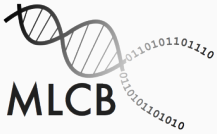
Building a library to evaluate generative protein models

Philip Hartout

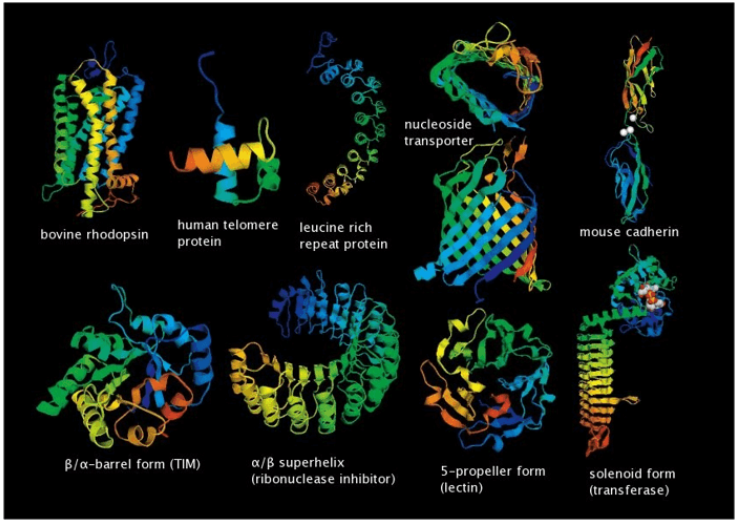
May 6, 2022



D BSSE

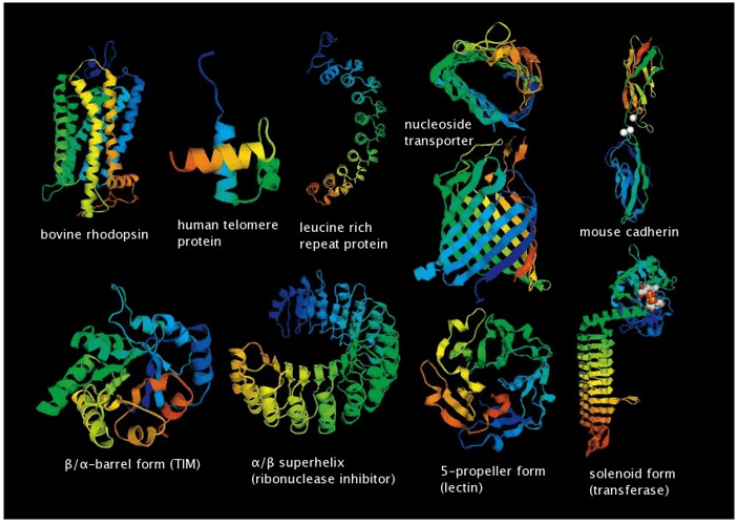
ETH zürich

Introduction



Proteins are diverse.

Introduction



Proteins are diverse.

Support all functions for life.

Generative Protein Modelling

Proteins

Generative Protein Modelling

Proteins

- well-defined (sequence)

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- large databases

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Evaluation Problem

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- large databases

Generative Model

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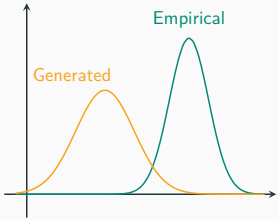
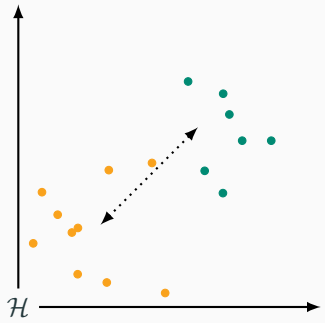
- generate samples following $P(X)$

Evaluation Problem

- Are the generated and empirical data distributions the same?



Maximum Mean Discrepancy (MMD)



MMD captures the distance between 2 sets on *any* RKHS $\mathcal{H}$.

Maximum Mean Discrepancy (MMD) – continued

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Currently accepted method to evaluate generative GNNs.

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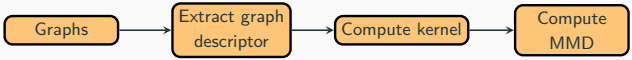

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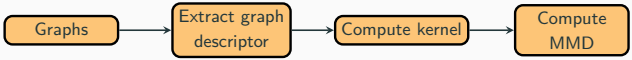

It's possible to leverage decades of kernel research!

Maximum Mean Discrepancy (MMD) – continued

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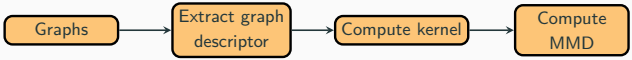

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Both a blessing and a curse:

Maximum Mean Discrepancy (MMD) – continued

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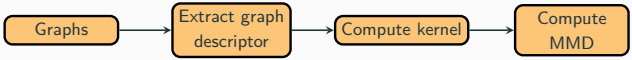

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Blessing Flexibility, Computation on multiple representations

Maximum Mean Discrepancy (MMD) – continued

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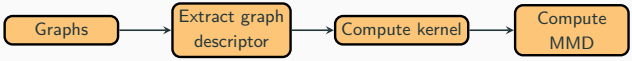

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Both a blessing and a curse:

Blessing Flexibility, Computation on multiple representations

Curse Instability (see O'Bray et al (2021)), hyperparameter tuning.

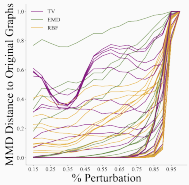


Figure 1: MMD computed from a clustering coefficient on synthetic graphs. TV: total variation kernel, RBF: radial basis function, EMD: earth mover's distance.

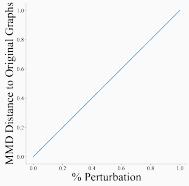


Figure 2: Ideal MMD behaviour.

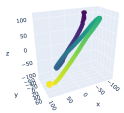
– Thesis Goal –

Build a library to evaluate generative protein models

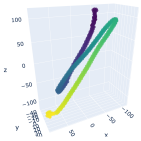
Experimental setup

Take 10 sets of 100 proteins from Alphafold DB (easy to work with)

Gaussian noise



Twist



Mutate

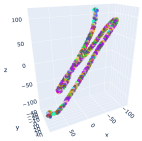
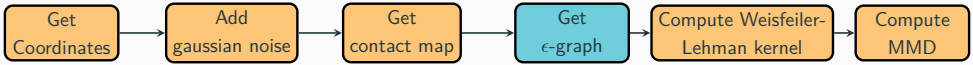


Figure 3: Adding Gaussian Noise. Color-coded according to the index.

Figure 4: Adding Twist. Color-coded according to the index.

Figure 5: Adding Mutations. Color-coded according to amino acid type.

Experiment 1 – Gaussian Noise



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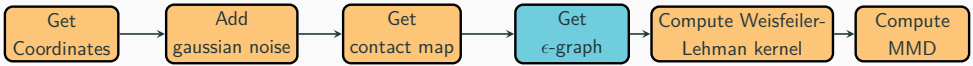

Each curve: different ε.

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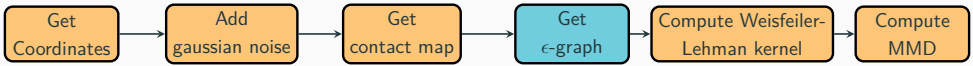

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2 sources of variance:

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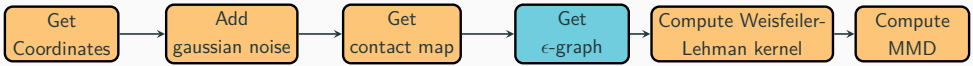

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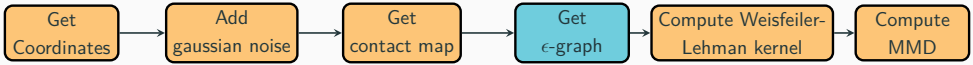

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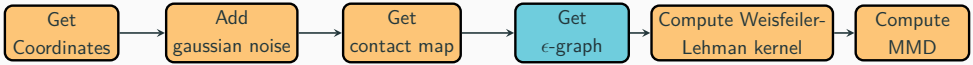

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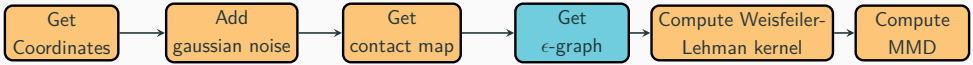

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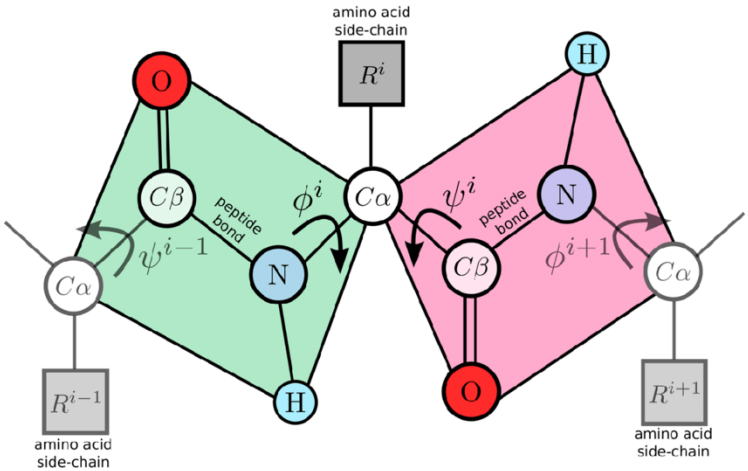
Conclusions

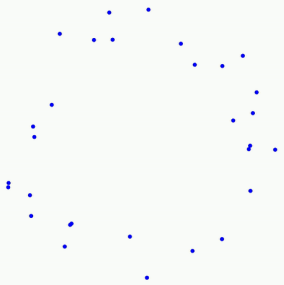
1. MMD is stable using the Weisfeiler-Lehman kernel
2. Choice of representation influences MMD

Dihedral angles



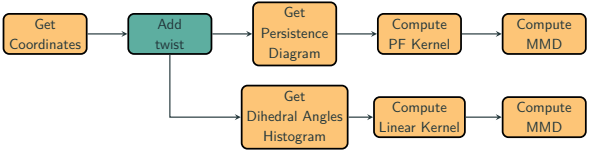
These angles *define* the shape of the protein.

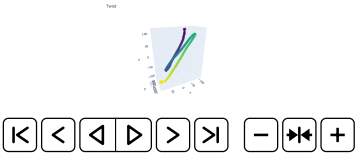
Čech filtrations



Čech filtrations captures connected components, cycles and holes by varying ε.

Experiment 2 – Twist





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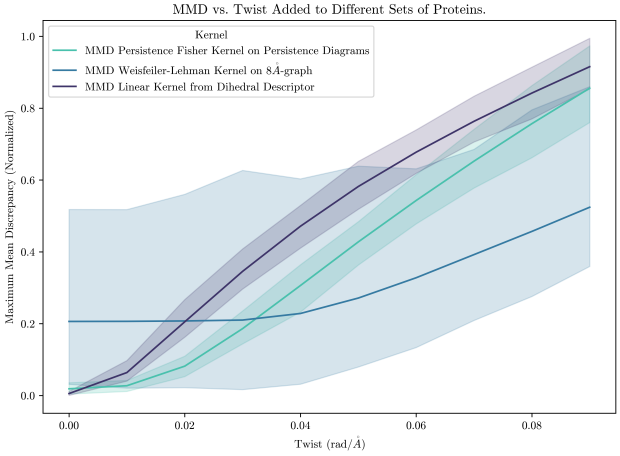

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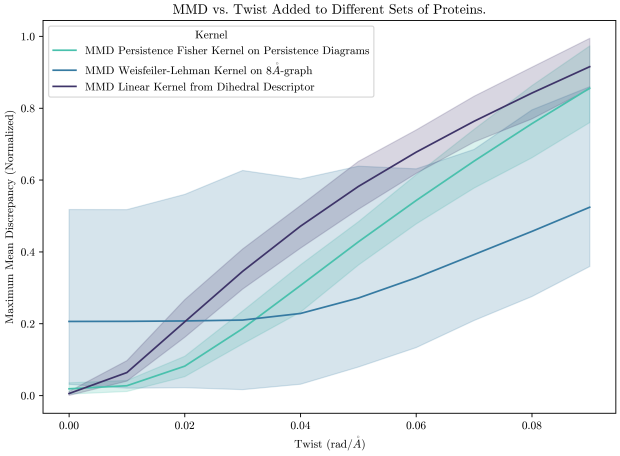

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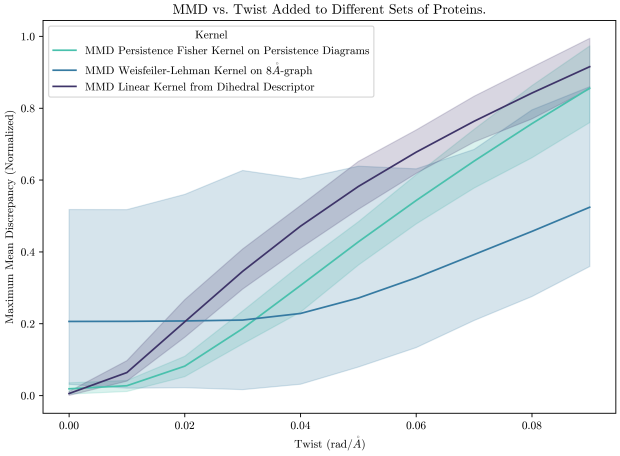

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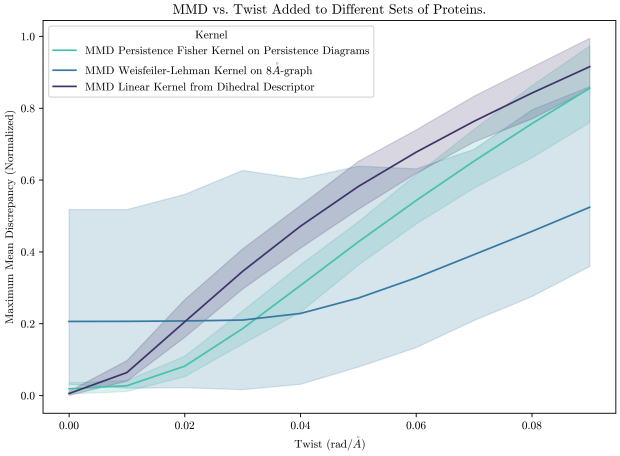

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Conclusions

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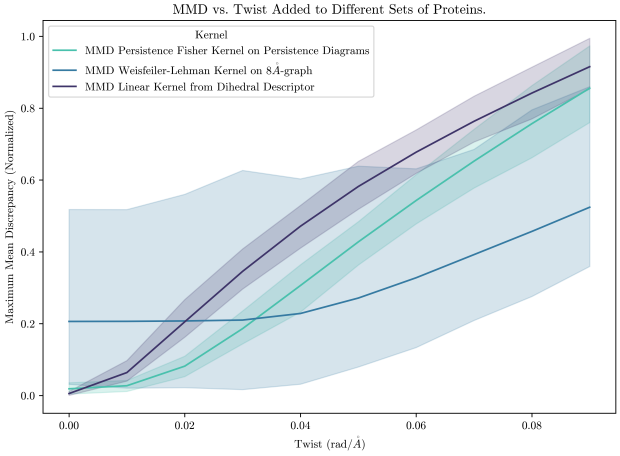

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2. Dihedral descriptor behave well, fast to compute

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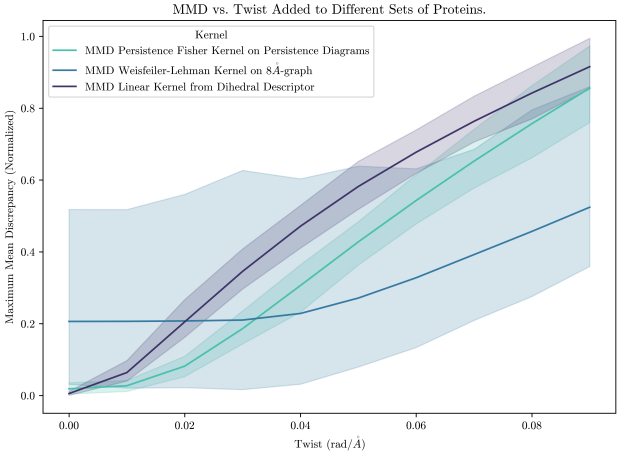

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3. Weisfeiler-Lehman kernel does not capture global shape changes

Experiment 3 – Mutate

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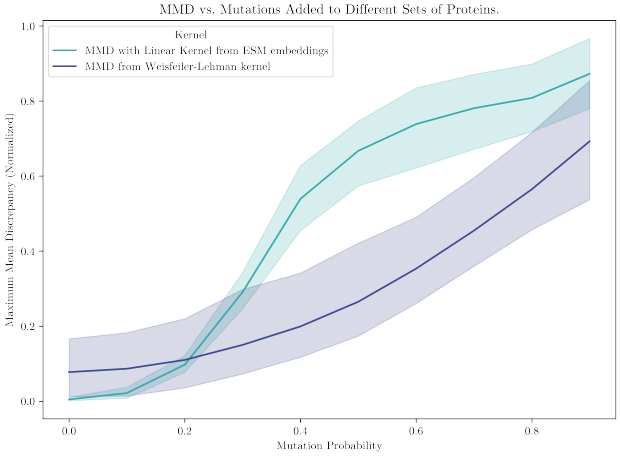

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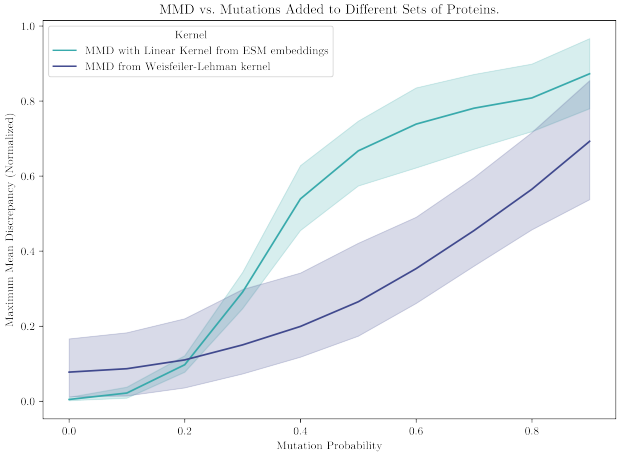

2 sources of variance:

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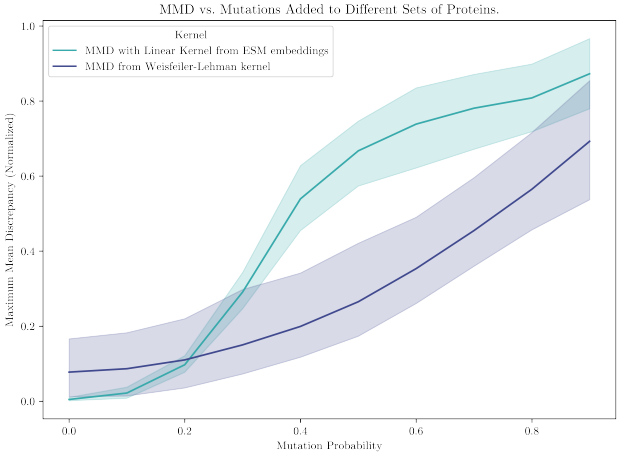

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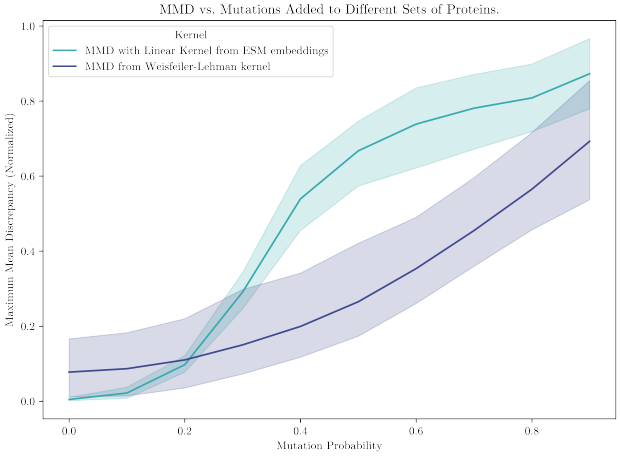
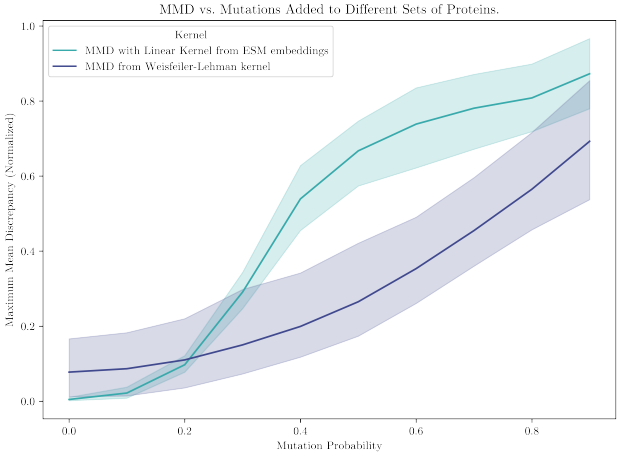


2 sources of variance:

- Data
- Mutation seed

Experiment 3 – Mutate



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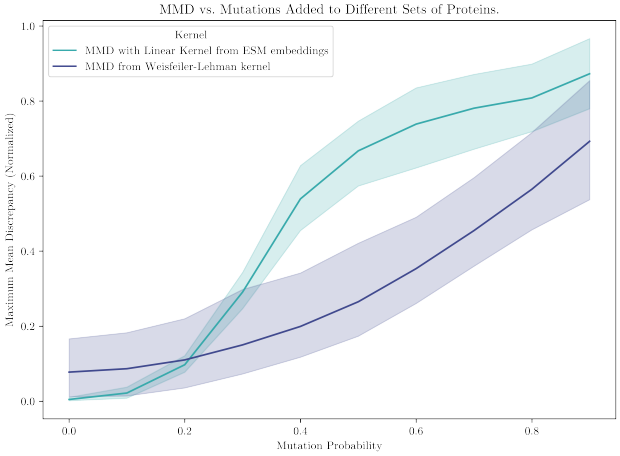

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Conclusions

1. Weisfeiler-Lehman kernel captures changes but noisy

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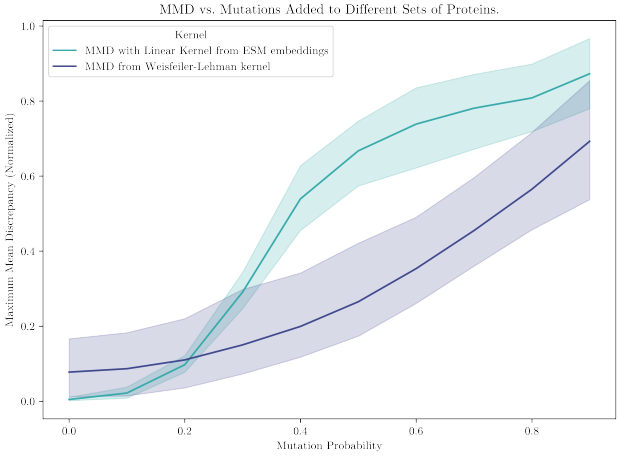

2 sources of variance:

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1. Weisfeiler-Lehman kernel captures changes but noisy
2. ESM captures changes.

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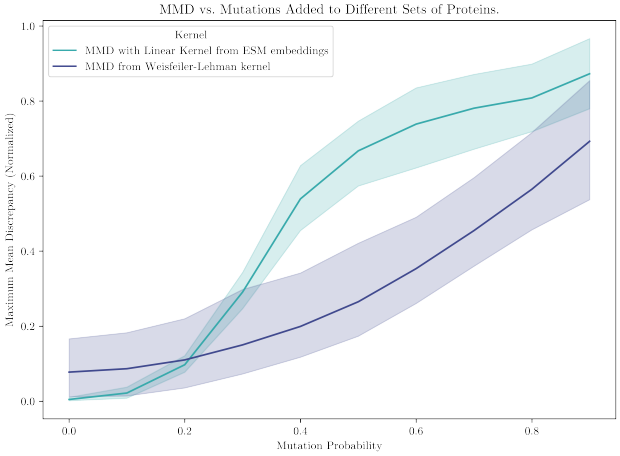

2 sources of variance:

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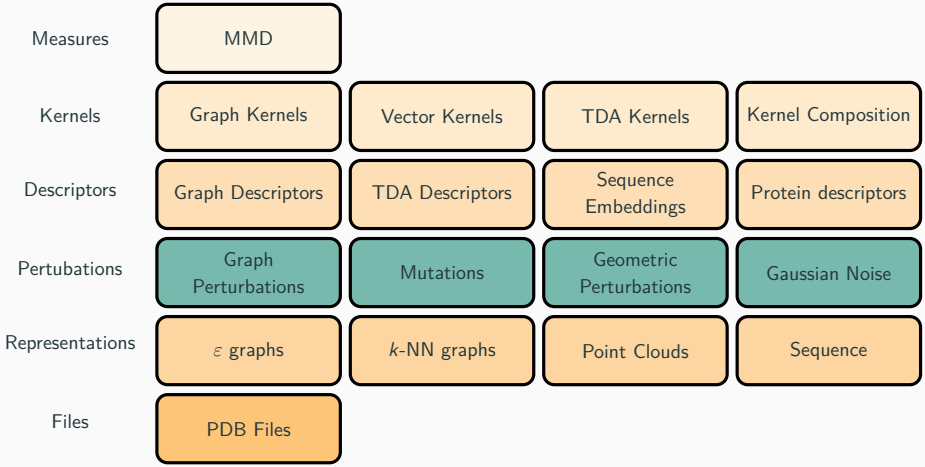
Conclusions

1. Weisfeiler-Lehman kernel captures changes but noisy
2. ESM captures changes.
3. Further study with lower mutation probabilities.

Questions - Overview



Maximum Mean Discrepancy (MMD)

$$\mathrm{MMD}(X, Y) := \frac{1}{n^2} \sum_{i,j=1}^{n} k(x_i, x_j) + \frac{1}{m^2} \sum_{i,j=1}^{n} k(y_i, y_j) - \frac{2}{nm} \sum_{i=1}^{n} \sum_{j=1}^{m} k(x_i, y_j)$$

where:

- $\mathcal{X}$ is some non-empty set.
- $x_i, x_j \subseteq \mathcal{X}$, n is the number of samples in $\mathbf{x}$;
- $y_i, y_j \subseteq \mathcal{X}$, m is the number of samples in $\mathbf{y}$;
- $k : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$ is a valid kernel.

MMD captures the distance between 2 sets on *any* RKHS $\mathcal{H}$.

API

```
base_feature_pipeline = pipeline.Pipeline(
    [
        ("coordinates", Coordinates(granularity="CA", n_jobs=12),),
        (
            "add gaussian noise",
            GaussianNoise(
                random_seed=42, noise_mean=0, noise_variance=10, n_jobs=12,
            ),
        ),
        ("contact map", ContactMap(metric="euclidean", n_jobs=12,),),
        ("epsilon graph", EpsilonGraph(epsilon=epsilon, n_jobs=12),),
    ]
)

proteins_perturbed = base_feature_pipeline.fit_transform(paths_to_pdb_files)
```

API

```
base_feature_pipeline = pipeline.Pipeline(
    [
        ("coordinates", Coordinates(granularity="CA", n_jobs=12),),
        (
            "add gaussian noise",
            GaussianNoise(
                random_seed=42, noise_mean=0, noise_variance=10, n_jobs=12,
            ),
        ),
        ("contact map", ContactMap(metric="euclidean", n_jobs=12,),),
        ("epsilon graph", EpsilonGraph(epsilon=epsilon, n_jobs=12),),
    ]
)

proteins_perturbed = base_feature_pipeline.fit_transform(paths_to_pdb_files)
```

```
graphs = load_graphs(proteins, graph_type="eps_graph")
graphs_perturbed = load_graphs(proteins_perturbed, graph_type="eps_graph")

mmd = MaximumMeanDiscrepancy(
    biased=True,
    squared=True,
    kernel=WeisfeilerLehmanKernel(
        n_jobs=12, n_iter=5, normalize=True, biased=True,
    ),
).compute(graphs, graphs_perturbed)
```

MMD with 8-Å-MMD with Weisfeiler-Lehman kernel