Simple Models Work Best in Peptide Function Prediction

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J. Adamczyk, P. Ludynia, W. Czech *"Molecular Fingerprints Are Strong Models for Peptide Function Prediction"*, ArXiv preprint

Peptide Function Prediction

Peptides:

- small proteins, up to 50 amino acids
- potential novel therapeutics, e.g. antibiotics or anticancer drugs
- SMILES, amino-acid sequences, graphs

Peptide function prediction:

- binary classification
- does a peptide have a certain property, e.g. antibacterial?

Popular Approaches

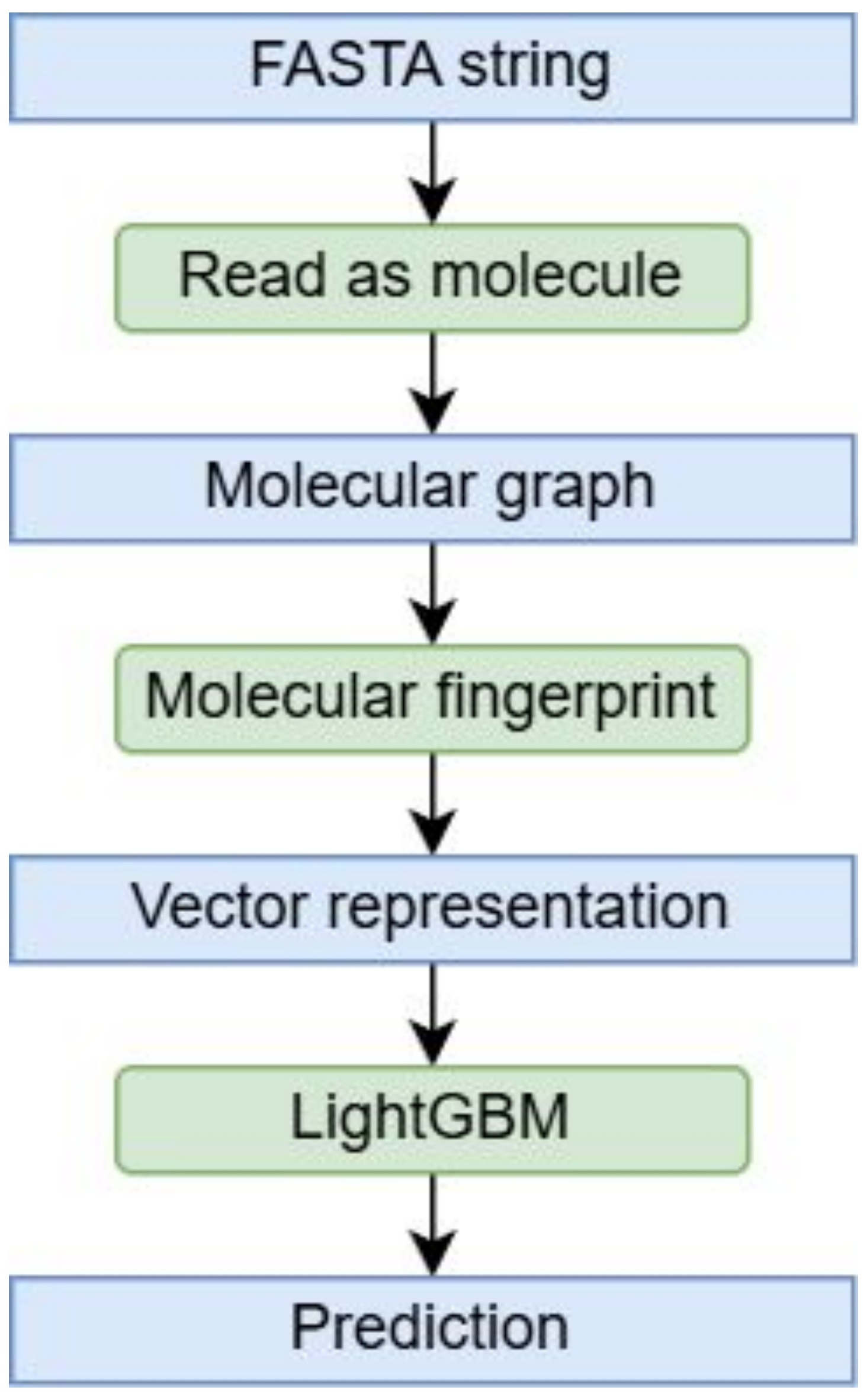
- protein language models (**PLMs**)
- graph neural networks (**GNNs**)
- complex multimodal feature engineering

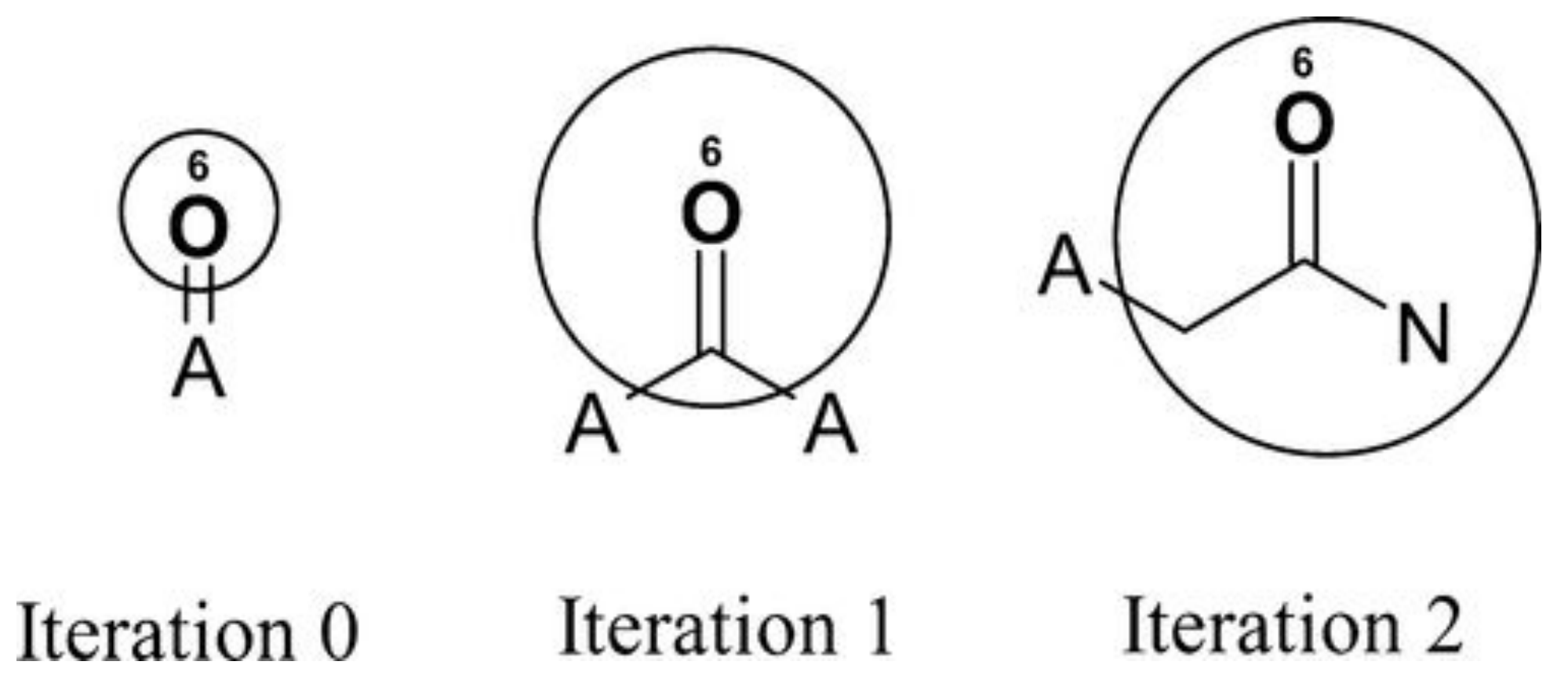
Long Range Graph Benchmark (LRGB)

- peptide benchmark for **graph learning**
- designed to require learning **long-range dependencies**
- benchmark mostly for graph neural networks (GNNs)
- **important assumption** - "proteins require long-range dependencies so peptides must require them too" - **but is it correct?**

Methods

- **molecular fingerprints**: ECFP, RDKit fp, Topological Torsion (TT)
- **vectorization algorithms** for molecules
- **hashed fingerprints** detect subgraphs of given shape and hash results onto feature vector
- **count fingerprints** count occurrences of subgraphs (binary would just detect if it exists)
- implemented using our own library for efficient computation of molecular fingerprints, **scikit-fingerprints**
- **LightGBM** classifier
- quickly trainable model with minimal number of parameters


FASTA string
Read as molecule
Molecular graph
Molecular fingerprint
Vector representation
LightGBM
Prediction



Example subgraph extraction in consecutive iterations of ECFP algorithm.

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Large Scale Benchnmarking

- **6** benchmarks, **126** datasets, **>215 thousand** unique peptides
- SOTA on 5 benchmarks:
  - LRGB
  - BERT-based models benchmark
  - XUAMP
  - AMPBenchmark
  - PeptideReactor
- AutoPeptideML - near SOTA but much faster and lighter

LRGB results:

Model	Peptides-func AUPRC ↑	Peptides-struct MAE ↓
Transformer	63.26 ± 1.26	0.2529 ± 0.0016
SAN	64.39 ± 0.75	0.2545 ± 0.0012
MOLTOP	64.59 ± 0.05	-
GraphGPS	65.35 ± 0.41	0.2500 ± 0.0005
GINE	66.21 ± 0.67	0.2473 ± 0.0017
GatedGCN	67.65 ± 0.47	0.2477 ± 0.0009
GCN	68.60 ± 0.50	0.2460 ± 0.0007
GraphViT	69.42 ± 0.75	0.2449 ± 0.0016
GRIT	69.88 ± 0.82	0.2460 ± 0.0012
CRaWl	70.74 ± 0.32	0.2506 ± 0.0022
GRED	71.33 ± 0.11	0.2455 ± 0.0013
DRew	71.50 ± 0.44	0.2536 ± 0.0015
HDSE	71.56 ± 0.58	0.2457 ± 0.0013
S^2GCN	73.11 ± 0.66	0.2447 ± 0.0032
RDKit	73.11	0.2459
TT	73.18	0.2438
ECFP	**74.60**	**0.2432**

- short-range model outperform the complex ones
  - conclusion: **peptides don't require long range dependencies**
  - short-range features contain enough information for accurate peptide function prediction
- why so many papers haven't used this simple method?
  - their fingerprint baselines used **binary** fingerprints instead of **count** variants
  - many scientists don't compare their models against **strong baselines!**

Conclusions and Lessons

- conclusions
  - molecular fingerprints are effective methods for peptide function prediction problem
  - simple vectorization + tree ensemble is able to **outperform deep-learning models**
  - assumption that peptides need long-range dependencies was false
- lessons
  - complex models might not always be the best
  - don't underestimate simple feature extraction methods
  - always compare your models against simple but strong baselines
  - design your baselines very carefully, read documentation and learn about the methods

References

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