Protein Secondary Structure Prediction with Long Short Term Memory Networks

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1. INTRODUCTION

Recently Long Short Term Memory (LSTM) [Hochreiter et al., 1997] recurrent neural networks (RNN) have shown good performance in a number of tasks, including machine translation [Sutskever et al., 2014], and speech recognition [Graves & Jaitly, 2014]. This paper uses the LSTM for prediction of protein secondary structure. Many machine learning algorithms have been applied to this problem: Qian & Sejnowski 1988 introduced neural networks, Jones 1999 discovered that the use of evolutionary information, through position specific scoring matrices, improved performance, and Baldi et al. 1999 introduced RNN’s for secondary structure prediction. Recent work includes conditional random fields hybrid models [Maaten et al., 2011; Peng et al., 2009; Wang et al., 2011] and generative stochastic networks [Troyanskaya, 2014].

A common approach to secondary structure prediction is to use a non-sequential model, typically feed-forward neural networks or SVM’s [Hua & Sun, 2001; Jones, 1999]. These models are not ideal for classifying data which cannot naturally be presented as a vector of fixed dimensionality, why a sliding window approach is typically used to circumvent this problem. Window based models can only learn dependencies within the input window, recent methods for learning other dependencies includes conditional random field hybrid models. RNN’s can be applied to sequential data of any length, and should theoretically be able to learn longterm dependencies. In practice RNN’s suffer from exploding or vanishing gradients [Bengio et al., 1994], and on a secondary structure prediction task Baldi et al. 1999 reported that their RNN’s were only able to learn dependencies of ±15 amino acids relative to the target. The LSTM cell was invented to solve the vanishing gradients problem and enables the network to learn dependences over 100’s of time steps. The contribution of this paper is the application of bidirectional LSTM networks [Graves, 2012] to protein secondary structure prediction. Our model architecture uses feed-forward neural networks for concatenation of predictions from the forward and backward networks in the bidirectional model and the model also includes feed-forward neural networks between hidden states in the recurrent network, See figure 1. The use of feed-forward neural networks ”inside” the reucrrent neural network has also been explored by [Pascanu et al., 2013]. This work primarily differs from the work by Baldi et al. 1999 in the introduction of the LSTM cell, the availability of much larger datasets and the possibility of training larger models by using a GPU.
2. MATERIALS AND METHODS

2.1. Model

The LSTM cell is implemented as described in [Graves, 2013], however without peepholes, because recent papers have shown good performance without peepholes [Sutskever et al., 2014; Zaremba & Sutskever, 2014; Zaremba et al., 2014]. When predicting target \( x_t \) a (forwards) RNN only know the past sequence, \( x_1...x_t \). In tasks where the entire sequence is known beforehand, e.g. secondary structure prediction, this is not desirable. Schuster & Paliwal 1997 introduced the bidirectional RNN as an elegant solution to this problem. One trains two separate RNN’s, the forward RNN starts the recursion from \( x_1 \) and goes forwards, the backwards model starts at \( x_n \) and goes backwards. The predictions from the forward and backward networks are combined and normalized, see Figure 1. The standard method for combining the forward and backward models is to normalize the activations from each layer in a softmax layer [Graves, 2012]. We expand the standard stacked bidirectional LSTM model by introducing a feed-forward network responsible for concatenating the output from the forward and backward networks into a single softmax prediction. Secondly we expand the model by inserting a feed-forward network between recurrent hidden states, see equation (7), along with shortcut connections between the recurrent hidden layers. Similar ideas have been explored for RNN’s by [Pascanu et al., 2013]. Figure 2 shows a LSTM cell. Equation (1) to equation (10) describes the forward recursions for a single LSTM layer, \( h_{t-\text{rec}} \) is forwarded to the next time slice and \( h_t \) is passed upwards in a multilayer LSTM.

\[
\begin{align*}
    i_t &= \sigma(x_t W_{xi} + h_{t-1} W_{hi} + b_i) \\
    f_t &= \sigma(x_t W_{xf} + h_{t-1} W_{hf} + b_f) \\
    o_t &= \sigma(x_t W_{xo} + h_{t-1} W_{ho} + b_o) \\
    g_t &= \tanh(x_t W_{xg} + h_{t-1} W_{hg} + b_g) \\
    c_t &= f_t \odot c_{t-1} + i_t \odot g_t \\
    h_t &= o_t \odot \tanh(c_t) \\
    h_{t-\text{rec}} &= h_t + \text{feedforwardnet}(h_t) \\
    \sigma(z) &= \frac{1}{1 + \exp(-z)} \\
    \odot &: \text{Elementwise multiplication} \\
    x_t &: \text{input from the previous layer: } \text{h}_{t-1} 
\end{align*}
\]

2.2. Data

We use the dataset from Troyanskaya 2014\(^1\). The dataset consists of amino acid sequences labeled with secondary structure. Sequences and structures were downloaded from PDB and annotated with the DSSP program [Kabsch & Sander, 1983]. In the literature it is common to map the 8-class DSSP output (Q8) to helix, sheets and coils (Q3), see Table 1. We use the original 8-class output, which is a harder problem. Each amino acid is encoded as an 42 dimensional vector, 21 dimensions for orthogonal encoding and 21 dimensions for sequence profiles. For further descriptions see Troyanskaya 2014. The full dataset has 6128 non-homologous sequences (identity less than 30%). This set is further filtered such that no sequences has more than 25% identity with the CB513 dataset [Cuff & Barton, 1999]. The dataset is divided into a training (n=5278) and a validation set (n=256), the CB513 dataset is used for testing.

2.3. Experimental setup

The LSTM is implemented in Theano [Bastien et al., 2012] using the Lasagne library\(^2\). The model has 3 layers with either 300 or 500 LSTM units in each layer. The feed-forward network, eq. (7), is a two layer ReLU network with 300 or 500 units in each layer, this network has skip connections. The output from the bidirectional forwards and backwards networks are concatenated into a single vector which is passed through a two layer ReLU network with 200 or 400 hidden units in

\(^1\)http://www.princeton.edu/~jzthree/datasets/ICML2014
\(^2\)https://github.com/benanne/Lasagne
The forward LSTM (red arrows) starts at time $t_1$ and the backwards LSTM (blue arrows) starts at time $n$, then they go forwards and backwards respectively. The errors from the forward and backward nets are combined using a feed forward net and the result is used for back propagation. Note the feedforward nets between time slices. The figure shows a single layer model, but the model is easily extended with more layers. Adapted from [Graves, 2012].

Each layer. The concatenation network is regularized using 50% dropout. In the LSTM cells all initial weights are sampled uniformly between -0.05 and 0.05 and biases are initialized at zero. In the fully connected layers weights are initialized using Lasagne’s default settings. The LSTM initial hidden and cell states are learned. The learning rate is controlled with AdaDelta using default settings ($\rho = 0.95$, $\epsilon = 10^{-6}$) [Zeiler, 2012]. After each epoch we calculate the norm of the gradients updates divided by the batch size:

$$
norm_2 = \frac{\|\text{gradient updates}\|_2}{\text{batch size}}$$

If the norm exceeds 0.5 all gradients are scaled with $\frac{0.5}{\norm_2}$. The batch size is 128.

Table 1. Description of protein secondary structure classes and class frequencies in the dataset. In the literature the 8-class DSSP output is typically mapped to 3 classes. The 8 to 3 class mappings are included for reference.

| 8-class (Q8) | 3 class (Q3) | Frequency | Name         |
|--------------|--------------|-----------|--------------|
| H            | H            | 0.34535   | $\alpha$-helix |
| E            | E            | 0.21781   | $\beta$-strand |
| L            | C            | 0.19185   | loop or irregular |
| T            | C            | 0.11284   | $\beta$-turn |
| S            | C            | 0.08258   | bend         |
| G            | H            | 0.03911   | $3_{10}$-helix |
| B            | E            | 0.01029   | $\beta$-bridge |
| I            | C            | 0.00018   | $\pi$-helix  |
3. RESULTS

The LSTM network has a correct classification rate of 0.674, better than current state of the art performance achieved by a generative stochastic network (GSN) [Bengio & Thibodeau-Laufer, 2013; Troyanskaya, 2014] and a conditional neural field (CNF) [Lafferty et al., 2001; Peng et al., 2009]. Furthermore the LSTM network performs significantly better than the bidirectional RNN (BRNN) used in SSpro8 having a correct classification rate of 0.511 [Pollastri et al., 2002], see Table 2.

4. DISCUSSION AND CONCLUSION

We used the LSTM RNN for prediction of protein secondary structure. To our knowledge the CB513 performance of 0.674 is currently state-of-the-art. Comparison with the SSpro8 method shows that the LSTM significantly improves the performance. Similarly the LSTM performs better than both Conditional neural fields and GSN methods. Inspired by Pascanu et al. 2013 we used a feedforward network between the recurrent connections. We showed that a LSTM with this architecture and a feedforward neural net for concatenation of the forward and backward nets performs significantly better than existing methods for secondary structure prediction. Future work includes investigation of different architectures for the feedforward networks.

5. AUTHORS CONTRIBUTIONS

SS is PhD student under the supervision of OW. SS developed the model and performed the experiments. Both authors read and approved the final version of the article.
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