# Automated Protein Function Description

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# Intro

- Machine learning for protein function prediction

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[2] Meet Barot et al. "NetQuilt: deep multispecies network-based protein function prediction using homology-informed network similarity". In: *Bioinformatics* 37.16 (Feb. 2021), pp. 2414–2422. DOI: 10.1093/bioinformatics/btab098.

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- NetQuilt[2]: integrating PPI networks of multiple organisms

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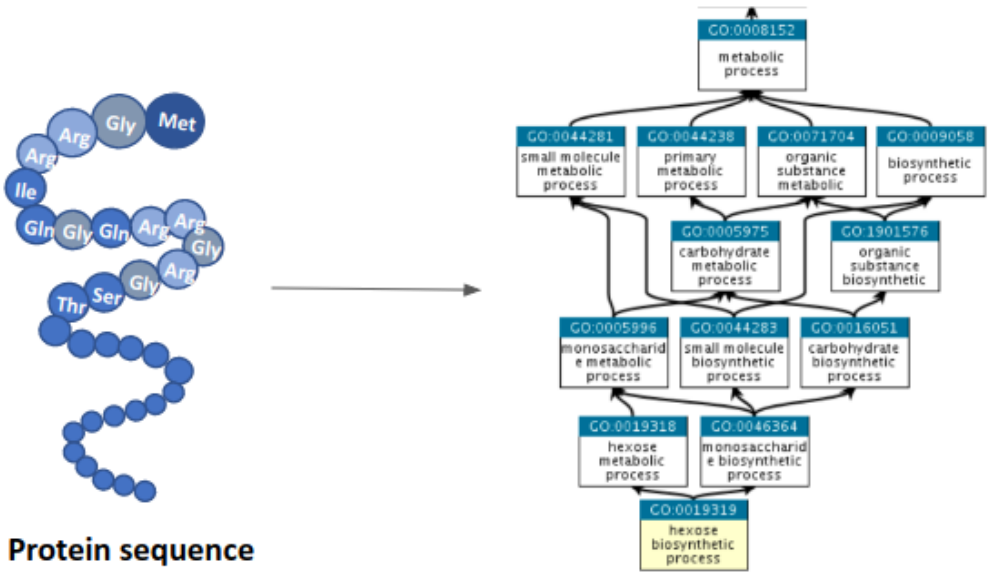
# Roadmap

1. Protein function prediction $\rightarrow$ protein function description
2. Motivation
3. Model
4. Evaluation metrics
5. Results

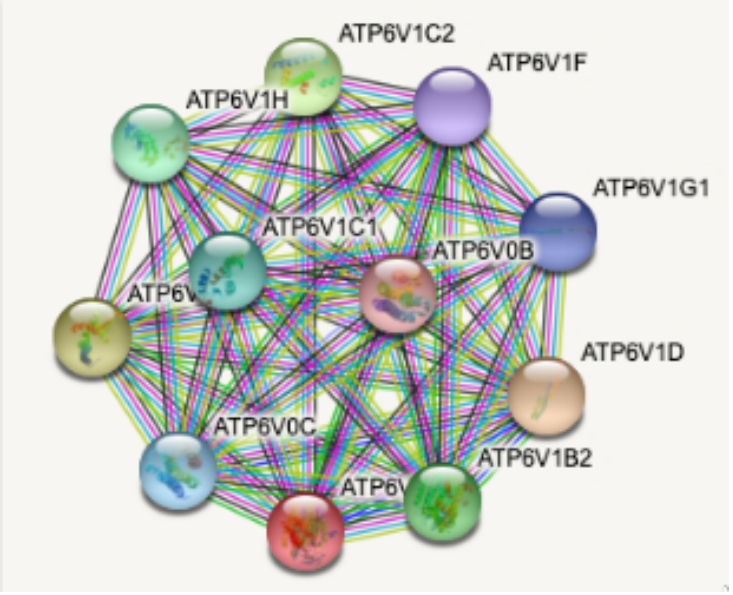
# Protein function prediction as it is

Supervised multilabel problem, where sequences are mapped to labels organized into a hierarchy, e.g. the Gene Ontology



# Protein function prediction as it **should be**

Given a set of proteins, describe their common function.




$\rightarrow$

"Proton-transporting atpase activity, rotational mechanism."

# Motivation for protein function description

Why make a model that describes the common functions of a set of proteins in natural language?

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To discover new categories of protein function with info to guide experimental design to test for them, we need a model that generates functional descriptions.

# Proposed model

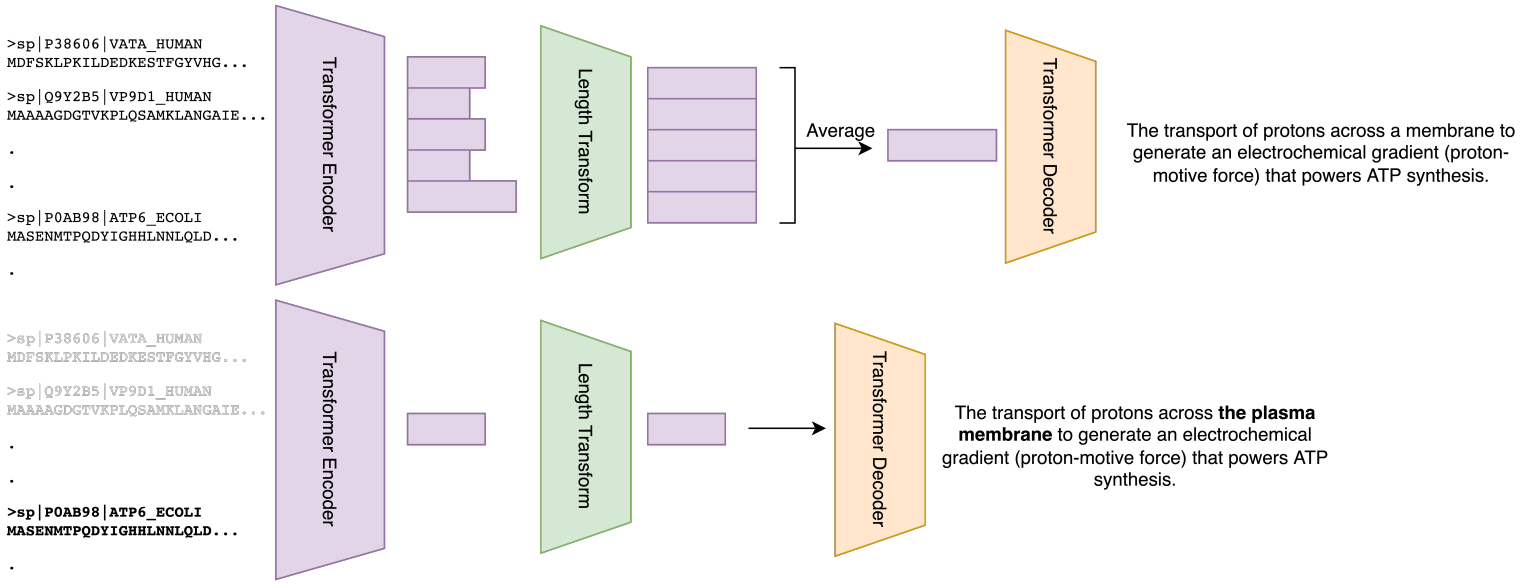


Figure: Transformer encoder-decoder model. Estimates $P(d|S)$ where S is a set of protein sequences and d is a given description.

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- Evaluating *generated* descriptions can really only be done manually.
  - This is not a solved problem in natural language processing.
  - Most work relies on manual ranking of generated text samples in terms of their similarity to a gold standard.
- We can, however, evaluate the scoring that the model assigns to pairs of sequence sets and their known descriptions.

# Evaluation metrics

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# Data

- Uniprot-KB Swiss-Prot (manually annotated and reviewed), 566,996 proteins total
  1. Maximum number of proteins per GO term: 1280
  2. Minmum number of proteins per GO term: 32
  3. Total number of proteins in training set: 316k
  4. Total number of proteins in validation set: 180k
  5. Total number of GO terms in training set: 9053
  6. Total number of GO terms in validation set: 2264

# Results

Table: Model Validation Set Performances

| Metric | Model scores | Term-normalized model scores |
|---|---|---|
| Correctness | 0.57 | 0.83 |
| Specificity | 0.52 | 0.58 |
| Robustness | 0.84 | 0.44 |

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- Taking a Gene Ontology term that was not included in training
- Sampling the proteins annotated with that term
- Use these proteins as input to the model
- Use beam search over token probabilities to generate tokens sequentially

# Validation set generation examples

GO:0032099: negative regulation of appetite
Actual description:
any process that reduces appetite .
Prediction:
any process that results in a change in state or activity of an organism ( in terms of a result of a leptin stimulus .

# Validation set generation examples

GO:0003725: double-stranded RNA binding
Actual description:
binding to double-stranded rna .
Prediction:
any process that activates or increases the rate or extent of rrna molecule .

# Validation set generation examples

GO:0035434: copper ion transmembrane transport
Actual description:
the directed movement of copper cation across a membrane .
Prediction:
the increase in size ( protons .

# Validation set generation examples

GO:0046992: oxidoreductase activity, acting on X-H and Y-H to form an X-Y bond
Actual description:
catalysis of an oxidation-reduction ( redox ) reaction in which x-h and y-h form x-y .
Prediction:
the formation of methane , the formula ch4 .

# Validation set generation examples

GO:0042023: DNA endoreduplication
Actual description:
regulated re-replication of dna within a single cell cycle , resulting in an increased cell ploidy . an example of this process occurs in the synthesis of drosophila salivary gland cell polytene chromosomes .
Prediction:
any process that modulates the frequency , rate or extent of chromatin organization .

# Future human-assisted evaluation of function discovery

- Human-assisted evaluation will be needed for the descriptions generated for a given set of novel proteins.

[3] Nisan Stiennon et al. "Learning to summarize with human feedback". In: *Advances in Neural Information Processing Systems* 33 (2020), pp. 3008–3021, Daniel M Ziegler et al. "Fine-tuning language models from human preferences". In: *arXiv preprint arXiv:1909.08593* (2019).

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  - This would be expensive, as the task needs to be done by an expert.
- This feedback could be used to fine-tune the model to produce more accurate, fluid or generally desirable descriptions of proteins, as has been done for document summarization models[3].

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