End-to-end multitask learning, from protein language to protein features without alignments

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Abstract

Correctly predicting features of protein structure and function from amino acid sequence alone remains a supreme challenge for computational biology. For almost three decades, state-of-the-art approaches combined machine learning and evolutionary information from multiple sequence alignments. Exponentially growing sequence databases make it infeasible to gather evolutionary information for entire microbiomes or metaproteomics. On top, for many important proteins (e.g. *dark proteome* and *intrinsically disordered proteins*) evolutionary information remains limited. Here, we introduced a novel approach combining recent advances of Language Models (LMs) with multi-task learning to successfully predict aspects of protein structure (secondary structure) and function (cellular component or subcellular localization) without using any evolutionary information from alignments. Our approach fused self-supervised pre-training LMs on an unlabeled big dataset (UniRef50, corresponding to 9.6 billion words) with supervised training on labelled high-quality data in one single end-to-end network. We demonstrated the effectiveness of the novel concept through the successful per-residue prediction of protein secondary structure (Q3=85%, Q8=72%) and through per-protein predictions of localization (Q10=69%) and the distinction between integral membrane and water-soluble proteins (Q2=89%). On top, multi-task predictions are 300-3000 times faster (where HHblits needs 30-300 seconds on average, our method needed 0.045 seconds). These new results push the boundaries of predictability towards grayer and darker areas of the protein space, allowing to make reliable predictions for proteins which were not accessible by previous methods. On top, our method remains scalable as it removes the necessity to search sequence databases for evolutionary related proteins.

Key words: Machine Learning; Language Modelling; Semi-Supervised Learning; Multi-Task Learning; Protein Secondary Structure Prediction; Protein subcellular-localization Prediction.

Abbreviations used: 1D, one-dimensional – information representable in a string such as secondary structure or solvent accessibility; **3D**, three-dimensional; **3D structure**, three-

dimensional coordinates of protein structure; **NLP** Natural Language Processing; **PIDE**, percentage of pairwise identical residues;

Introduction

Successful combination of evolutionary information and artificial intelligence. Predicting structural and functional aspects of proteins based on their amino acid sequence has been one of the most challenging problems for computational biology. Researchers have been working on this problem for nearly five decades in order to bridge the sequence-structure/function gap, i.e. the gap between 180M proteins of known sequence (UniProt (Consortium, 2018)) and about 560K proteins with experimental annotations about function (SwissProt (Boutet et al., 2016)) or 150K with high-resolution experimental structures (PDB (Berman et al., 2000)). The biggest single improvement in prediction performance was achieved over two decades ago through the combination of achine learning (ML) and evolutionary information, i.e. the profiles extracted from Multiple Sequence Alignments (MSA) of related proteins as input feature for protein secondary structure prediction (Rost & Sander, 1993a, 1993b, 1994a). Evolutionary information was quickly adopted by the field (Frishman & Argos, 1995; Jones, 1999; Mehta, Heringa, & Argos, 1995) and has become the *de facto* standard for encoding protein sequences for most machine learning applications, including the prediction of transmembrane helices (Rost, Casadio, Fariselli, & Sander, 1995), solvent accessibility (Pollastri, Baldi, Fariselli, & Casadio, 2002; Rost & Sander, 1994b), protein flexibility (Capriotti, Fariselli, & Casadio, 2005; Radivojac et al., 2004), inter-residue contacts (Hayat, Sander, Marks, & Elofsson, 2015), protein-protein interactions (Hamp & Rost, 2015; Zhang et al., 2012), and subcellular localization (Casadio, Martelli, & Pierleoni, 2008; Tatyana Goldberg et al., 2014; Nair & Rost, 2003).

With protein sequence data exploding exponentially, evolutionary information becomes even more valuable (Jones, 1999; Rost, 2001). However, even today's fastest solutions, HHBlits3 (M. Steinegger et al., 2019) and MMSeqs2 (Steinegger & Söding, 2017), can hardly cope with all 2.5B sequences in BFD (Steinegger, Mirdita, & Söding, 2019). On top, evolutionary information is more tricky to obtain for proteins that are difficult to align such as intrinsically disordered proteins (IDPs), or proteins from the Dark Proteome (Perdigao et al., 2015).

Mining the wealth of unlabeled bio-data through transfer learning. What if we could replace the search for evolutionary related proteins by semi-supervised multi-task (MT) learning? Such an approach would build upon the recent success of language models (LMs) (Devlin, Chang, Lee, & Toutanova, 2018; Howard & Ruder, 2018; Peters et al., 2018) applied to protein sequences (Heinzinger et al., 2019; Rives et al., 2019). Language models are trained on large unlabeled text-corpora to predict the most probable next word in a sentence, given all previous words in this sentence (auto-regression). As only a sequence of words (sentence) is needed to train, such approaches are referred to as *self-supervision*, i.e. the learning of syntax and semantics through data without requiring expert knowledge. The same idea can be adopted to computational biology by considering single amino acids as words and their sequences as sentences. This simple transfer unleashes the power of big data sets easily outgrowing text-corpora used in NLP such as Wikipedia by orders of magnitude (Heinzinger et al., 2019; Howard & Ruder, 2018; Rives et al., 2019).

So far applications of LMs to protein sequences have split the training into two phases (Alley, Khimulya, Biswas, AlQuraishi, & Church, 2019; Heinzinger et al., 2019; Howard & Ruder, 2018): (1) self-supervised pre-training on unlabeled data learns vector representations (embeddings), which is followed by (2) supervised training of a second network on labeled data using the embeddings as input. Although transfer learning succeeds to an amazing extent to extract some principles relevant for the understanding the language of life, databases of protein sequences do not capture any explicit information about the molecular constraints shaping proteins in evolution. Not surprisingly, the simple two-step

solution self-supervised transfer-learning followed by supervised deep-learning fails to beat the best methods using evolutionary information. For NLP, multi-task (MT)_learning merges the two steps in an end-to-end trainable machine, e.g. through transformer models currently reaching the state-of-the-art in NLP (Dai et al., 2019; Devlin et al., 2018; Radford et al., 2019).

Here we hypothesized that multi-task (MT)_learning, aka. merging of the two aforementioned steps (self-supervised transfer-learning followed by supervised deep-learning) into one end-to-end network might enable the fine tuning of the application of NLP models to particular supervised problems. More specifically, we trained a MT transformer model on five different tasks: (1) The language modeling task was trained on 35M sequences from UniRef50 (Suzek et al., 2015); (2) The per-residue (word-level) tasks included the prediction of secondary structure in three (helix, strand & other) and eight states (3-turn helix, 4-turn helix, 5-turn helix, hydrogen bonded turn, extended strand in parallel and/or anti-parallel β-sheet conformation, residue in isolated β-bridge, bend, coil)(DSSP (Kabsch & Sander, 1983)); (3) The per-protein (sentence-level) tasks included the predictions of protein subcellular localization in ten classes and a binary classification into membrane-bound and soluble proteins. In order to simplify the comparability of results between different approaches, we used two datasets from recent state-of-the-art publications (Almagro Armenteros, Sonderby, Sonderby, Nielsen, & Winther, 2017; Klausen et al., 2019).

Materials & Methods

Data

Language modeling. The self-supervised, language modelling task was trained on UniRef50 a subset of UniProt (Consortium, 2018) clustered at 50% pairwise sequence identity (PIDE). The database contained 33M protein sequences with 9,577,889,953 residues and a vocabulary of 25 words: the standard 20 and two rare amino acids (U and O) along with three letters for ambiguous (B, Z) or unknown amino acids (X). Each protein was treated as a sentence and each amino acid was interpreted as a single word. The model was trained using 99.9% of the data, while randomly keeping 0.01% (~33k) of the proteins for validation. In this case, since the goal is self-supervision, homology doesn't play a major role and thus train/validation splits could be drawn at random. The maximal model length was set to 1024; for proteins longer than 1024 residues only the first 1024 residues were used.

Per-residue: secondary structure. Using a data set of protein secondary structure previously published (Klausen et al., 2019) simplified comparisons of this task to state-of-the-art prediction methods, including: NetSurfP2.0 (Klausen et al., 2019), Spider3 (Heffernan, Yang, Paliwal, & Zhou, 2017), RaptorX (S. Wang, Li, Liu, & Xu, 2016) and JPred4 (Drozdetskiy, Cole, Procter, & Barton, 2015). For training, 10,837 sequence-unique (at 25% PIDE) proteins with high-quality 3D structures (<2.5Å or 0.25nm) were collected by the PISCES server (G. Wang & Dunbrack Jr, 2003) from the Protein Data Bank – PDB (Berman et al., 2000). DSSP (Kabsch & Sander, 1983) assigned secondary structure; residues without atomic coordinates (*REMARK-465*) were removed. The seven DSSP states (+ one for unknown) were mapped to three states as in previous works (Rost & Sander, 1993b): [G,H,I] → H: helix, [B,E] → E: strand, all others to O: other). Since the NetSurfP-2.0 data only published the pre-computed protein profiles, protein sequences were extracted through SIFTS (Velankar et al., 2012). During this mapping step, 56 proteins were removed from the training and three from the test set due to differences in lengths between SIFTS and NetSurfP-2.0 (two from CB513 (Cuff & Barton, 1999); one from CASP12 (Abriata, Tamò, Monastyrskyy, Kryshtafovych, & Dal Peraro, 2018); none from TS115 (Y. Yang et al., 2016)). Proteins longer than 512 residues were also removed due to constraints of our transformer

models. Three test sets (also referred to as validation sets) were distinguished: TS115: 115 proteins from high-quality structures (<3Å) released after 2015 (and at most 30% PIDE to any protein of known structure in the PDB at the time); CB513: 513 non-redundant sequences compiled 20 years ago (511 after SIFTS mapping); CASP12: 21 proteins taken from the CASP12 free-modelling targets (20 after SIFTS mapping; all 21 fulfilled a stricter criterion toward non-redundancy than the two other sets; non-redundant with respect to all 3D structures known until May 2018 and all their relatives). The NetSurfP-2.0 authors removed all proteins from the training set which had more than 25% PIDE to any protein in their test sets.

Per-protein data: subcellular localization and membrane/soluble. The prediction of subcellular localization (also referred to as *location* or *cellular component*) was trained and evaluated through data introduced by the authors of DeepLoc (Almagro Armenteros et al., 2017), one of the state-of-the-art prediction methods for this task. The performance of several other methods was also evaluated on this set, namely: LocTree2 (T. Goldberg, Hamp, & Rost, 2012), MultiLoc2 (Blum, Briesemeister, & Kohlbacher, 2009), SherLoc2 (Briesemeister et al., 2009), CELLO (Yu, Chen, Lu, & Hwang, 2006), iLoc-Euk (Chou, Wu, & Xiao, 2011), WoLF PSORT (Horton et al., 2007) and YLoc (Briesemeister, Rahnenfuhrer, & Kohlbacher, 2010). This data set pools proteins with experimental annotation (code: ECO:0000269) from UniProtKB/Swiss-Prot (release: 2016_04, (Consortium, 2018)). To facilitate training and evaluation, the authors of DeepLoc mapped the plain localization annotations to ten classes, removing all proteins with multiple annotations. Additionally, all proteins were labelled as *water-soluble* or *membrane-bound* (some with ambiguous annotations as *unknown*). The resulting 13,858 proteins were clustered to 8,464 representatives with PSI-CD-HIT (Fu, Niu, Zhu, Wu, & Li, 2012; Li & Godzik, 2006) (version 4.0; at 30% PIDE or E-val<10-6; the alignment had to cover at least 80% of the shorter protein). The remaining proteins were split into training and testing by using the same proteins for testing as DeepLoc. Similar to DeepLoc, proteins longer than the maximum processed by the method (1000 for DeepLoc, 1024 for the method presented here) remained in the data set and were simply cut (keeping the first and the last 512 residues).

Evaluation measures. For simplicity of comparison, the evaluation measures followed previous publications (Almagro Armenteros et al., 2017; Klausen et al., 2019), namely three-state per-residue accuracy (Q3 (Rost & Sander, 1993b)) as the percentage of residues correctly predicted in three secondary structure states (helix, strand, other), the corresponding eight-state per-residue accuracy (Q8), the two-state per-protein accuracy (Q2) to describe the percentage of proteins correctly predicted as membrane-bound/water-soluble, and the ten-state per-protein accuracy (Q10) for the ten classes of localization. All numbers reported constituted averages over all proteins in the final test sets.

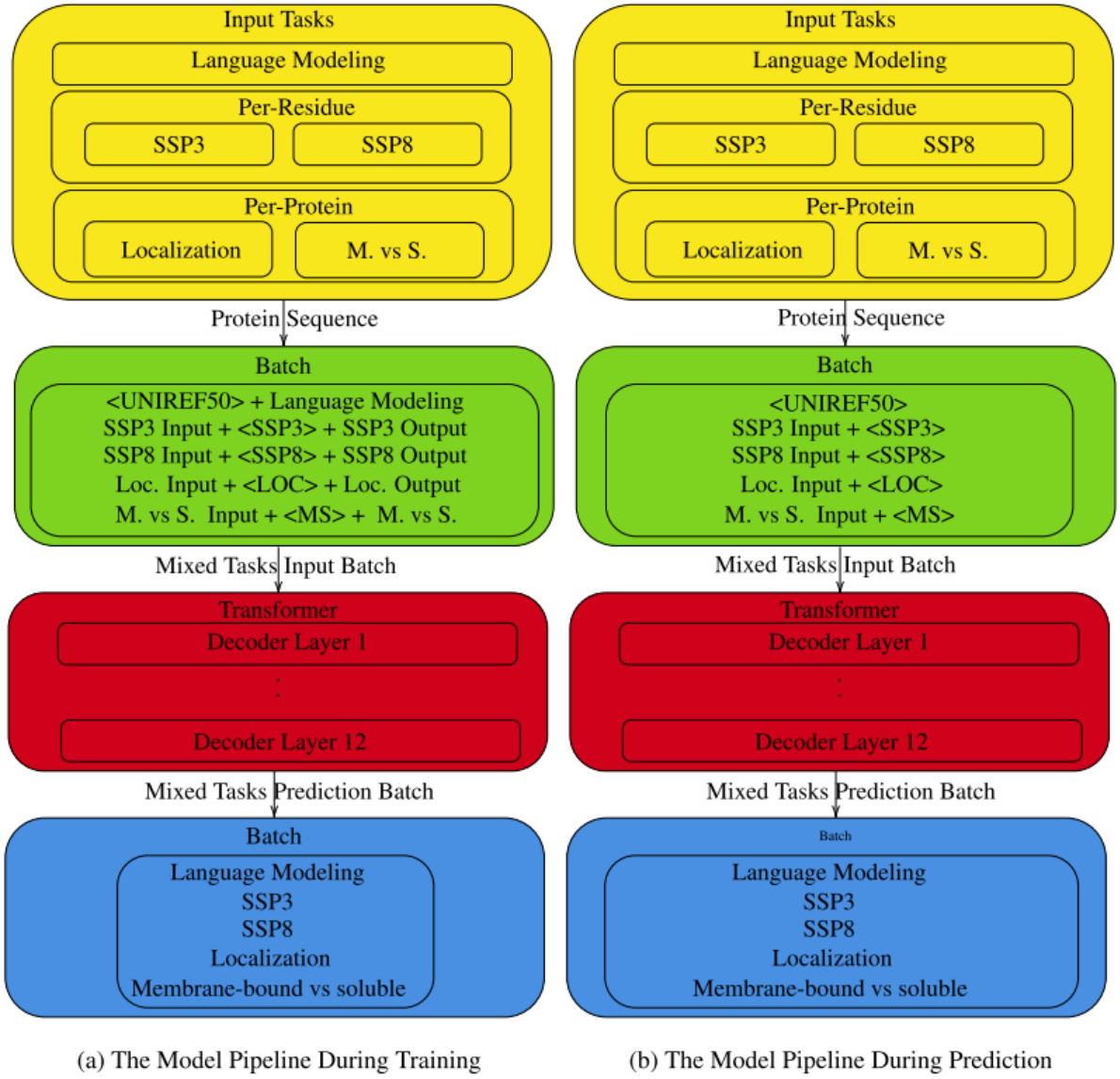
Deep Biology Multi-Task Learning (MT-ALF Zero)

Concept. Thus far, successful applications of NLP techniques in computational biology (Alley et al., 2019; Heinzinger et al., 2019; Howard & Ruder, 2018; Rives et al., 2019) used a two-step approach: Step 1: training of a self-supervised model on protein sequences without annotations to learn vector representations (embeddings). Step 2: use embeddings as input to train supervised models on annotated data (e.g. secondary structure or localization prediction). MT-ALF Zero merged the two steps into a single model trained end-to-end. This was achieved by applying a joint loss consisting of the four supervised tasks ((I) 3- and (II) 8-state secondary structure prediction, (III) 10-state per-protein localization and (IV) 2-state per-protein membrane/globular) and (V) the semi-supervised language modeling task. Thereby, the model could learn biochemical and biophysical properties of amino acids together (I, II & V) with the global properties of the macromolecules they constitute (III & IV).

The idea was borrowed from the NLP transformer model (Vaswani et al., 2017). These models consist of two building blocks, namely an encoder and a decoder. Here, we tested only the first approach (decoder only (Radford et al., 2019)).

Architecture and training. The model used for MT-ALF Zero consists only of the decoder part of the transformer model (Fig. 1a: training, Fig. 1b: prediction/testing). We used 12 attention layers with maximum length of 1024 for inputs and outputs. The number of hidden layers was set to 1024, while the number of heads was set to 16. A dropout rate of 0.2 reduced the risk of over-fitting. For this model, the input differed between training and prediction (Fig. 1). During training, both the input and the output of each task were concatenated inserting a control token between them. During prediction, the model saw only the input followed by the control token. Each task had its own control token allowing the model to learn what to predict next: <*UNIREF50*> (Language Modelling), <*SSP3*> and <SSP8> (secondary structure prediction in 3 and 8 states), <LOC> (localization), <MS> (membrane-bound vs. water-soluble proteins).

The model was trained using 6 Titan GPUs with local batch size of 512 and global batch size of 3072. The Adam optimizer was used with 0.0002 learning rate, with a warm-up rate of 16k steps, after that the learning rate decayed until 250k steps. The model was trained for a total number of 500K steps.



(a) The Model Pipeline During Training (b) The Model Pipeline During Prediction

Figure 1: Sketch of MT-ALF Zero architecture. DBTML Model Architecture. (a) shows the model during training time and (b) shows the model during prediction time. The yellow block shows that the model supports the input from 5 different tasks. The green block is the only different block between training and prediction, during training it concatenate both input and output separated by a special control token, while during prediction it only append to the input the special control token. The red block shows the transformer model which contains 12 layers using only the decoder. The blue block shows that the output could be a mixed of different tasks output.

Results

Per-residue: secondary structure prediction competitive. Using evolutionary information from multiple sequence alignments (MSAs), NetSurfP-2.0 (Klausen et al., 2019) is the top method for secondary structure prediction, reaching Q3=83-87% (depending on data set, Fig. 2a: marked by dashed horizontal lines) and Q8=71-74% (Fig. 2b). Almost equally top are Spider3 (Heffernan et al., 2017) and RaptorX (S. Wang et al., 2016), both also using MSAs (all methods marked by red stars in Fig. 2 used evolutionary information as input). Without using evolutionary information from multiple sequence alignments (MSAs), MT-ALF Zero achieved on average numerically the same, or even higher, performance for Q3 (Q3=83-87%, Fig. 2a) and Q8 (Q8=71-74%, Fig. 2b).

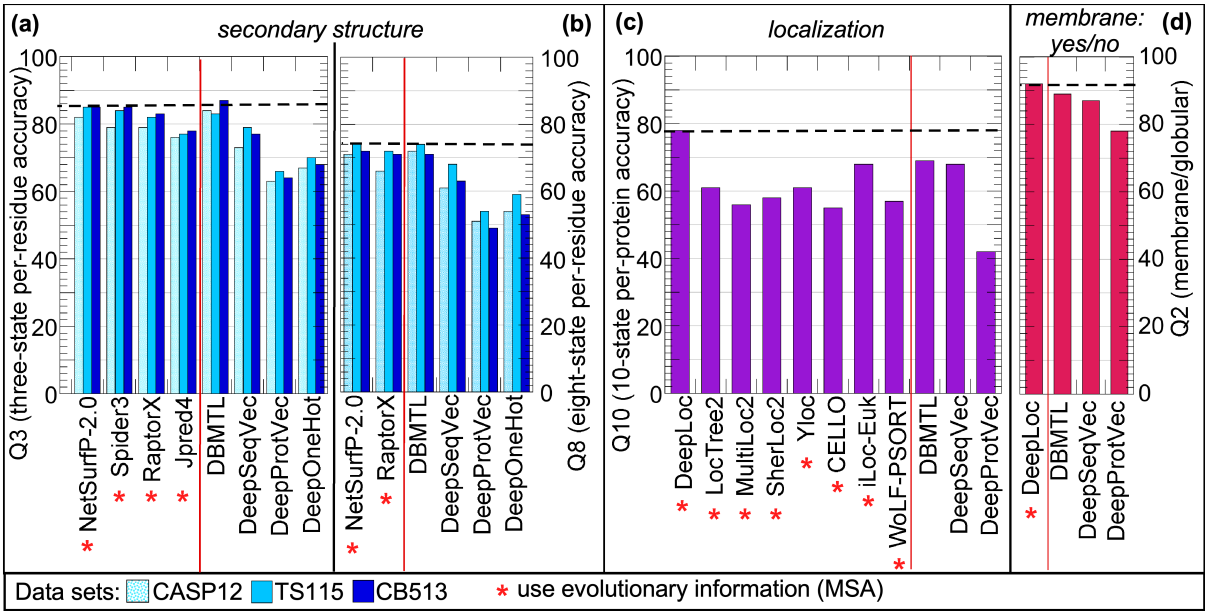


Figure 2: **Performance comparison.** Panel a: We used three different data sets (CASP12, TS115, CB513) to compare three-state secondary structure prediction performance (y-axis: Q3). The proposed MT-ALF Zero, our previous transfer-learning approach DeepSeqVec and the uncontextualized DeepProtVec use only single protein sequences as input. All other methods use evolutionary information encoded as protein profiles. The performance of other methods was extracted from (Klausen et al., 2019) and (Heinzinger et al., 2019). Panel b: The same three data sets as in (a) were used to compare the eight-state secondary structure prediction performance (y-axis: Q8). Panel c: The predictive power of MT-ALF Zero on the prediction of subcellular localization was also compared to top methods (numbers for Q10 taken from DeepLoc (Almagro Armenteros et al., 2017) using evolutionary information. Panel d: The same data set as in Panel c was used to assess the predictive power of MT-ALF Zero for the classification of a protein into membrane-bound and water-soluble.

The comparison of MT-ALF Zero to other methods also not using evolutionary information (DeepSeqVec, DeepProtVec, DeepOneHot) demonstrated the breakthrough achievements. *ProtVec* (Asgari & Mofrad, 2015) was one of the first approaches to successfully adopt NLP solutions (namely Google's Word2vec (Mikolov, Chen, Corrado, & Dean, 2013)) to problems in computational biology by extracting rules from languages that are context-independent. DeepProtVec uses ProtVec embeddings (Asgari & Mofrad, 2015)

as input for a straightforward supervised deep learning with levels of Q3 and Q8 15-20 percentage points below MT-ALF Zero (DeepProtVec Fig. 2ab). Using only sequence as input performed slightly better (DeepOneHot: Fig. 2), however, the real jump originated from self-supervised learning using the NLP model ELMo (Peters et al., 2018) as embeddings (DeepSeqVec Fig. 2). The difference between MT-ALF Zero and DeepSeqVec (Q3: 8.3 percentage points (average over all three data sets); Q8: 8.3 percentage points (average over all three data sets)) signified the improvement from the end-to-end problem specific solution realized by MT-ALF Zero. For secondary structure prediction, this difference implied to boost the approach from the level of "best method amongst those not using evolutionary information to "one of the best methods".

Per-protein performance high but not top. For both per-protein prediction tasks explored (localization and membrane-bound/water-soluble globular) MT-ALF Zero **did not** reach the top performance level (Fig. 2cd). For the prediction of localization, the best method DeepLoc reached Q10=78%, while the approach introduced here (MT-ALF Zero) remained nine percentage points below Q10=69% (Fig. 2c, Table SOM_3). MT-ALF Zero was numerically higher than other popular prediction methods using evolutionary information, namely (sorted by date): WoLF PSORT (Horton et al., 2007), CELLO (Yu et al., 2006), MultiLoc2 (Blum et al., 2009), SherLoc2 (Briesemeister et al., 2009), YLoc (Briesemeister et al., 2010), iLoc-Euk (Chou et al., 2011), and LocTree2 (T. Goldberg et al., 2012). However, for localization prediction, the end-to-end solution MT-ALF Zero hardly outperformed the two-step approach realized earlier through SeqVec (Heinzinger et al., 2019) embeddings (DeepSeqVec Fig. 2c). In contrast, the Word2vec-like approach ProtVec (Asgari & Mofrad, 2015) realized in DeepProtVec again performed much worse (over 20 percentage points: Fig. 2c).

The situation was similar for the other per-protein task, namely the binary classification into membrane-bound and water-soluble, globular proteins. Although for this task, MT-ALF Zero missed the top level only by a smaller margin of three percentage points: Q2(DeepLoc)=92% vs. Q2(MT-ALF Zero)=89% (Fig. 2d, Table SOM_4). Once again, the novel end-to-end solution realized by MT-ALF Zero outperformed other solutions not using evolutionary information, e.g. the two-stage approach DeepSeqVec and the non-contextualized transfer-learning approach DeepProtVec by (Fig. 2d).

Blazingly fast predictions. One of the main advantages of the transformer model over LSTM-based models such as ELMo (Peters et al., 2018) is speed reached by processing input tokens in parallel through self-attention mechanisms (Bahdanau, Cho, & Bengio, 2014). Using a single 1080Ti GPU, the model took ~35 seconds to load, and with a batch size of 32, the prediction for a 1024-residue protein took, on average, 0.033 seconds. This was similar to the LSTM-based transfer-learning model SeqVec (Heinzinger et al., 2019). In comparison to methods that use evolutionary information and have to first build the MSA, MT-ALF Zero reached a speed-up of approximately 110-fold compared to NetSurfP-2.0 using MMSeqs2 for creating alignments.

Discussion

Semi-supervised multi-task learning: the future for bioinformatics? Essentially, we confirmed our hypothesis that an end-to-end solution realized by the multi-task learning approach MT-ALF Zero could become competitive for various tasks of predicting aspects of protein structure and function directly from sequence without needing any multiple sequence

alignment (MSA). Previous work showed how transfer-learning from self-supervised unannotated databases such as UniRef50 provide a substantial advance toward understanding the language of life as realized in protein sequences (Heinzinger et al., 2019). However, the step from a solution impressively accurate without MSA to one being competitive constituted a substantial jump in improvement (Fig. 2ab) that might help to establish the end-to-end concept in computational biology.

Less gain for per-protein prediction tasks. While the novel end-to-end solution (MT-ALF Zero) improved over our earlier two-step solution (DeepSeqVec), it reached the top of the state-of-the-art only for the tasks of per-residue predictions of secondary structure and three and eight states. For both per-protein tasks explored (localization and membrane-bound/not), the best competitors using evolutionary information still performed substantially better (Fig. 2cd). For localization prediction, our approach still outperformed many popular solutions that use MSA (Fig. 2c). However, a recent publication might suggest this view to be possibly slightly distorted by the choice of data set and number of states (Savojardo, Martelli, Fariselli, Profiti, & Casadio, 2018). Another reason for this result could be attributed to the the technical limitation forcing proteins to be chopped to 1024 residues (using only the first and last 512 residues for protein longer than 512 amino acids). This clearly affected the per-protein data sets more than the per-residue data sets as the latter were taken from the PDB (Consortium, 2018), which tends to contain domain-like, aka. shorter fragments of long proteins. However, the same pre-processing (aka. sequence chopping) was performed for the classification into membrane-bound/not, whilst here performance was not as much below the top-performer (DeepLoc). This could be explained by two observations. Firstly, the signal of membrane-bound proteins is among the most dominant signals captured during language modeling (Heinzinger et al., 2019). Secondly, subcellular localization relies heavily on certain short sequence motifs which might be removed when chopping the sequences (Almagro Armenteros et al., 2017).

Another possible explanation as to why the end-to-end solution MT-ALF Zero improved less over the two-step approach for localization and membrane classification w.r.t. secondary structure prediction might be the smaller data sets for the former. All per-protein tasks had many orders of magnitude fewer samples than the per-residue tasks. Possibly, these were too few to tap into the full potential of the end-to-end solutions with many free parameters.

How can semi-supervised multi-task learning be so successful? Two factors may have contributed to the impressive improvement in secondary structure prediction: (1) semi-supervised learning and (2) model type. (1) *Semi-supervised learning*: previously, models tapping into the power of transfer learning capabilities of self-supervised language modeling might have pushed what can be achieved from single sequences to the limit without end-to-end training, i.e. coupling the pre-training phase and the task-specific fine-tuning phase. The MT-ALF Zero model tapped into the possibility of leveraging large amounts of unlabeled sequence (big data) while transferring knowledge between annotated proteins and proteins without any labels. This might have allowed the model to transfer the knowledge not only from the language model task to other tasks, but between tasks. (2) *Model type*: In NLP, the transformer model is currently achieving state-of-the-art results in various sequence to sequence problems (Dai et al., 2019; Devlin et al., 2018; Z. Yang et al., 2019). Leveraging this concept for biological sequences helped to push the boundaries of methods which do not rely on evolutionary information. The core module of all transformer models is the attention mechanism. This mechanism allows transformers to learn which regions in the input space (aka. sequence) contribute most to a prediction at a certain position (residue). Simply put, each output of the self-attention module is a weighted sum over all its inputs. One crucial advantage of this approach is that the length of the computational graph computing the dependency between any two residue positions i and j in a protein is independent of their

sequential distance |i-j|, allowing to better capture long-range dependencies (Dai et al., 2019).

Speed-up. Most importantly, MT-ALF Zero speeds up over other state-of-the-art methods by not having to compile MSAs. How much time is gained through this step depends on how the MSAs are built. Compared to NetSurfP-2.0 we increase the speed ~3000x (HHBlits3 is used to compute alignments) – 110x (MMseqs2 (Steinegger & Söding, 2017) is used to compute the alignments) On top, the advantage of using alignment-free predictors is growing hand-in-hand with the growth of bio-databases. These figures explain why, for many applications, even slightly less accurate, but faster predictors might be preferable to users when the top predictors become inexecutable due to limited computing resources.

Conclusion

27 years after the proof that the combination of machine learning and evolutionary information from multiple sequence alignments (MSAs) substantially and significantly improves protein structure prediction (Rost & Sander, 1992, 1993a), we presented a new method, MT-ALF Zero, pushing artificial intelligence to a level at which it can compete with methods using evolutionary information in an alignment-free manner. MT-ALF Zero (Fig. 1) demonstrated how semi-supervised learning can be applied to the language of life, distilled in the form of protein sequences. By fusing self-supervised language modelling and supervised fine-tuning into one model which is trained with a joint loss that characterizes various protein properties, knowledge is transferred between different tasks, allowing the model to build a multi-modal understanding of proteins. In order to share as much knowledge between the tasks as possible, while still enabling the network to learn task-specific features, the MT implementation used in this work provides task-specific input signals. So far we have implemented four supervised tasks: two on the level of residues (word-level), namely secondary structure prediction in 3- and 8-states, and two on the level of proteins (sentence-level), namely subcellular localization prediction and the classification membrane-vs-soluble proteins.

MT-ALF Zero performed similar or better than many top methods using evolutionary information from MSAs. For secondary structure prediction it even reached the very top of the line. As this is achieved without the costly step of building MSAs, our new method speeds up over competitors by about two orders of magnitude. On top, this increase will grow as exponentially as the sequence databases. Thus, semi-supervised MT approaches, as the one described in this work, may become a new frontier in computational biology and medicine, in particular in situations in which a wealth of unannotated data (sequences) contrasts with very constrained annotations (about protein structure and function).

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