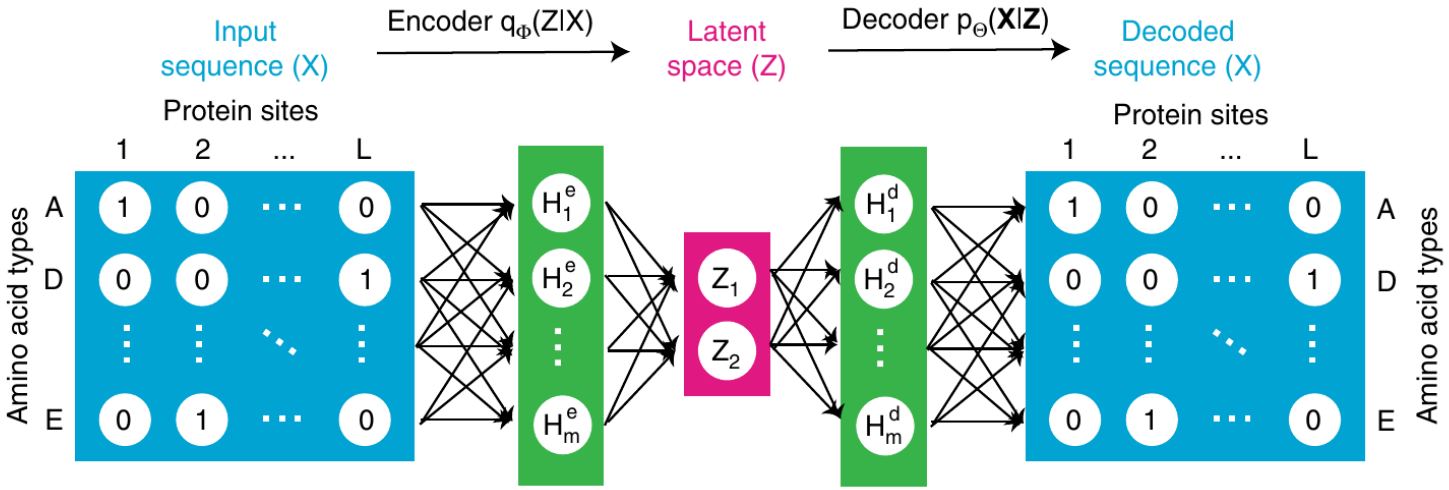


Variational Autoencoders (VAEs) in Protein Design

- VAEs: Generative models that learn to encode and decode data.
- Difference from standard autoencoders: Introduces probabilistic encoding.
- Application: Generating functional protein sequences efficiently.



Variational autoencoder framework [Ding *et al*, 2020, Nat. Com.]



- Linear dense NN: $H = W \times S + b$
- Activation function: $ReLU(H_i) = max(0, H_i)$
- Output function: $Softmax(X) = \hat{S} = \frac{exp\{X_i\}}{\sum_j expX_j}$
- $Z \sim \mathcal{N}(\mu = 0, \sigma^2 = Id)$

$$ELBO(\theta, \phi) = \sum_Z q_\phi(Z|X) \log p_\theta(X|Z) - \sum_Z q_\phi(Z|X) \log \frac{q_\phi(Z|X)}{p_\theta(Z)} \quad (1)$$

$$ELBO(\theta, \phi) =< \mathcal{L}(\hat{S}) > -D_{KL}(Encoder(S)||\mathcal{N}(Z|\mu, \sigma^2))$$

Training of a VAE

Architecture chosen by 5-fold cross validation

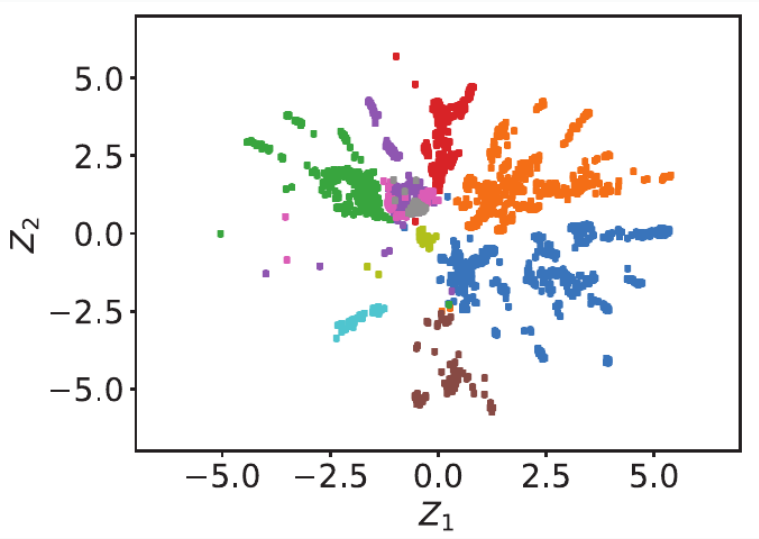
- 1 $\times$ hidden (linear) layer fully connected (Encoder and Decoder)
- 512 units per hidden layer
- Latent space dimension = 10
- Parameter space (W) dense layer: L $\times$ 21 $\times$ 512 $\rightarrow 10^6$

Training paramerters

- Re-weigting sequences (reduce redundancy and emphasize diversity)
- 10^4 optimization steps (ADAM optimizer)
- Regularization

Latent space representation of sequence space

[Ding *et al*, 2020, Nat. Com.]

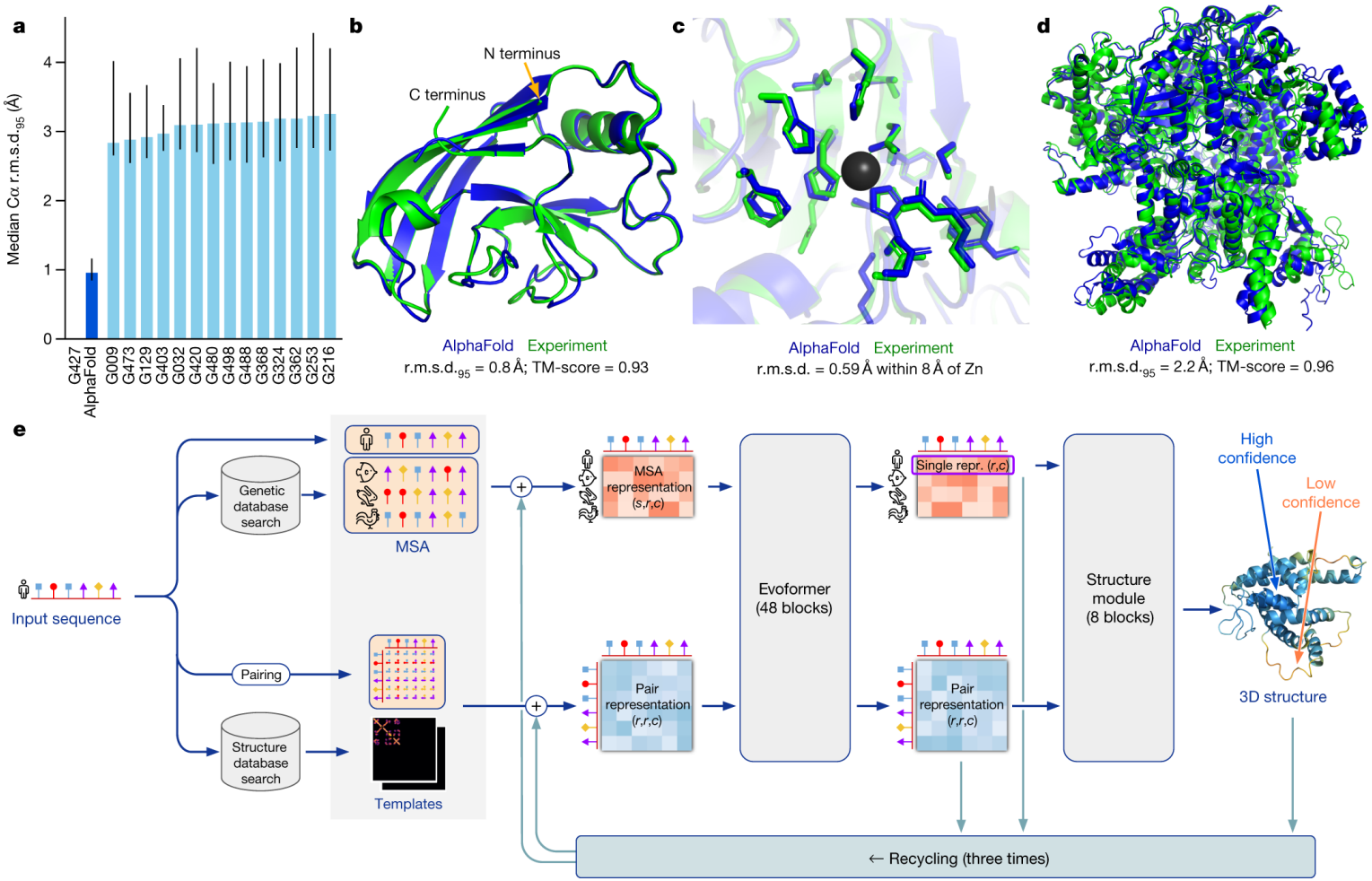


Use a structure predictor to deduce sequences

{AlphaFold is so good at predicting the structure, can't we just invert it?}

Yes, we can!

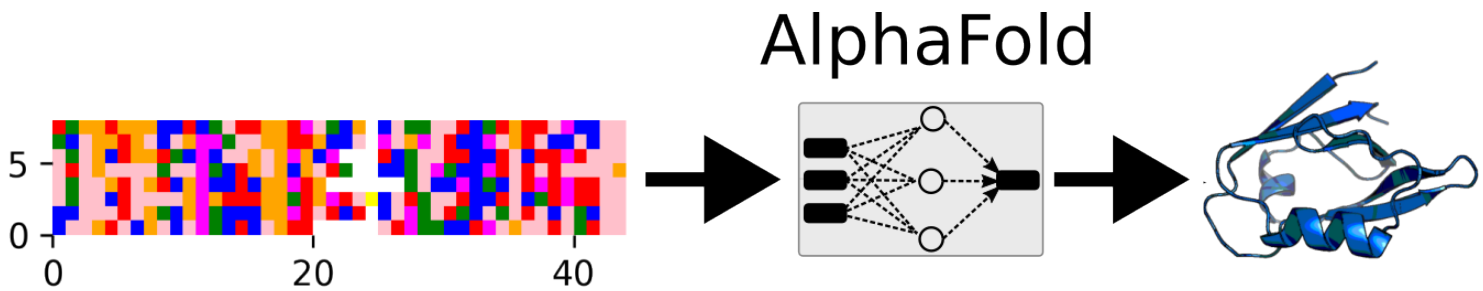
AlphaFold structure prediction



End-to-End prediction model accounting for evolutionary information as well as geometric information → Any parameter on the way is differentiable, even the input sequences.

AlphaFold: inverting the prediction

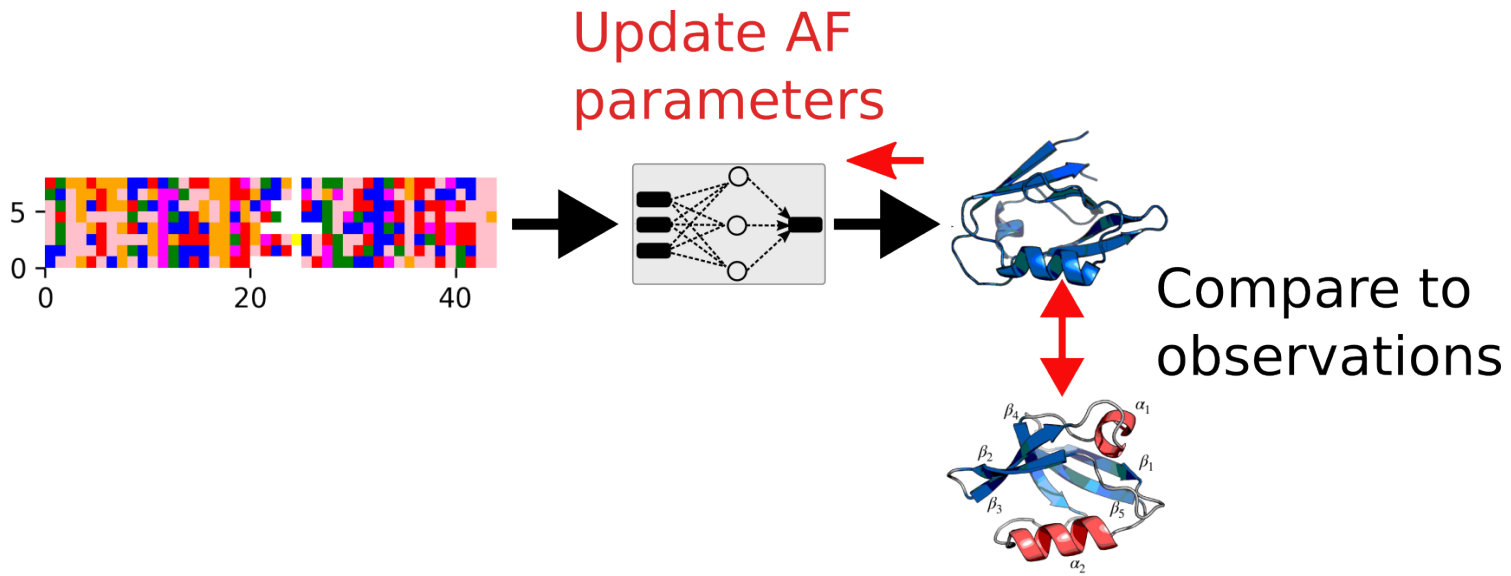
Prediction of a structure's fold.



(J. Jumper *et al*, 2020, Nature)

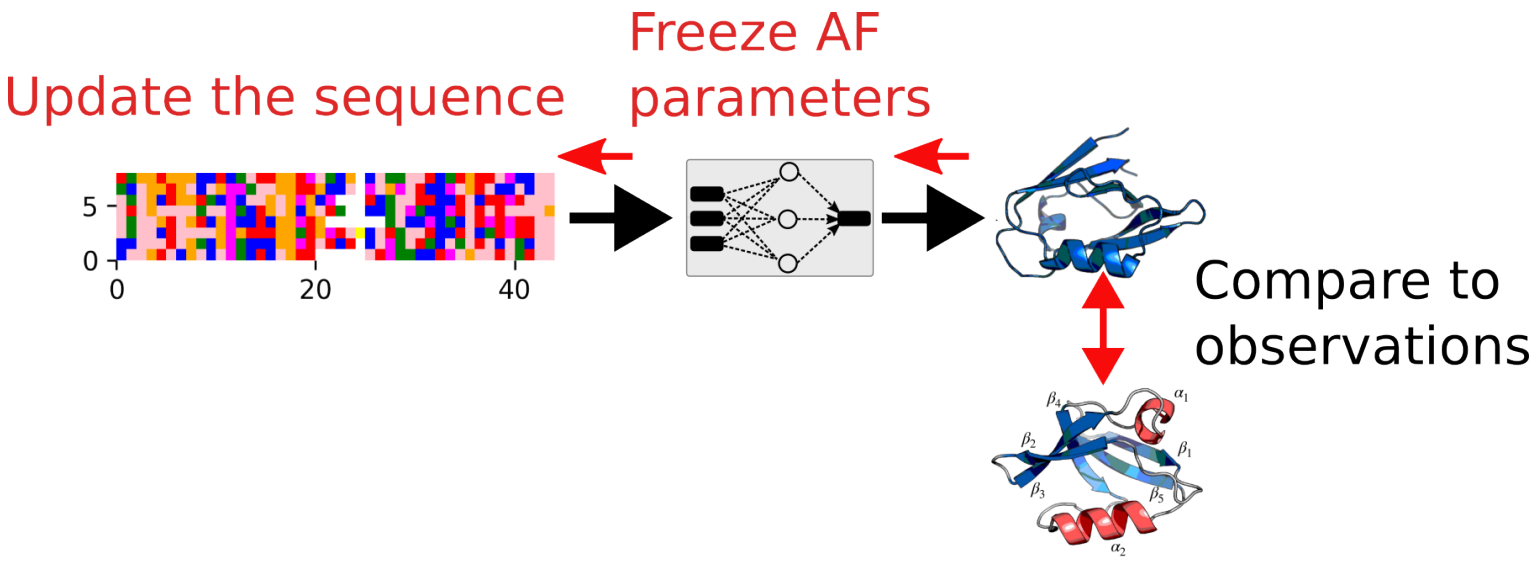
AlphaFold: inverting the prediction

Compare the prediction to the true structure and update accordingly the parameters of AlphaFold using the gradient of the loss function.



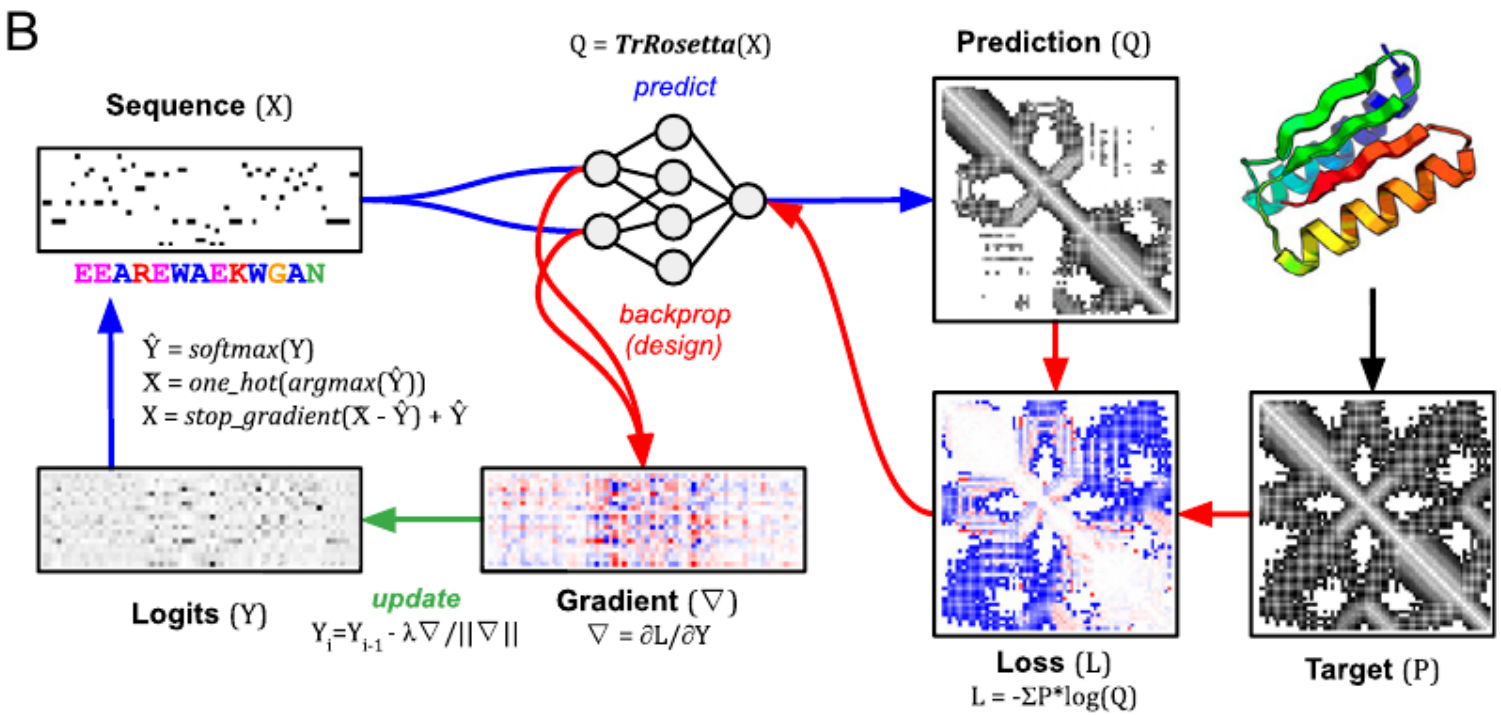
AlphaFold: inverting the prediction

To design: use the gradient with respect to the input only to search for sequences that give the correct fold.



(Norm *et al*, 2021, PNAS)

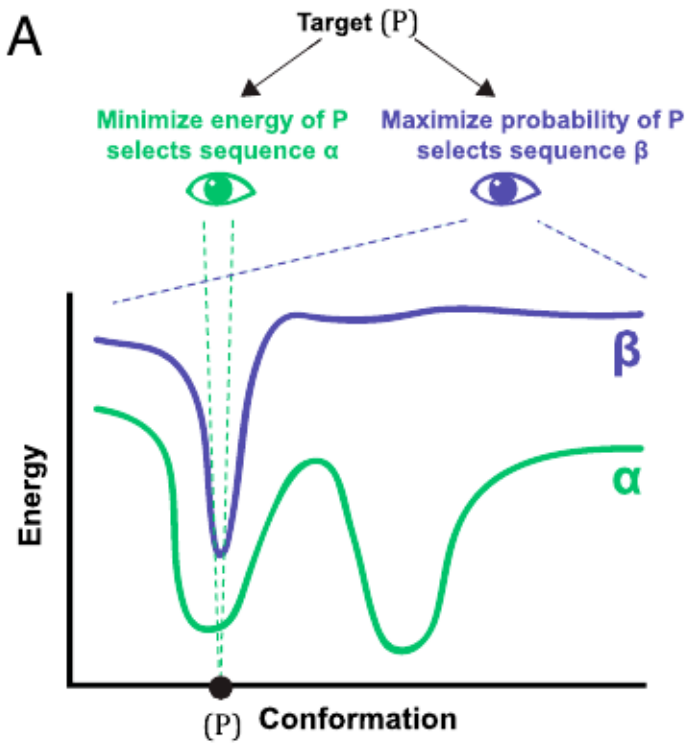
Encode the structure into distance matrices ($D_{i,j}$ = distance between residues i and j).



(Norm *et al*, 2021, PNAS)

Why doing so?

- Positive design: searching for sequences that fold into the target structure.
- Negative design: searching for sequences that fold only into the target structure.



(Norm *et al*, 2021, PNAS)

Graph neural network to design proteins conditioned on the structure