Molecular language models

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What are language models?

Natural language processing basics

Natural language

The patient complaints of severe (Severity) left-sided (Location) chest (Anatomy) pain (Problem). He underwent angioplasty (Procedure) & had 2 stents (Medical Device) placed a year ago. His BP (Body Measurement) and cardiac enzymes test (Lab Data) were normal. He is on aspirin & plavix (Medicine). He has a history of alcohol & marijauana abuse (Substance Abuse).

How do we learn language?

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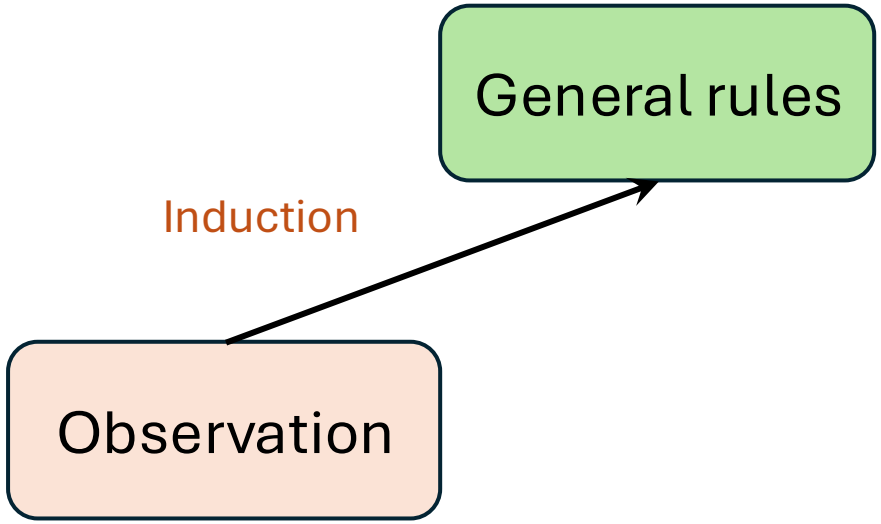
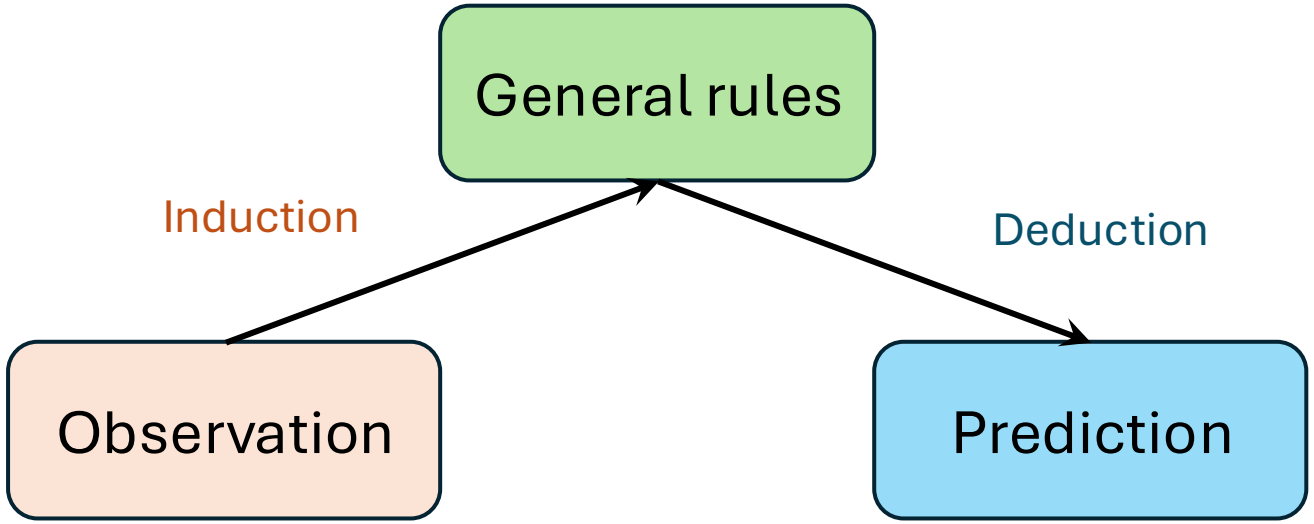


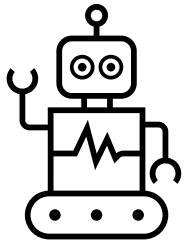
How do we learn language?

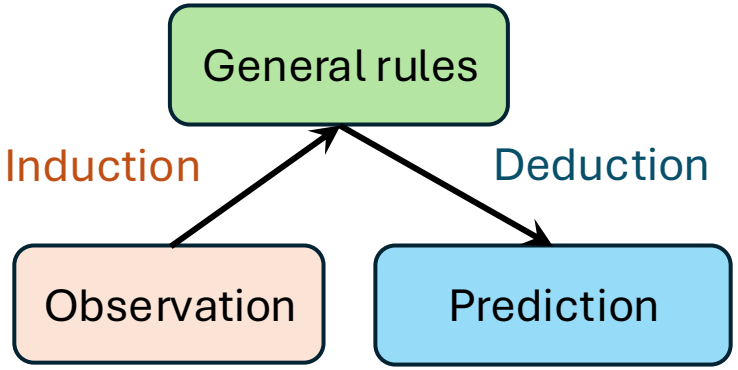


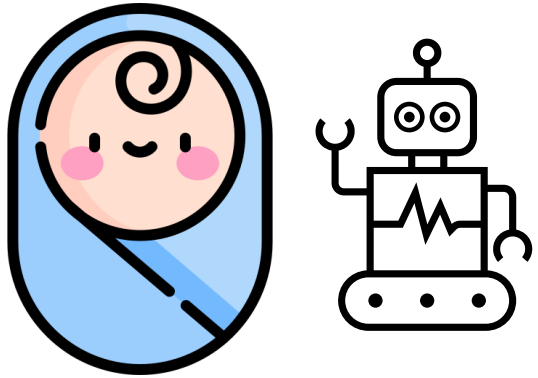
- **Induction**: Process of inferring general rules from discrete observations
- **Deduction**: Process of deriving discrete predictions from general rules

How can we teach a model languages?

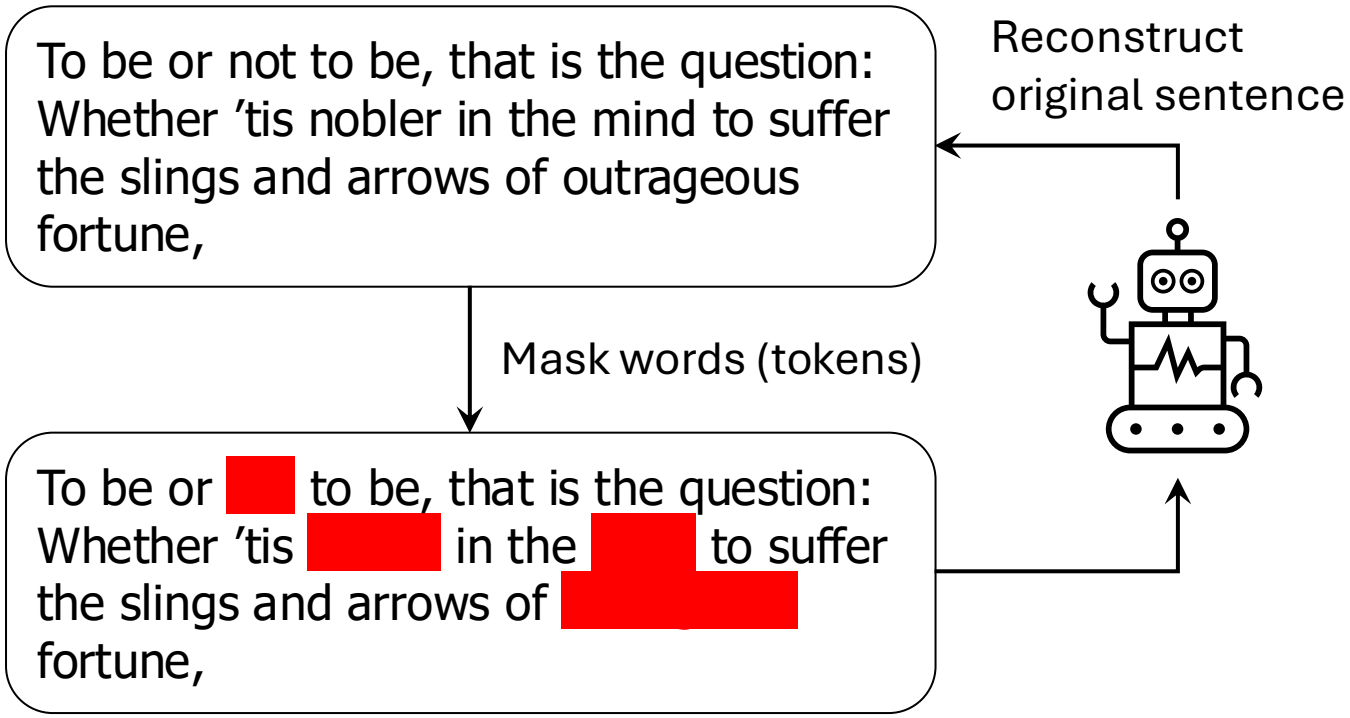
To be or not to be, that is the question:
Whether ’tis nobler in the mind to suffer
the slings and arrows of outrageous
fortune,

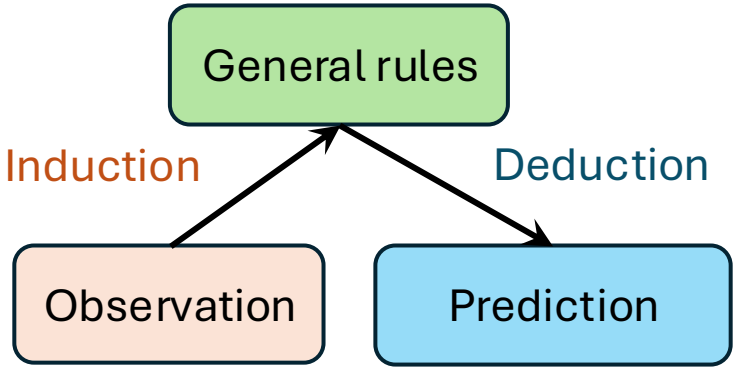


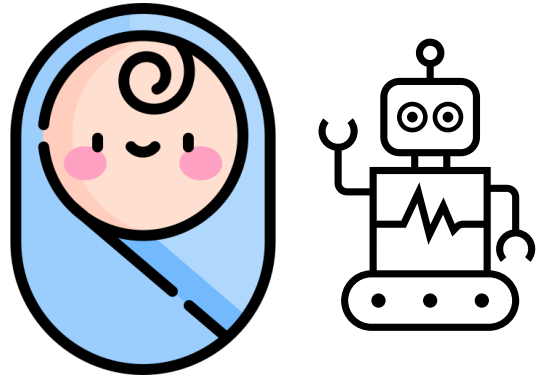




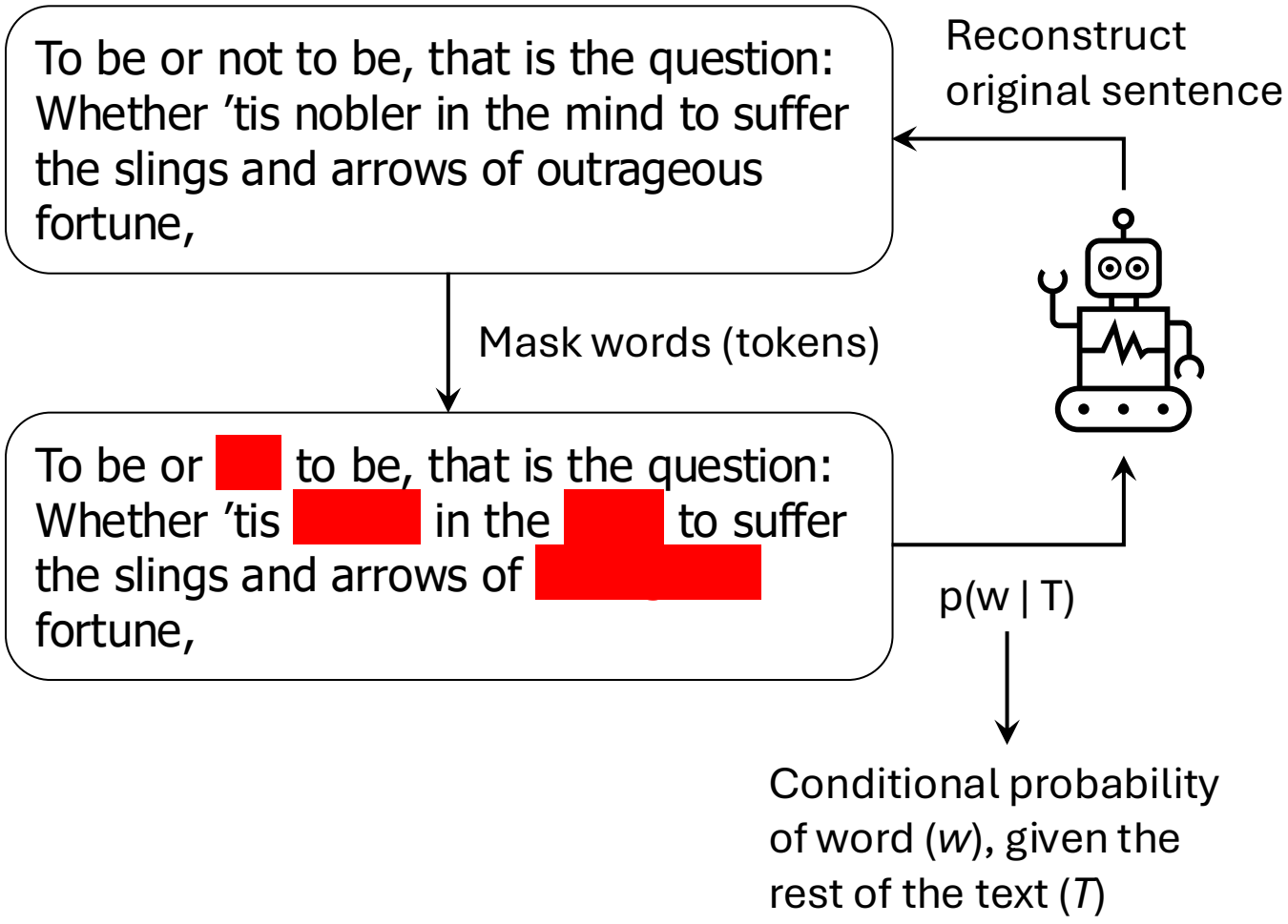
How can we teach a model languages?

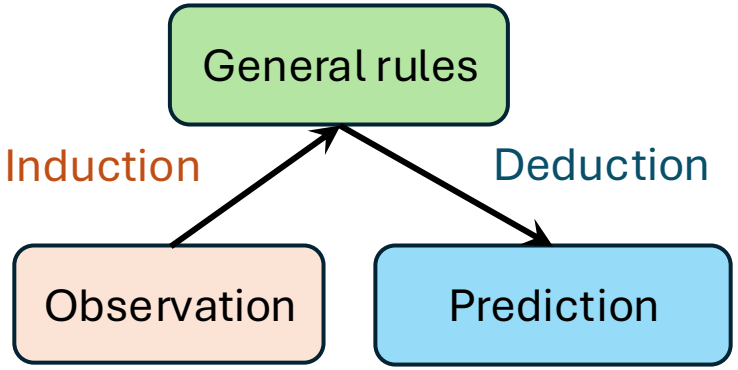


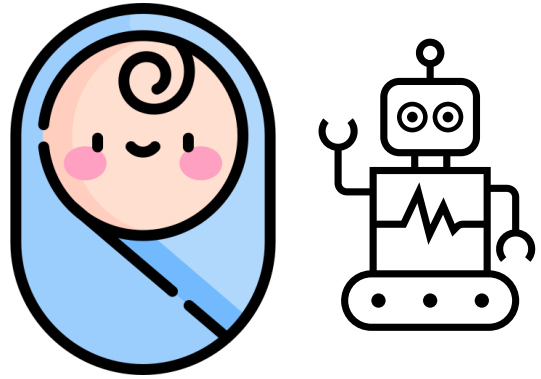




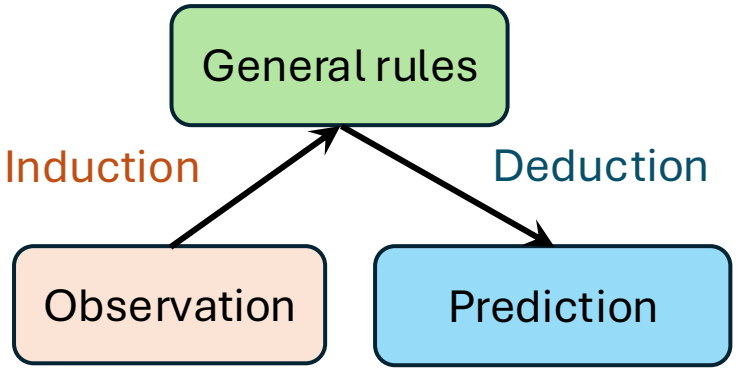
How can we teach a model languages?

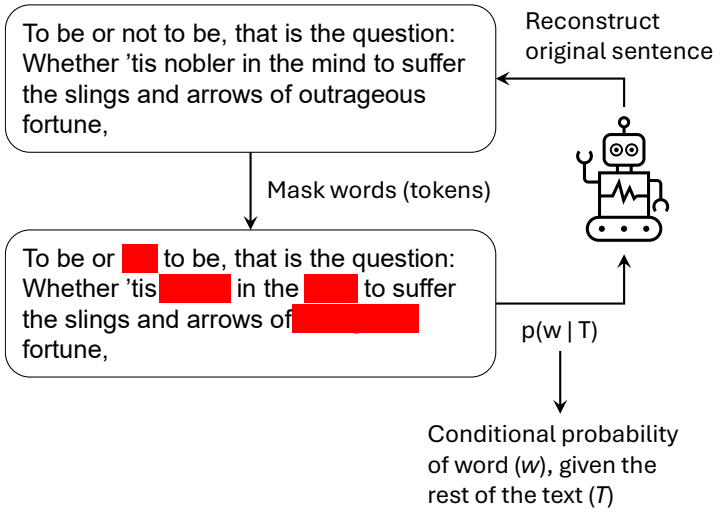




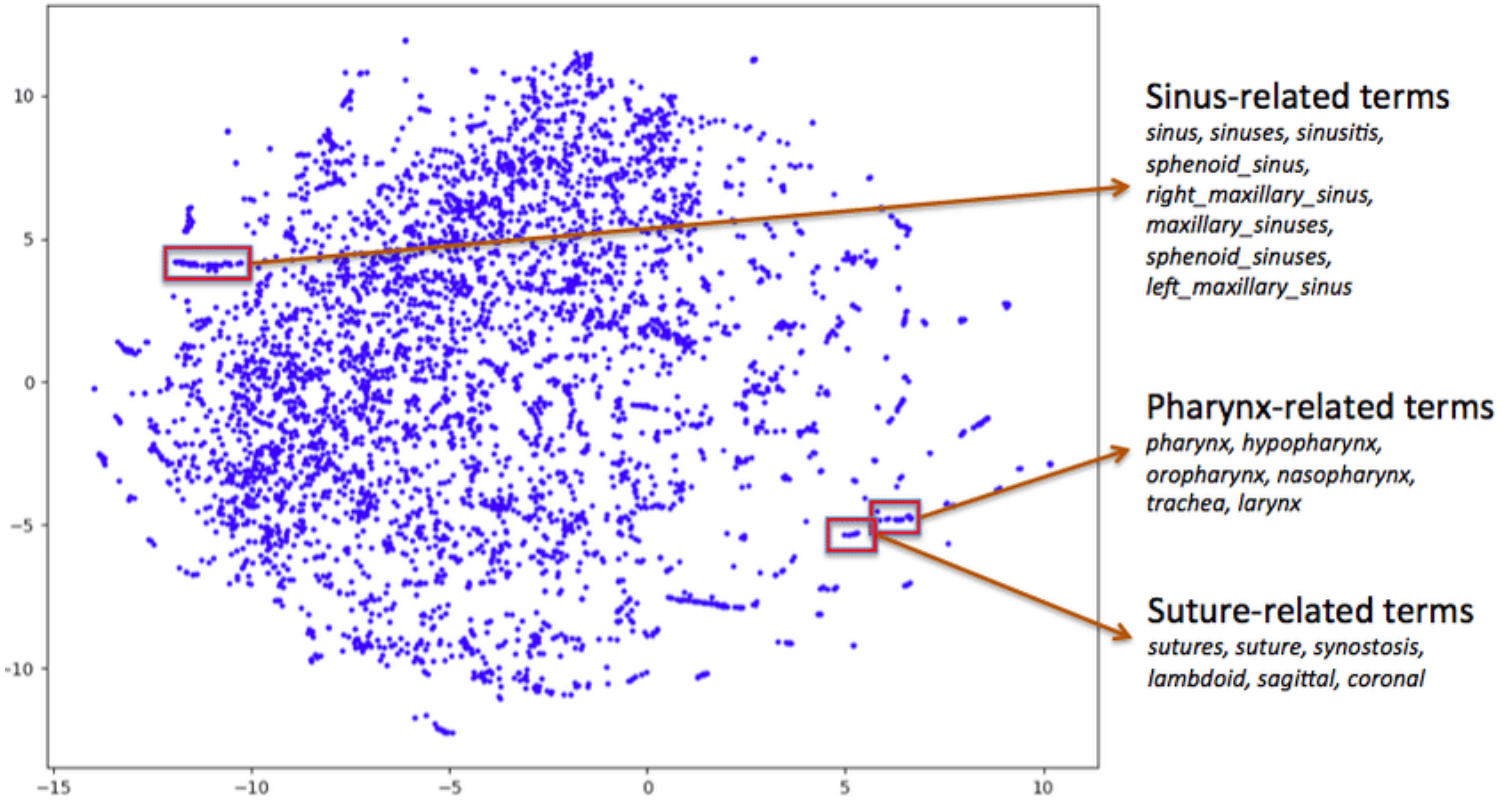


Words are embedded as vectors





2D representation of multidimensional space



Similar words are close together in the embedding/representation space

Resources

Model comparison

- https://arena.ai/

Language modelling visual explanation

- https://www.youtube.com/watch?v=LPZh9BOjkQs
- https://www.youtube.com/watch?v=eMlx5fFNoYc

How can we model language?

Transformers and the attention mechanism

Objective: pay attention to the right words

- The girl went to her grandma’s <mask>. <mask> had made cookies.
- The ship was lost in the <mask>.
- There was <mask> in the M50.

Objective: pay attention to the right words

- The girl went to her grandma's house. <mask> had made cookies.
- The ship was lost in the <mask>.
- There was <mask> in the M50.

Objective: pay attention to the right words

- The girl went to her grandma’s house. She had made cookies.
- The ship was lost in the <mask>.
- There was <mask> in the M50.

Objective: pay attention to the right words

- The girl went to her grandma’s house. She had made cookies.
- The ship was lost in the sea/ocean.
- There was <mask> in the M50.

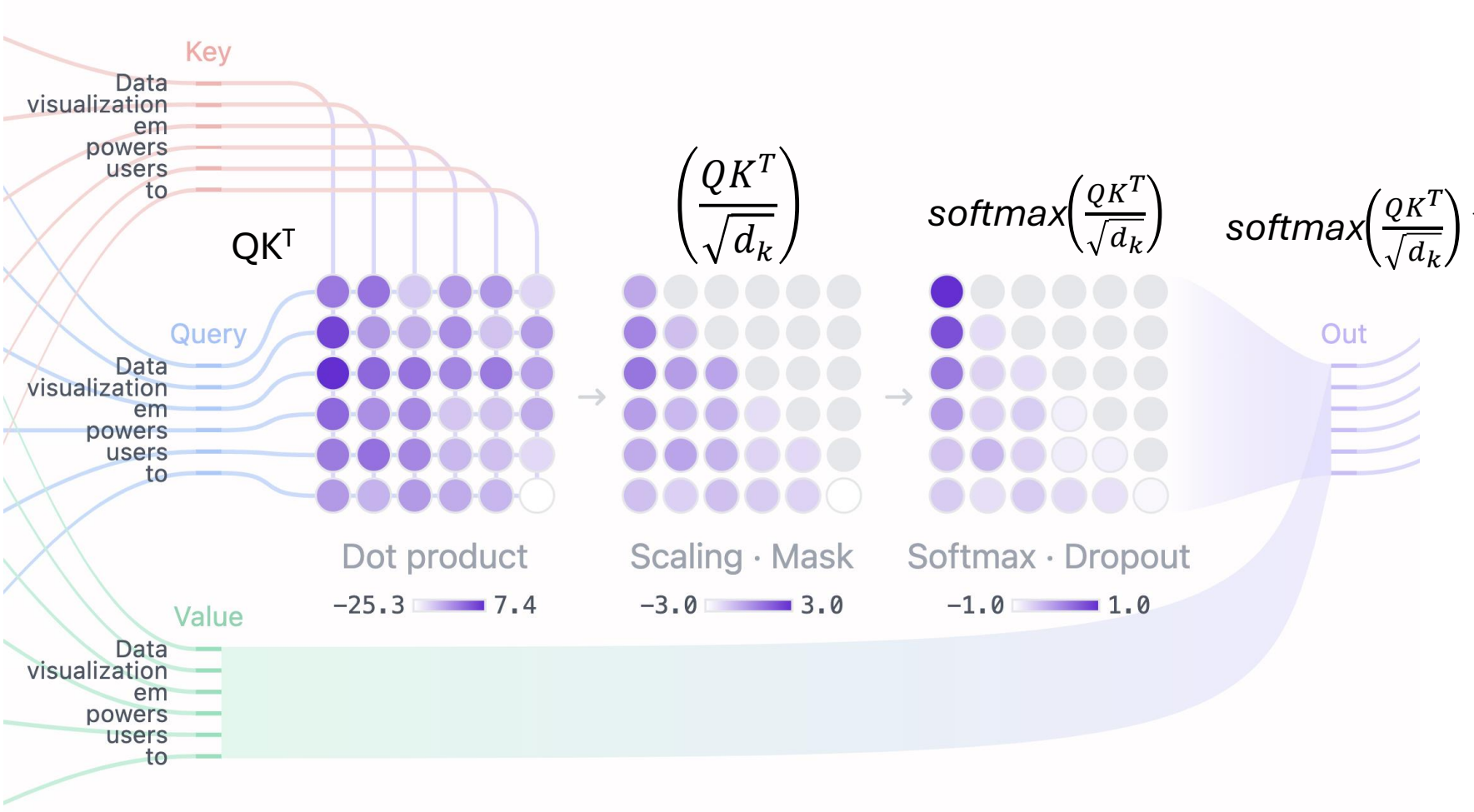
Objective: pay attention to the right words

- The girl went to her grandma’s house. She had made cookies.
- The ship was lost in the sea/ocean.
- There was traffic/an accident in the M50.

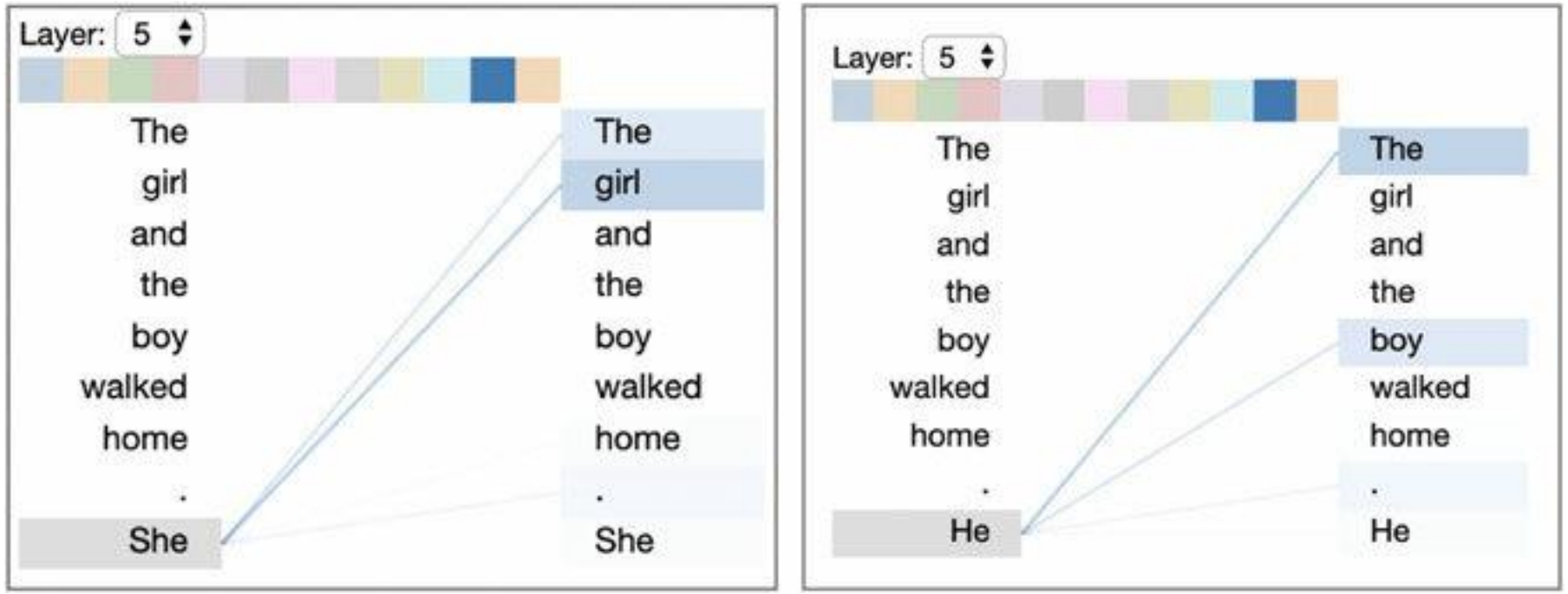
Attention Layer: Query, Key, Value

Attention: $softmax\left(\frac{QK^T}{\sqrt{d_k}}\right)V$

- **Key:** embedding of word we are interested in
- **Quey:** embedding of words we want to see if they are worth attending to
- **Value:** embedding of all words

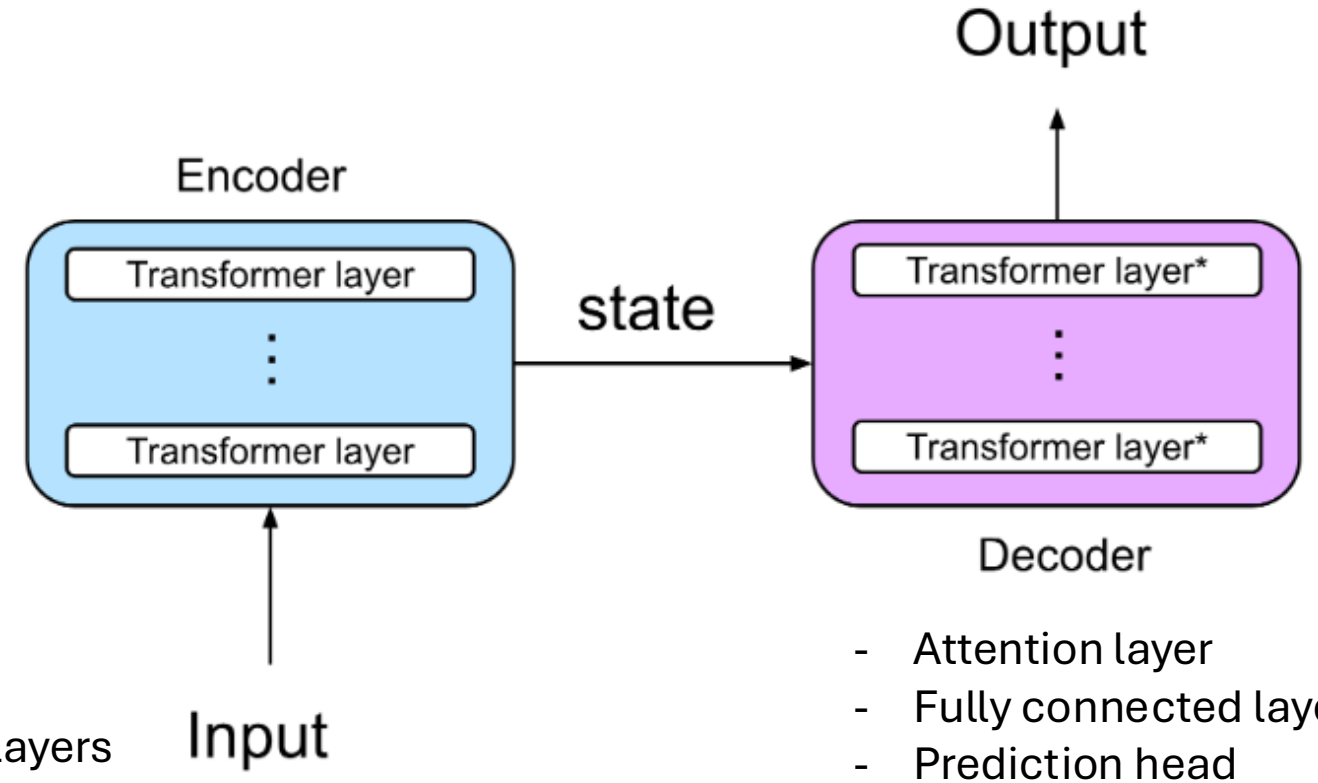


Objective: pay attention to the right words



Transformer architecture

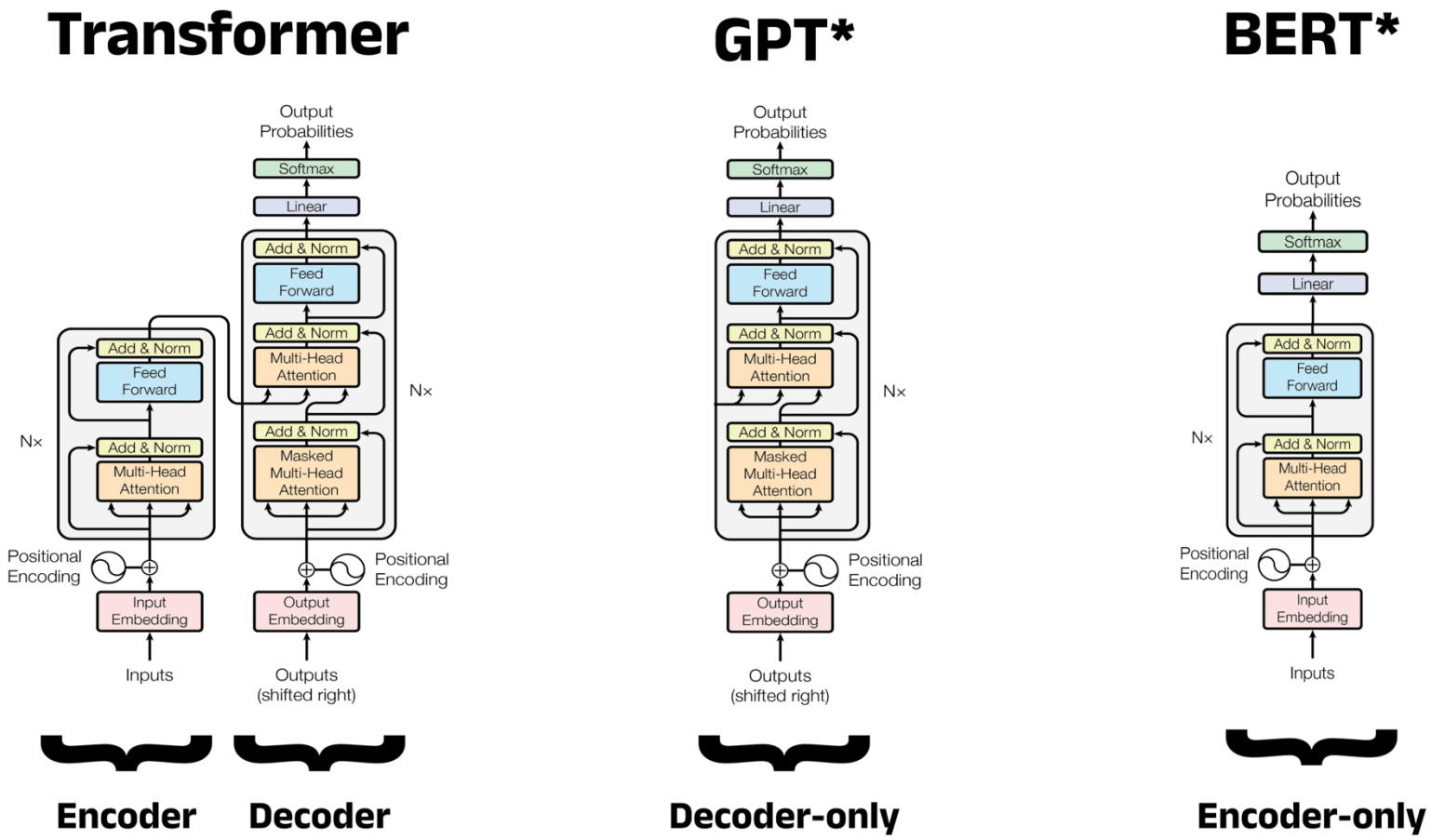
- **Encoder:** Text to numerical vector
- **Decoder:** Numerical vector to text



- Tokenizer
- Embedding layer
- Attention layer
- Fully connected layers

- Attention layer
- Fully connected layers
- Prediction head

Types of architecture

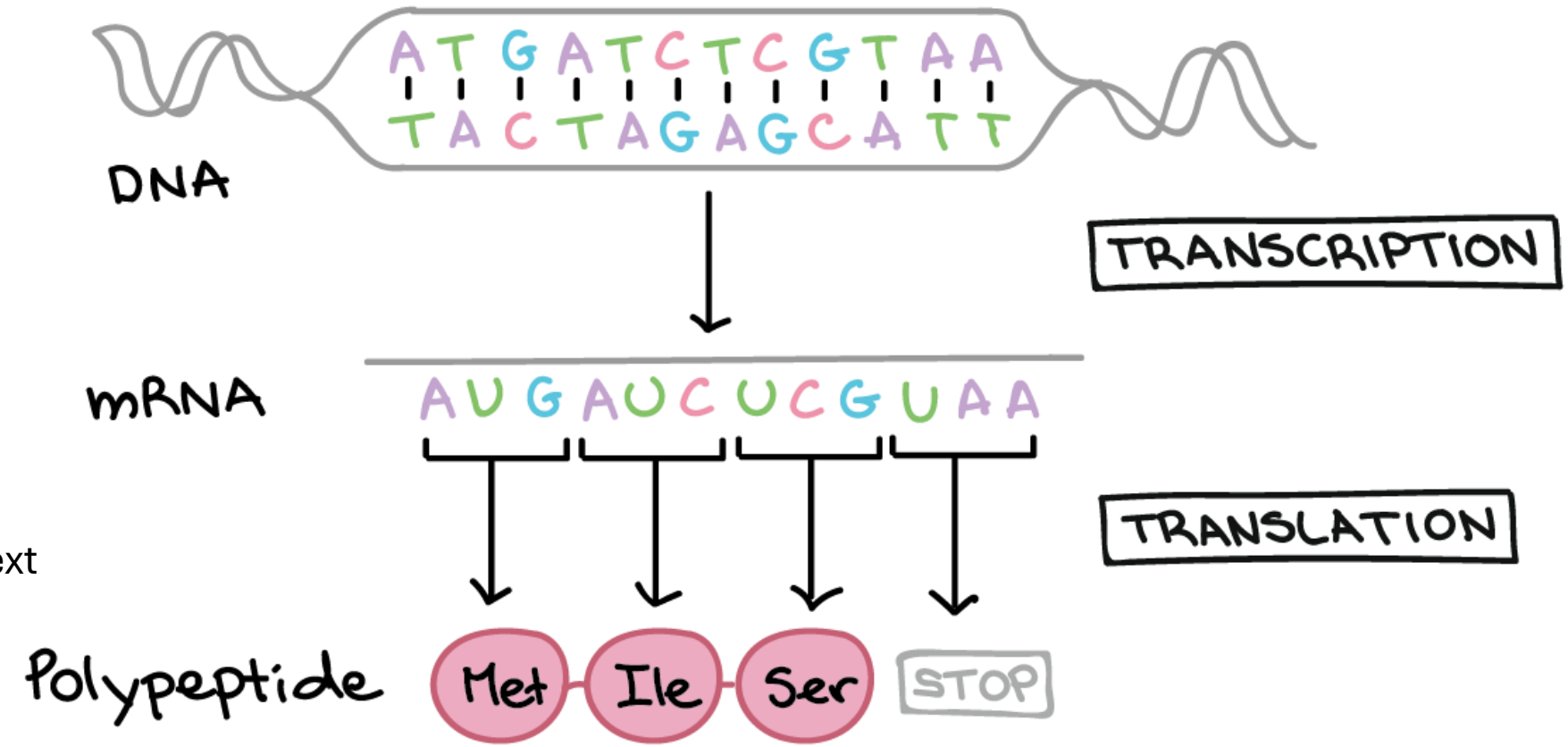


What are the molecular languages?

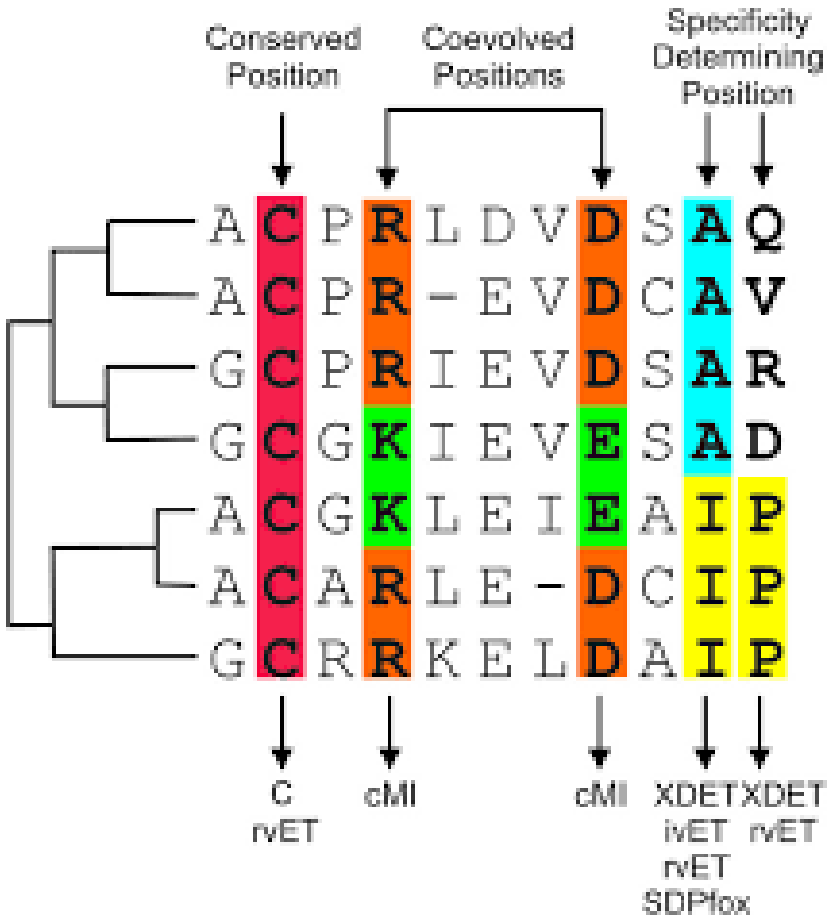
Transforming biomolecules into strings

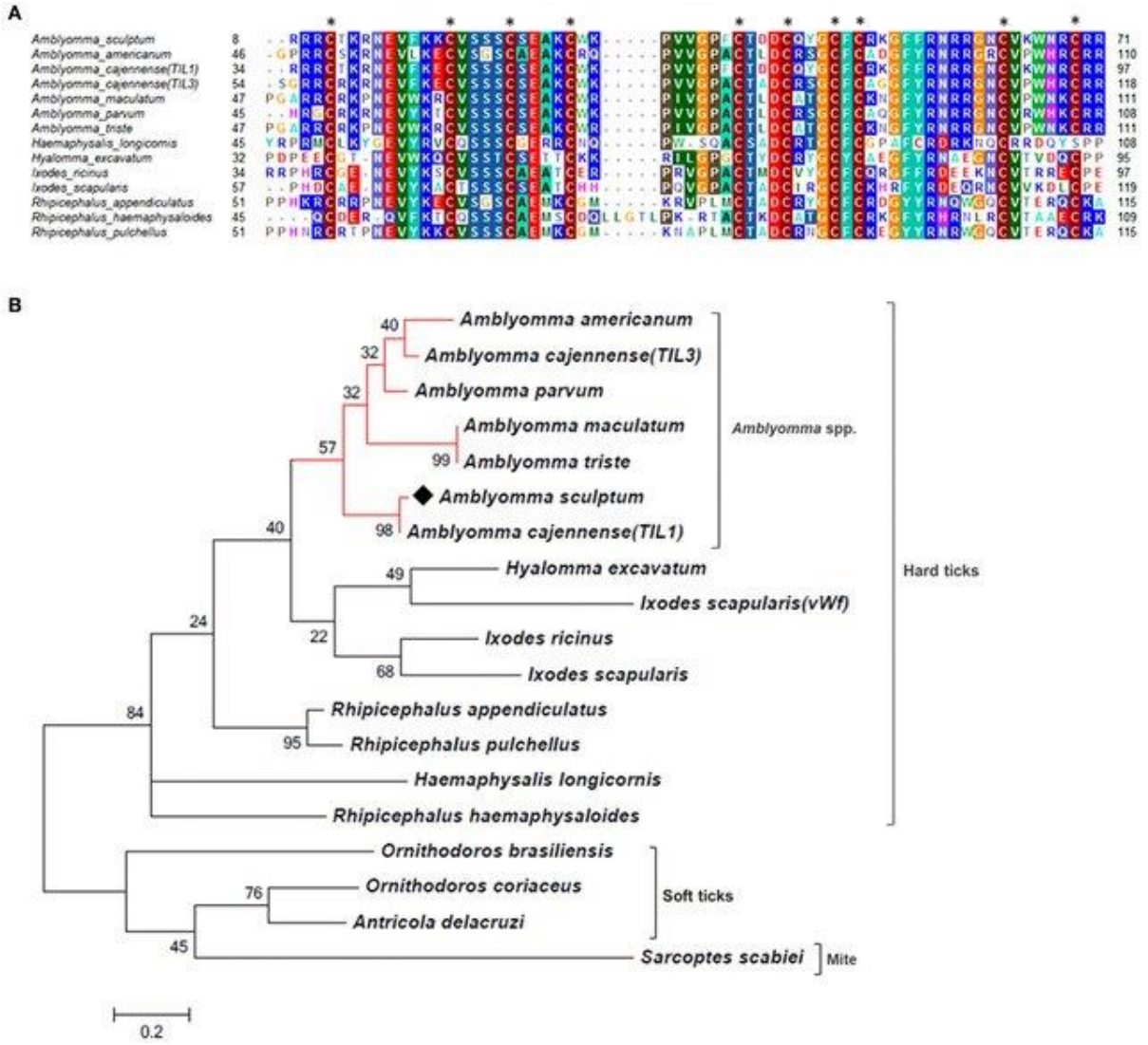
Biosequences

- **DNA and RNA:** 4 letter alphabet, huge context
- **Proteins:** ~20 letter alphabet, smaller context

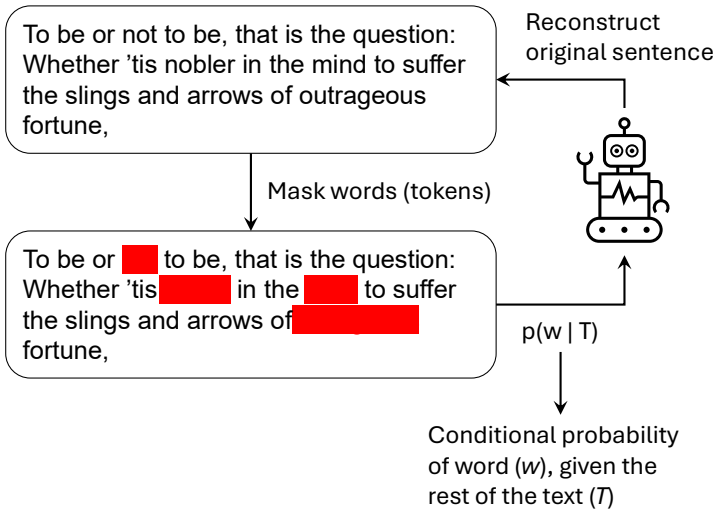


Biosequence evolution

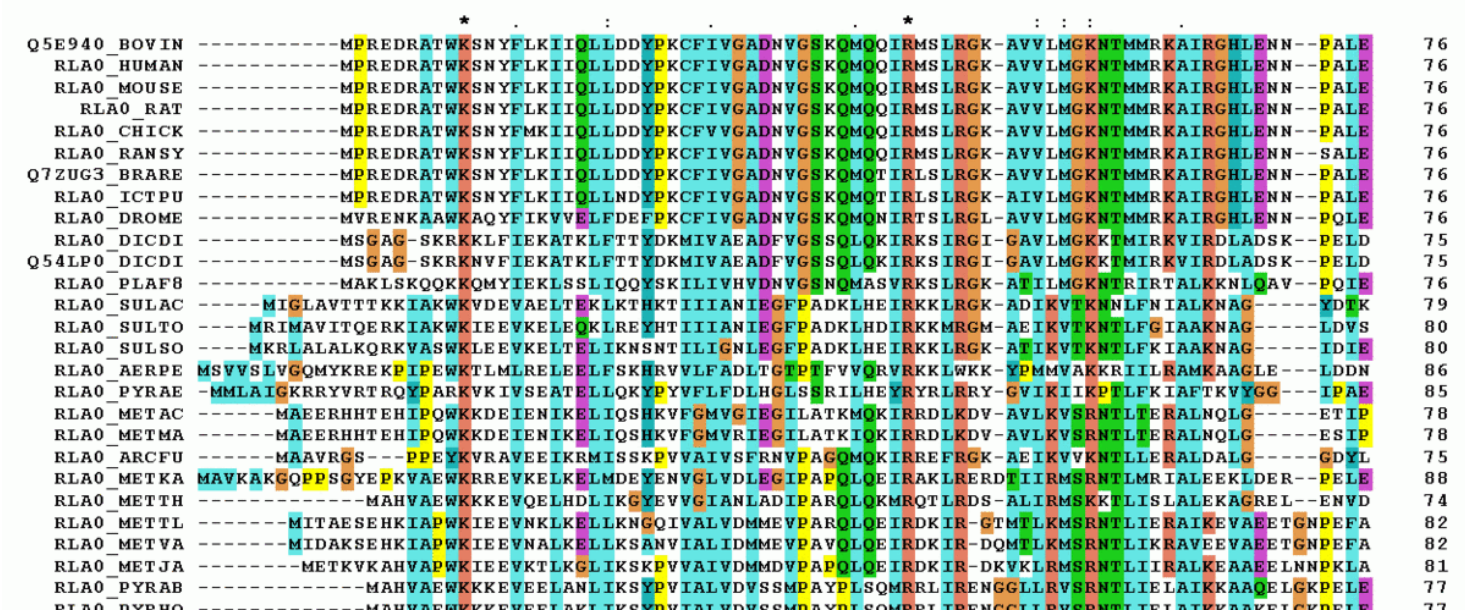




Biosequences



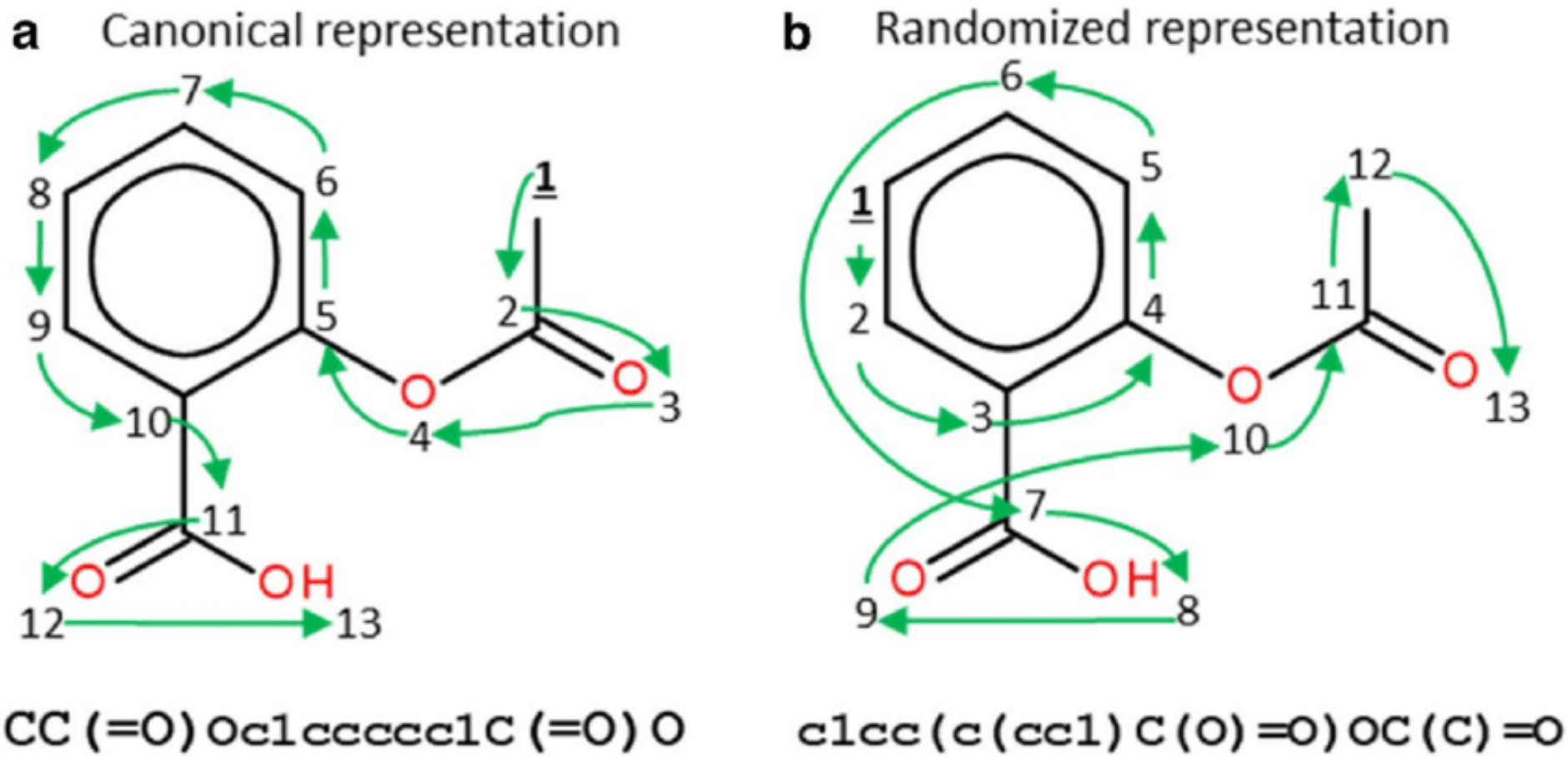
Language models learn evolutionary conservation



Protein Language Models

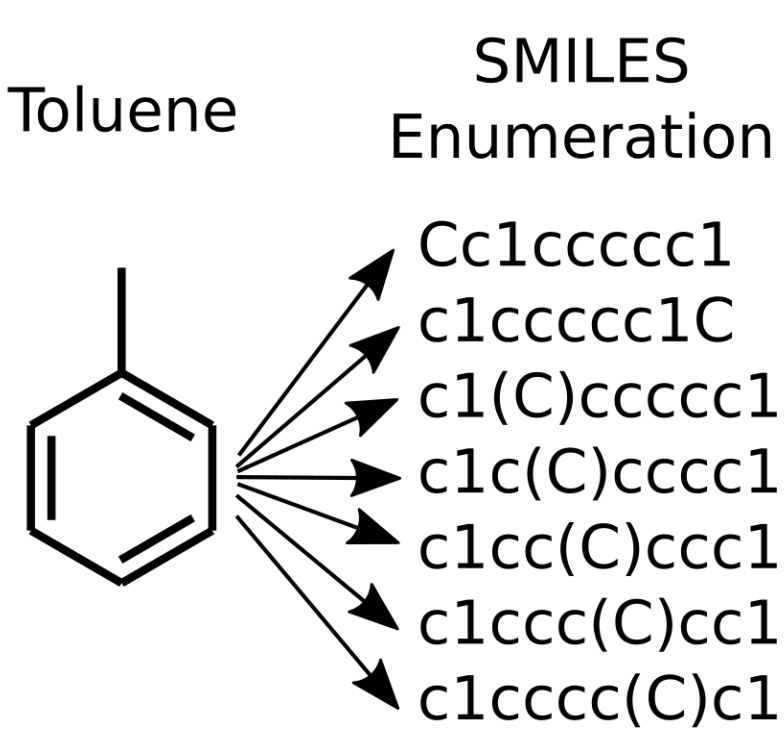
Name	Num params	Laboratory	Year
ESM-1b	650M	Meta	2019
ProtBERT	400M	RostLab	2020
Prot-T5-XL	560M	RostLab	2020
ProtGPT2	730M	Noelia Ferruz Lab (Barcelona)	2022
ESM-2	8M, 35M, 150M, 650M, 3B y 15B	Meta	2022
ESM-Fold	3B (+ 690M)	Meta	2022
ProstT5	560M (From Prot-T5-XL)	RostLab	2023

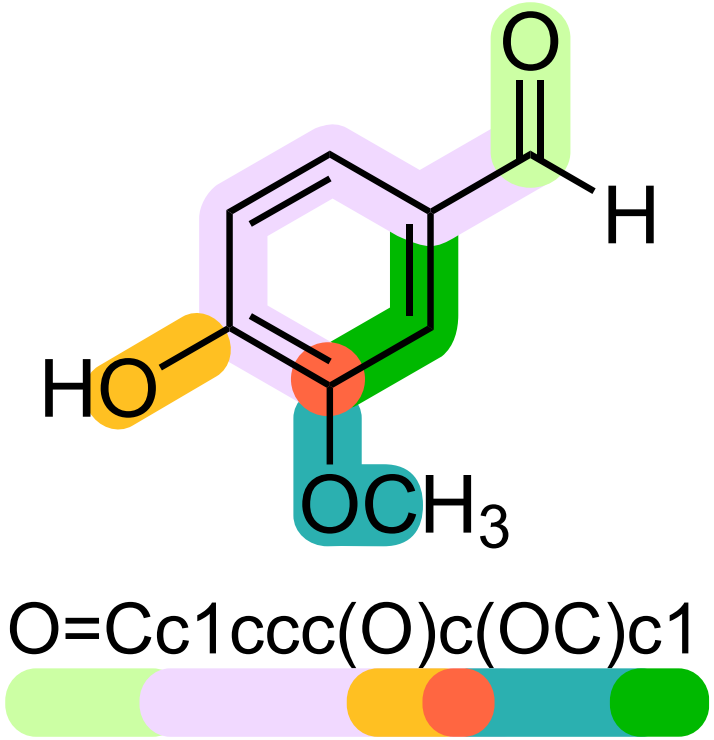
Small molecules: SMILES



Simplified Molecular Input Line Entry System

SMILES


Toluene
SMILES
Enumeration
Cc1ccccc1
c1ccccc1C
c1(C)ccccc1
c1c(C)cccc1
c1cc(C)ccc1
c1ccc(C)cc1
c1cccc(C)c1


O
H
HO
OCH3
O=Cc1ccc(O)c(OC)c1

Chemical fingerprints

1. Define circular substructures
2. Hash the substructures
3. Fold the hashes into bit-vector

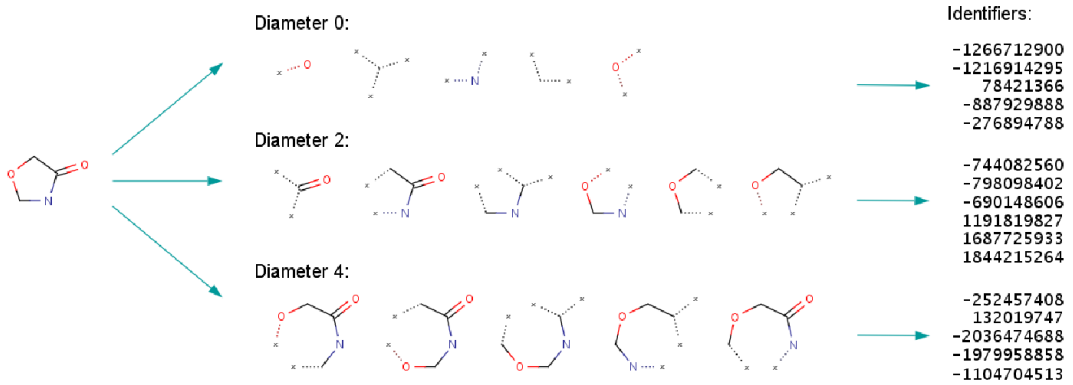


Fig. 2. ECFP generation process

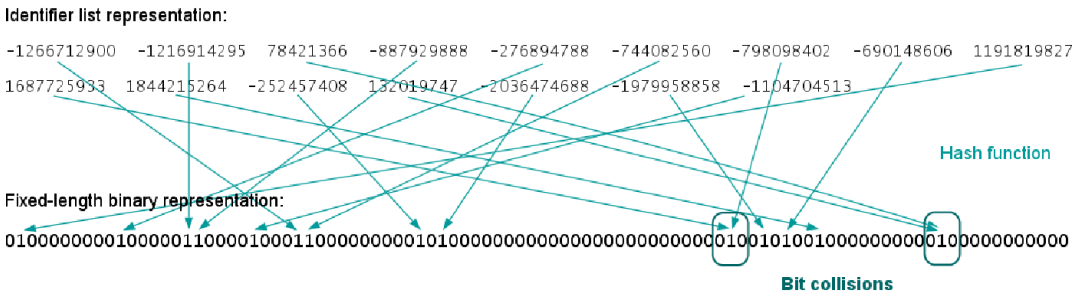


Fig. 3. Generation of the fixed-length bit string ("folding")

Chemical Language Models

Name	Num params	Laboratory	Year
ChemBERTa	3.5M	Ramsudar Lab	2020
Molformer-XL	45M	IBM	2022
ChemBERTa-2	3.5M	Ramsudar Lab	2022
ChemBERTa-3	3.5M	Ramsudar Lab	2025

Tutorial 1: Representation learning

Transforming biomolecules into vectors

Objective

1. Get models from huggingface
2. Generate representations
    1. What's the best strategy?
    2. Can you improve efficiency?
3. Train machine learning model
    1. What's the best model?
    2. How to properly evaluate?

Tutorial materials

- https://github.com/RaulFD-creator/ucd-teaching
- raul.fernandezdiaz@ucdconnect.ie