Generative Models of protein sequences

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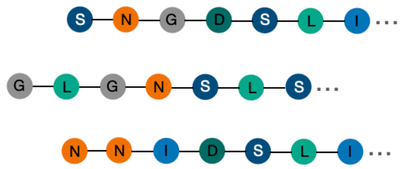
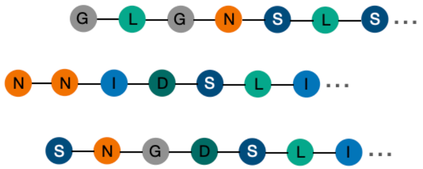
Journées de la Physique Statistique

UMR 7083 Gulliver ESPCI PARIS TIMC UGA Université Grenoble Alpes

Generative Models



Training data $\sim P_{data}$



Artificial data $\sim P_{model}$

1. Learn P_{model} similar to P_{data}
2. Generate samples from P_{model}

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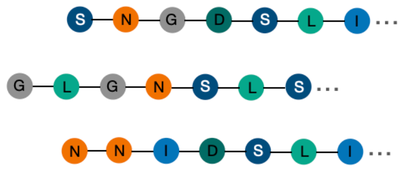

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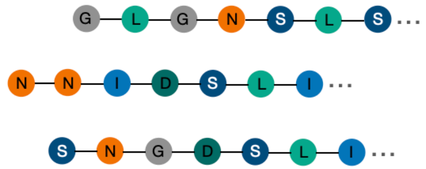

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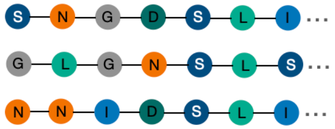
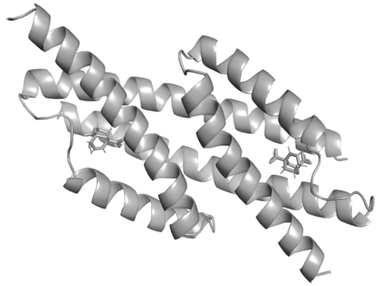
Homologous sequences

Amino-acid chains



3d structure



Function

Catalyse a specific reaction

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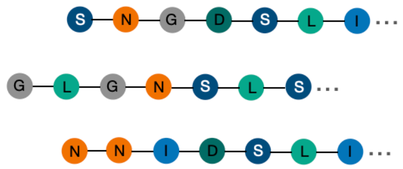
Generative Models



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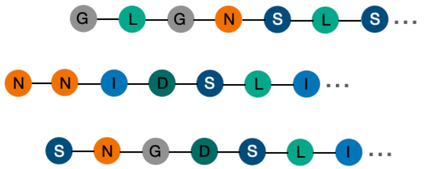

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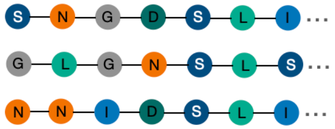

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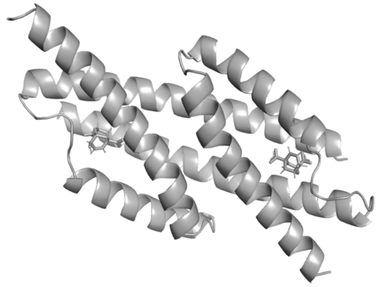

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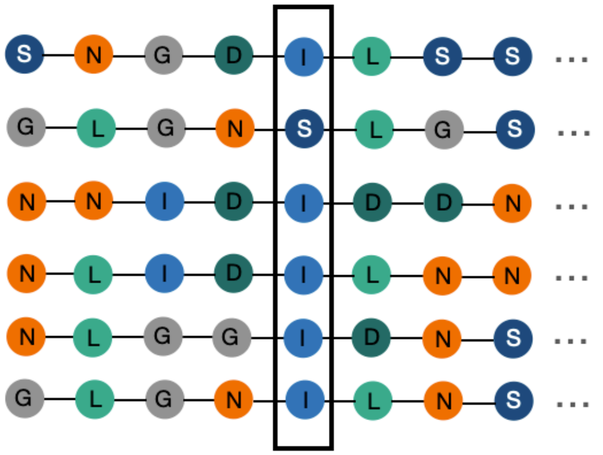
Catalyse a specific reaction

Conservation



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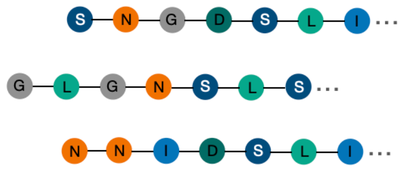
Generative Models



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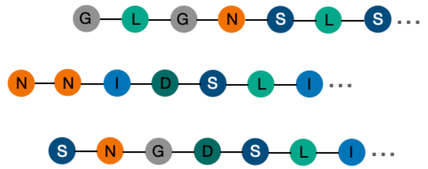

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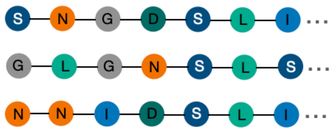

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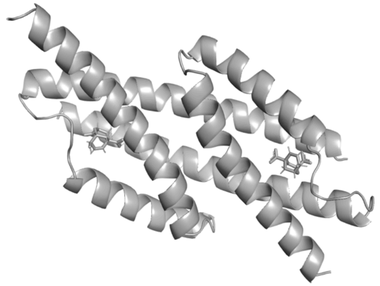

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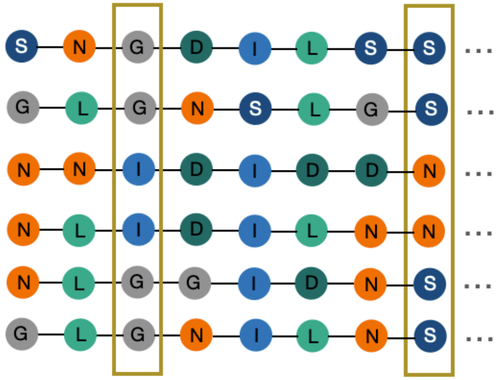

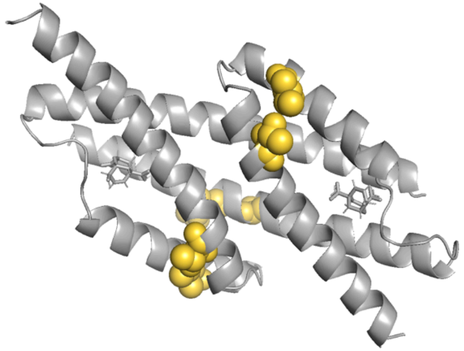

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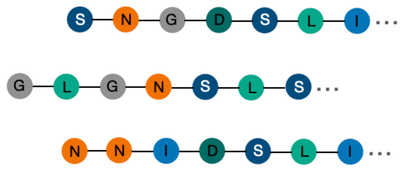

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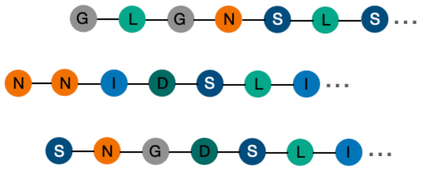

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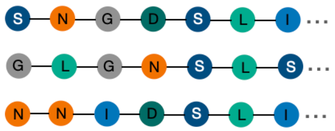

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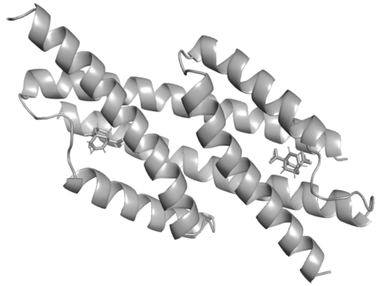

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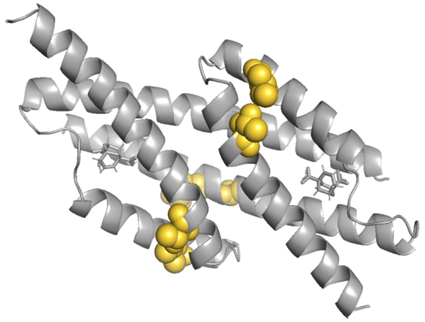
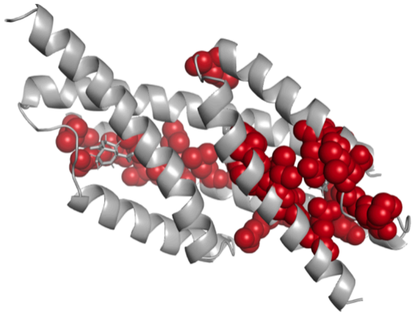


Local

Functional Positions



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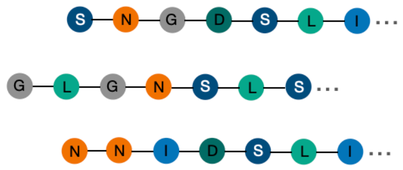

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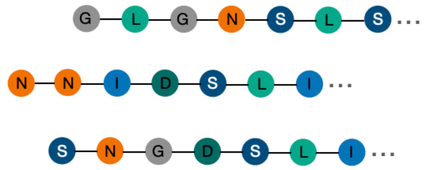

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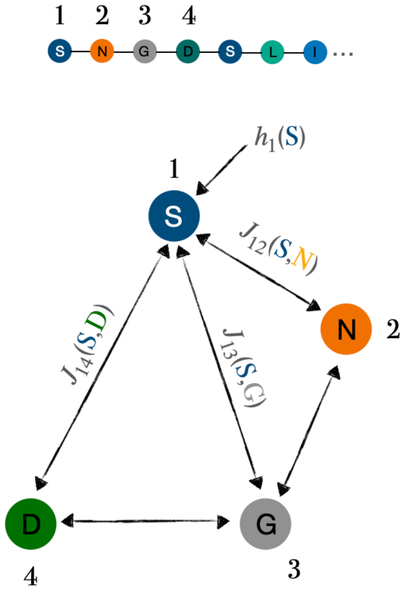
Potts Model

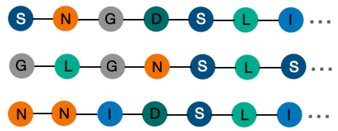


$$p(\{\sigma_i\}_{i=1,\dots,L}) = \frac{1}{Z(\boldsymbol{h},\boldsymbol{J})} \prod_{i=1}^{L} e^{h_i(\sigma_i)} \prod_{i<j} e^{J_{ij}(\sigma_i,\sigma_j)}$$

- Parameters inferred with Gradient descent algorithm
- Boltzmann Machine algorithm (BM)

Homologous sequences

Amino-acid chains



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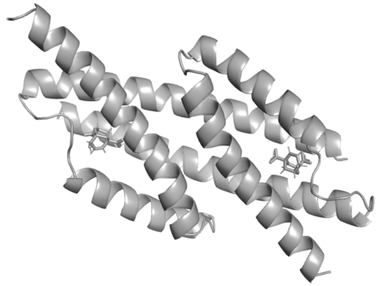

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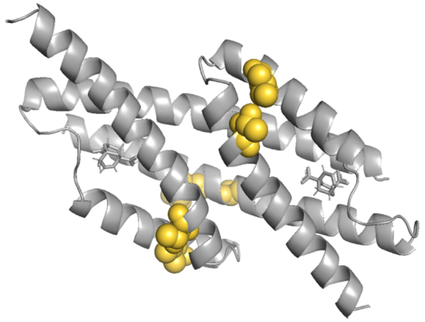

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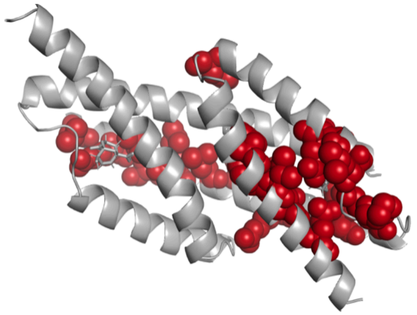

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Different features

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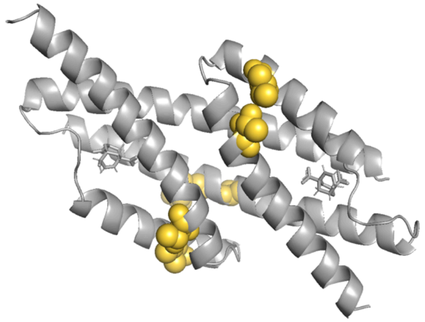

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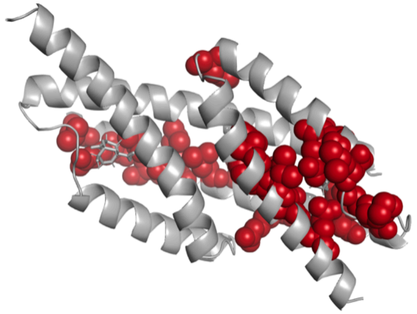

Y. Kleeorin, W. P. Russ, O. Rivoire, and R. Ranganathan, 2021

Different features

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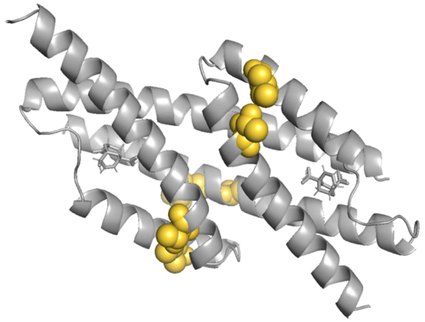

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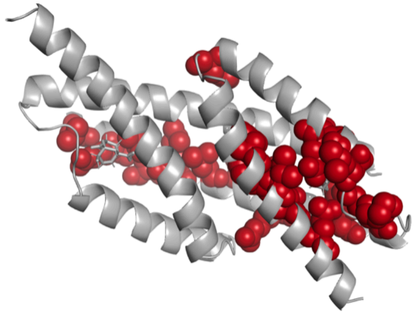

Undersampling

$$\text{Number of natural sequences} << \begin{cases} \text{Number of possible sequences} \\ \text{Number of parameters} \end{cases}$$

$$\text{L2-Regularization}: \quad \text{Loss} + \lambda \times \text{Penalty}$$

L2-norm of the parameters

Y. Kleeorin, W. P. Russ, O. Rivoire, and R. Ranganathan, 2021

Different features

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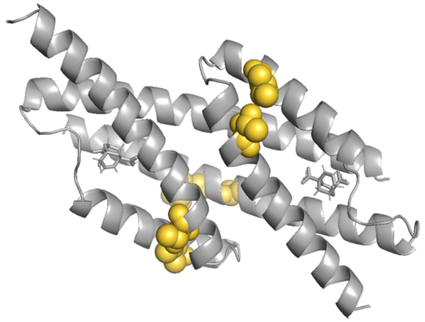

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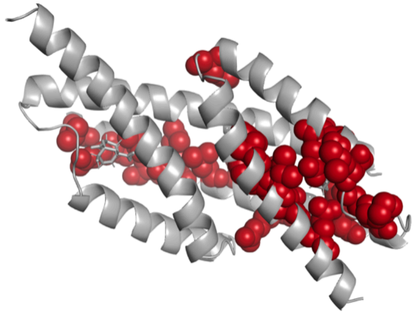

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→ Introduce a bias

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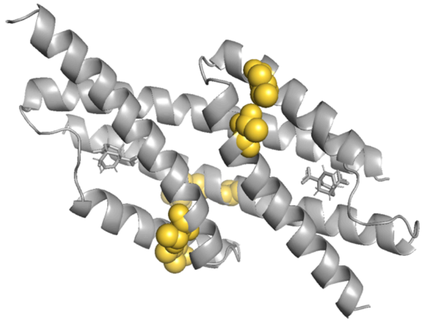

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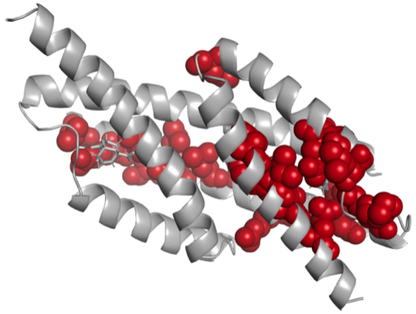

High regularization

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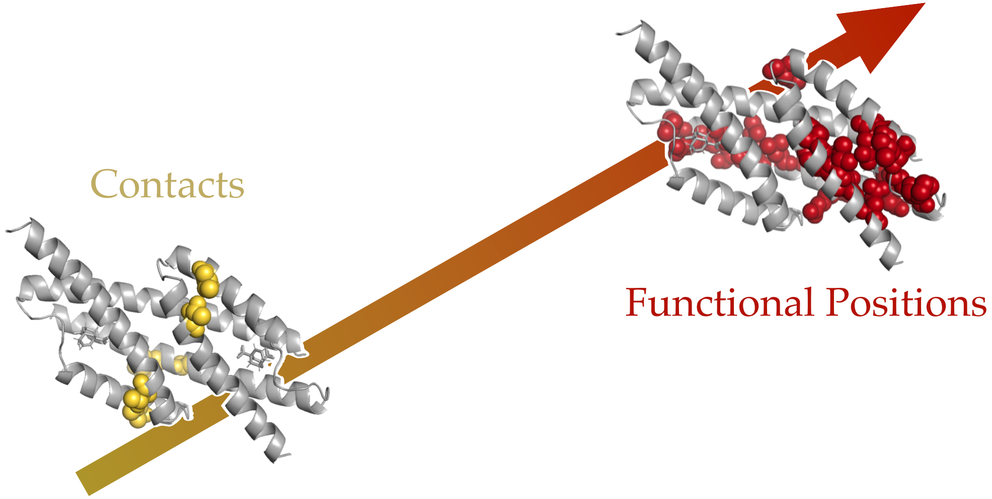

Functional Positions

Low regularization

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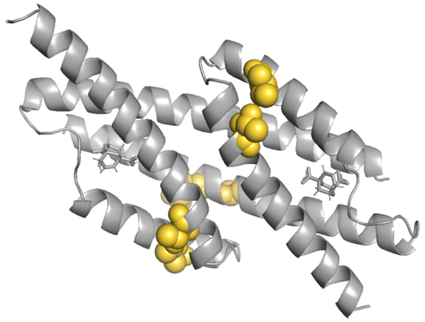

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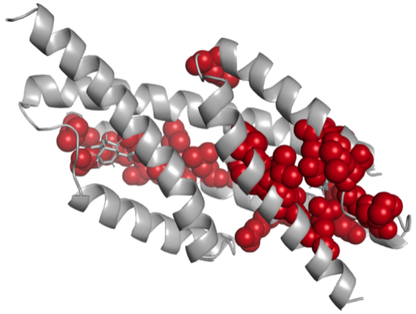

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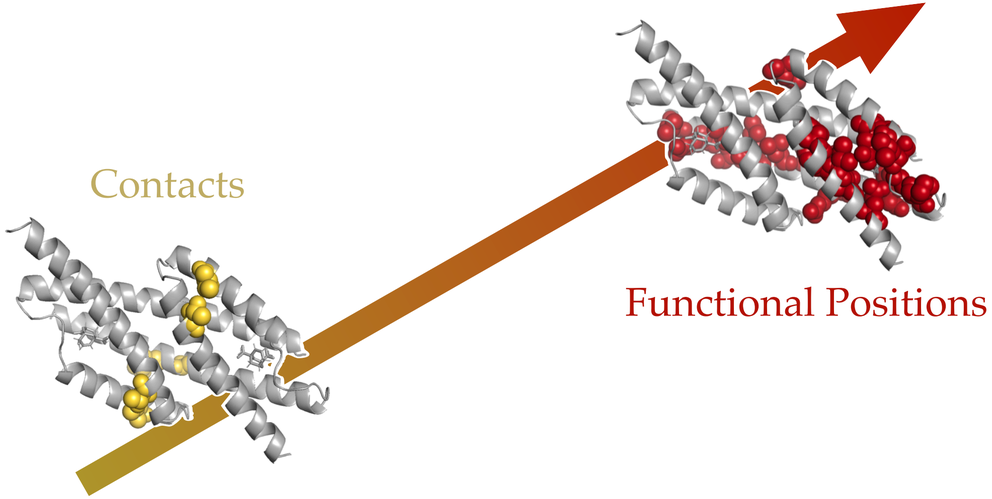

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→ Introduce a bias

Infer Generative Models that:

- Combine the inference of both local & Collective features
- Reproduce the diversity of natural protein families
- Capture other statistics

  (1^{st}, 2^{nd}, 3^{rd} order statistics, PCA, energy distributions…)

→ **SBM (stochastic Boltzmann Machine) ***

Y. Kleeorin, W. P. Russ, O. Rivoire, and R. Ranganathan, 2021

*Yaakov Kleeorin