Attention and Transformer Models for Genomics

BMI/CS 776

www.biostat.wisc.edu/bmi776/

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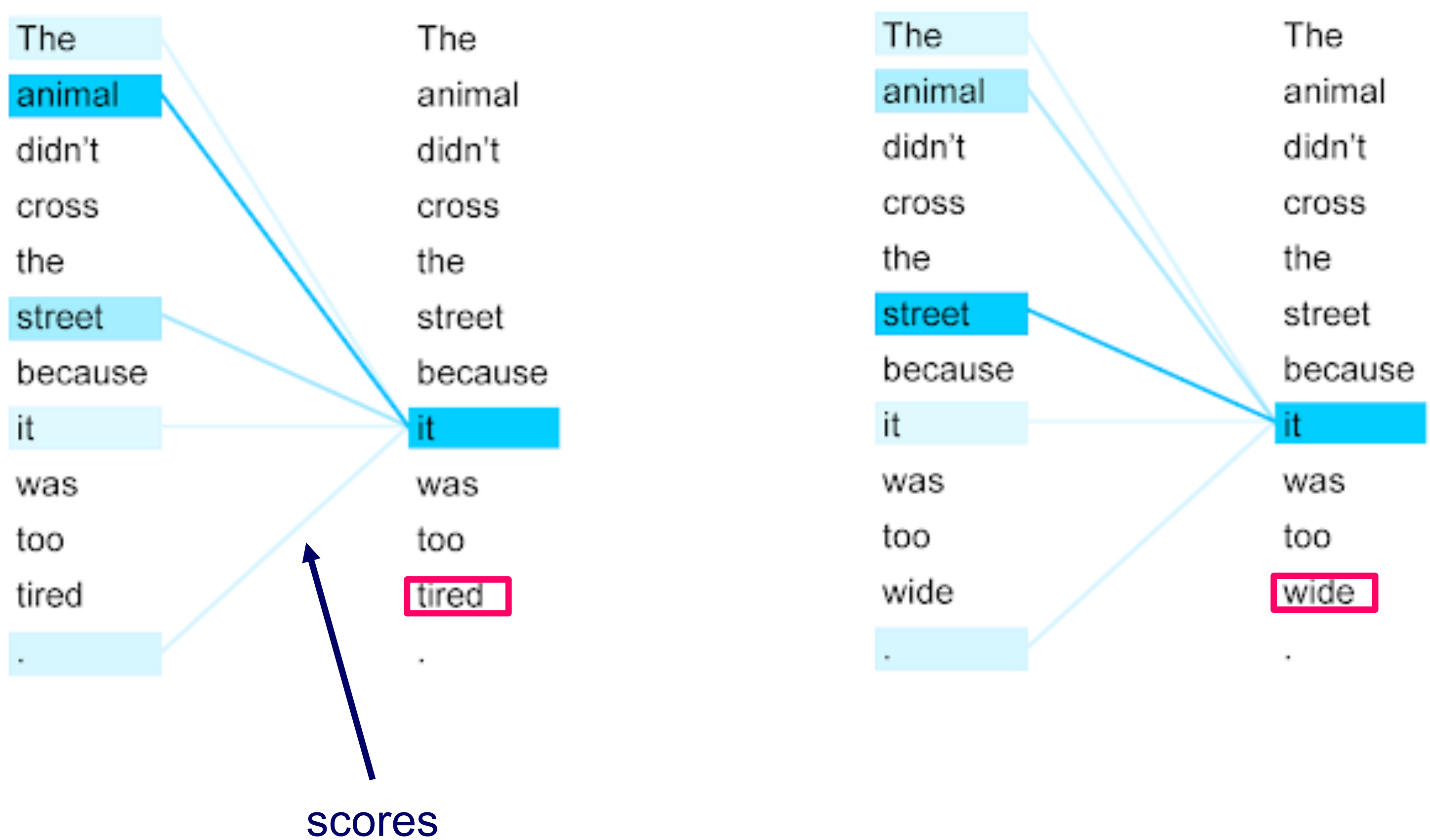
Goals for lecture

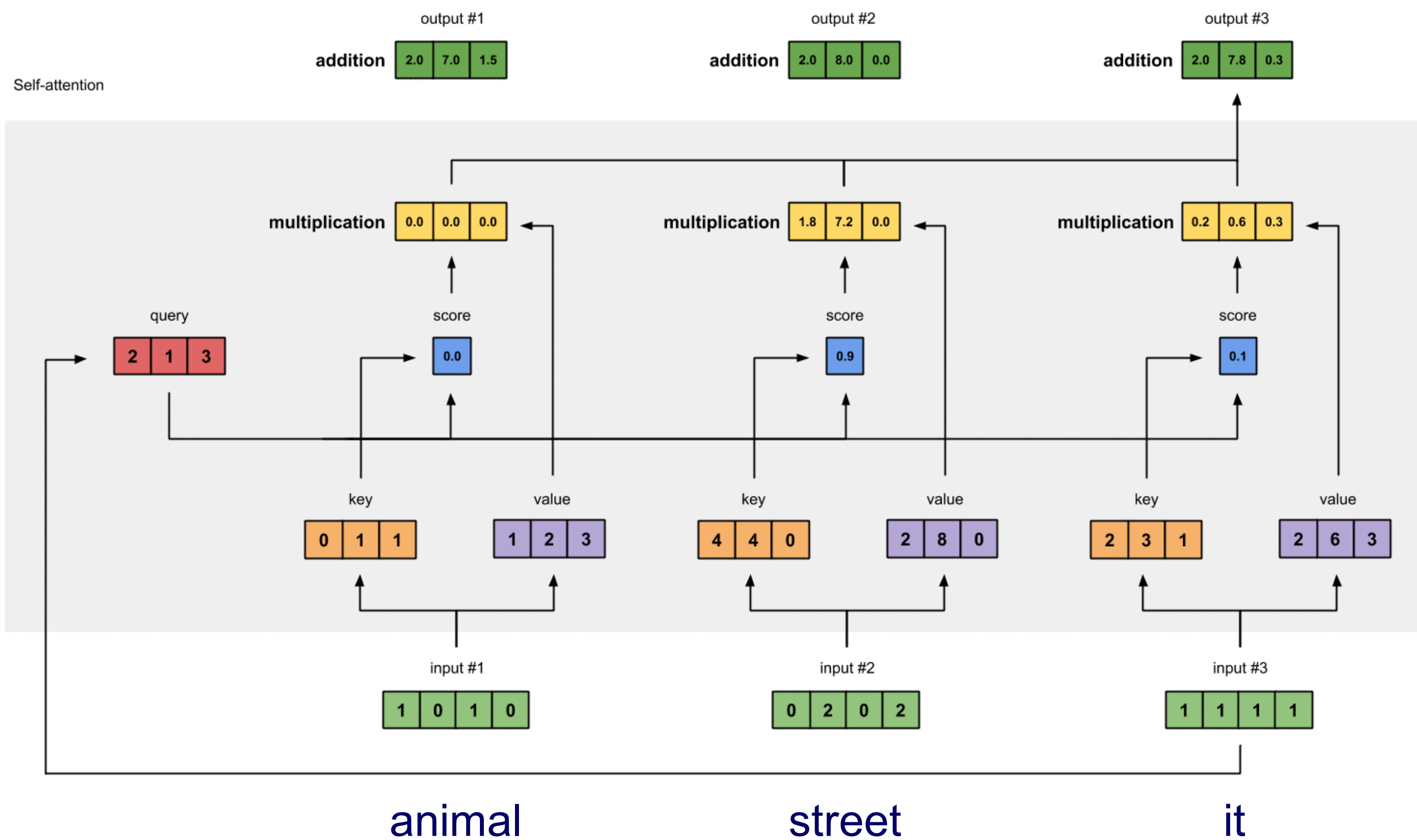
- Attentions
  - Interpretation
  - Self and Cross-Attention Calculation
  - Multi-Head Attention
- Transformer architecture
  - Positional Encoding
  - Generative Output
- Applications to bioinformatics

Attention Interpretation



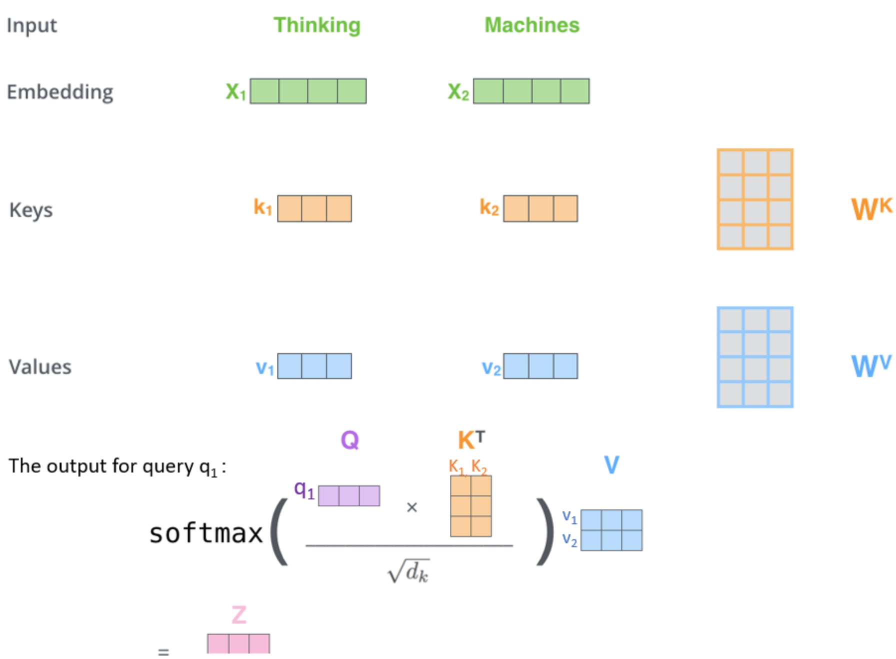
https://blog.research.google/2017/08/transformer-novel-neural-network.html

Attention Calculation



https://towardsdatascience.com/illustrated-self-attention-2d627e33b20a

Attention Calculation

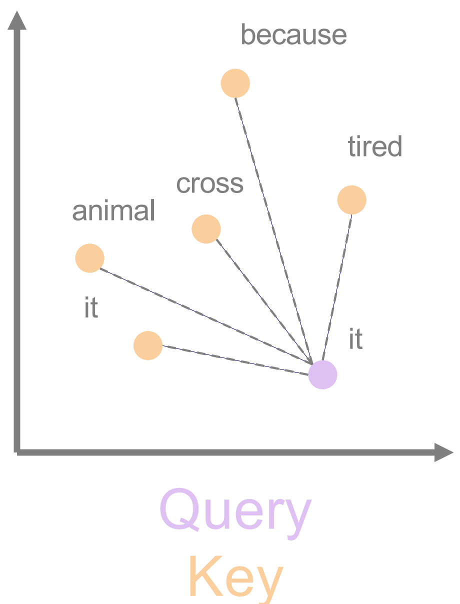


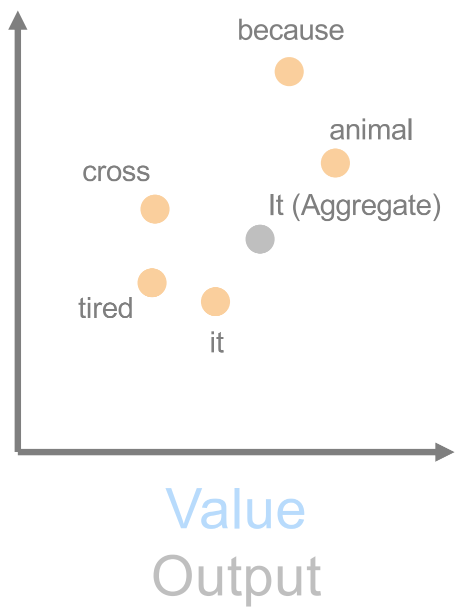
- Embeddings are passed through feed-forward networks to produce a **query** vector, as well as **key** and **value** vectors

- **Value** vectors are summed proportionally to the similarity between their corresponding **keys** and the **query**

https://medium.com/@YanAlx/step-by-step-into-transformer-79531eb2bb84

Attention Calculation

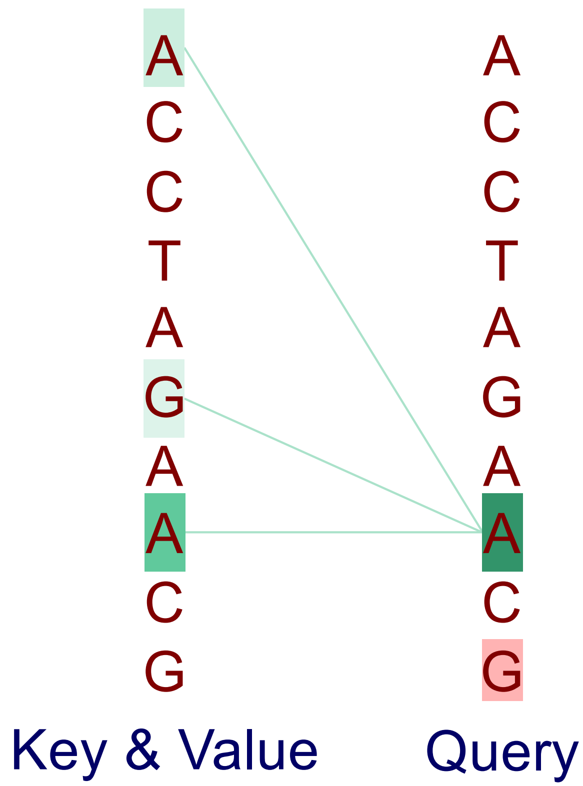




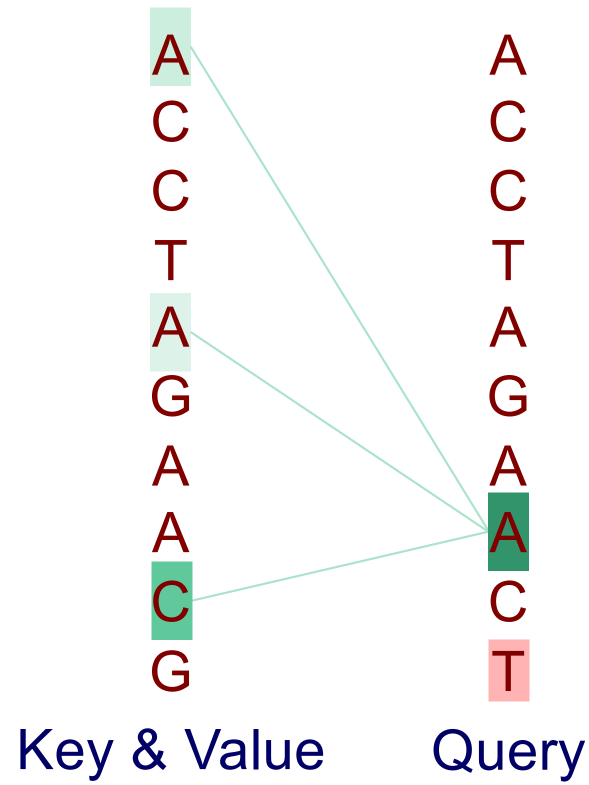
- **Key** and **query** vectors can be thought of as sharing a latent space
- The distance between the **query** and **keys** then determines the final **output** in **value** space

https://medium.com/@YanAIx/step-by-step-into-transformer-79531eb2bb84

Types of Attention

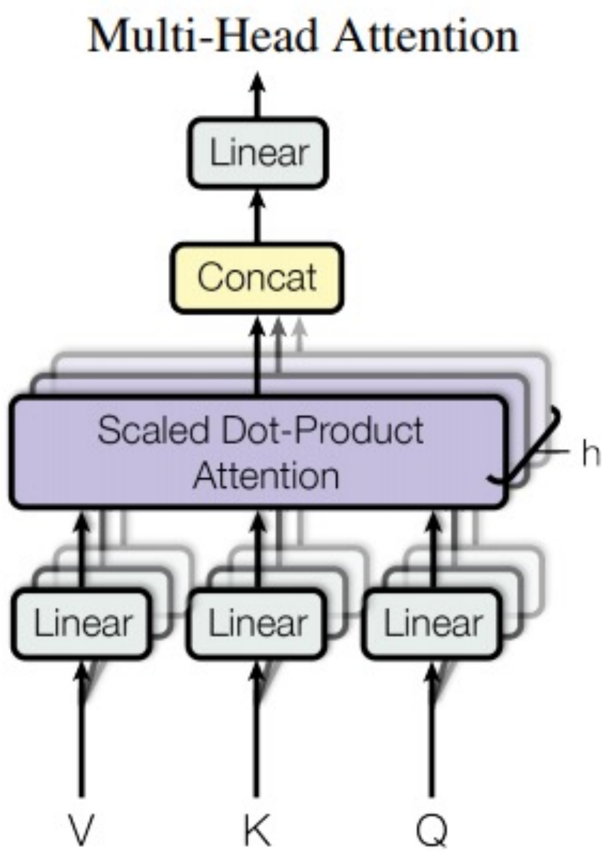


Self-Attention



Cross-Attention

Multi-Head Attention



Each attention module is known as a ‘head’

Multi-head attention involves aggregating multiple heads, usually culminating in average pooling

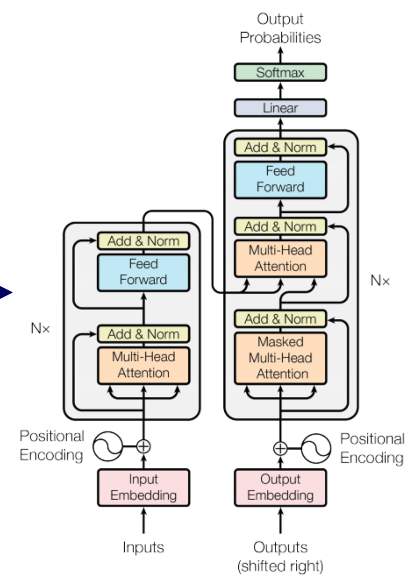
This allows each head to prioritize differing features of the sequence (e.g. noun-noun relationships, noun-verb relationships)

https://www.tensorflow.org/text/tutorials/transformer

Transformer Outline

Input Sequence

A C C T A G A A C G



Output Sequence

A C G .. T C G A A T

Example: Generative Text

Find the bug with this code:

```
for (var i = 0; i < 5; i++) {
  setTimeout(() => console.log(i), 1000)
}
```

The code contains a bug that will cause it to always print the number 5 to the console, rather than the expected sequence of numbers from 0 to 4. This is because the `setTimeout` function creates a closure that captures the value of the `i` variable, but the `i` variable is changed before the callback function is executed.

To fix this bug, the code can be modified to create a new variable in the loop that is passed to the `setTimeout` callback function, rather than using the loop variable directly. This will ensure that each callback function captures the correct value of the loop variable, and the expected output will be produced. Here is an example of how the code could be fixed:

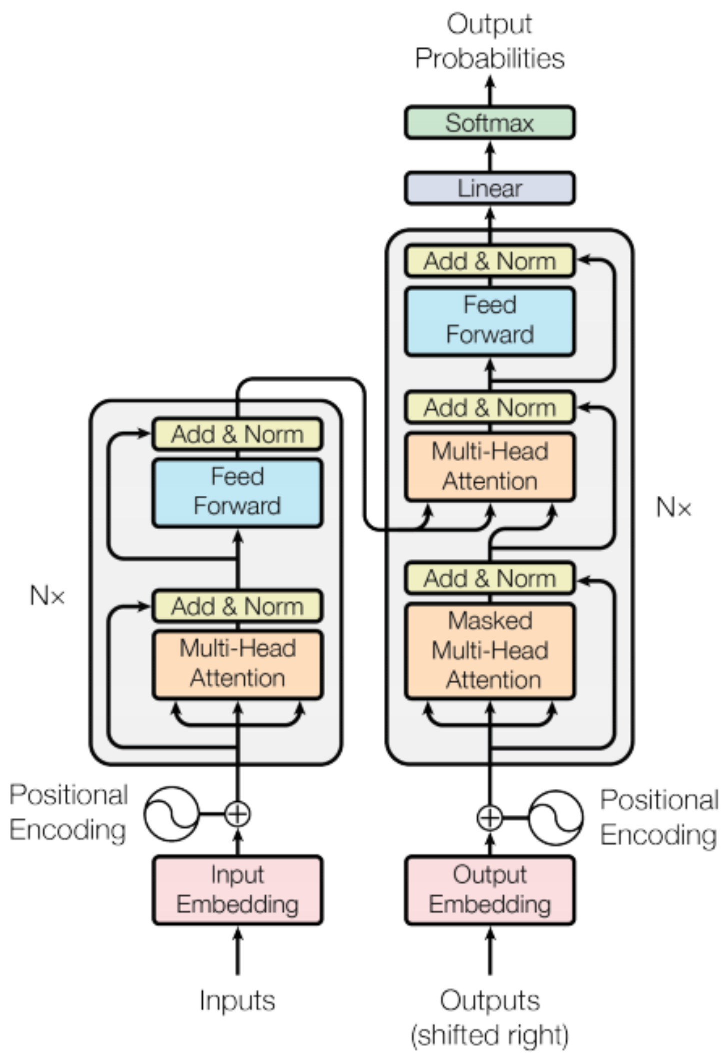
Copy code

```
for (var i = 0; i < 5; i++) {
  // Create a new variable and pass its value to setTimeout
  const value = i;
  setTimeout(() => console.log(value), 1000)
}
```

This code will print the numbers 0 to 4 to the console, as expected. Alternatively, the `let` keyword can be used in place of `var` to declare the loop variable, which will automatically create a new variable for each iteration of the loop and avoid the need to create a new variable manually. This is a common pattern for avoiding closure-related bugs in JavaScript.

https://www.springboard.com/blog/news/chatgpt-revolution/

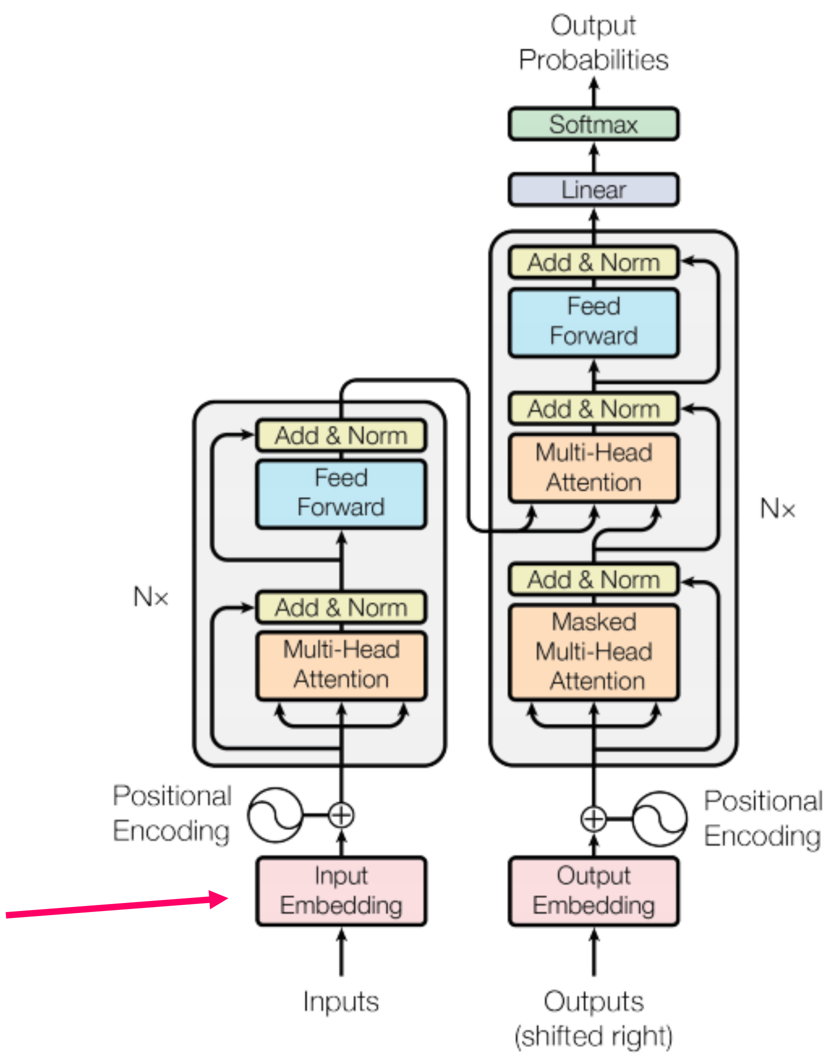
Transformer Architecture



Encoder Decoder

https://www.tensorflow.org/text/tutorials/transformer

Input Embedding



Input Sequence

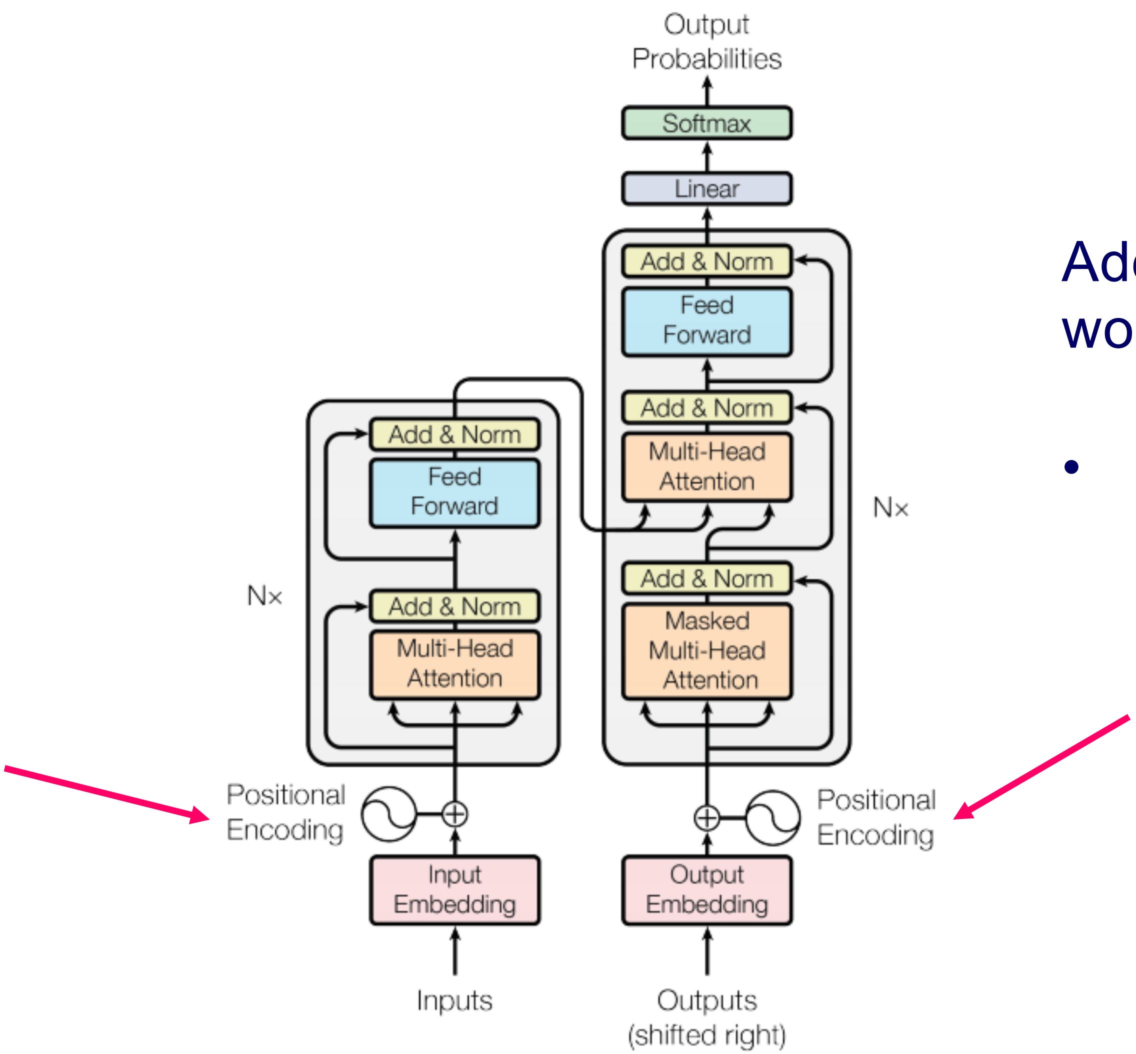
A C C T A G A A C G

Learned
Embeddings

0 4 4 5 0 8 0 0 0 8
2 8 8 8 2 3 2 2 8 3
5 5 5 2 5 0 5 5 5 0
3 8 8 8 3 6 3 3 8 6

https://www.tensorflow.org/text/tutorials/transformer

Positional Encoding

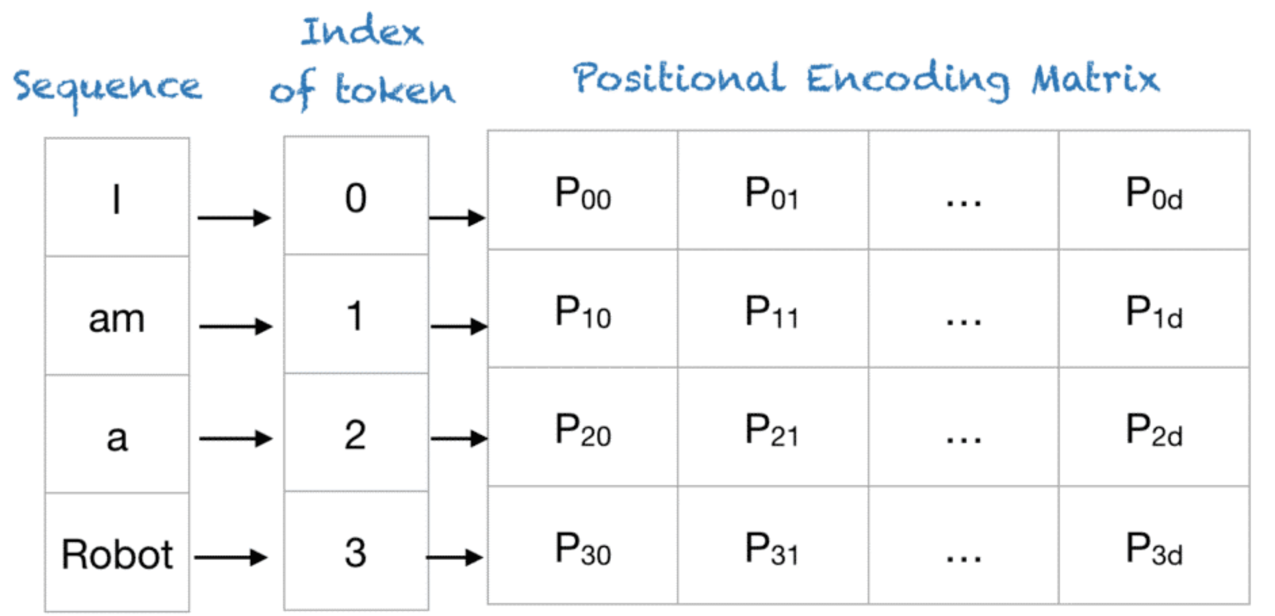


Add positional representations to word embeddings

- Allows the network to consider word proximity

https://www.tensorflow.org/text/tutorials/transformer

Positional Encoding



Positional Encoding Matrix for the sequence 'I am a robot'

https://machinelearningmastery.com/a-gentle-introduction-to-positional-encoding-in-transformer-models-part-1/

Positional Encoding

$$P(k, 2i) = \sin\left(\frac{k}{n^{2i/d}}\right)$$

$$P(k, 2i+1) = \cos\left(\frac{k}{n^{2i/d}}\right)$$

Positional Encoding Matrix with d=4, n=100

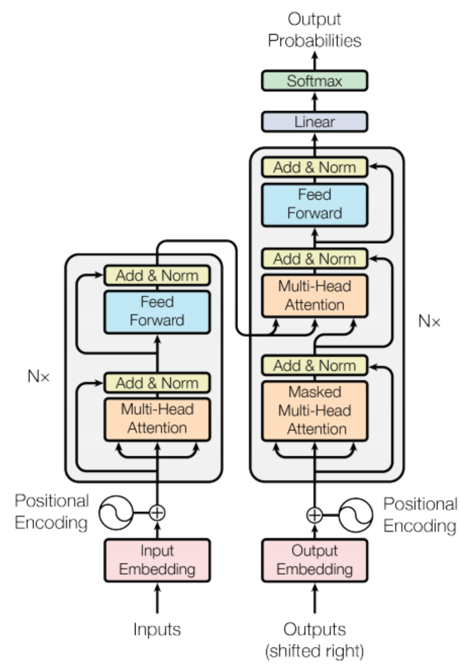
Sequence	Index of token, k	i=0	i=0	i=1	i=1
I	0	$P_{00}=\sin(0)$ = 0	$P_{01}=\cos(0)$ = 1	$P_{02}=\sin(0)$ = 0	$P_{03}=\cos(0)$ = 1
am	1	$P_{10}=\sin(1/1)$ = 0.84	$P_{11}=\cos(1/1)$ = 0.54	$P_{12}=\sin(1/10)$ = 0.10	$P_{13}=\cos(1/10)$ = 1.0
a	2	$P_{20}=\sin(2/1)$ = 0.91	$P_{21}=\cos(2/1)$ = -0.42	$P_{22}=\sin(2/10)$ = 0.20	$P_{23}=\cos(2/10)$ = 0.98
Robot	3	$P_{30}=\sin(3/1)$ = 0.14	$P_{31}=\cos(3/1)$ = -0.99	$P_{32}=\sin(3/10)$ = 0.30	$P_{33}=\cos(3/10)$ = 0.96

Positional Encoding Matrix for the sequence 'I am a robot'

https://machinelearningmastery.com/a-gentle-introduction-to-positional-encoding-in-transformer-models-part-1/

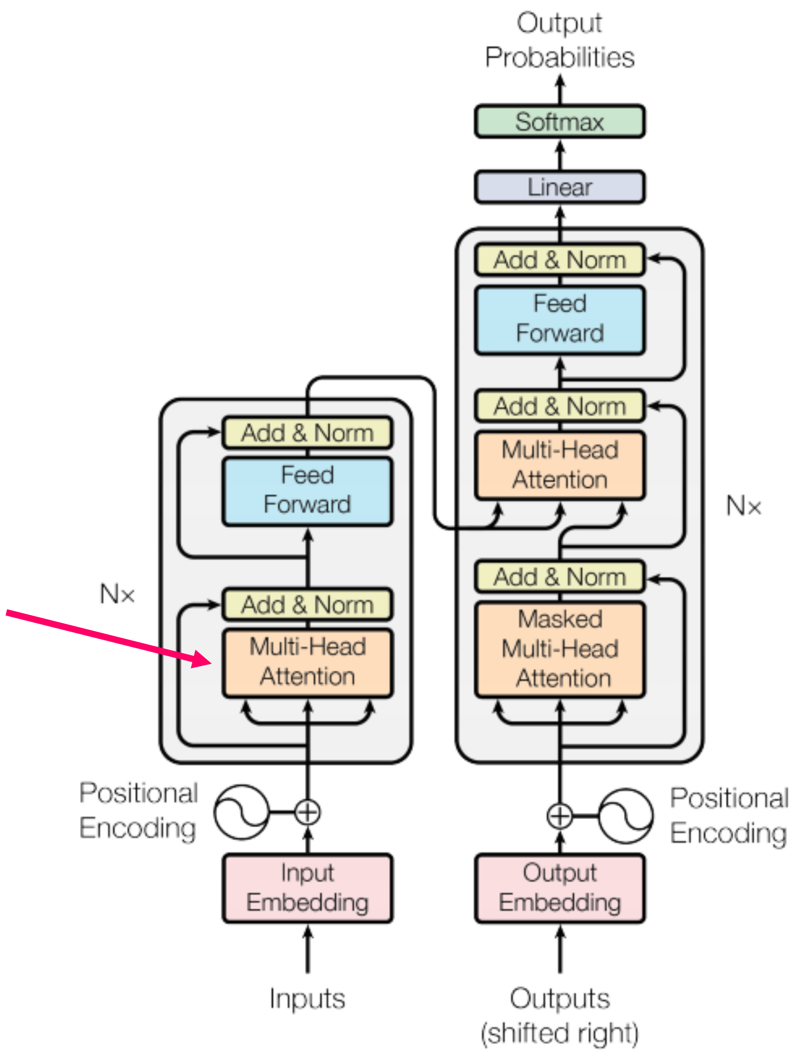
Positional Encoding

Learned Embeddings		Positional Encoding		Temporal Embeddings
0 4 4 5 0 8 0 0 0 8				0 6 0 6 0 2 3 8 5 9
2 8 8 8 2 3 2 2 8 3	→	Addition	→	2 2 2 0 9 7 4 9 1 2 7
5 5 5 2 5 0 5 5 5 0				4 7 1 5 3 3 7 6 3 1
3 8 8 8 3 6 3 3 8 6				3 5 7 1 2 5 3 0 3 9



https://www.tensorflow.org/text/tutorials/transformer

Attention Modules



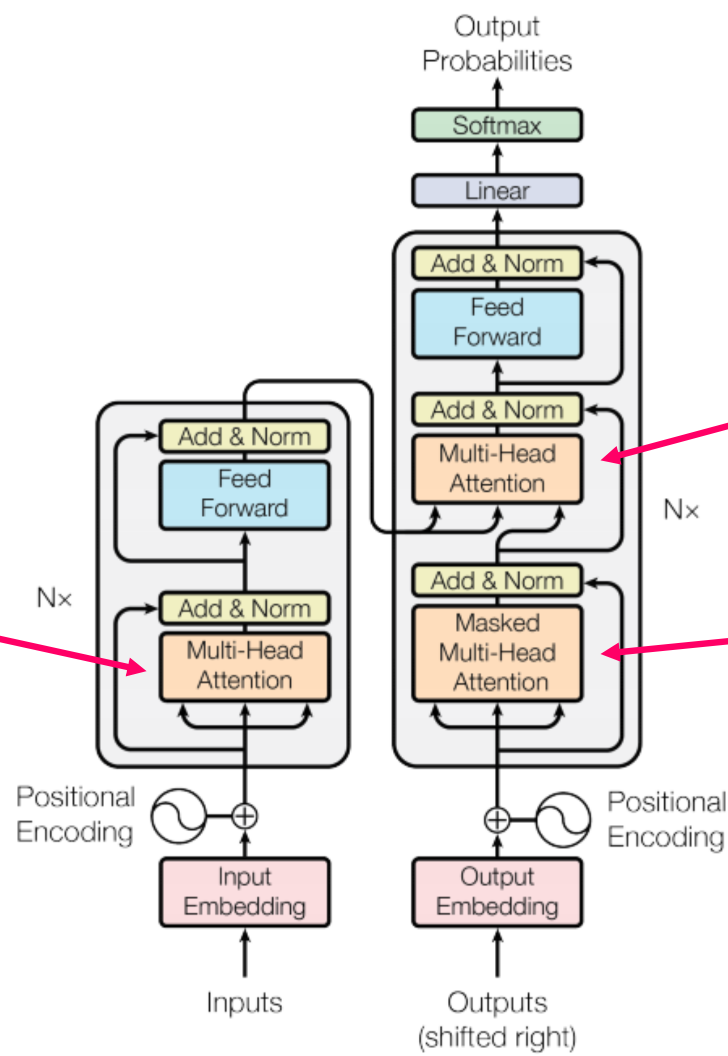
Prioritize bases relative to each other

- This is the primary mechanism which allows transformers to work
- Essentially adds context to existing embeddings

https://www.tensorflow.org/text/tutorials/transformer

Self and Cross-Attention

Self-attention
(Q=K=V)



Cross-attention
(Q from decoder)
(K=V from encoder)

Self-attention
(Q=K=V)

https://www.tensorflow.org/text/tutorials/transformer

Transformer Attention

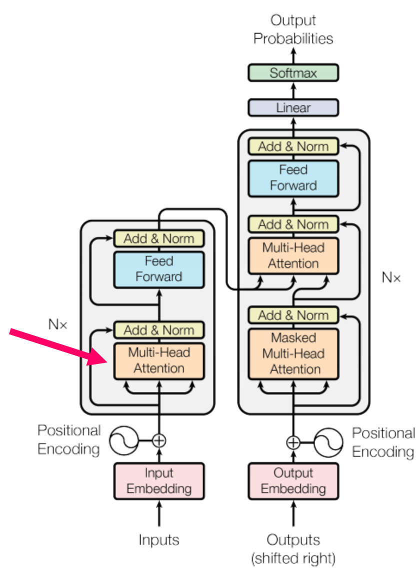
Temporal
Embeddings

0 6 0 6 0 2 3 8 5 9
2 2 2 0 9 7 4 9 1 2 7
4 7 1 5 3 3 7 6 3 1
3 5 7 1 2 5 3 0 3 9

Multi-Head
Attention
+Feed-Forward

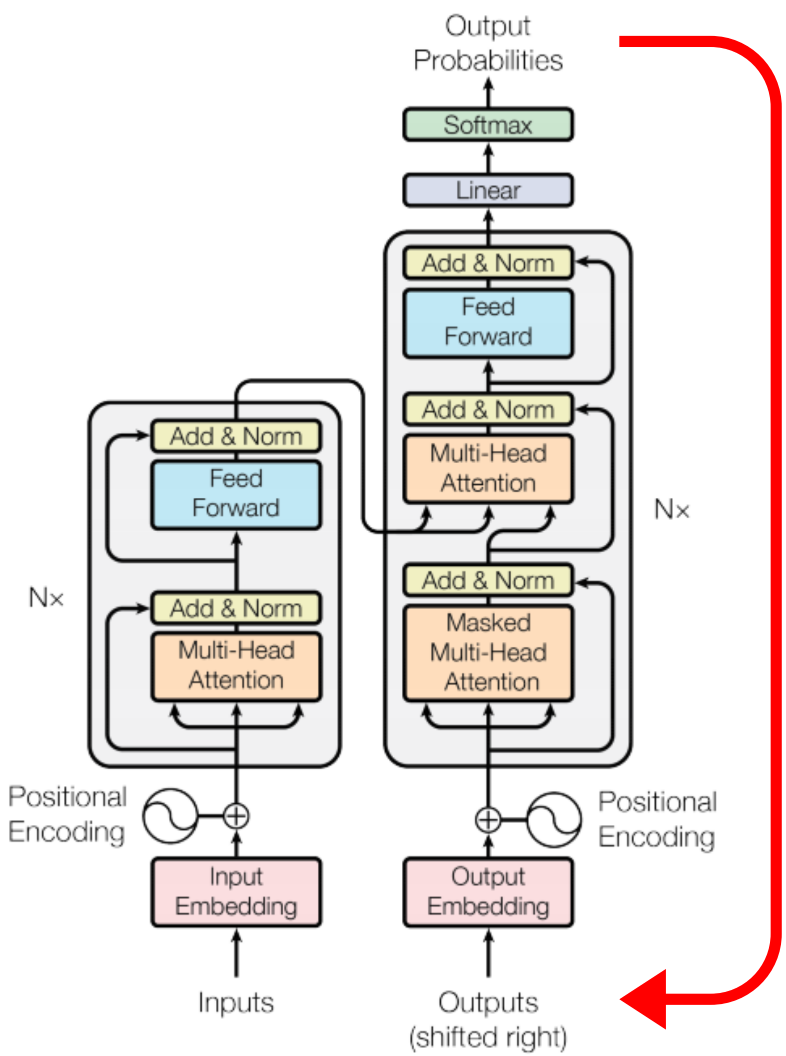
Encoded
Representations

0 5 7 5 5 2 3 7 7 0
5 6 1 8 1 2 3 1 2 4
0 8 3 7 6 1 7 8 8 3
2 7 7 3 9 0 0 4 0 0



https://www.tensorflow.org/text/tutorials/transformer

Transformer Decoder

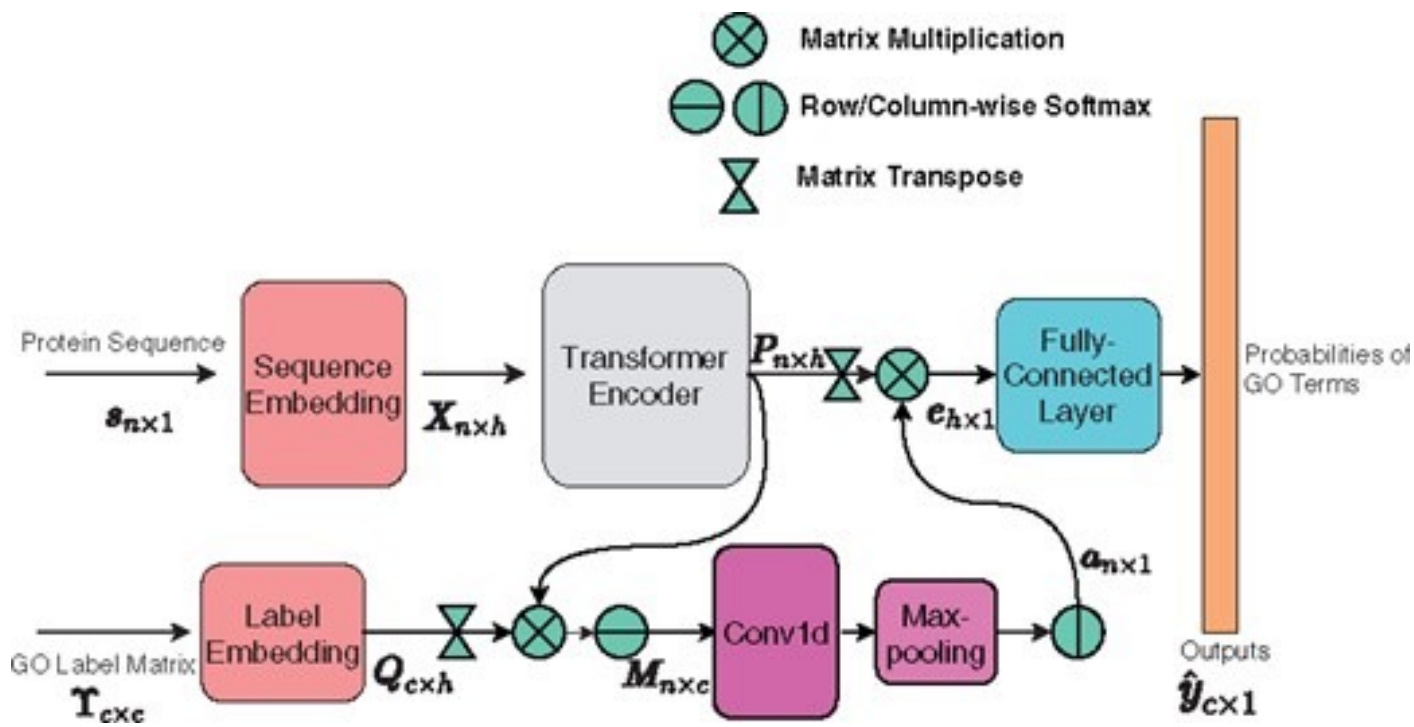


https://www.tensorflow.org/text/tutorials/transformer

For generative outputs, repeatedly choose the most likely next element until the end of the sequence

0. <start>
1. <start> A
2. <start> A T
3. <start> A T T
4. <start> A T T G
5. <start> A T T G <end>

Example: Protein Function Annotation

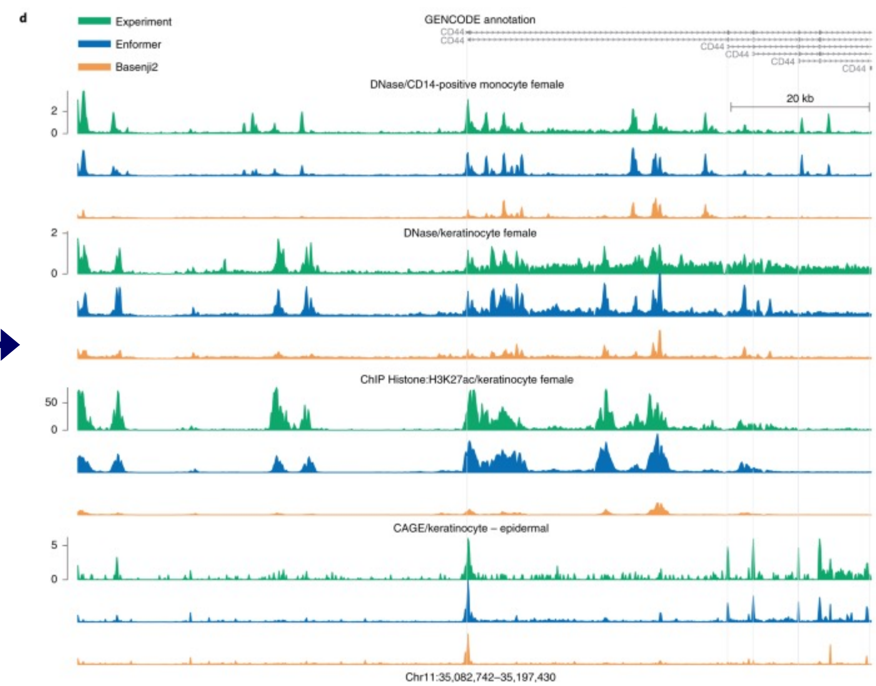


Yue Cao et al. Bioinformatics 2021; 37:18

Example: Enhancer Prediction from DNA Sequence

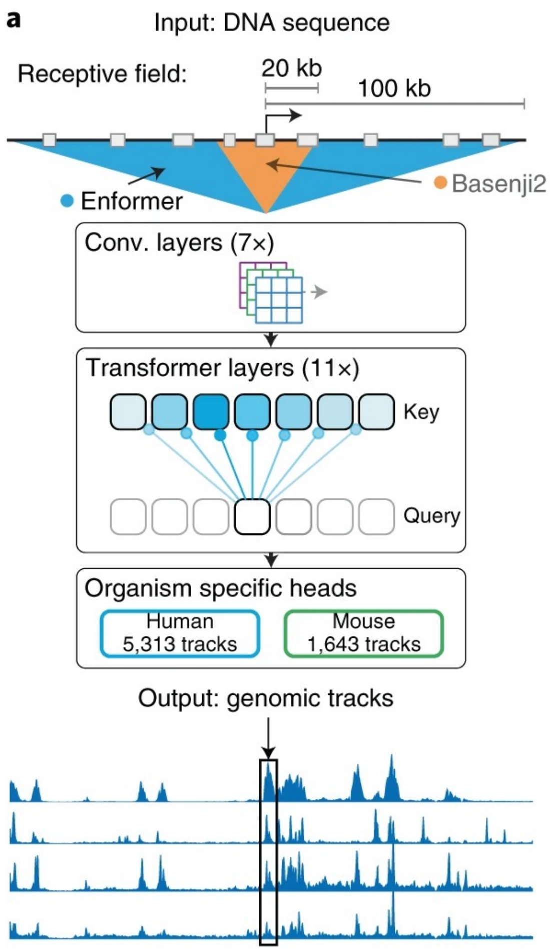
Transformers have applications other than sequence generation as well

A C C T A G A A C G $\xrightarrow{\text{Enformer}}$



Žiga Avsec et al. Nature Methods 2021; 18

Example: Enhancer Prediction from DNA Sequence



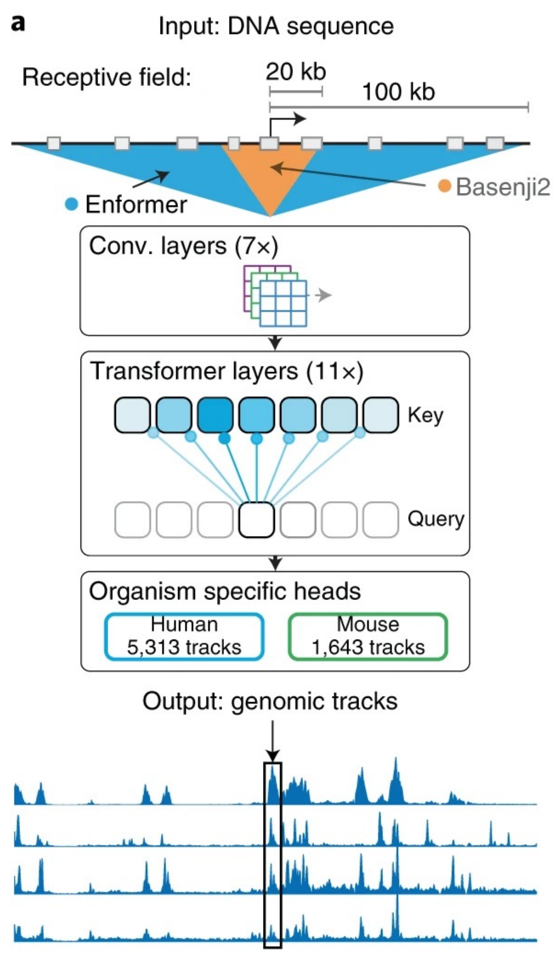
Instead of generating a DNA sequence, genomic tracks (e.g. TF binding, accessibility) can be generated instead

- Convolve 100kb to produce features for each base with attention pooling
- Feed to multiple self-attention blocks (transformer encoder)
- Apply final convolutions to predict tracks for humans or mice

Žiga Avsec et al. Nature Methods 2021; 18

Example: Enhancer Prediction from DNA Sequence

Transformers allow for broader search regions with fewer computational limits



Predict attribute-correlated locations based on DNA sequence

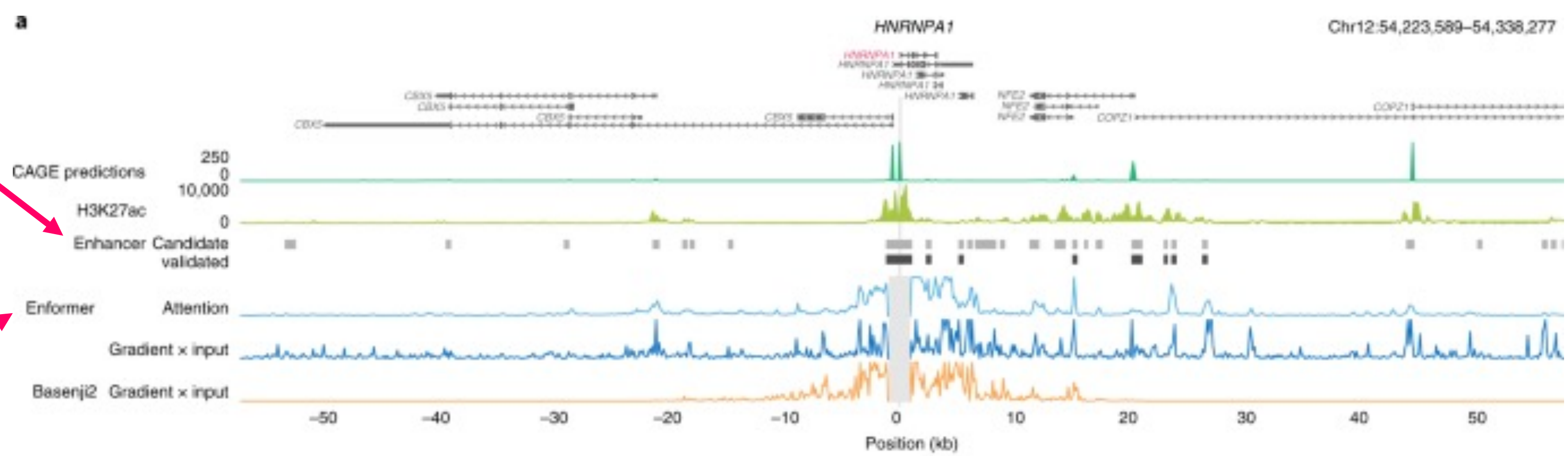
Žiga Avsec et al. Nature Methods 2021; 18

Example: Enhancer Prediction from DNA Sequence

After predicting tracks, known enhancers line up with calculated attention scores

CRISPRi Validation

Attention Scores



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