White Box : Website Frontend & Network visualization using Guided Backpropagation

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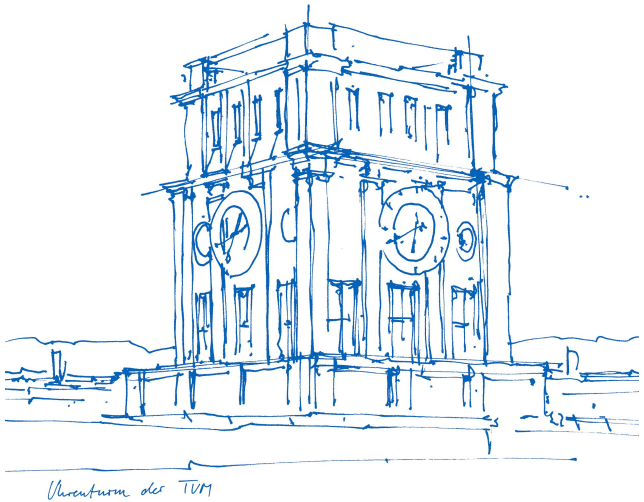
München, 12. April 2018



Outline

- Goals and Motivation
- Web Interface
  - Proposed System
  - Technical Details
  - Results
- Guided Backpropagation
  - Theoretical Background
  - In Context of Protein Distance Prediction
  - Results and Observations
- Summarization
- Future Work

Goals and Motivation

- Web interface that accepts a protein sequence (primary structure) and predicts the distances between each pair of the sequence (tertiary structure) using a Deep Neural Net

  Motivation

  - Need for an open and simple interface to predict protein structure
  - Single pipeline that abstracts the intermediate steps between the input & output

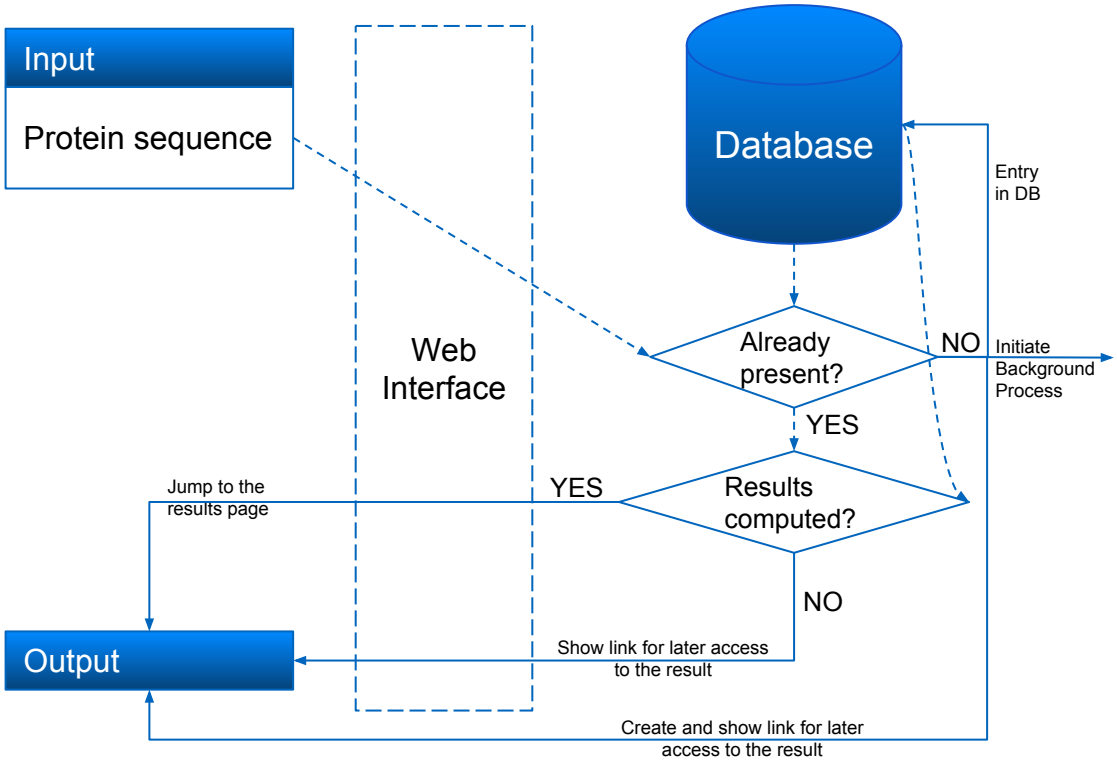
- Visualization of the DNN using guided backpropagation

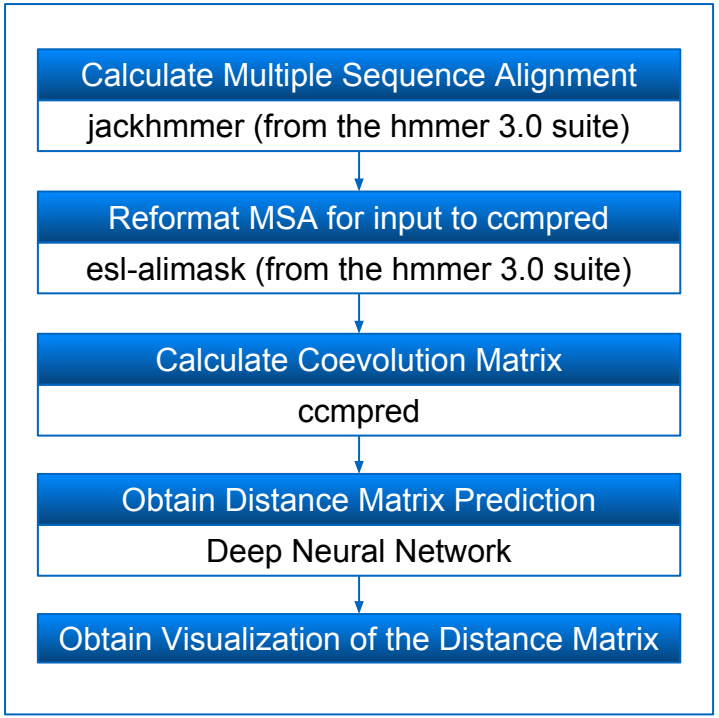
  Motivation

  - To understand the intuition behind the predictions from the Deep Neural Net

Web Interface

Web Interface Pipeline

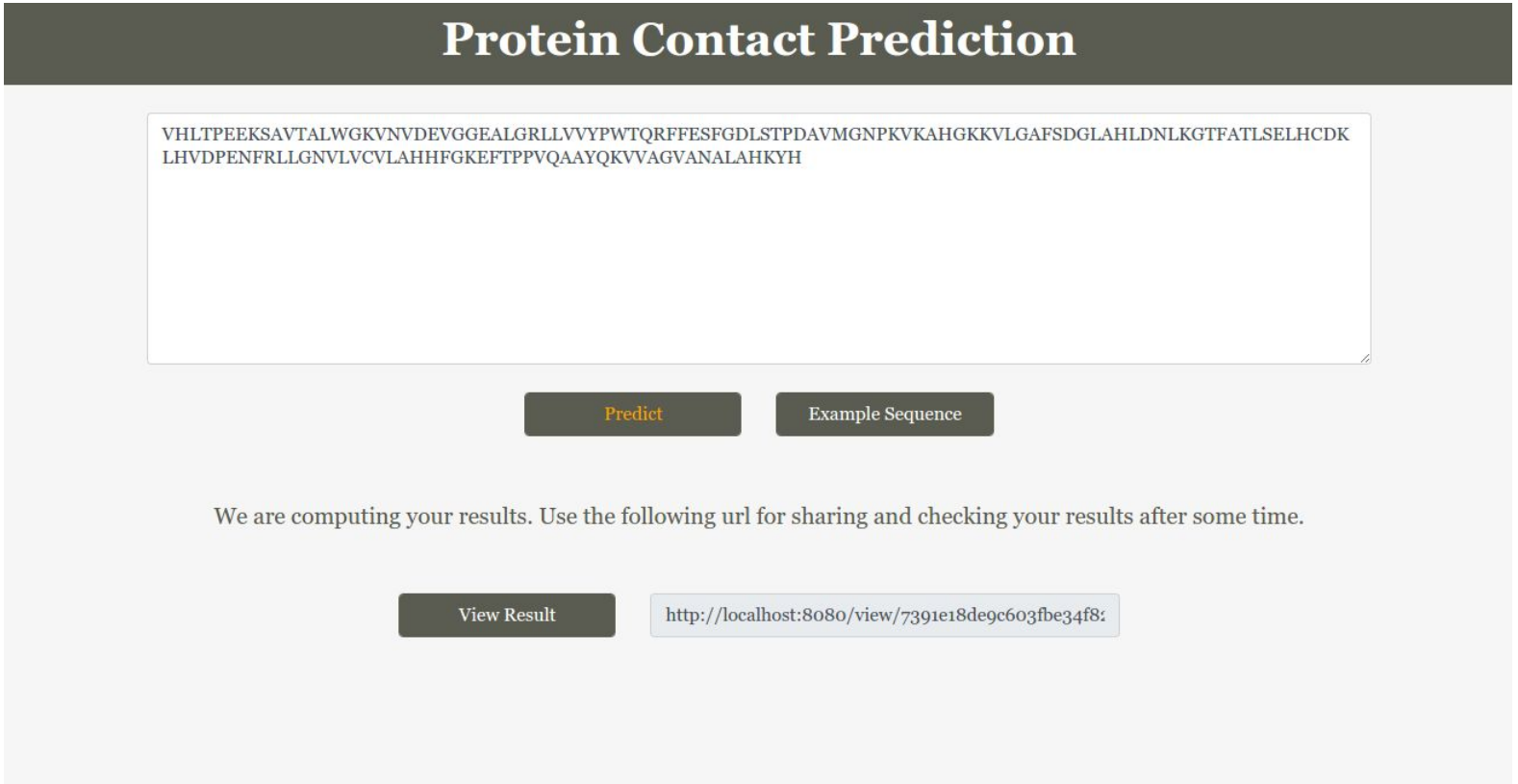




Technology Used

- Framework - Flask 0.12.0
- Database - SQLite
- For the pipeline
  - Compute MSAs - JackHMMer
    - Computation ran against the Uniref-100 DB
  - Compute Co-evolution Matrices - ccmpred
    - Output a coevolution matrix of LxLx21x21.
  - Compute Distance Matrix predictions - Deep Neural Network
    - Courtesy of Matthias Baur and Omer Dolev, build on Pytorch
    - Derived from the NIPS paper by Vladimir Golkov et.al
    - Uses 3 Convolutional Layers and Dropouts in-between with ReLu non-linearities at each layer
    - Total receptive field - 15x15

Results - New protein sequence submitted for prediction



Results - Prediction result page with download link

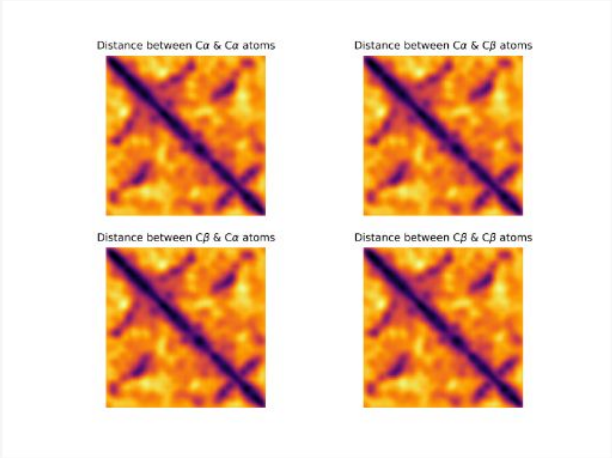
Back to Prediction

Protein Contact Prediction

Values for the Predicted Distances

```
[[[[14.784979  13.48749   12.582673  12.35956   12.731022
13.575727  14.689992  15.893319  17.059916  18.246597
19.22058   20.033127  20.619339  21.071295  21.556519
21.965202  22.108734
    22.305288  22.351646  22.444418  22.495945  22.624033
22.71798   22.794687  22.936514  23.071259  23.40327
23.614328  23.763374  23.90229   23.918566  23.995262
23.972977  23.847668
    23.84865   23.92982   23.993912  24.186884  24.294575
24.420267  24.432446  24.372395  24.231634  23.952837
23.553322  23.18491   22.875723  22.598354  22.518726
22.58587   22.7896
    23.150423  23.551117  23.90246   24.248568  24.42588
24.552217  24.52873   24.446562  24.251257  24.06741
23.931532  23.729584  23.694914  23.619432  23.554947
23.664295  23.781809
    23.901031  23.888157  23.890314  23.591152  23.222052
22.773478  22.31707   21.78776   21.371721  21.125128
21.075558  21.351625  21.755829  22.15758   22.54271
22.944006  23.242756
    23.33889   23.344349  23.25695   23.142015  23.038727
22.903646  22.826412  22.783583  22.896877  22.964088
23.20372   23.369822  23.542053  23.717321  23.852446
23.891457  23.868319
    23.755865  23.713825  23.67262   23.715204  23.776411
23.877964  23.966188  24.166292  24.289675  24.412405
24.453985  24.486525  24.425549  24.327272  24.229849
24.13049   23.856766
    23.612608  23.279634  22.931135  22.616386  22.425797
22.209623  22.144041  22.034185  21.946014  21.900238
21.975492  22.058119  22.186363  22.52303   22.828335
```

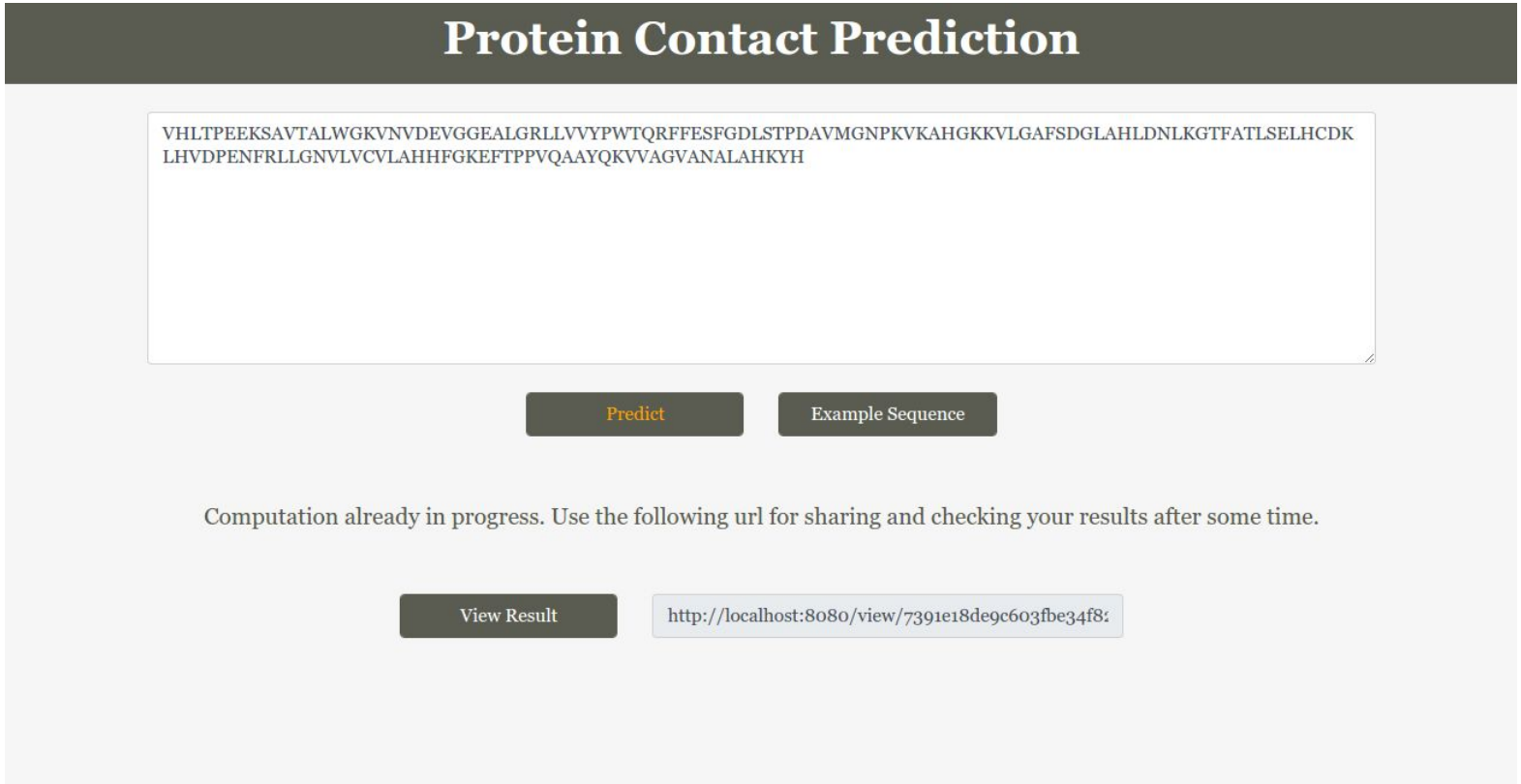
Visualization of Predicted Distances



Download Result

http://localhost:8080/download/7391e18c

Results - Same protein sequence submitted again

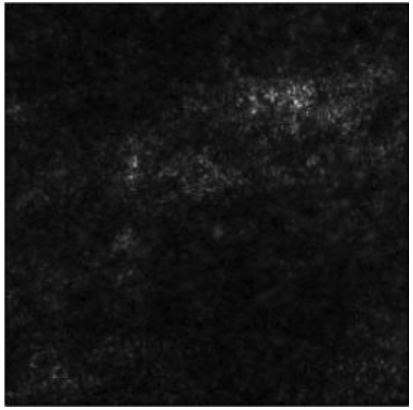


Guided Backpropagation

Introduction - Basic Approach

- Aim : To visualize the parts of the input (I) that affect the output (O)
- Basic approach : Visualize δO/δI
    - The magnitude of gradient in a portion of the visualization is proportional to the degree of influence the corresponding input region exerts over the output

Input Image



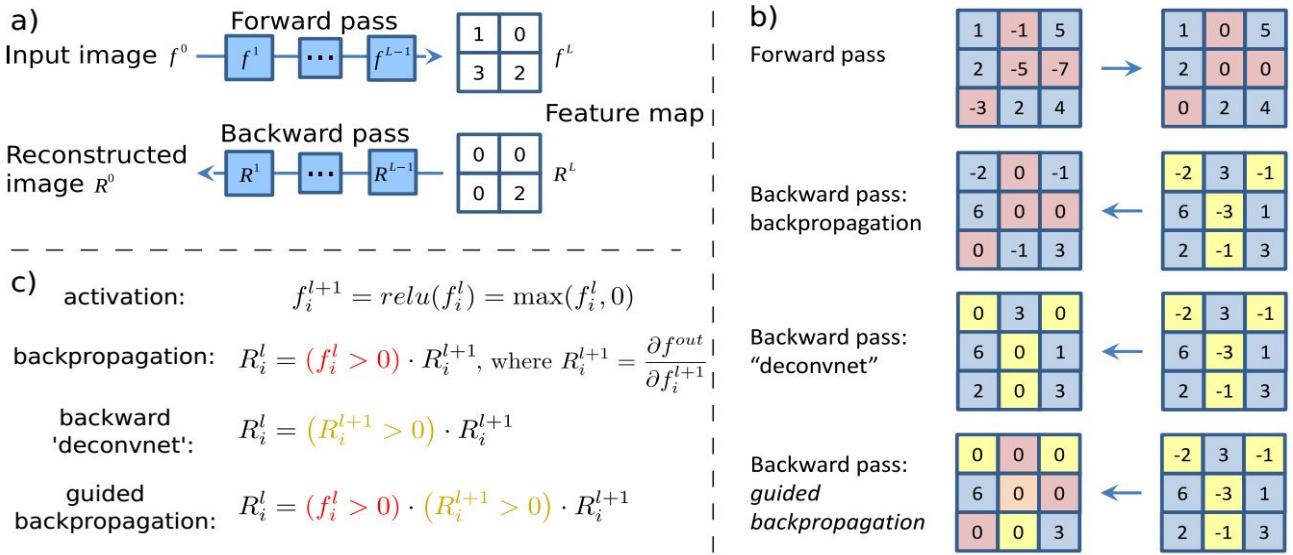
Plain gradient

Fig1: We consider a classification network that for examples takes the image of a snake and outputs the class snake.

Jan Schlüter. (2015). Guided Backpropagation. [online] Available at: https://github.com/Lasagne/Recipes/blob/master/examples/Saliency%20Maps%20and%20Guided%20Backpropagation.ipynb [Accessed 2018]

Introduction - Variants of the Basic Approach

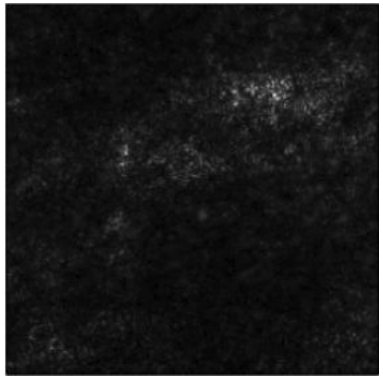
- Variants of the basic approach - dealing with ReLu in different ways:
  - Basic Approach - Guidance only from the Input
  - Backward Deconvnet - Guidance only from the Output
  - Guided Backpropagation - Guidance from both the Input and Output



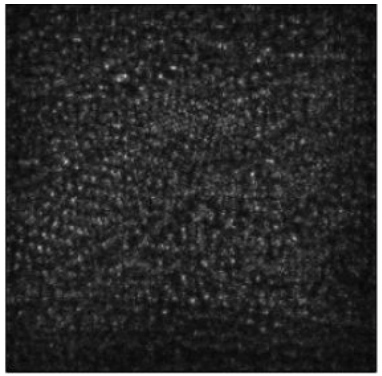
Jost Tobias Springenberg and (2014). Striving for Simplicity: The All Convolutional Net. CoRR, abs/1412.6806,

Introduction - Examples of Visualization

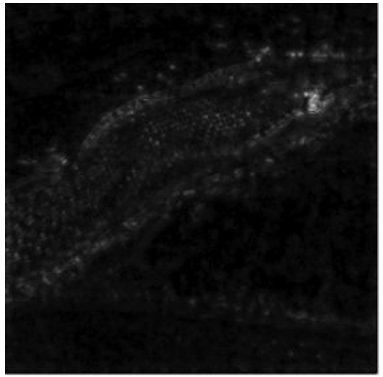
Input Image



Plain Gradients



Backward Deconvnet



Guided Backpropagation

Jan Schlüter. (2015). Guided Backpropagation. [online] Available at: https://github.com/Lasagne/Recipes/blob/master/examples/Saliency%20Maps%20and%20Guided%20Backpropagation.ipynb [Accessed 2018]

Method - In Context of Protein Distance Prediction

- The deep learning network for protein distance prediction has an :
  - Input (I) size of (441, L, L), where the input is a coevolution matrix and L is the sequence length
  - Output (O) size of (4, L, L), where the first dimension stands for the 4 connection types - alpha-alpha, alpha-beta, beta-alpha and beta-beta
- Thus, the size of the gradient (or Jacobian) $\delta O/\delta I$, in this case comes out to be (4xLxL, 441xLxL)
- We can however reduce the gradient size to (4xLxL, 441x15x15), since the final receptive window size of our convolutional neural network is (15,15)
- We visualize these gradients using 4xLxL plots containing 441 (21x21) subplots of size (15x15). Each subplot, thus shows the influence of inputs on the distance predicted between a certain position pair of amino acids for one of the four channels

Results - Visualization Example

- Neural Network
  - CNN with 33% precision on non locals
- Input Sequence
  - ID: 1ABA_A
  - Sequence Length: 87
  - Coevolution size: (87,87,21,21)
- Guided Gradients (Jacobian):
  - Size: (87,87,21,21,15,15) - beta-beta
- Selected Output Position: We will be showing the visualizations for the output at (20,32) of the predicted matrix since it has a contact and is a true-positive for our network

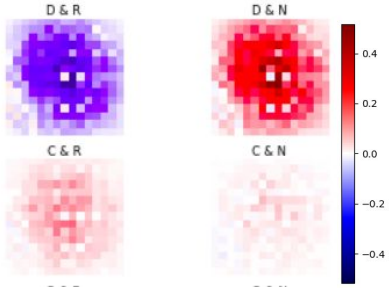


Fig1: Subset from the full Jacobian, contains gradients of the output at (20,32) wrt input coevolution for amino acid pairs (D,R), (D,N), (C,R) and (C,N)*

Fig2: Corresponding subset from the coevolution matrix focusing on the (15,15) receptive window around the position (20,32)*

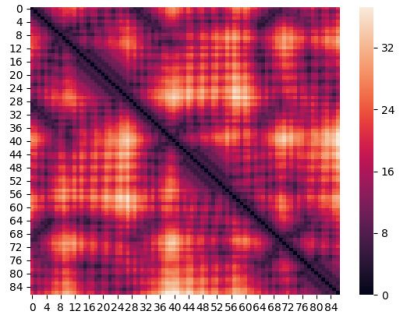


Fig3: Ground Truth Distance visualization for the beta-beta channel

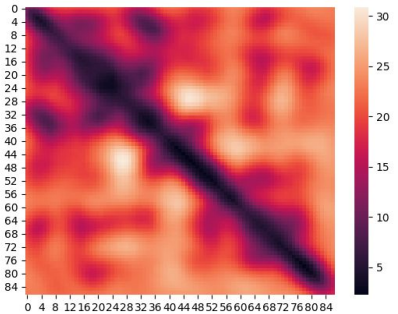


Fig4: Predicted Distance visualization for the beta-beta channel

* We only plot the area in the effective receptive field - (15,15) around the output position (20,32), as only those are taken into consideration by the current network architecture

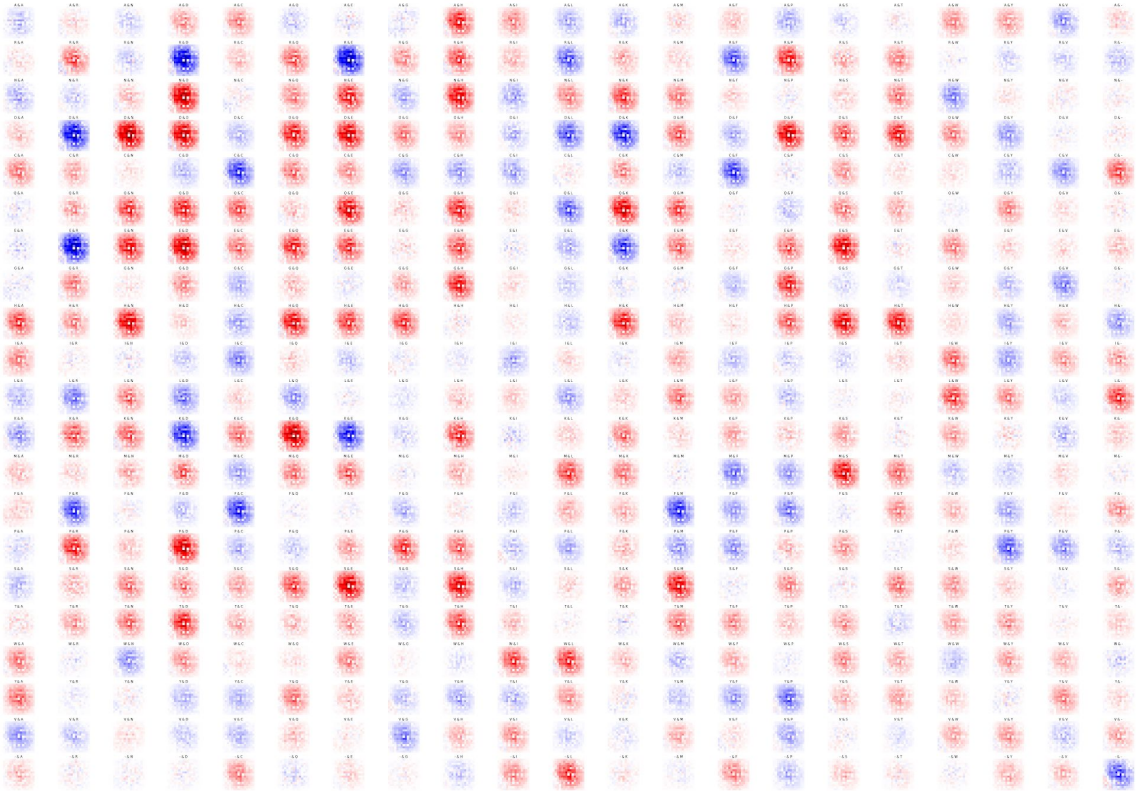


Fig1: Subset from the full Jacobian, contains gradients of the output at (20,32) wrt input coevolution for 21x21 amino acid pairs

Observations and Inferences

Correlation of gradients and co-evolutions:

- We observed mostly positive linear correlation between gradients and coevolution values in Fig. 1
- Another related observation can be seen in Fig. 2 where we weigh the gradients with the sign of the corresponding coevolution value

Inference:

The areas with positive correlation may indicate that increasing the coevolution values there, will also increase the predicted distance (We recheck the interpretation of the gradient in Fig. 3). This however, was in contrast to our expectations since a high coevolutional value is usually indicative of a contact.

Conclusion:

Correlation values may be misleading as they are indicative of a linear relationship, whereas in this case it is quite non-linear.

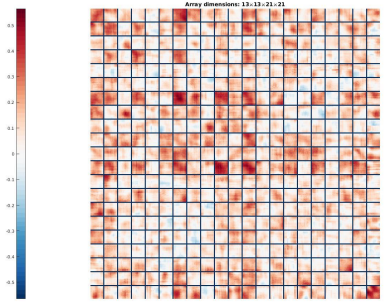


Fig1: Correlation values between coevolutions and gradients over window (15x15) for all the amino acid pairs (dim 1&2) for output positions (20:32,20:32) (dim 3&4)

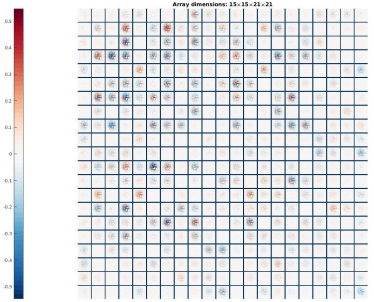


Fig2: Gradients weighted by sign of corresponding coevolution values. The amount of + and - values in the weighted gradient are nearly equal (47% and 51% resp.)

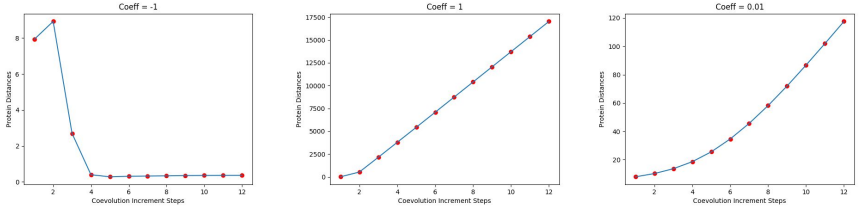


Fig3: These are the plots for predicted distance values at position (20,32) against coevolution change steps. In this experiment we increased the coevolution value by a fraction of the gradient values (indicated by coeff) to check the effect on output when the input moves in the direction of the gradient. As evident from the above, the output was shown to increase

Observations and Inferences

Receptive Field:

We observed that the gradient magnitudes are strongest in the center of the image and gradually move to zero as we move towards the edges of the receptive field (see Fig. 1). Notice that the coloration is almost circular.

Inference:

This can be interpreted as evidence in support of the receptive window size chosen as (15,15).

If the actual window size had been larger (i.e influence from neighbors farther away), then we would have expected to see stronger gradients at the edges of out current receptive window too.

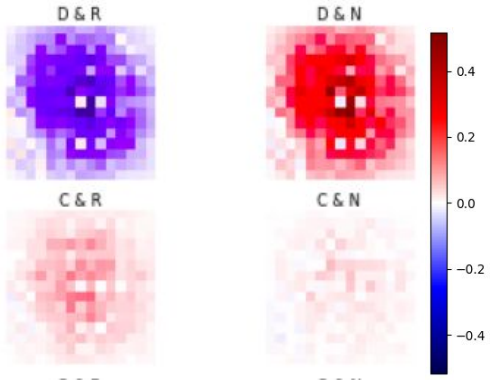


Fig1: Notice the circular pattern of the gradient coloration and how it fades out as we move to the window edges.

Observations and Inferences

Patterns:

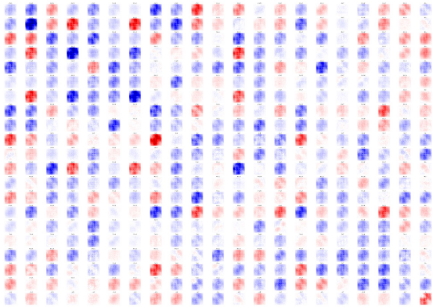
We observed that a certain spatial pattern, linked to the identity of amino acid pairs, tended to appear in our gradient visualization (see Figures on the right). The gradient pattern lightened or darkened (or inverted) according to the coevolution input, but was otherwise unaffected

Inference:

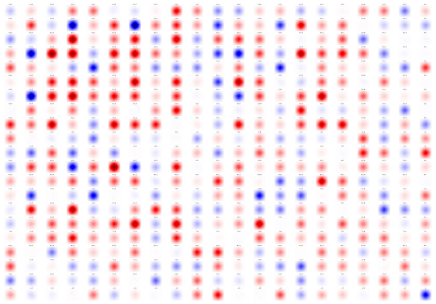
This behavior may indicate that the network has strong notions about particular pairs of amino acids and steers the output according to this notion, paying less attention to the actual coevolution values there.

Conclusion

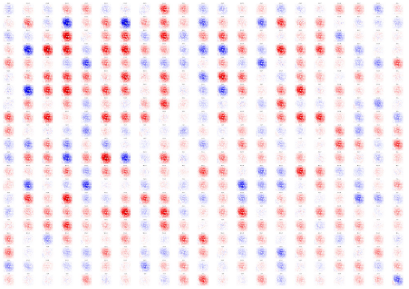
This is not an expected behavior. Further analysis is required to understand this. Investigation of this behavior for a network with higher precision may also lead to some results.



All input coevolutions are highly negative ~ -0.3



All input coevolutions are highly positive ~ +0.3



Original input coevolutions

Fig 1,2,3: Gradients for the position (20,32)

Summarization

In our work, therefore, we have

- Created and presented a web interface for predicting the distances between various amino acids in a protein, given a protein sequence.
- Implemented guided backpropagation to visualize the inner workings of the Deep Neural Network (an intermediate step for the above) that predicts Protein Distance Matrix, given its coevolution matrix.

Future Work

Future Work

- Integrate some tool on the website to show the visualizations from guided backpropagation.
- Comparison with other visualization techniques.
- Host the website for public use.
- Further analysis of the visualization results.

References and Source Code

References

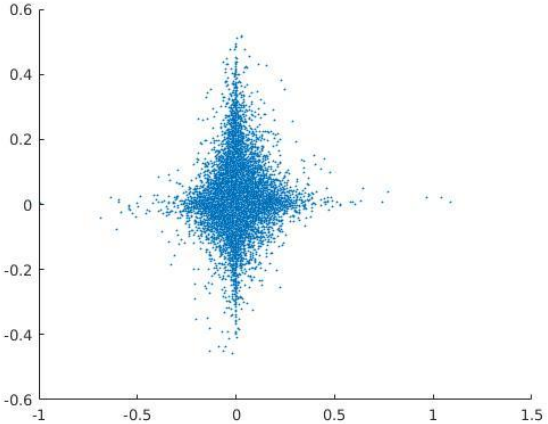
- Golkov, V. et al. (2016). Protein contact prediction from amino acid co-evolution using convolutional networks for graph-valued images. In Advances in Neural Information Processing Systems (pp. 4222-4230).
- Springenberg, J. et al. (2014). Striving for simplicity: The all convolutional net. arXiv preprint arXiv:1412.6806.
- Ozbulak, U. (2017). utkuozbulak/pytorch-cnn-visualizations. [online] Available at: https://github.com/utkuozbulak/pytorch-cnn-visualizations [Accessed 2018].: The All Convolutional Net. CoRR, abs/1412.6806,
- Golkov, V. (2016). show & scroll - Visualize arbitrary N-dimensional arrays - File Exchange - MATLAB Central. [online] De.mathworks.com. Available at: https://de.mathworks.com/matlabcentral/fileexchange/52374-show---scroll-visualize-arbitrary-n-dimensional-arrays [Accessed 2018].

Source Code

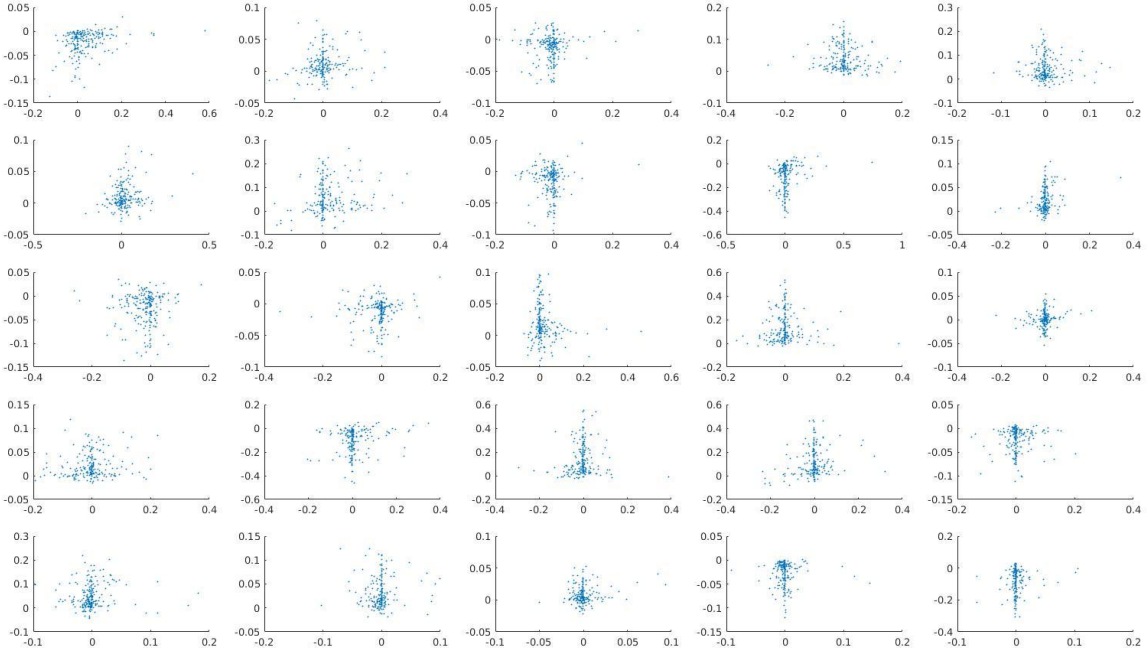
- https://gitlab.lrz.de/dugarsumit/dlcvbm
- https://gitlab.lrz.de/ge72xax/dl4cv_prak

Additional Results*

Coevolution (X-Axis) vs Gradients (Y-Axis) for Position 20,32



Coevolution (X-Axis) vs Gradients (Y-Axis) for Position 20,32 individually for the first 25 pairs of Amino Acids

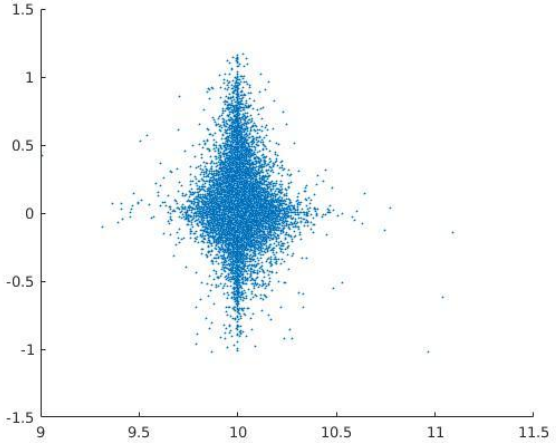


The scatter plots for the rest of the amino acid pairs are as scattered as these ones, indicating that there is no direct correlation between coevolution and gradients. We also plotted the results for the first 25 amino acids for highly negative (we subtracted a large value from) coevolutions and highly positive (we added a large value to) coevolutions. We again, did not notice any significant pattern in those. You can see these plots on the following slides

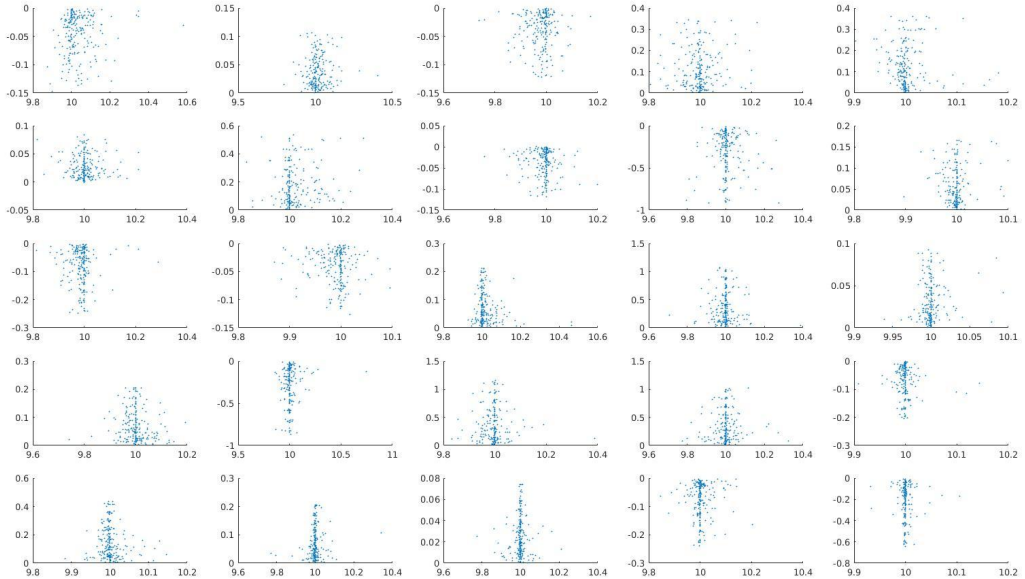
*all results for sequence 1ABA_A

Additional Results*

Highly positive Coevolution (Added 10 to every value) (X-Axis) vs Gradients (Y-Axis) for Position 20,32



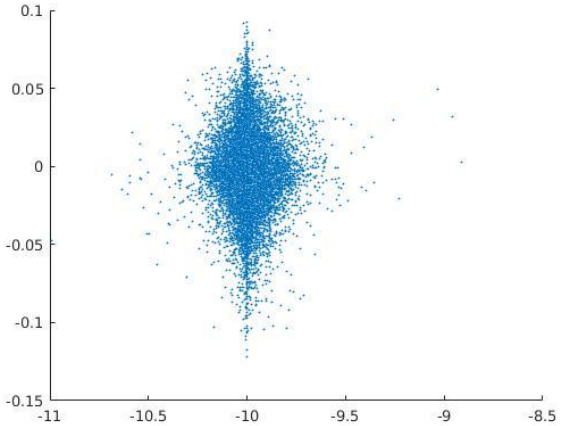
Highly positive Coevolution (Added 10 to every value) (X-Axis) vs Gradients (Y-Axis) for Position 20,32 individually for the first 25 pairs of Amino Acids



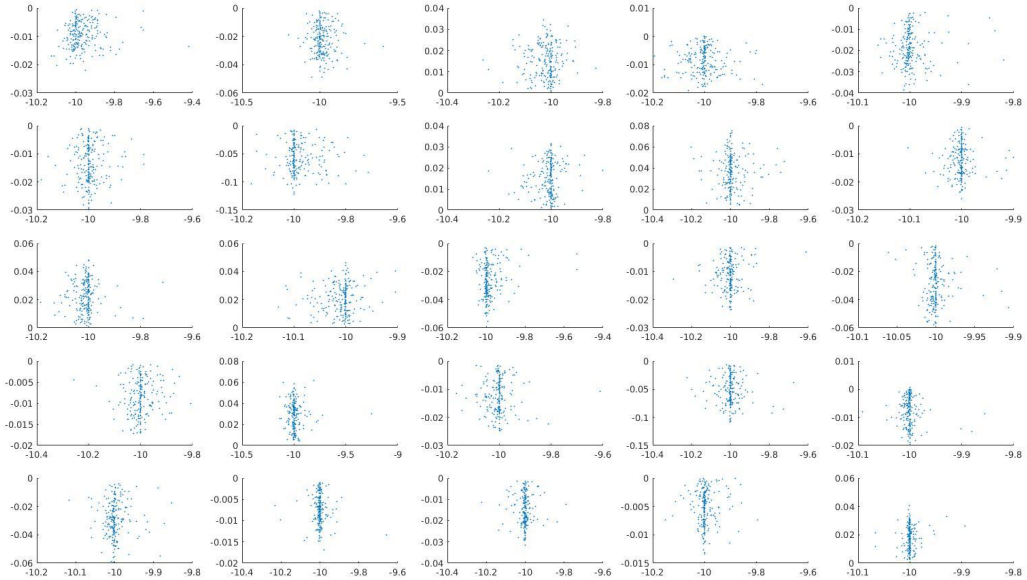
*all results for sequence 1ABA_A

Additional Results*

Highly negative Coevolution (Subtracted 10 from every value) (X-Axis) vs Gradients (Y-Axis) for Position 20,32



Highly negative Coevolution (Subtracted 10 from every value) (X-Axis) vs Gradients (Y-Axis) for Position 20,32 individually for the first 25 pairs of Amino Acids



*all results for sequence 1ABA_A