

**Heidelberg University**  
**Institute of Computer Science**

**Project report for the lecture Advanced Machine  
Learning**

**Prediction of the next SARS-CoV-2  
variants**

`https://github.com/nilskre/AML-covid-project`

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## List of Abbreviations

<b>DNA</b>	Deoxyribonucleic Acid
<b>GAN</b>	Generative Adversarial Network
<b>GISAID</b>	Global Initiative on Sharing All Influenza Data
<b>GPU</b>	Graphics Processing Unit
<b>LSTM</b>	Long Short-Term Memory
<b>ORF</b>	Open reading frames
<b>ReLU</b>	Rectified Linear Unit
<b>RNA</b>	Ribonucleic Acid
<b>RNN</b>	Recurrent Neural Network
<b>SARS-CoV-2</b>	severe acute respiratory syndrome coronavirus 2
<b>UTR</b>	Untranslated region

## 0 Project Setup

For a detailed description of how to set up the project, please have a look at [https://github.com/nilskre/bomberman\\_rl/blob/master/README.md](https://github.com/nilskre/bomberman_rl/blob/master/README.md).

## 1 Introduction

## 2 Fundamentals and Related Work

### 2.1 Basics from molecular biology

This chapter gives a brief introduction into the underlying biological domain.

The human genome is encoded as Deoxyribonucleic Acid (DNA). The DNA carries genetic instructions how DNA based organisms develop and behave. It is structured as a double helix and consists of two nucleotide pair combinations: adenine (A), thymine (T) and cytosine (C), guanine (G). [7, p. 8]

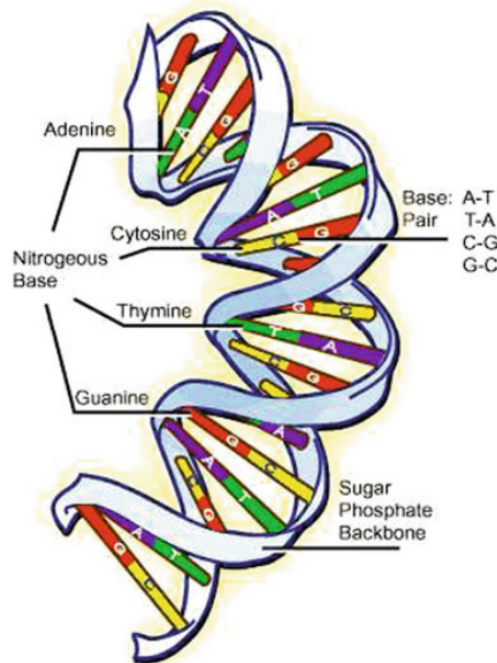


Figure 1: DNA double helix [7, p. 8]

The protein biosynthesis (also known as the central dogma of molecular biology) describes how proteins are produced based on DNA sequences. The proteins then produce characteristics (e.g. human hair color). So the DNA directly influences which human characteristics are developed. [11, p. 6]

The process of the protein biosynthesis can be seen in figure 2. The single steps are described in the following:

1. Transcription: The DNA is transcribed by the RNA-Polymerase into pre-messenger RNA. As part of this process the nucleotide thymine is replaced by uracil (U). [11, p. 9]

2. mRNA Processing: The pre-messenger RNA is transformed into the messenger RNA by removing the non-coding regions (introns). So the main difference between DNA and Ribonucleic Acid (RNA) is that the DNA is structured as a double helix, whereas the RNA consists of a single strain. [11, p. 9]
3. Translation: Ribosomes translate the mRNA into amino acids. Three nucleotides (one codon) decode one amino acid. The matching which codons decode for which amino acid can be seen in figure 3. [11, p. 9]

## Central dogma of molecular biology

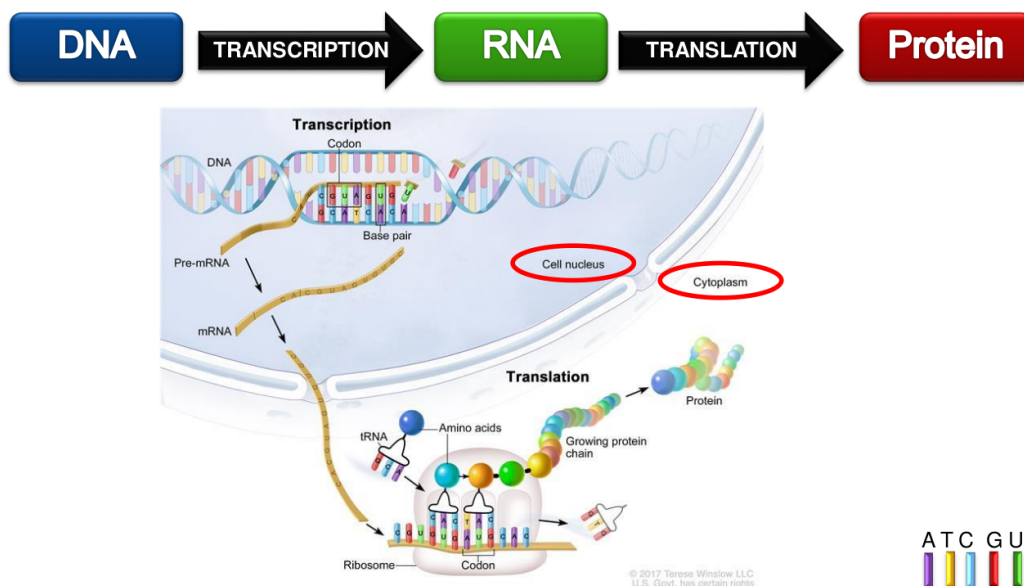


Figure 2: Protein biosynthesis [11]

RNA based viruses (like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) use RNA to encode their genetic information. That means that the genetic information is present as a single strained RNA sequence. This sequence contains for example the information which proteins form the surface structure of the SARS-CoV-2 virus and how this surface looks like. [9]

Based on Naqvi et al. [9] the four proteins forming SARS-CoV-2 are:

- spike (S)
- envelope (E)



	U	C	A	G	
U	UUU Phe UUC UUA Leu UUG	UCU Ser UCC UCA UCG	UAU Tyr UAC UAA STOP UAG STOP	UGU Cys UGC UGA STOP UGG Trp	U C A G
C	CUU Leu CUC CUA CUG	CCU Pro CCC CCA CCG	CAU His CAC CAA Gln CAG	CGU Arg CGC CGA CGG	U C A G
A	AUU Ile AUC AUA AUG Met	ACU Thr ACC ACA ACG	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
G	GUU Val GUC GUA GUG	GCU Ala GCC GCA GCG	GAU Asp GAC GAA Glu GAG	GGU Gly GGC GGA GGG	U C A G

Figure 3: Genetic code [11]

- membrane (M)
- nucleocapsid (N)

A structural representation of SARS-CoV-2 and a host cell is visualized in figure 4. [9]

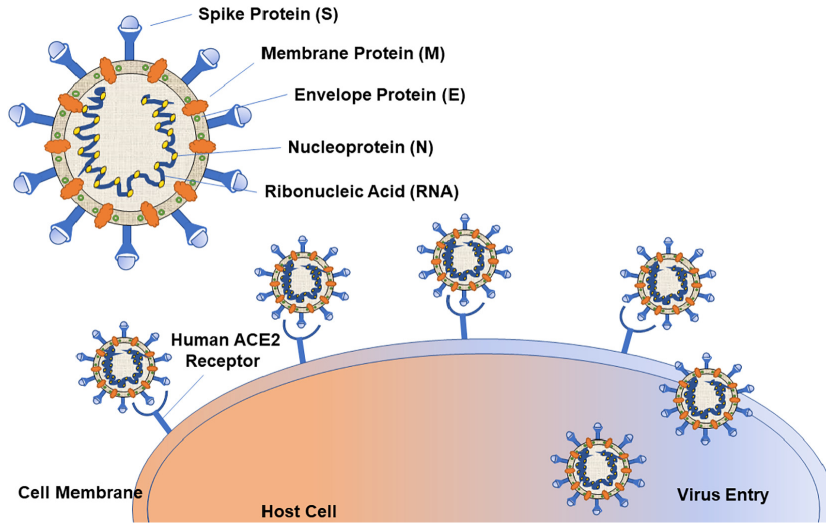


Figure 4: SARS-CoV-2 structure [9]

Furthermore figure 4 shows the RNA in the center. The SARS-CoV-2 RNA consists of about 30,000 nucleotides, which belong to different subgroups, as shown in figure 5. Padded by a 5' Untranslated region (UTR) at the beginning and a 3' UTR in the end, the middle part contains 12 functional Open reading frames (ORF), which contain the four coding regions for the proteins S, E, M and N.



Figure 5: SARS-CoV-2 genome structure [9]

## 2.2 From Probabilistic Language Models to modeling Evolution Theory

A probabilistic language model tries to approximate the probability distribution

$$P(w_1, \dots, w_n) = \prod_{t=1}^n P(w_t | w_1, \dots, w_{t-1}) \quad (1)$$

with  $w_t$  being a word at position (time step)  $t$  in a sentence of length  $n$ . To build language models Recurrent Neural Networks (RNNs) were used to model such probability distributions.

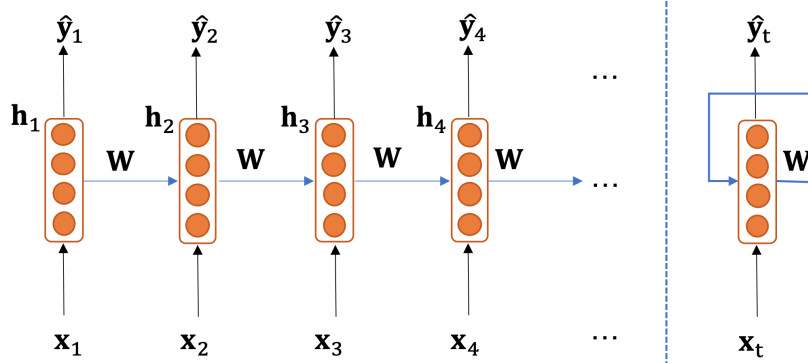


Figure 6: Architecture of a conventional RNN [4]

At each time step  $t$  it outputs a probability distribution  $P(w_t | w_1, \dots, w_{t-1})$  given the words read so far in the current instance (see Figure 6). Words are read as a vectorized numerical representation, often given by pretrained so-called word embeddings  $x_t$  which are lower dimensional and more semantically-enriched compared to simple one-hot encodings. One then calculates the hidden state  $h_t$  by

$$h_t = f(W^{(h)}h_{t-1} + W^{(x)}x_t + b_1) \quad (2)$$

and the corresponding output probability distribution by

$$\hat{y}_t = \text{softmax}(U^{(h)}h_t + b_2). \quad (3)$$

The applied weight matrix is always the same for each time step  $t$  giving the RNN its name. One can therefore simplify the unrolled RNN architecture on the left side of Figure 6 to the one on the right, where the hidden state is continuously passed as an input to the next time step. To achieve a better convergence behavior during training, one can also provide the expected hidden state of time step  $t - 1$  instead of using the predicted hidden state, which is called teacher forcing. RNNs are able to process input of arbitrary length and are by their recurrent character capable to use information from previous time steps. Unfortunately, they are vulnerable to vanishing and exploding gradient problems. Long Short-Term Memory (LSTM) is a special RNN architecture that solves such vulnerabilities by owning a separate long-term cell state besides a short-term hidden state and is introduced in subsection 2.6. It is able to preserve information over many time steps. [4]

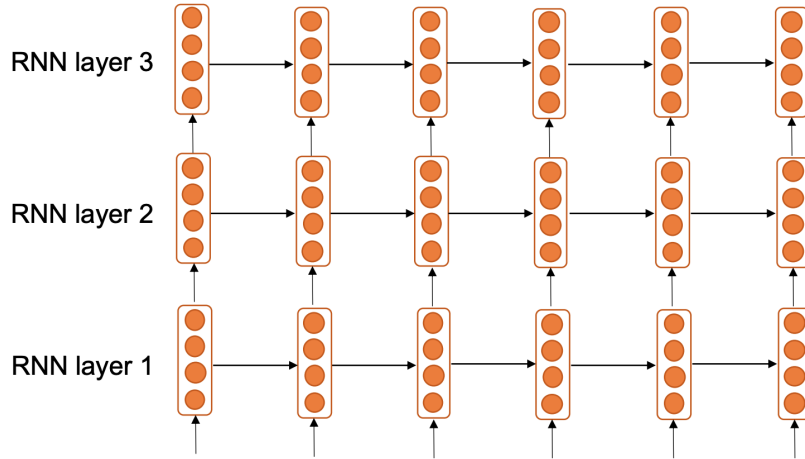


Figure 7: Architecture of a multi-layer RNN [4]

One can also use two RNNs, one traversing a sentence from left to right and another one vice versa, with two different weight matrices to model the probability distribution bidirectionally. One therefore simply concatenates the hidden states of each RNN before applying the weight matrix  $U$  and the *softmax()* function. Also multi-layer RNN can be utilized to generate higher-order features (hidden states) for the prediction task (see Figure 7). [4]

The RNNs or even better LSTMs architectures used for probabilistic language modeling can be reused in a more complex domain called sequence to sequence modeling for neural machine translation from one language to another. Here one first tries to learn a fixed-dimensional input representation

from an input sequence using an encoder architecture based on an LSTM. The so-called context vector is then decoded by a second LSTM into a new sequence of words preserving the grammar but owning a different meaning. [13]

Sequence to sequence models are introduced together with the LSTM architecture in subsection 2.6. Here the connection to evolution theory can be drawn. RNA sequences made of a concatenation of nucleotides <sup>1</sup> can be represented textually using the FASTA format. A sequence to sequence model can then transferably be applied in the domain of RNA sequences to model how RNA-based viruses change their structure to avoid the detection by the human immune system but still to preserve their infectivity and evolutionary fitness [5].

## **2.3 GISAID EpiFlu Data Platform**

## **2.4 Domain-Specific Methodologies to create Evolutionary Datasets for Mutation Prediction**

## **2.5 Previous Work on Mutation Prediction**

Even before the rise of Covid-19 there had been studies trying to predict mutations of RNA viruses. In the collection of [16, 15, 17] the authors predict the mutation positions in hemagglutinins from influenza A virus using logistic regression and plain neural networks and then use the resulting amino acid mutating probabilities to derive possible mutated amino acids. The same approach is further used for H5N1 neuraminidase proteins.

[10] proved that nucleotides in an RNA sequence can change based on their local neighborhood. Neural networks are used to predict new strains of the Newcastle virus and subsequently a rough set theory based algorithm is introduced to extract the according point mutation patterns.

[8] uses a more modern sequence to sequence approach based on LSTMs to learn nucleotide mutations between time-series species of H1N1 Influenza virus and the Newcastle virus as mutations can also be influenced by long-distance relations of amino acids. Therefore one hot-encoded RNA sequences of a parent generation preprocessed to words is given as an input and the output is the predicted offspring generation evaluated by accuracy to the compared true offspring generation. The achieved accuracy in this paper is questionably high with 98.9% on the H1N1 Influenza virus and 96.9% on the

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<sup>1</sup>We restrict the representation of nucleotides solely to their nucleobases parts consisting of the distinct nucleobases guanine, adenine, cytosine and thymine. We therefore do not include the phosphate group and the five-carbon sugar components.

Newcastle virus, possibly because of overfitting to the few 4.609 samples for H1N1 Influenza virus and only 83 for the Newcastle virus. Our approach therefore tries to increase the number of samples available for training when building the dataset.

Our approach will neither use any of the just mentioned architectures, but uses a transformer based architecture coupled with a GAN-style training architecture. Nevertheless a short introduction into sequence to sequence models and the underlying long short-term memory components shall be given to better point out our architectural decisions .

## 2.6 Sequence to Sequence Models based on Long Short-Term Memory

The original LSTM unit was introduced in [6] and can be used for language modeling instead of using plain RNNs to prevent running into vanishing or exploding gradient problems [12]. The architecture of an LSTM is shown in the following figure:

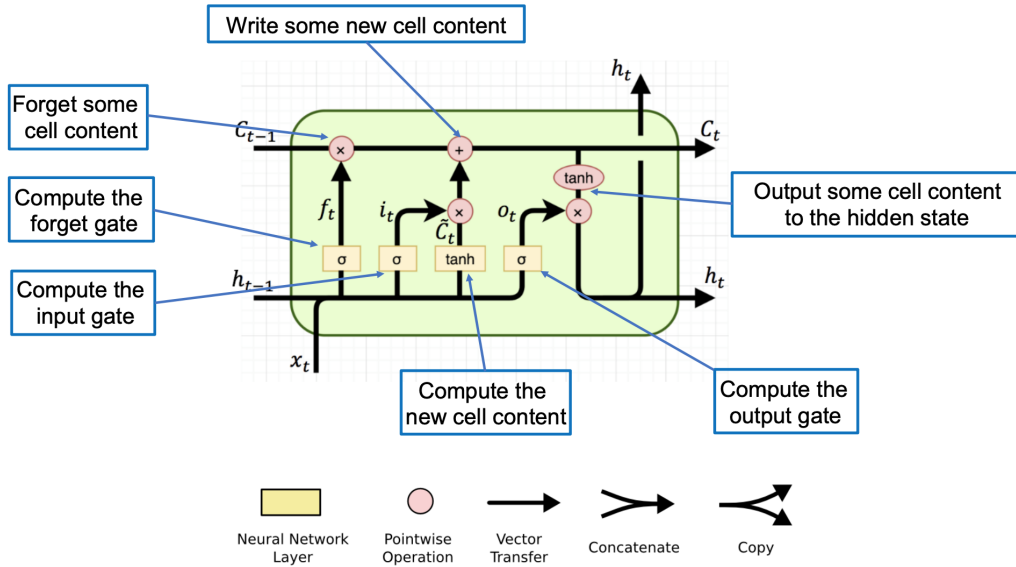


Figure 8: Architecture of an LSTM [4]

It consists of a hidden state  $h_t$  and an additional cell state  $c_t$ . The cell state stores long-term information and is used to derive a new hidden state. Information flows through three different gates inside the LSTM. The forget gate is used to control which parts of the cell state are potentially carried on to the next time step, the input gate is responsible to decide which parts

of the cell state should be updated and the output gate determines what is being passed on as the new hidden state. All three gates depend on the previous hidden state and the current input. They provide factors limited to the interval  $[0,1]$  by the sigmoid function and are multiplied with the cell state, the changes to be added to the cell state and the new hidden state derived from the cell state. Through the cell state an LSTM therefore makes it possible to capture long-distance dependencies. [4]

[13] introduced sequence to sequence learning following a multi-layer encoder-decoder style model architecture. One layer consists of one LSTM that is used as an encoder to learn a large fixed-dimensional vector representation of a size-unrestricted input sequence called the context vector. This vector consists of the last cell and hidden state of the encoder and incorporates the structure of the input sequence helping the following decoder LSTM to provide qualitative predictions for the output sequence. The second LSTM therefore serves as a beam search<sup>2</sup> decoder to map the context vector to a corresponding output sequence whose length does not need to match with the length of the input sequence. The output probability distribution is therefore given by the equation

$$p(y_1, \dots, y_{T'} | x_1, \dots, x_T) = \prod_{t=1}^{T'} p(y_t | v, y_1, \dots, y_{t-1}) \quad (4)$$

with  $v$  being the context vector. Using an LSTM is preferred over a normal RNN as it is used to capture the long range temporal dependencies of the input data. The encoder-decoder architecture uses four layers in total partitioned onto four Graphics Processing Units (GPUs). A corpus of 160k words for the input sequence and another one of 80k words for the target sequence was used to create the word embeddings of dimension 1000. Unknown words were replaced by a *UNK* token. The sequence to sequence model approach was evaluated for neural machine translation and reached a 34.81 BLEU score. One finding during training was that reversing the input sequence introduces many short term dependencies as the minimal time lag of the problem is reduced making optimization easier. [13]

## 2.7 Applying Generative Adversarial Networks

Using a plain sequence to sequence model for mutation prediction does not necessarily guarantee that the generated sequences are evolutionary offsprings of a parent generation as not being included as is in the ground truth

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<sup>2</sup>Do not choose the most probable word but the  $B$  most likely word hypothesis and pass them to the next time step in the LSTM. Whichever hypothesis results in the lowest loss is kept. To avoid combinatorial explosion limit the beam depth size.

data. The generated sequences might occur realistic and biologically relevant, but a plain sequence to sequence architecture does not inherently check for natural parental descent and therefore does not make sure whether the predicted mutations lead to improved fitness. [3] developed a novel sequence to sequence framework based on the Generative Adversarial Network (GAN) idea to predict genetic mutations and future biological polulations of the influenza virus (see Figure 9). MutaGAN describes a sequence to sequence generator within an adversarial framework that predicts protein sequences augmented with possible mutations. By using a sequence to sequence generator and a discriminator specialized on separating fake evolutionary mutations from real ones, one can then guarantee to a certain degree that the evolutionary parent-childhood coherence is given. In MutaGAN a mutation is considered correct if the change in amino acid and location within the RNA sequence is equal to the parent's true offspring. [3]

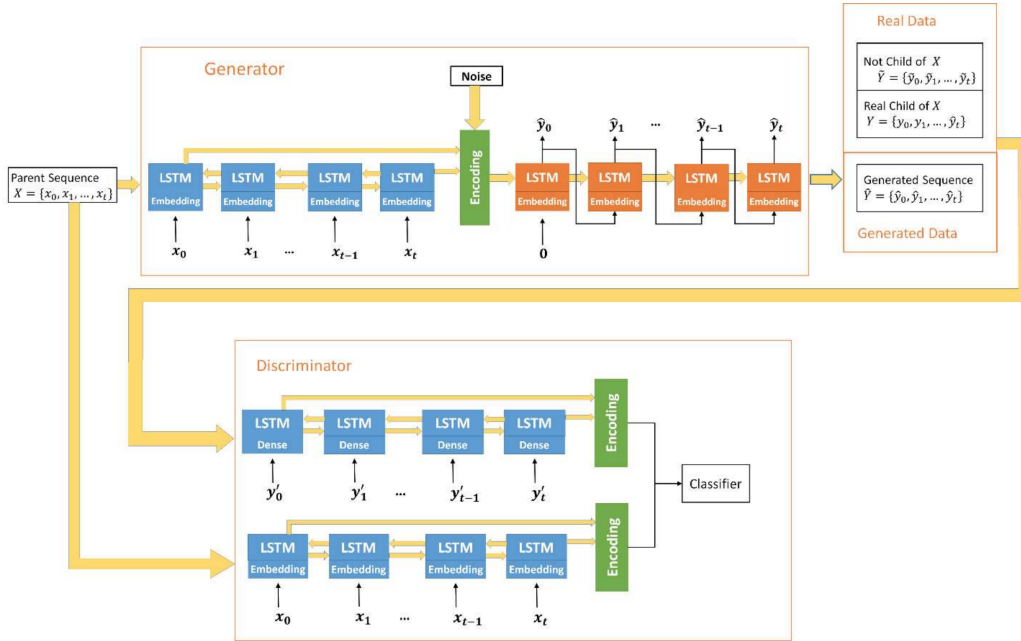


Figure 9: Architecture of MutaGAN [3]

MutaGAN's generator consists of a sequence to sequence model. The encoder is built from of a bidirectional LSTM and the resulting context vector of dimensionality 512 is combined with noise from a standard normal distribution. The decoder LSTM predicts the resulting sequence of amino acids greedily using the  $\text{argmax}()$  of the  $\text{softmax}()$  output for every time step. The discriminator is trained on three different parent-child pair configurations to

optimally compete against the generator, real parent-child pairs, real parent and generated child pairs and pairs of real sequences that are not parent-child pairs. Two bidirectional LSTM encoders sharing the same weight matrix as the encoder of the generator produce a fixed-dimensional encoding of the provided parent-child pair used for classification of evolutionary descent by a plain neural network. The child encoder in the discriminator uses a dense layer having the same weight matrix as the embedding layer of the encoder of the generator. The dense layer is required to directly input the predicted child sequence as its probability distribution rather than the final output after applying the  $\text{argmax}()$  as it would not enable backpropagation to train the generator. In case of a true child sequence is given a simple one-hot encoding is used. [3]

Interestingly [3] states planned improvements by utilizing bigger datasets acquired from the Global Initiative on Sharing All Influenza Data (GISAID) database EpiFlu and by using more length-robust attention-based models to directly work on nucleotide sequences instead of sequences of amino acids. Therefore transformers and the attention mechanism are introduced in the following section.

## 2.8 Transformer and Attention Mechanism

Using a sequence to sequence model as introduced based on an encoder-decoder architecture of LSTM cells has some drawbacks. First the input needs to be process sequentially in time steps which makes parallelization difficult and increases training time, especially for longer sequences. Furthermore the hidden and cell state vector passed through every timestep tries to encode information of *all* previous time steps without knowing which information is especially important for the current time step. This not only makes long distance dependencies hard to capture, but also might not get the prioritization of the previous time step inputs right. [2, 14]

To tackle these problems the so-called transformer architecture was introduced in [14]. It feeds an entire sequence into the encoder to be processed in parallel denying any concept of recurrence or convolution. Only using a so called self-attention mechanism the transformer makes sure that during processing every input position, each of them receives the information that is most important to them. This way modeling long dependencies becomes much more easy compared to LSTMs as the view on the input sequence is more global. In this architecture, the encoder also passes all computed hidden states of every position to the decoder, which therefore [14] can generate the target sequences based on more semantically enriched features and also in parallel for every position. [14]



The transformer architecture achieved state-of-the-art quality results with a BLEU score of 41.8 on the WMT 2014 English-to-French translation task (cf. BLEU score of [13] was 34.8), while still being much faster to train due to its parallelization capabilities. State-of-the-art results are already achieved after just twelve hours of training on eight P100 GPUs. As this is still far beyond the scope and resources given for this project, this projects provides a proof-of-concept transformer model trained for far shorter and fewer sequences as one would need to predict entirely new RNA sequences. [14]

First the transformer architecture should be introduced in the following:

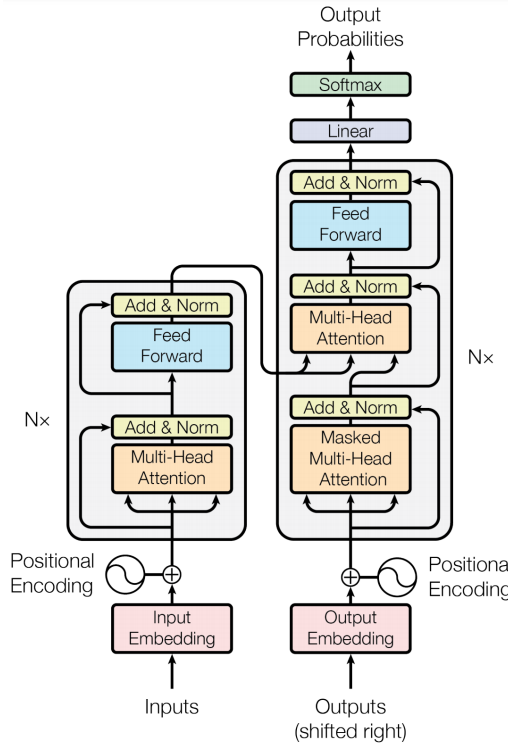


Figure 10: Architecture of the transformer [14]

The transformer consists of an encoder and a decoder part just as normal sequence to sequence models. One layer of the encoder contains a self-attention layer before passing the hidden state representations of an input sequence to a feed forward neural network consisting of two linear transformations separated by Rectified Linear Unit (ReLU). Thus it makes sure that semantic and contextual dependencies between different positions in the input sequence are also modeled. Also skip connections are added for both components with subsequent layer normalization. [1, 14]

To calculate the self-attention output of a sequence, a query  $Q$ , key  $K$  and value  $V$  matrix is calculated through multiplication of the sequence representation<sup>3</sup> with learned transformation matrices. Each row of the three received matrices corresponds to a specific input position. The output of the self-attention layer is then calculated through

$$(ScaledDot - Product)Attention(Q, K, V) = softmax(\frac{QK^T}{\sqrt{d_k}})V. \quad (5)$$

The dot product between  $Q$  and  $K$  calculates scores that are used as weighting factors for  $V$ . This models for every input position how relevant all other input positions are for each of the hidden state encodings. The scores are divided by the square root of the dimensionality of the query/key values of the hidden state representations, which is chosen to be 64 (square root eight), to receive more stable non-vanishing gradients. The softmax guarantees that the positional scores lie between zero and one and add up to one. Note that the score of the current input position itself will most likely have the highest score. [1, 14]

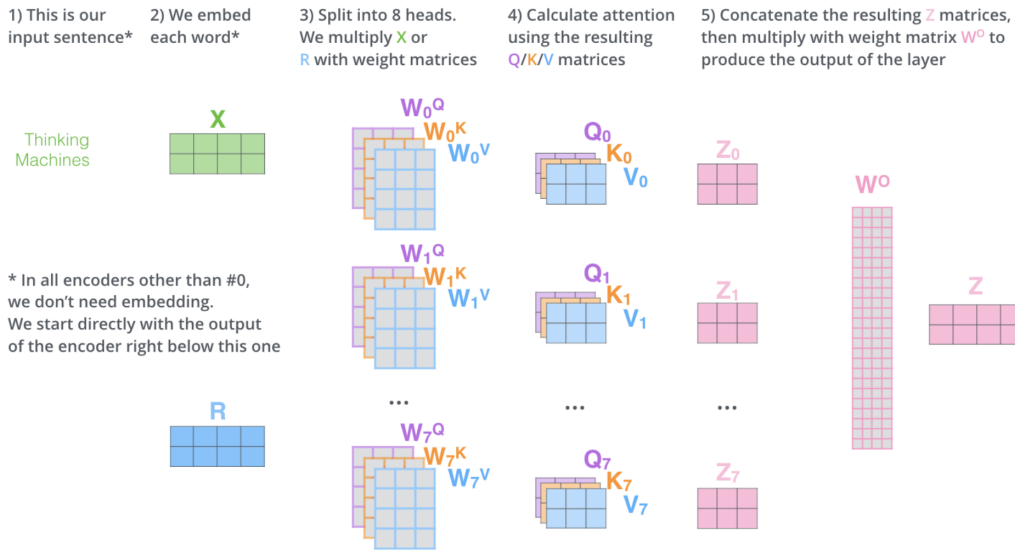


Figure 11: Multi-head attention architecture [1]

One can expand self-attention towards a multi-head attention. In this configuration each head produces its own query, key and value matrices and therefore its own self-attention output in its own representation subspace.

<sup>3</sup>A matrix containing the hidden state representations of every input position

The resulting hidden state is calculated by concatenating each hidden state output of the different heads and multiplying it with a contraction matrix that outputs a hidden state vector in its single-head dimensionality. Multi-head attention is needed to be able to better focus on multiple parts of the input sequence when encoding an input position, otherwise it might happen that most of the focus is set on the input position itself. [14] uses 8 heads. [1, 14]

Overall six layers of encoder and decoder components having individual weight matrices are stacked on top of each other to capture low-level as well as high-level features. The dimensionality of the hidden state is 512. Note that each position of the input sequence is encoded on an individual path through the transformer, which makes parallelization possible compared to LSTM based architectures. [1, 14]

The decoder uses almost the same architecture as the encoder, but contains an additional multi-head attention component that integrates all the hidden state encodings from the encoder. Therefore the final hidden state encodings resulting from the top most encoder are transformed into key and value attention vectors and given to the integrating multi-head attention component of every decoder. Once again this helps to better focus on the relevant input positions for the current output position based on hidden state information extracted from the encoder. Note that the decoder works in a sequential manner again meaning that the input to the decoder are the already decoded sequence tokens of previous time steps, future input positions are masked away. The first multi-head attention component therefore captures inter-dependencies in the generated output sequence, the second one, the so called encoder-decoder attention, enriches the hidden state encoding with the information given from the encoder hidden states. Finally a linear layer mapping the hidden state vector to a logits vector with dimensionality of the given output dictionary and a *softmax()* function produce the output sequence using the greedy or beam search approach. The *EOS* token symbolizes the end of the output to be generated. [1, 14]

Input to the transformer are word embeddings also of fixed dimensionality of 512. Onto each word embedding a positional encoding following a specific pattern is added. These patterns are either learned or fixed and make sure that the distances of the input positions are projected onto the query, key and value representations to be utilized during scaled dot-product attention. This also enables self-attention to be scaled to unseen lengths of sequences. Transformers usually contain an upper bound of sequence length to be processed, which is different to recurrent architectures that can process inputs of arbitrary length. Input sequences are usually padded up until the specified sequence length, the used *PAD* tokens are masked to be excluded from the self-

attention components. [1, 14]

## 2.9 Other Techniques

- NNs/SVMs: <https://bsb-urasipjournals.springeropen.com/articles/10.1186/s13637-016-0042-0>
- BiLSTM: <https://science.sciencemag.org/content/371/6526/284>

## **3 Approach**

TODO: Pipeline image

### **3.1 Dataset Creation**

hier irgendwo das Zielschema des Datensatzes beschreiben

#### **3.1.1 Raw data selection from GISAID**

focus: Germany from 4.5. - 6.8. (new variant arised in the recent past -> lambda, delta, ...) only Germany, to make it possible to handle the data about 35000 genomes in our raw dataset

beispiel record: genome sequence and metadata

#### **3.1.2 Generation of a phylogenetic tree**

#### **3.1.3 Phylogenetic tree to dataset**

### **3.2 Data Preprocessing**

two steps: - to make the dimensionality managable not the whole 30000 nucleotides are evaluated. We take a subpart of X nucleotides from position A to B - Transform string to numeric for model input

#### **3.2.1 Dimensionality reduction by selecting subpart of the genome**

#### **3.2.2 Transform genome sequence to numeric model input**

- DNA Sequencing (Done during dataset creation, given from GISAID)
- DNA Sequence Tokenization for Amino Acid Dictionary
- DNA Sequence Padding

### **3.3 Model Architecture**

### **3.4 Training Process**

## 4 Experimental results

## 5 Conclusion

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