The influence of non-domain regions' composition on the activity of multi-domain protein kinases

Bachelor's thesis

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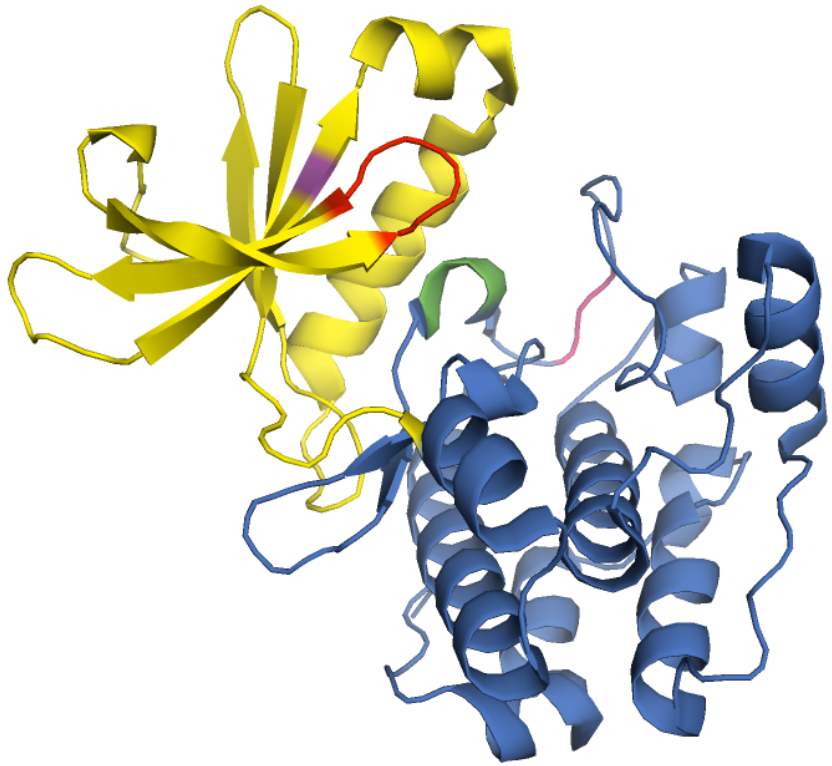
Overview

- Hypothesis: General linker composition traits influence the function and specificity of the adjoint domains.
- Key consequence: Prediction of protein domain function based on the analysis of the non-domain regions.
- Method: On human two-domain proteins with one PK domain do:
  1. acquire physicochemical attributes of the linkers and average them over their sequences,
  2. cluster the proteins by the averaged physicochemical attributes,
  3. embed GO terms and EC numbers into the clustering.
- Result: No colocalization of like GO or EC terms associated with proteins with different architectures was observed.

Protein kinase domain

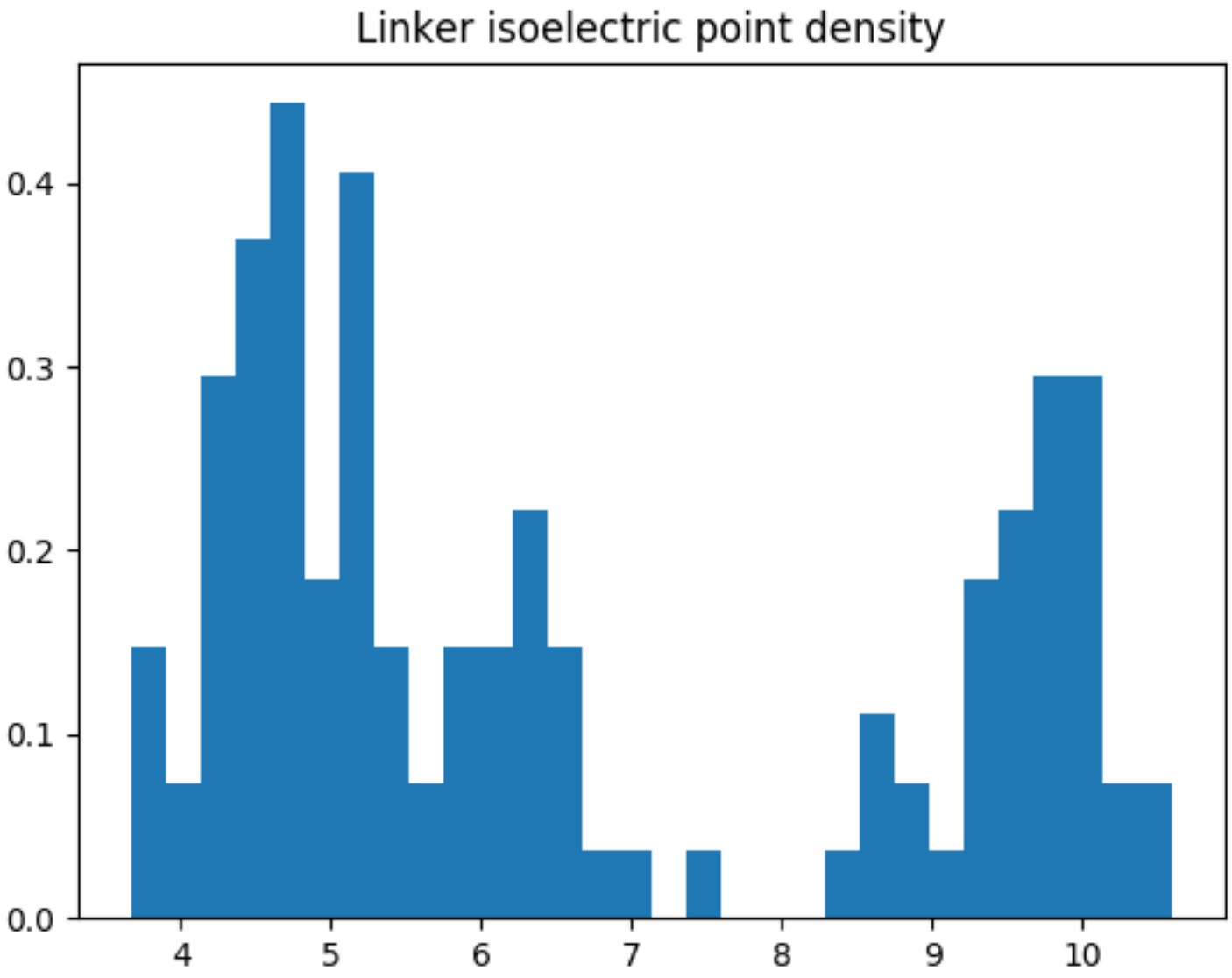
- Large and diverse family, involved in signal transduction.
- Phosphate group transfer from a phosphate donor onto a substrate.
- Bilobal structure with following conserved regions:
  - Gly-X-Gly-X-X-Gly motif
  - Invariant lysine
  - DFG motif
  - APE motif



Dataset

- 117 human two-domain proteins with one PK domain
- 32 different architectures
- Averaged physicochemical attributes of their inter-domain regions:
  - logarithm of the linker sequence length
  - isoelectric point
  - percentage of charged amino acids
  - GRAVY index

2D representation of the feature space performed by UMAP.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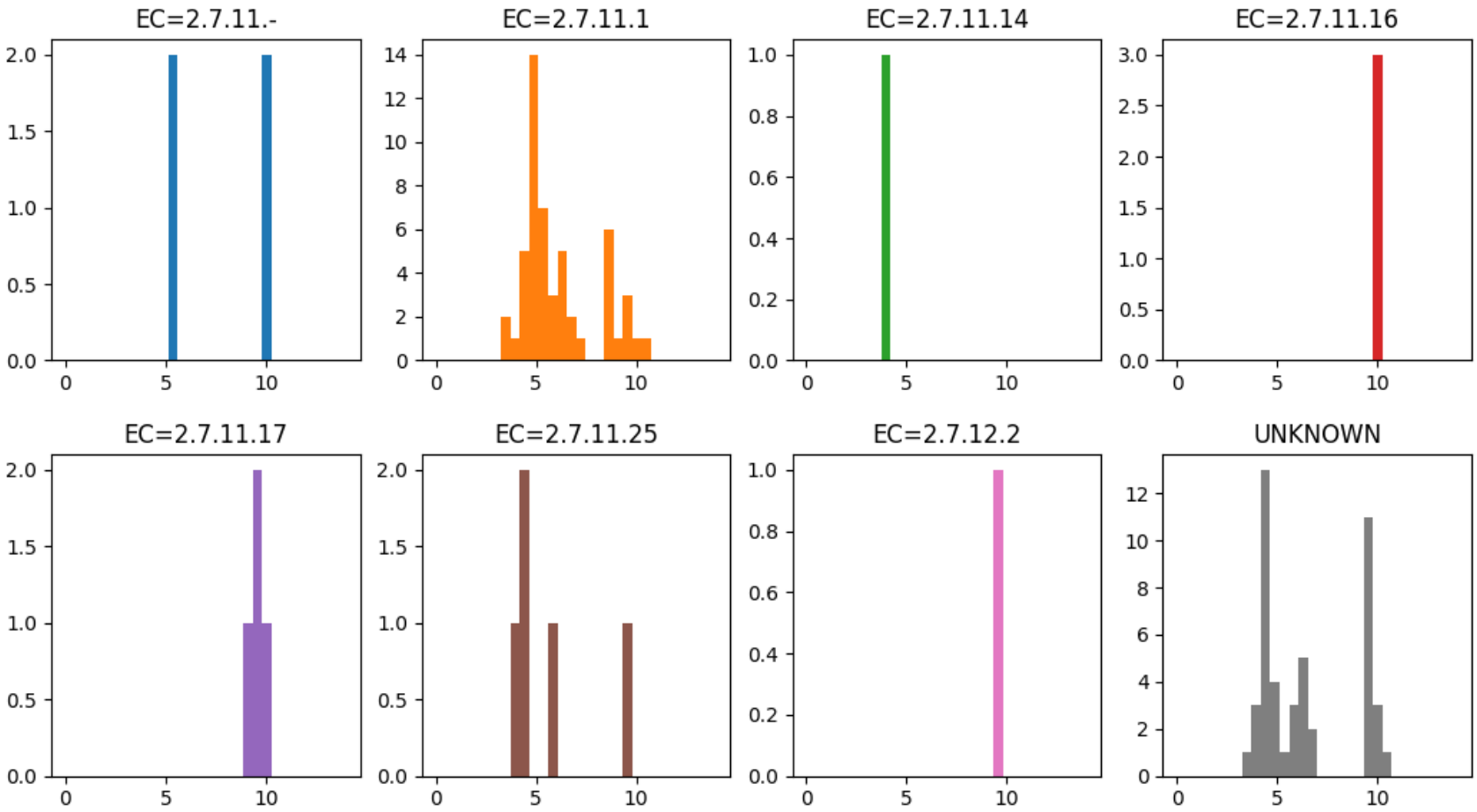
4
5
6
7
8
9
10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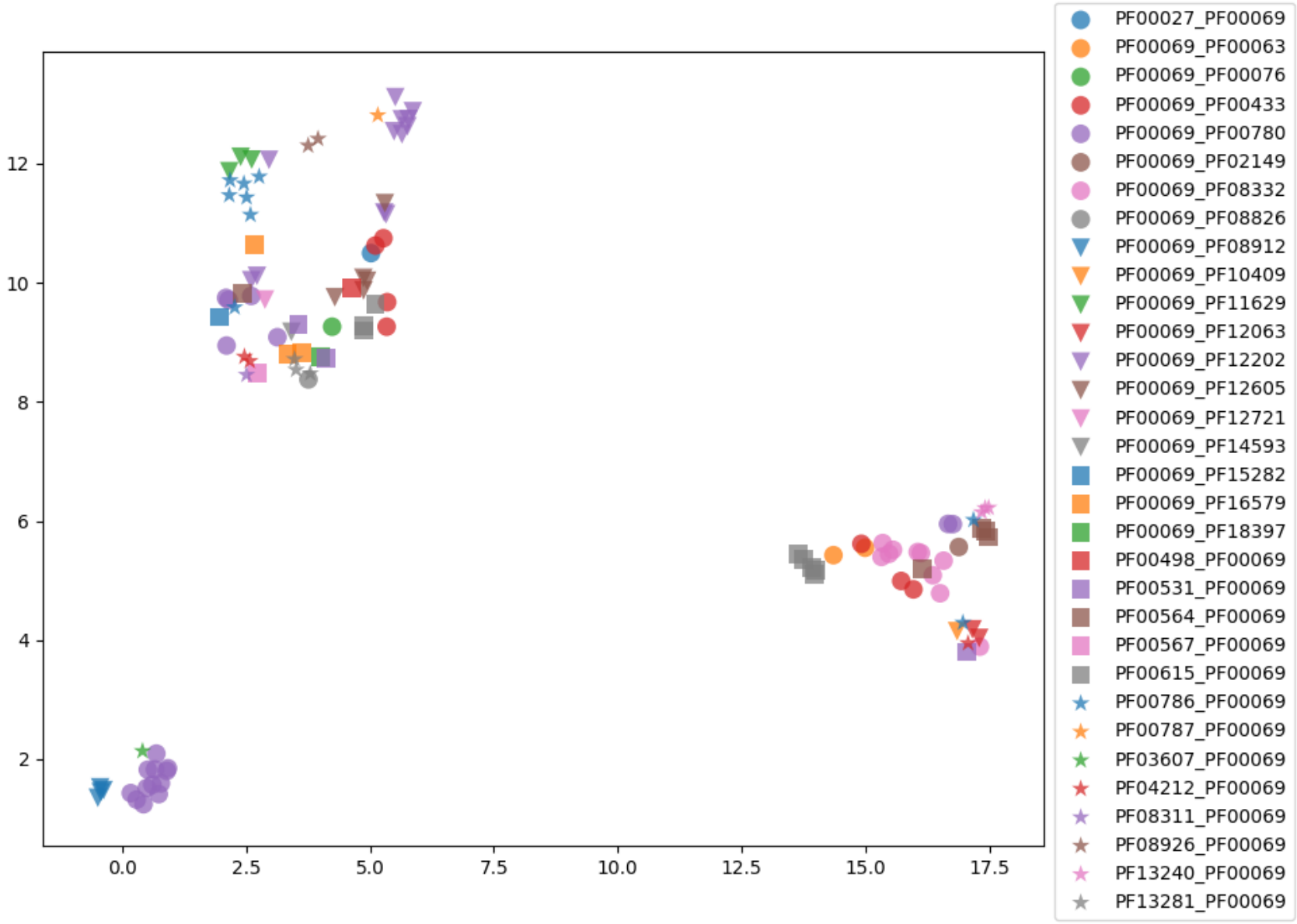
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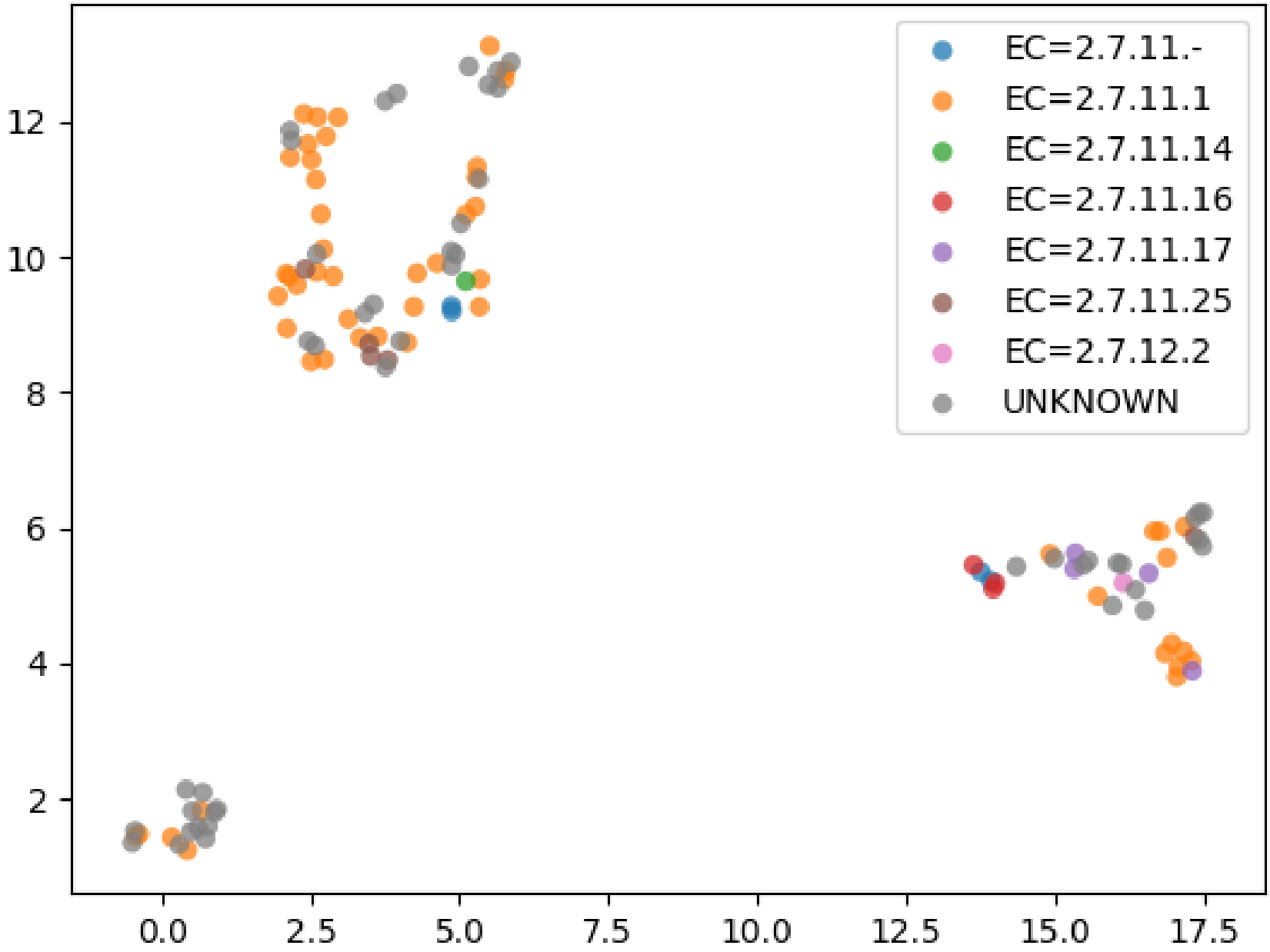
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15.0
17.5

Conclusion

- No general influence of the linkers' composition on the overall protein function observed.
- Problems:
  - 3.65625 proteins per architecture on average
  - GO and EC are too general and too precise, respectively
  - Observed linker types are determined by UMAP parametrization