Challenges of Physics-Based Approaches

- Computational Intensity: Demanding molecular dynamics simulations.
- Incomplete Modeling: Often neglects complex environmental interactions.

Nature's Blueprint

- Evolutionary optimization: Natural proteins are optimized to the physical diffusion limits.
- Homology Modeling: Borrowing structures from evolutionarily related proteins.
- Evolutionary Couplings: Pinpointing residues crucial for function.
- Advantages:
  - Sidestep computational hurdles.
  - Tap into nature's tried-and-tested designs.

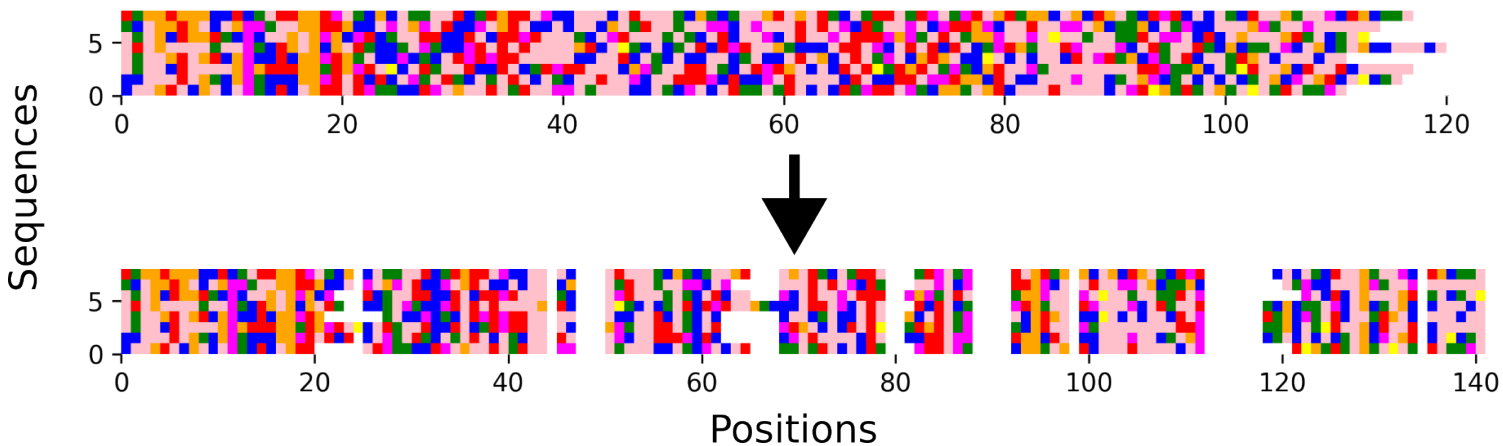
Given a target natural function, search for natural counterparts

Typical approach

1. Search natural counterparts for a targeted function.
2. Extract statistical signature from the collection of natural sequences.
3. Use the statistical signature to sample novel sequences.

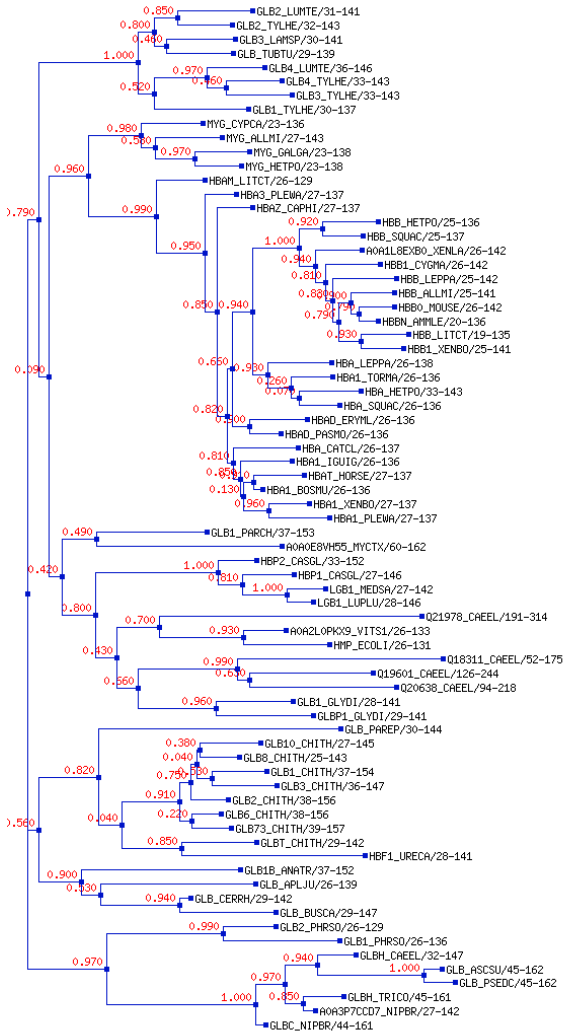
Multiple Sequence Alignments (MSAs) - the data

- Definition: Aligning multiple sequences to identify regions of similarity.
- Importance in bioinformatics:
  - Studying phylogenetics and evolutionary processes.
  - Identifying protein domains.



Multiple Sequence Alignments (MSAs) - the data

- Information extraction from MSAs:
  - Phylogenetic trees: Tracing evolutionary pathways.
  - Functional domains & conserved motifs: Identifying patterns.
  - Critical residues for protein function or stability.
- Popular tools & databases for MSAs:
  - Clustal: Widely used for sequence alignment.
  - Pfam: Database of protein families based on MSAs.
  - Uniprot: Comprehensive protein database.



Encoding MSAs for numerical use

- MSA is discrete qualitative data type

How to use them?

Encoding

- One-hot:

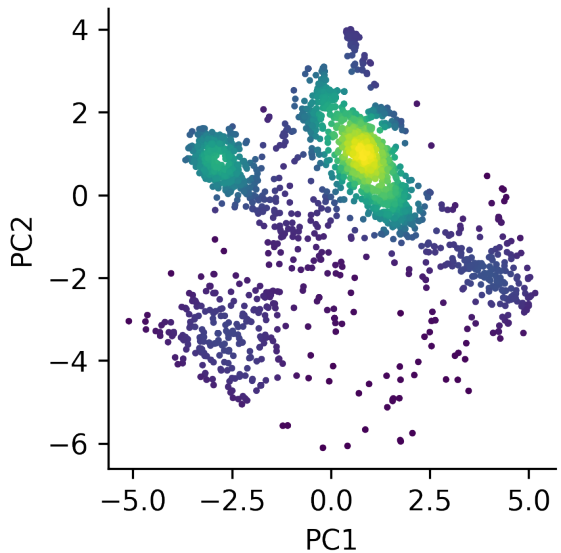
$$A \rightarrow \begin{pmatrix} 1 \\ 0 \\ \dots \\ 0 \\ 0 \end{pmatrix}, C \rightarrow \begin{pmatrix} 0 \\ 1 \\ \dots \\ 0 \\ 0 \end{pmatrix}, \dots Y \rightarrow \begin{pmatrix} 0 \\ 0 \\ \dots \\ 1 \\ 0 \end{pmatrix}, W \rightarrow \begin{pmatrix} 0 \\ 0 \\ \dots \\ 0 \\ 1 \end{pmatrix}.$$

- Random projection
- Deep learning embeddings

Since we have numerical data, we can also use dimensionality reduction techniques

Singular Value Decomposition (SVD) for Protein Data

- Application: Extracting meaningful patterns from vast protein datasets.
- Dimensionality Reduction: Simplifies complex data, retaining essential information.
- Pattern Recognition: Reveals underlying structures and relationships in protein data.



Mathematics behind SVD

Introduction

- Fundamental technique in linear algebra.
- Decomposes a matrix into three other matrices.
- Widely used in data compression, noise reduction, and more.

Mathematical Representation

- Given a matrix MSA:

$$MSA = U\Sigma V^T$$

Where:

- U - Left singular vectors (orthogonal matrix).
- Σ - Diagonal matrix of singular values.
- V^T - Transpose of right singular vectors (orthogonal matrix).

What's in those singular vectors ?

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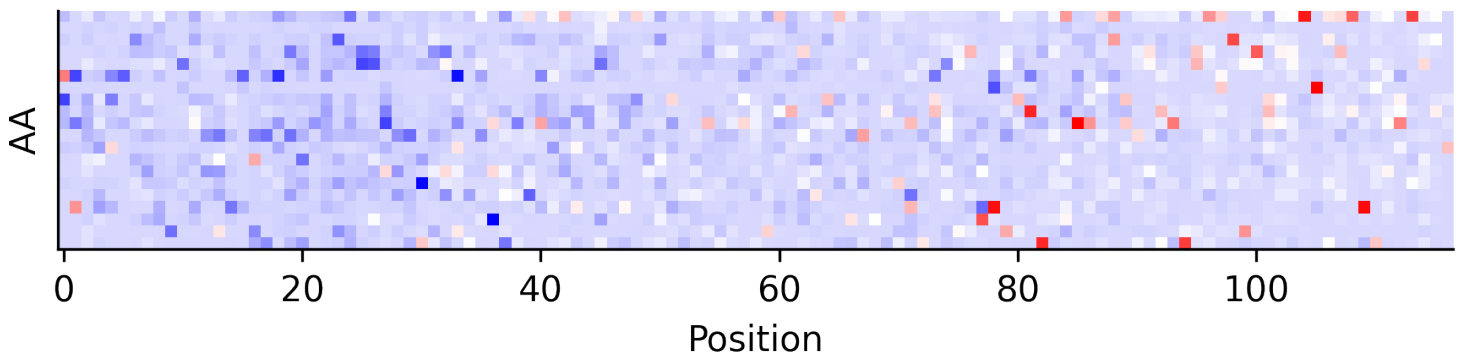
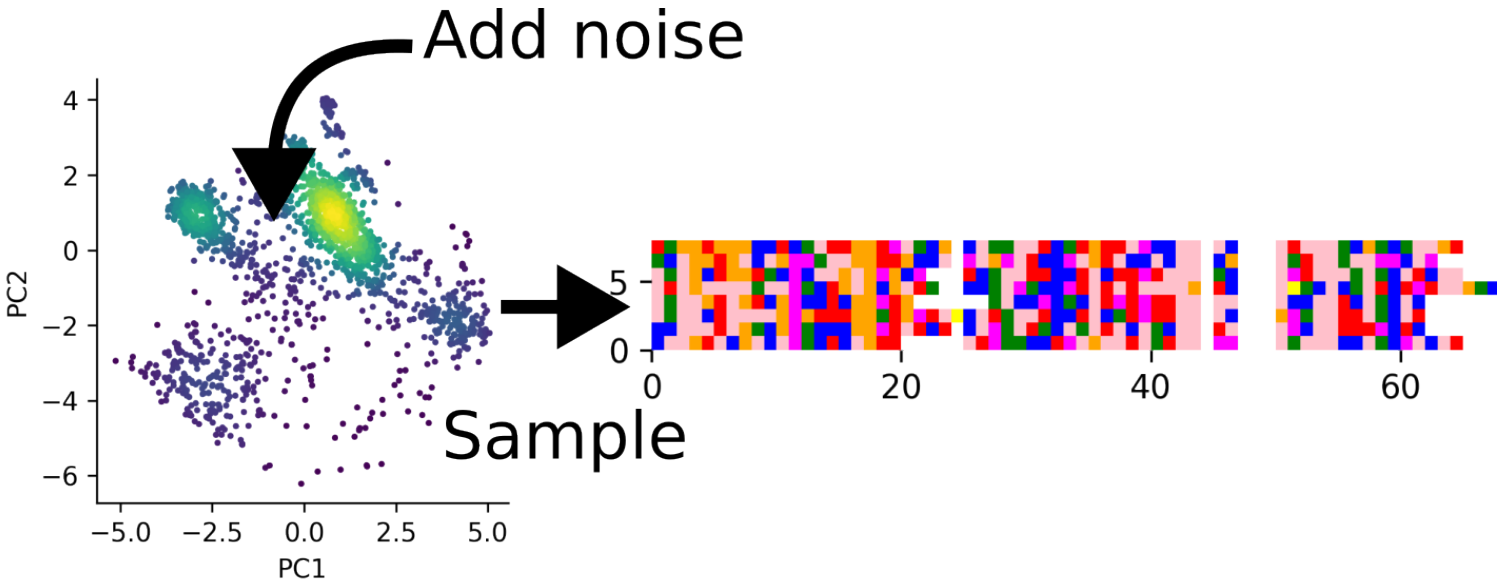
- The right singular vectors correspond to compositional motifs (in terms of sequences).



Sample the compositional motifs observed in the MSA to form novel sequences

Sequence Generation using SVD

- Concept of reverse mapping: Generating functional sequences from reduced-dimensional data.



Introduce a Gaussian blank noise to sample the PCs:

$$\tilde{U} = U + \mathcal{N}(0, 1)$$

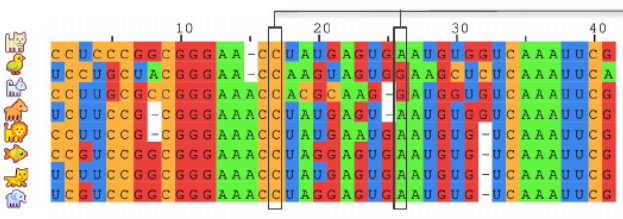
$$\hat{MSA} = \tilde{U}\Sigma V^T$$

Direct coupling analysis

F. Morcos *et al*, PNAS 2011

Markov Random Field for Protein Analysis

- Parametrize a probability distribution describing the distribution of sequences.
- Decompose the complex distribution of sequences into a pairwise potential — the Potts model.



$$\mathbb{P}(s_1, s_2, \ldots, s_8) \propto \exp\left\{ \sum_i h_i s_i + \sum_{i<j} J_{ij}(s_i, s_j) \right\}$$

MSA probabilistic model [Morcos *et al*, PNAS, 2011]

- Probability associated to a Sequence given a MSA:

$$P_{\mathcal{H}}(S) \propto \exp\{-\beta \times \mathcal{H}(S)\}$$

- Energy of a sequence (Potts models):

$$\mathcal{H}(S) = \sum_i h_i(S_i) + \sum_{i<j} J_{ij}(S_i, S_j)$$

- Energy parameters:
  - $\mathcal{H} = \{h_i; J_{ij}\}$ (lookup table)
  - Parameter space: $5 \times L + 5^2 \times \frac{L \times (L-1)}{2} = 464165$

Contact predictions based on coupling terms J_{ij}:

$$F_{ij} = \sqrt{\sum J_{ij}(A,B)^2} \quad \rightarrow \quad F_{ij}^{APC} = F_{ij} - \frac{F_{i.}F_{.j}}{F_{..}}$$

DCA learning technique

Turn into an optimization procedure

- Fit low-order statistics such as f_i and f_{ij}: Find $\mathcal{H}$ such that:

$$\hat{f}_i(A) = f_i(A) \quad ; \quad \hat{f}_{ij}(A, B) = f_{ij}(A, B)$$

Boltzmann machine learning [Figliuzzi *et al*, Mol. Biol Ev., 2018; Cuturello *et al*, RNA, 2020]

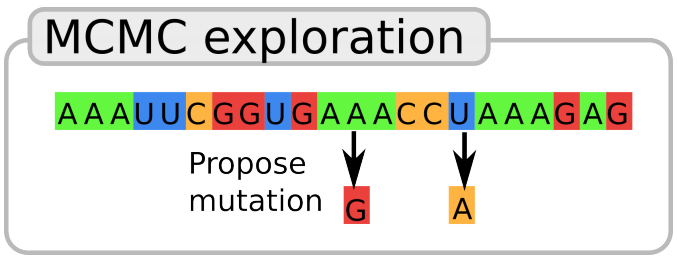
Initialize with a guess for $\mathcal{H}$ (could be zeros)

1. Generate a sample given $\mathcal{H}$ (MCMC) and compute $\hat{f}_i, \hat{f}_{ij}$
2. $\mathcal{H}$ parameters are updated following the log-likelihood

$$h_i(A) \leftarrow h_i(A) + \eta(\hat{f}_i(A) - f_i(A))$$

- Sampling sequences: sampling new protein variants.
- Ensuring biological relevance: Satisfying coevolutionary constraints.

Perform mutations:



Select using the parametrized distribution:

$$P_{\mathcal{H}}(S) \propto \exp\{-\beta \times \mathcal{H}(S)\}$$