Automated Protein Function Description

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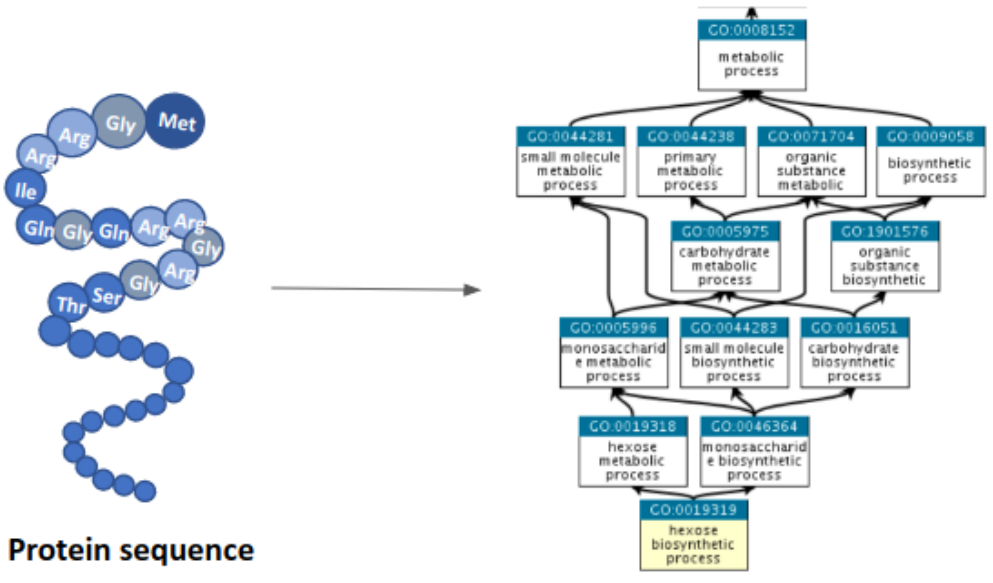
Roadmap

1. Protein function prediction $\rightarrow$ protein function description
2. Motivation
3. Evaluation metrics
4. Results
5. Performance issues
6. Experiments to do

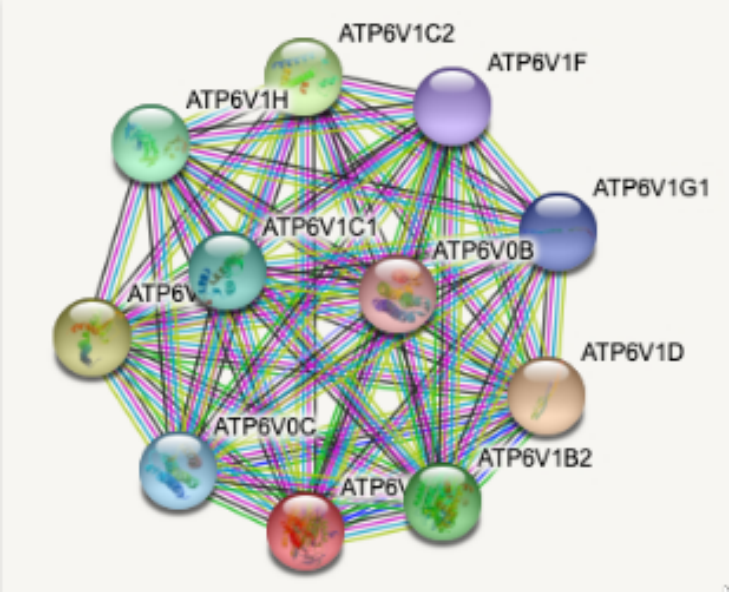
Protein function prediction as it is

Supervised multilabel problem, where sequences are mapped to labels organized into a hierarchy, i.e. 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.

Current methods for function discovery

- Many methods exist for function prediction, but most do not consider the problem of discovering novel functions.

[1] Maxat Kulmanov and Robert Hoehndorf. "DeepGOZero: Improving protein function prediction from sequence and zero-shot learning based on ontology axioms". In: *bioRxiv* (2022). DOI: 10.1101/2022.01.14.476325. eprint: https://www.biorxiv.org/content/early/2022/01/14/2022.01.14.476325.full.pdf. URL: https://www.biorxiv.org/content/early/2022/01/14/2022.01.14.476325.

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- DeepGOZero[1] predicts for terms not included in the training set, but this is limited to terms with ontological relations with known terms.

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Proposed model

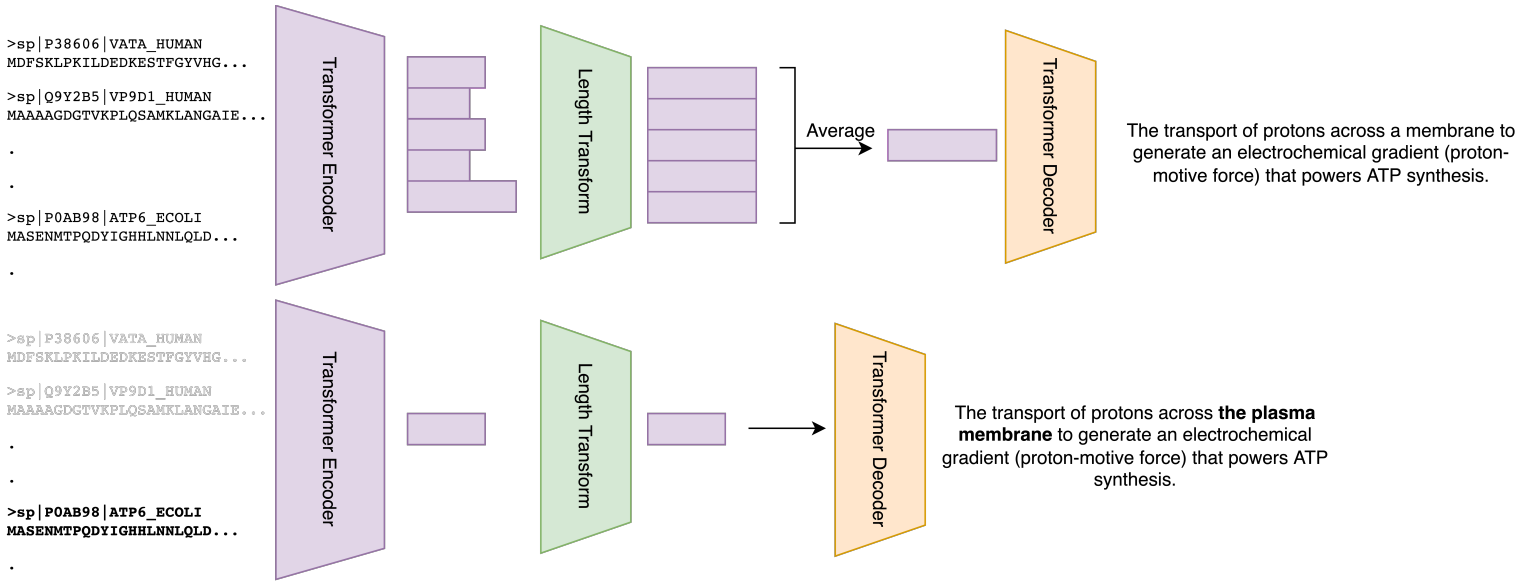

Figure: Transformer encoder-decoder model. Estimates $P(d|S)$ where S is a set of protein sequences and d is a given description.

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   - Generation using beam search

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- We can, however, evaluate the scoring that the model assigns to pairs of sequence sets and their known descriptions.

Evaluation

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2. Specificity
3. Robustness

Attribute 1: Annotation correctness.

Descriptions of GO terms that annotate the entire sequence set should be scored higher than terms that do not.

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We can calculate the average number of times a correct description outranks an incorrect one:

$$\frac{1}{|D_S| * |D_S^c|} \sum_{d_i \in D_S, d_j \notin D_S} \mathbb{1}(P(d_i|S) > P(d_j|S))$$

where D_S^c is the complement of D_S and $\mathbb{1}$ is the indicator function.

Attribute 2: Specificity preference.

Among correct terms, the model should score child terms higher than their parent terms.

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We can calculate the average number of times a correct child term outranks its parent term(s):

$$\frac{1}{|D_S|} \sum_{d_i \in D_S} \mathbb{1}(P(d_i|S) > P(A(d_i)|S))$$

Attribute 3: Annotation robustness.

Any pair of sequence sets that have the same GO descriptions in common should produce scores with the same rankings for those GO descriptions.

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We can calculate the average Spearman's rank correlation of the rankings for all sequence sets' correct descriptions.Let $R_{S_i} = R(P(D_{S_i}|S_i))$:

$$\frac{1}{N * (N-1)} \sum_{S_i, S_j} \frac{\text{cov}(R_{S_i}, R_{S_j})}{\sigma_{R_{S_i}} \sigma_{R_{S_j}}}$$

where N is the total number of sequence sets that have the exact set of GO descriptions D_{S_i}.

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 Performances

Metric	Validation set peformance
Annotation Correctness	0.54
Specificity Preference	0.57
Annotation Robustness	0.88

Training set generation examples

- Prediction: any process that modulates the frequency , rate or extent of calcidiol 1-monooxygenase activity .
- Actual description: any process that modulates the rate , frequency or extent of calcidiol 1-monooxygenase activity . calcidiol 1-monooxygenase activity is catalysis of the reaction calcidiol + nadph + h+ + o2 = calcitriol + nadp+ + h2o .

Training set generation examples

- Prediction: the modification of histone h4 by the addition of the addition of histone h2a .
- Actual description: the process involved in retention of aberrant or improperly formed mrnas , e . g . those that are incorrectly or incompletely spliced or that have incorrectly formed 3 ' -ends , within the nucleus at the site of transcription .

Training set generation examples

- Prediction: the process in which the developmental fate .
- Actual description: the multiplication or reproduction of cells , resulting in the expansion of a cell population that contributes to the shaping of the heart .

Training set generation examples

- Prediction: catalysis of the reaction (+ h2o + phosphate + phosphate .
- Actual description: enables the transfer of a solute or solutes from one side of a membrane to the other according to the reaction atp + h2o + thiamine (out) = adp + h (+) + phosphate + thiamine (in) .

Validation set generation examples

- Prediction: catalysis of the reaction sinapaldehyde + nadph = nadp+ = h+ .
- Actual description: binding to fructose 6-phosphate .

Validation set generation examples

- Prediction: catalysis of the reaction 2-deoxy-d-ribose 5-phosphate = d-glyceraldehyde 3-phosphate + acetaldehyde + acetaldehyde + acetaldehyde ...
- Actual description: catalysis of the reaction n6- (1 , 2-dicarboxyethyl) amp = fumarate + amp .

Validation set generation examples

- Prediction: the chemical reactions and pathways resulting in the formation of asparagine , the fundamental heterocyclic group of asparagine , from simpler precursors , the formation of the formation of the formation of the formation of the multisubunit water-soluble proteins , the formation of the multisubunit water-soluble proteins , the multisubunit water-soluble proteins , the multisubunit water-soluble proteins , the formation of the formation of the formation ...
- Actual description: the chemical reactions and pathways involving of salicylic acid (2-hydroxybenzoic acid) , a derivative of benzoic acid .

Current experiments to do

- Remove restriction of training/testing on functions with 32 to 1280 examples
- Architecture search
- Add oversmoothing regularization[2]
- Train on TREMBL annotations (more than 100 million proteins with some GO annotation, unreviewed)

[2] Ilia Kulikov, Maksim Eremeev, and Kyunghyun Cho. "Characterizing and addressing the issue of oversmoothing in neural autoregressive sequence modeling". In: *ArXiv* abs/2112.08914 (2021).

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