Integrating Knowledge Graphs and Large Language Models for Advancing Scientific Research

Qiang Zhang, Jiaoyan Chen, Zaiqiao Meng

Tutorial at Learning on Graph Conference (LoG)
26th November, 2024

About Me

Dr. Jiaoyan Chen

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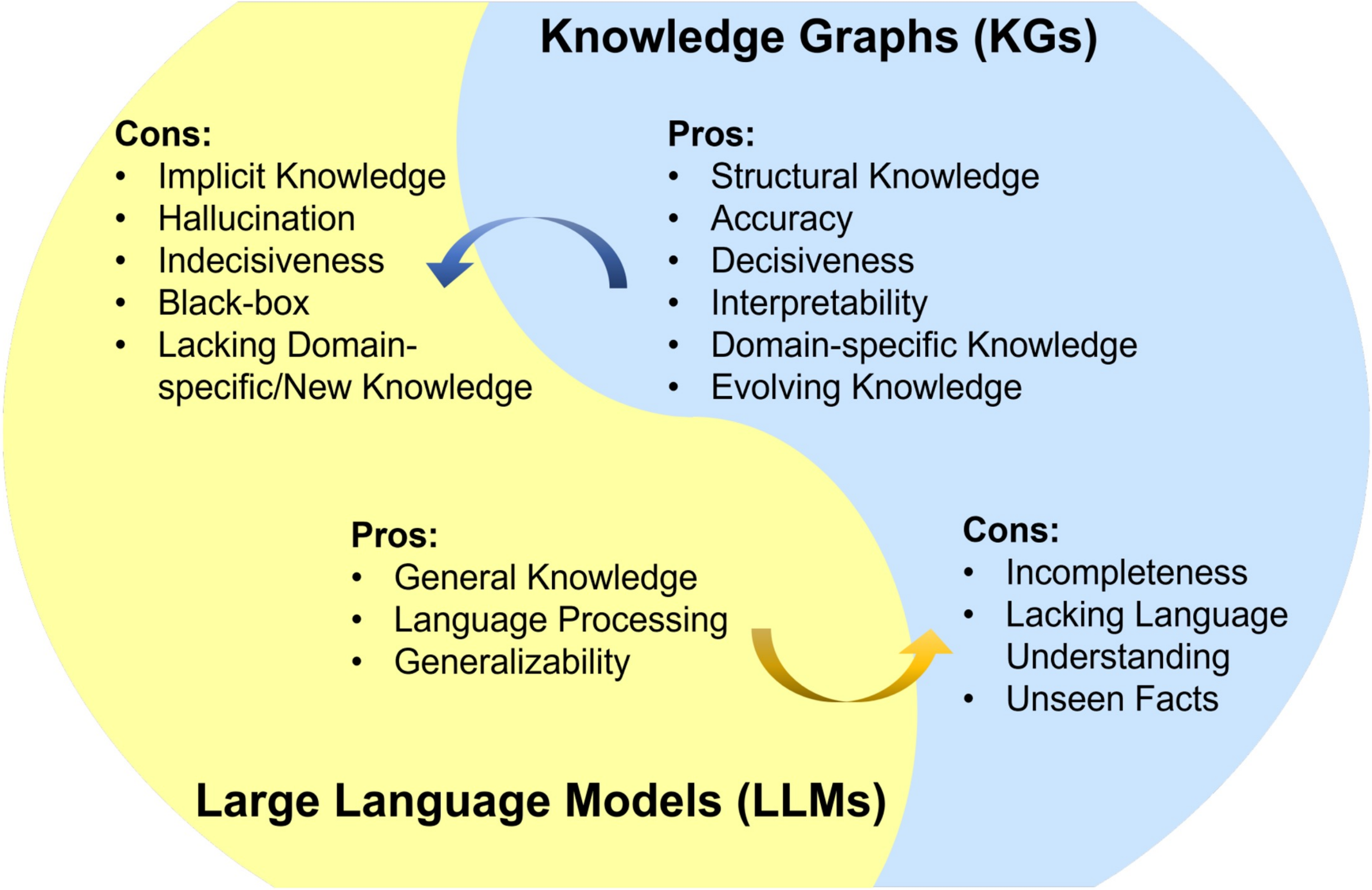
- UK Lecturer (Assistant Professor) at the Department of Computer Science, University of Manchester (2022.11 – now)
- Senior researcher at the Department of Computer Science, University of Oxford (part-time: 2022.12 – now; full time: 2017.11-2022.10)
- Ph.D. degree in Computer Science from Zhejiang University (2016)

- Knowledge Graph & Ontology
- Knowledge Representation
- Semantic Web & Semantic Techniques
  - Integration with Machine Learning & Language Models
  - Neural-symbolic AI

Why combine KGs and LLMs?



Knowledge Graphs (KGs)

Cons:
- Implicit Knowledge
- Hallucination
- Indecisiveness
- Black-box
- Lacking Domain-specific/New Knowledge

Pros:
- Structural Knowledge
- Accuracy
- Decisiveness
- Interpretability
- Domain-specific Knowledge
- Evolving Knowledge

Pros:
- General Knowledge
- Language Processing
- Generalizability

Cons:
- Incompleteness
- Lacking Language Understanding
- Unseen Facts

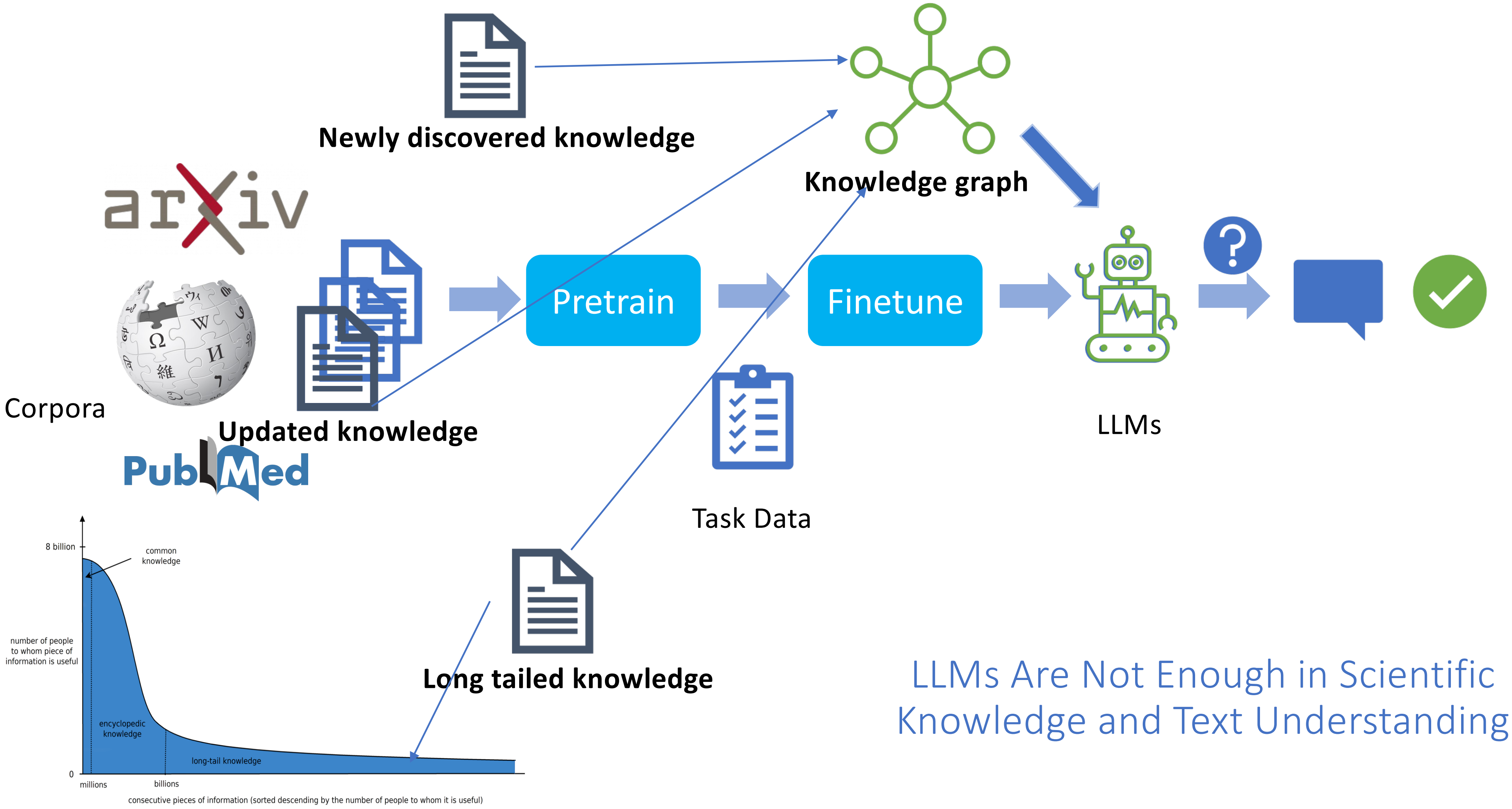
Large Language Models (LLMs)

Pan, Shirui, et al. "Unifying large language models and knowledge graphs: A roadmap." *IEEE Transactions on Knowledge and Data Engineering* (2024).

More similar perspectives recently, e.g.,

Pan, Jeff, et al. "Large Language Models and Knowledge Graphs: Opportunities and Challenges." Transactions on Graph Data and Knowledge (2023).

Why combine KGs and LLMs?



LLMs Are Not Enough in Scientific Knowledge and Text Understanding

Part I: Knowledge Graphs for Science

Jiaoyan Chen

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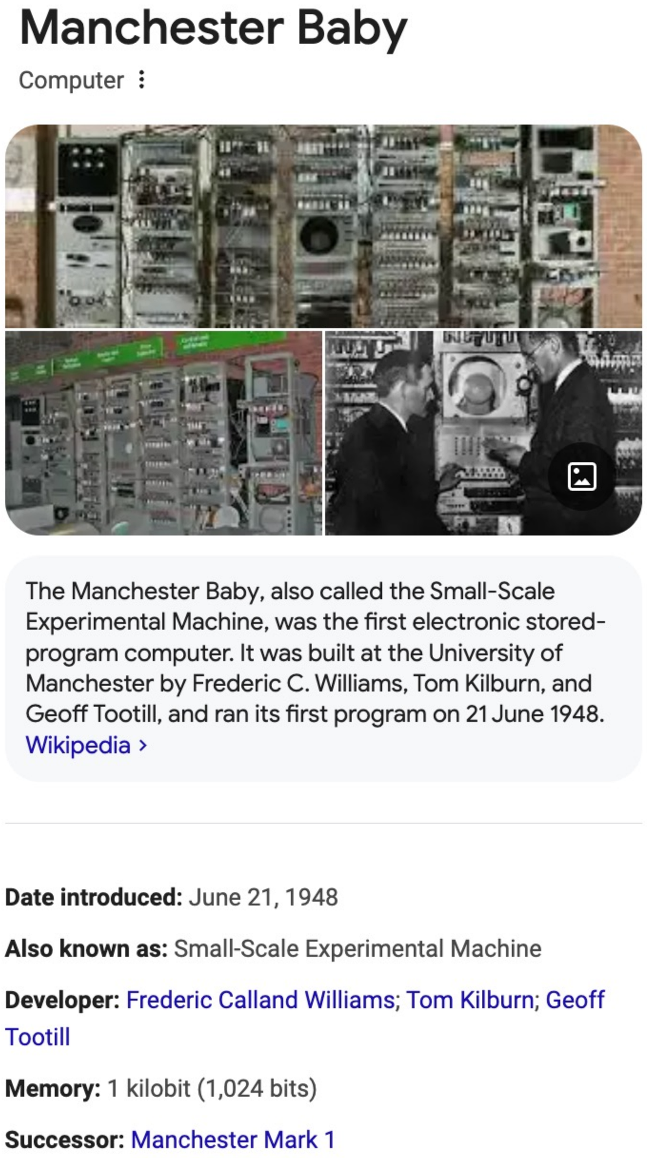
Outline

1. **KG Definitions and Core Concepts**
2. Ecotoxicological Effect Prediction: A Simple Case
3. KG for Life Science: Review & Challenges

The Knowledge Graph

- The Knowledge Graph is a knowledge base used by **Google** and its services to enhance its search engine's results with knowledge gathered from a variety of sources.
  - Proposed around 2012

  - Knowledge ≈ **Instances + Facts**
  - KG ≈ **Linked Structured Data** (can be regarded as a multi-relational graph)



Manchester Baby

Computer

The Manchester Baby, also called the Small-Scale Experimental Machine, was the first electronic stored-program computer. It was built at the University of Manchester by Frederic C. Williams, Tom Kilburn, and Geoff Tootill, and ran its first program on 21 June 1948. Wikipedia ›

Date introduced: June 21, 1948

Also known as: Small-Scale Experimental Machine

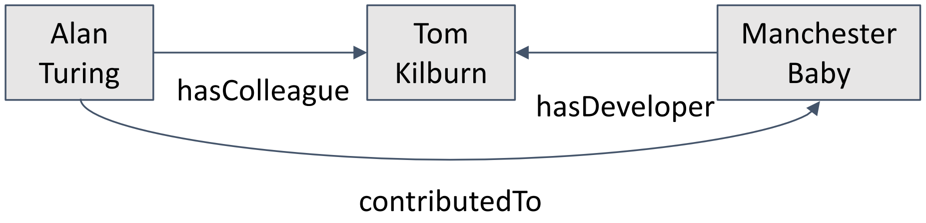
Developer: Frederic Calland Williams; Tom Kilburn; Geoff Tootill

Memory: 1 kilobit (1,024 bits)

Successor: Manchester Mark 1

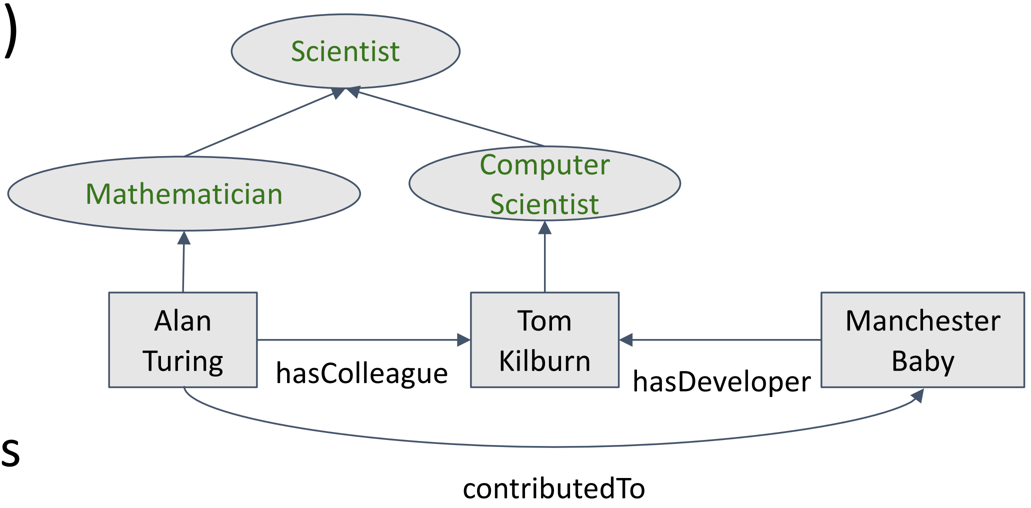
A Knowledge Representation Perspective

- **RDF** (Resource Description Framework)
  - Triple: <Subject, Predicate, Object>
  - Representing facts:
    - E.g., <Manchester Baby, hasDeveloper, Tom Kilburn>



A Knowledge Representation Perspective

- **RDF** (Resource Description Framework)
  - Triple: <Subject, Predicate, Object>
  - Representing facts:
    - E.g., <Manchester Baby, hasDeveloper, Tom Kilburn>
- **RDF Schema**
  - Meta data (schema) of instances and facts
    - E.g., class, property domain and range



A Knowledge Representation Perspective

- **Web Ontology Language** (OWL)
  - Taxonomies and vocabularies

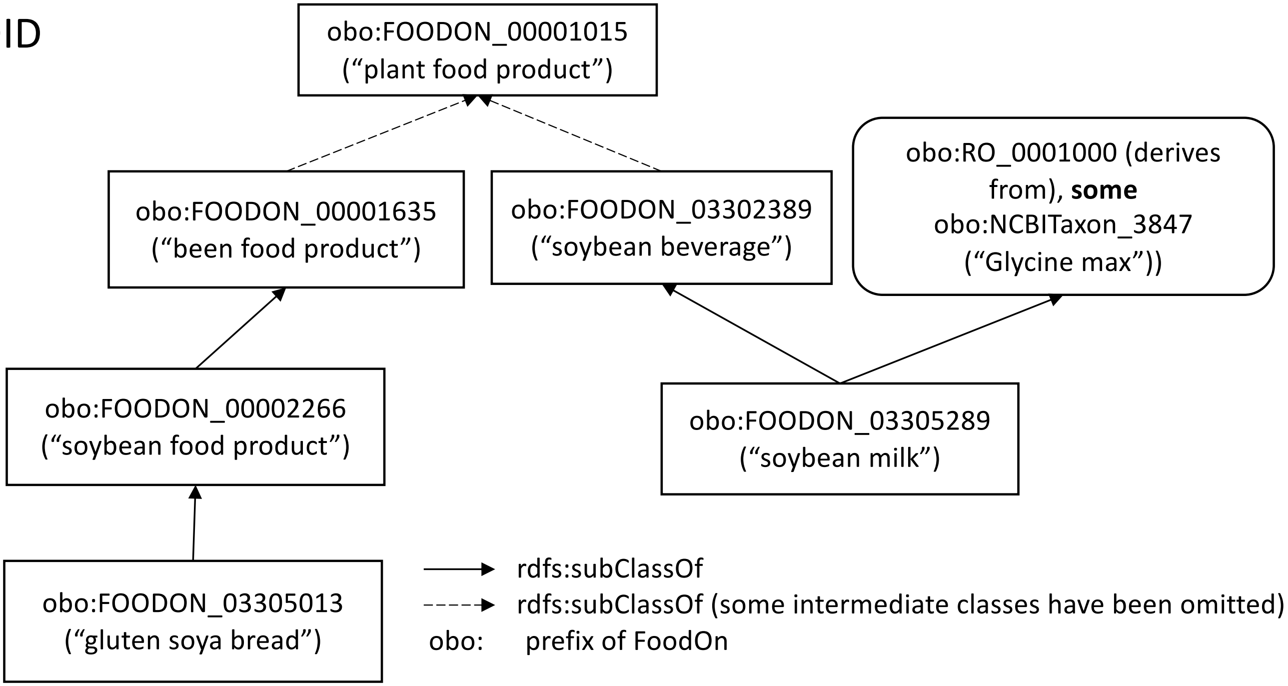
    E.g., FoodOn, SNOMED CT, GO, DOID

  - Constraints and logical relationships (> schema)

    Underpinned by **Description Logic (⊓, ⊔, ∃, ∀, ¬)**

    E.g., 'food material' ≡ 'environmental material' *and* ('has role' *some* 'food')

    E.g., the cardinality of "hasParent" is 2



obo:FOODON_00001015 ("plant food product")

obo:FOODON_00001635 ("been food product")

obo:FOODON_03302389 ("soybean beverage")

obo:RO_0001000 (derives from), **some** obo:NCBITaxon_3847 ("Glycine max"))

obo:FOODON_00002266 ("soybean food product")

obo:FOODON_03305289 ("soybean milk")

obo:FOODON_03305013 ("gluten soya bread")

→ rdfs:subClassOf

⇢ rdfs:subClassOf (some intermediate classes have been omitted)

obo: prefix of FoodOn

A segment of the food ontology FoodOn

What is a Knowledge Graph?

RDF facts

- relational graph
- as Google

RDF facts + schema

(OWL) Ontology

- graph + reasoning agent
- logic-equipped KG

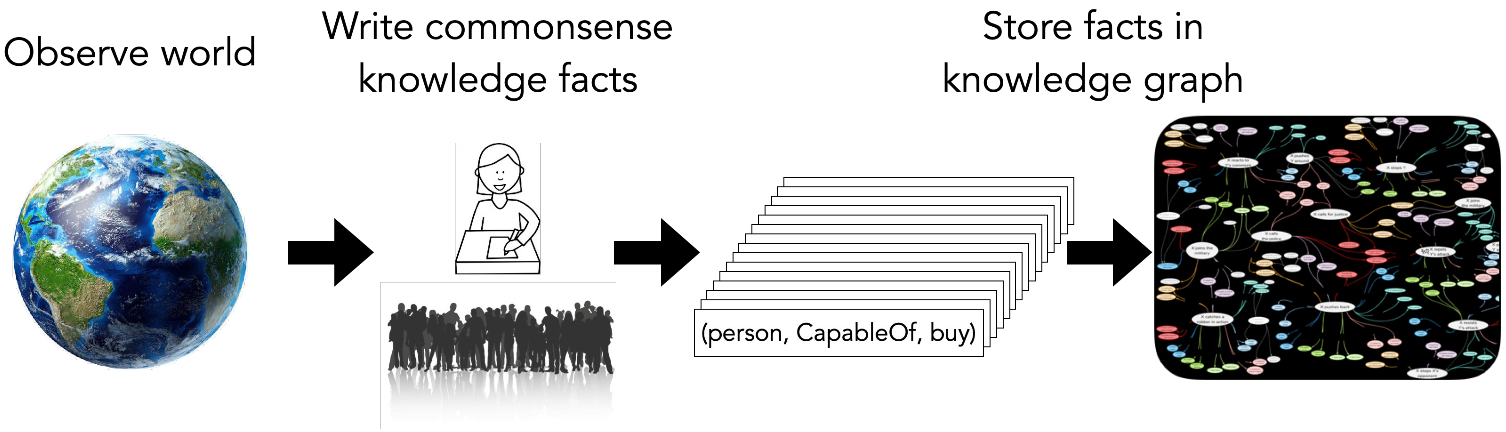
Knowledge Graph Advantages (w.r.t. Database)

- ✓ Intuitive (e.g., no “foreign keys”)
- ✓ Data + schema (ontology)
- ✓ URI not strings
- ✓ Flexible & extensible
- ✓ Rule language
  - Location + capital → location
  - Parent + brother → uncle
- ✓ Other kinds of query
  - Navigation
  - Similarity & Locality

(From Ian Horrocks)

Knowledge Graph Construction

- **Crowdsourcing (Encyclopedias) & Domain Experts**
    - DBpedia, Wikidata, Zhishi.me (中文), LinkedGeoData, GeoName
    - Domain ontologies like GO, SNOMED CT, FoodON



Observe world

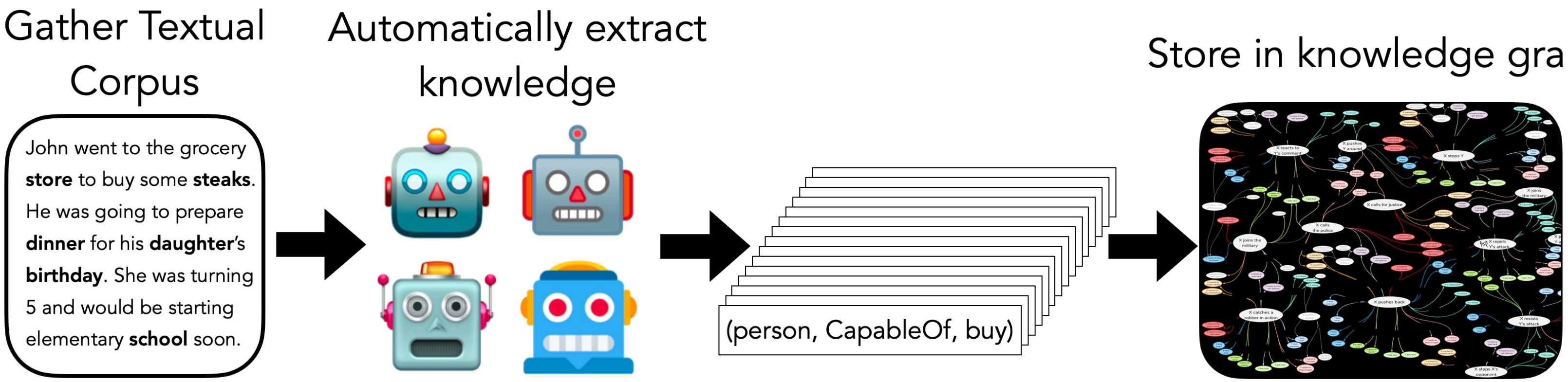
Write commonsense knowledge facts

Store facts in knowledge graph

(person, CapableOf, buy)

Knowledge Graph Construction

- **The Web, Natural Language Text**
    - Open Information Extraction, Web Mining



Gather Textual Corpus

John went to the grocery **store** to buy some **steaks**. He was going to prepare **dinner** for his **daughter**'s **birthday**. She was turning 5 and would be starting elementary **school** soon.

Automatically extract knowledge

(person, CapableOf, buy)

Store in knowledge graph

NLP and ML techniques: NER, Categorization, Relations extraction, Entity linking, etc.

Knowledge Graph Construction

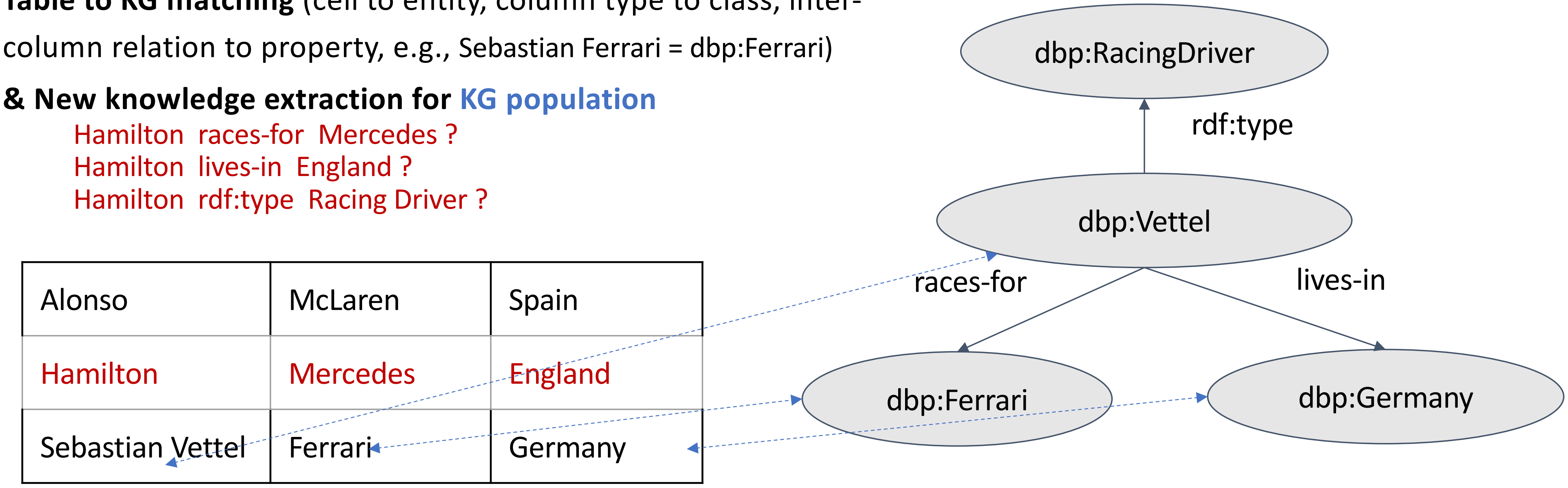
- **Semi-structured and structured data**
  - DBs, Web Tables, Excel Sheets, CSV files, etc.

Table to KG transformation (by e.g., rules)

Table to KG matching (cell to entity, column type to class, inter-column relation to property, e.g., Sebastian Ferrari = dbp:Ferrari)

& New knowledge extraction for KG population

Hamilton races-for Mercedes ?
Hamilton lives-in England ?
Hamilton rdf:type Racing Driver ?



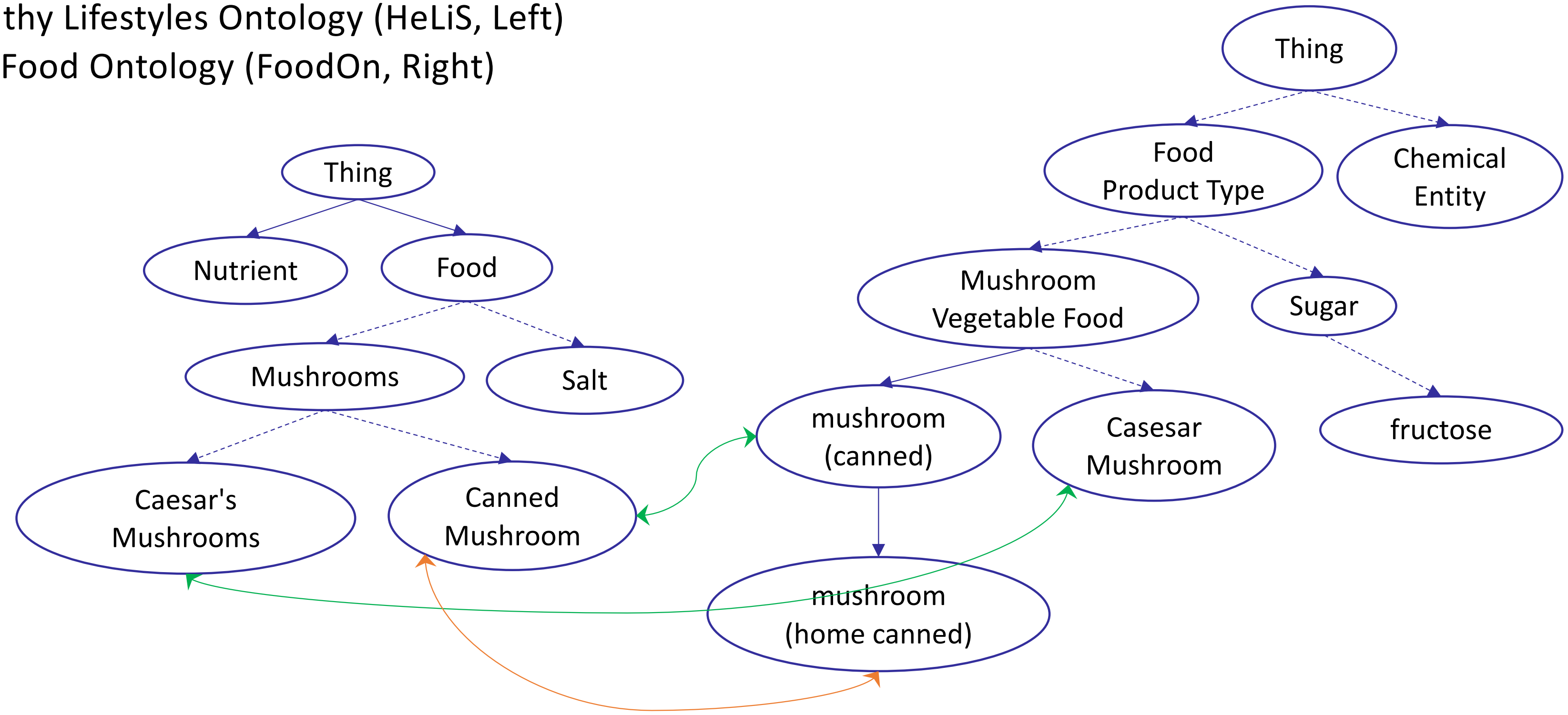
Alonso	McLaren	Spain
Hamilton	Mercedes	England
Sebastian Vettel	Ferrari	Germany

Existing KG on F1

Knowledge Graph Construction

- **Data integration (alignment, modulization, canonicalization, etc.)**

An example of alignment between
Healthy Lifestyles Ontology (HeLiS, Left)
and Food Ontology (FoodOn, Right)

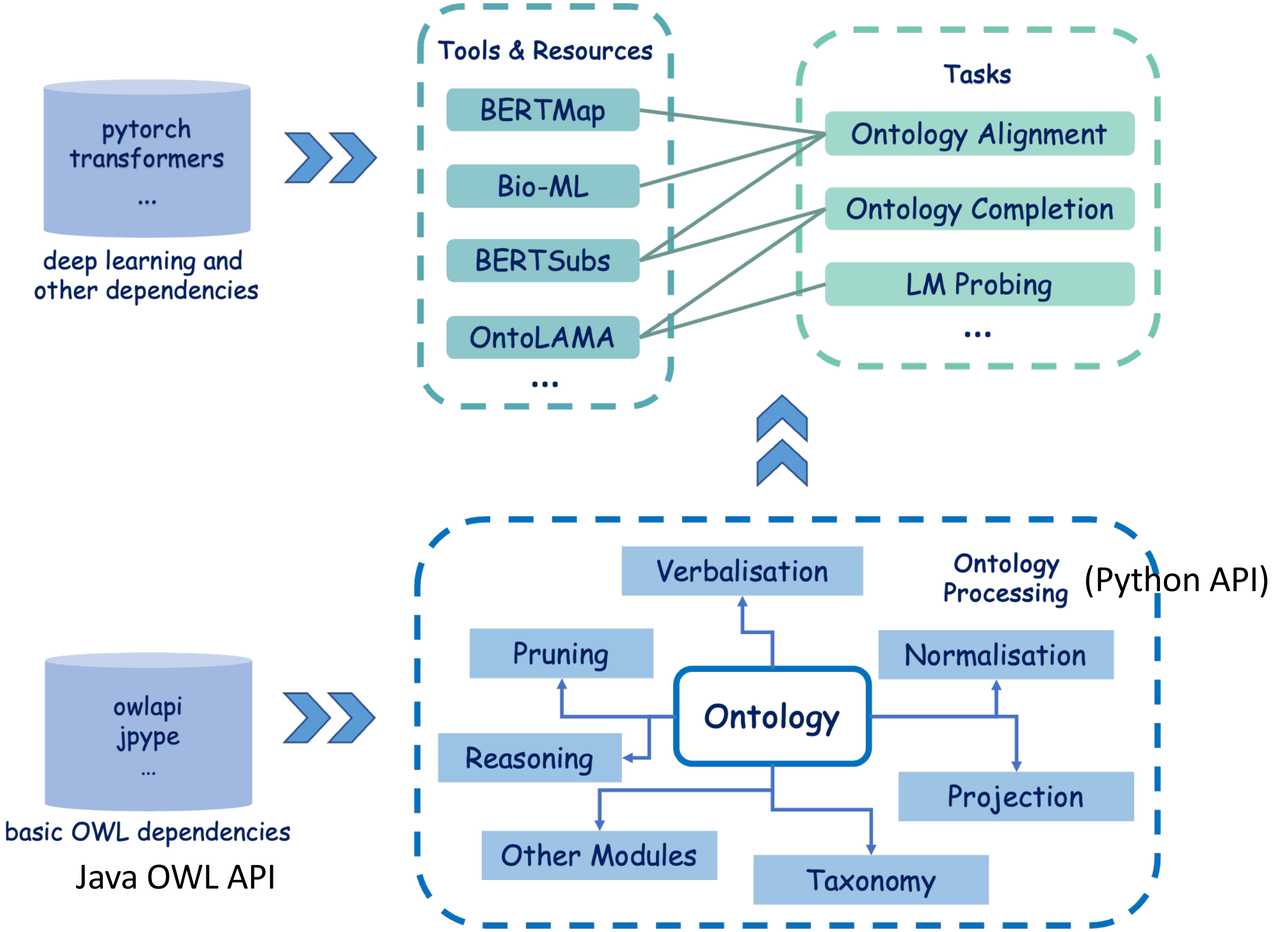


Knowledge Graph Construction

DeepOnto

An LM-based Ontology Engineering Library

https://github.com/KRR-Oxford/DeepOnto



pytorch
transformers
…
deep learning and other dependencies

Tools & Resources
BERTMap
Bio-ML
BERTSubs
OntoLAMA
…

Tasks
Ontology Alignment
Ontology Completion
LM Probing
…

owlapi
jpype
…
basic OWL dependencies
Java OWL API

Ontology Processing (Python API)
Ontology
Verbalisation
Pruning
Normalisation
Reasoning
Projection
Other Modules
Taxonomy

He, Y., et al. "DeepOnto: A Python package for ontology engineering with deep learning." Semantic Web Journal (2024).

Outline

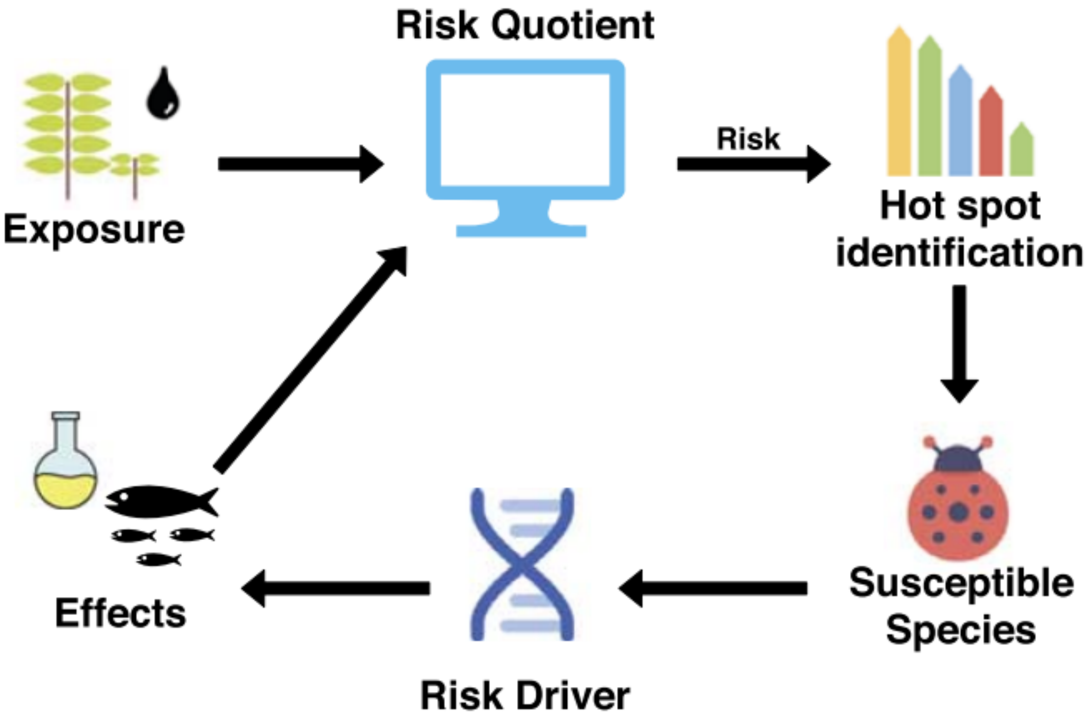
1 KG Definitions and Core Concepts

2 **Ecotoxicological Effect Assessment: A Simple Case**

3 KG for Life Science: Review and Challenges

Ecotoxicological Effect Assessment

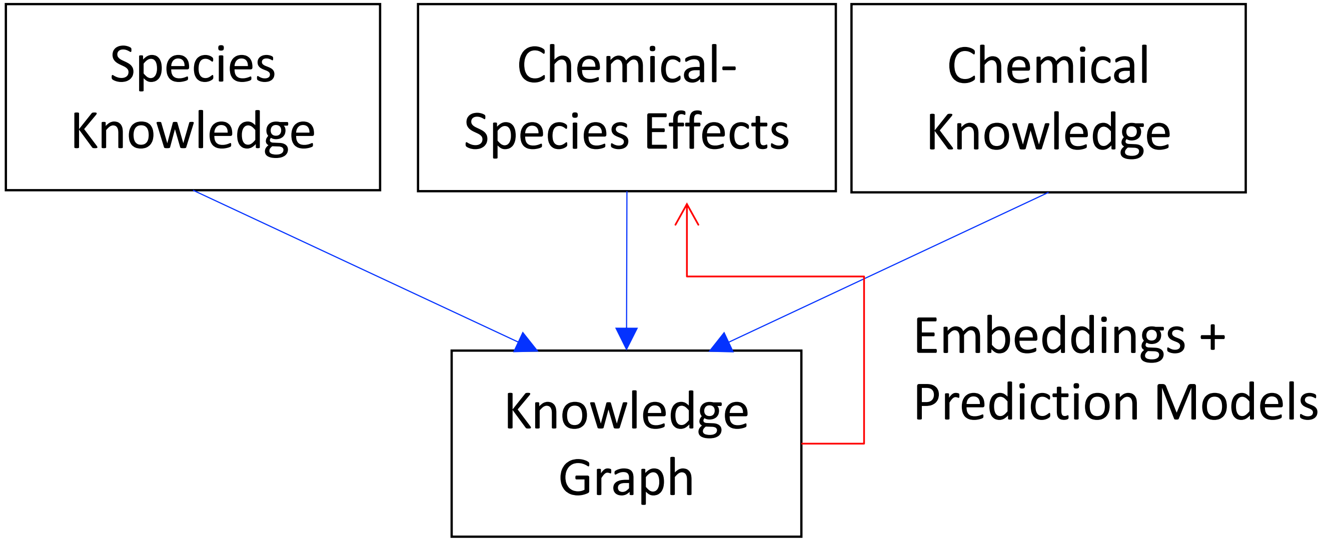
Norwegian Institute for Water Research



Simplified pipeline used in Norwegian Institute for Water Research

Chemical effect data gathered from laboratory experiments

Ecotoxicological Effect Assessment



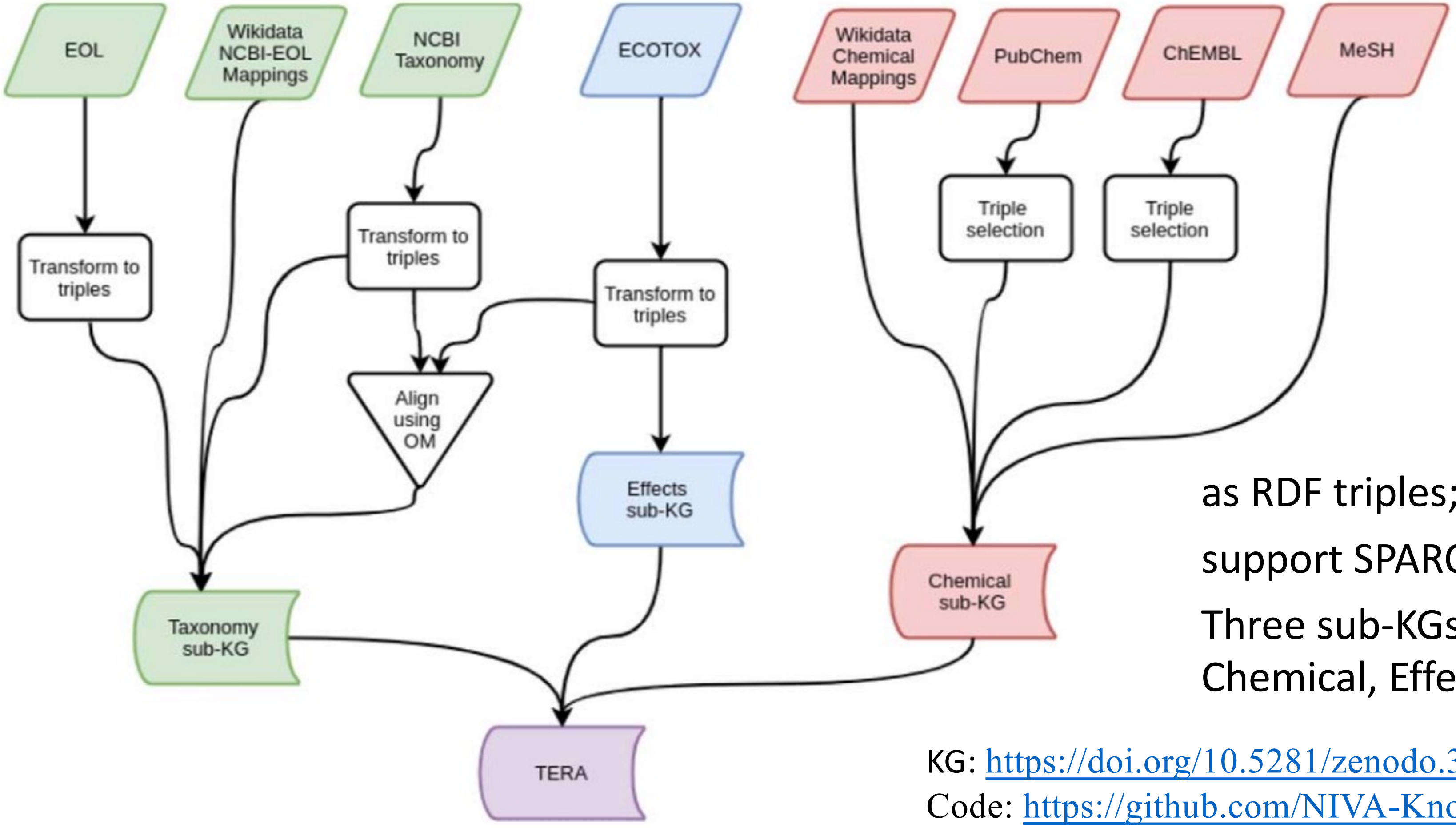
[Myklebust et al. 2022]: use **KG and its embeddings**, focus on **mortality**, i.e., lethal concentration to 50% of test population (LC50) measured at 48 hours

Myklebust, Erik B., et al. "Prediction of adverse biological effects of chemicals using knowledge graph embeddings." *Semantic Web* 13.3 (2022): 299-338.

How to Construct a Knowledge Graph?

- Data sources
  - Biological effects: ECOTOXicology database (~1M results, ~12K compounds, ~13K species, ~0.6% coverage of chemical-species pair coverage)
  - Biological: NCBI Taxonomy, Encyclopedia of Life (EOL; for species traits)
  - Chemical: PubChem, ChEMBL, MeSH
- Data integration
  - Wikidata mappings of species and chemicals
  - Ontology alignment tools
    - LogMap, AML: Lexical matching & index, reasoning
    - Levenshtein distance
    - Alternative: BERTMap (https://github.com/KRR-Oxford/DeepOnto): BERT fine-tuning, lexical matching & index, reasoning-based repair

TERA: Toxicological Effect and Risk Assessment KG



as RDF triples;

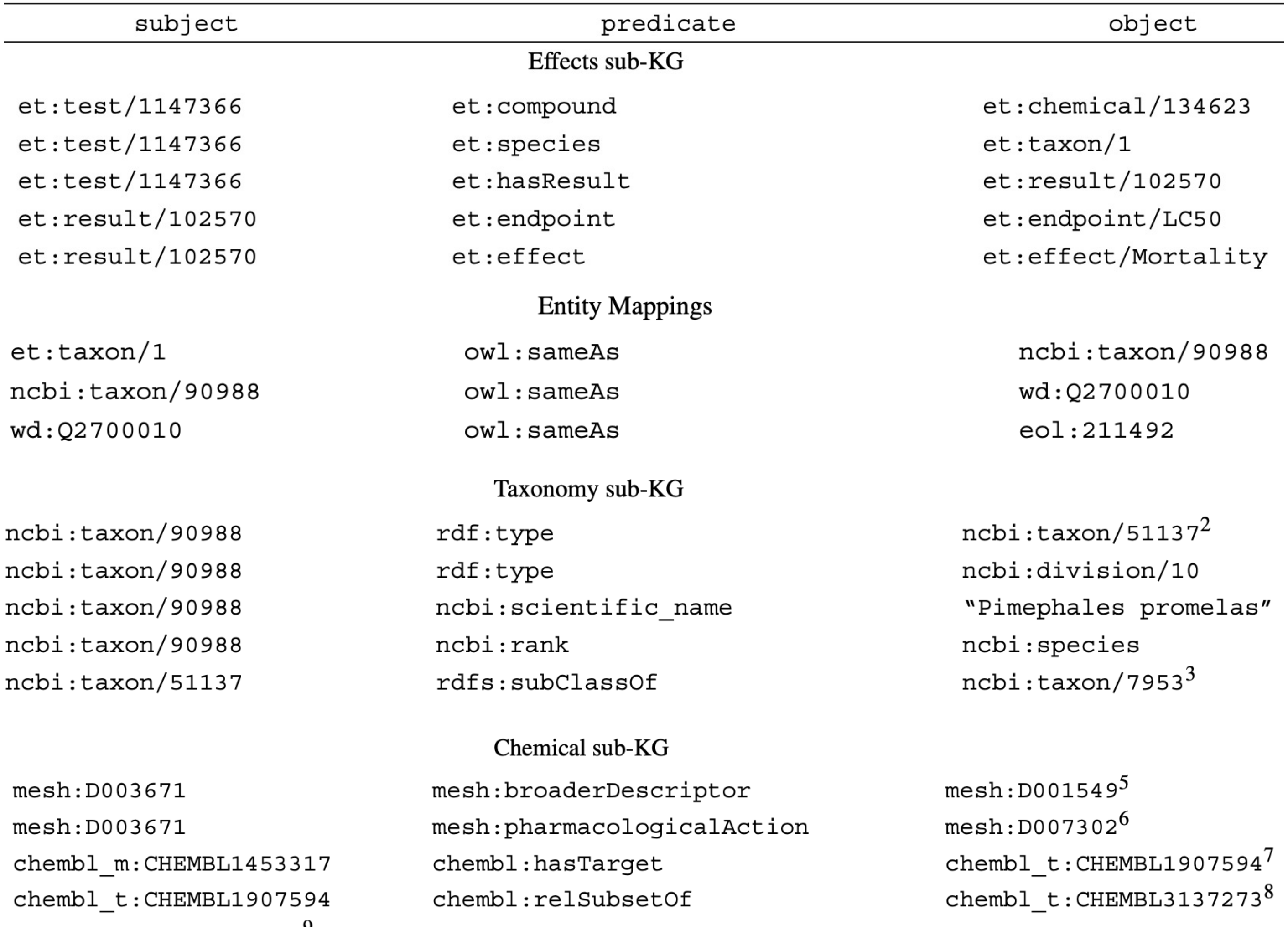
support SPARQL query

Three sub-KGs: Species, Chemical, Effect

KG: https://doi.org/10.5281/zenodo.3559865
Code: https://github.com/NIVA-Knowledge-Graph/TERA

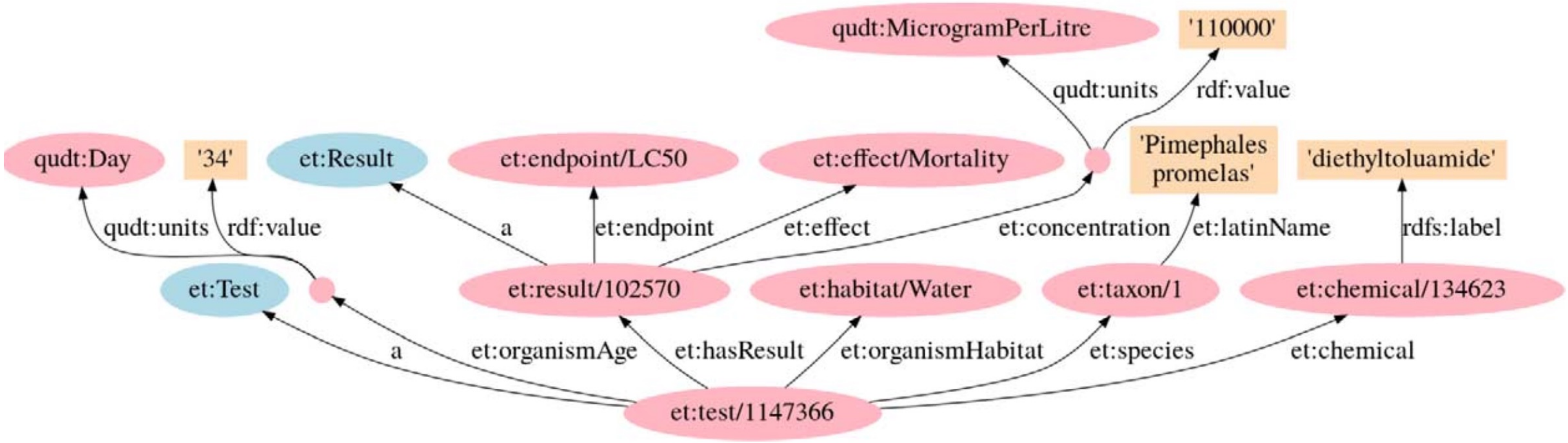
TERA: Toxicological Effect and Risk Assessment KG

Examples of RDF Triples



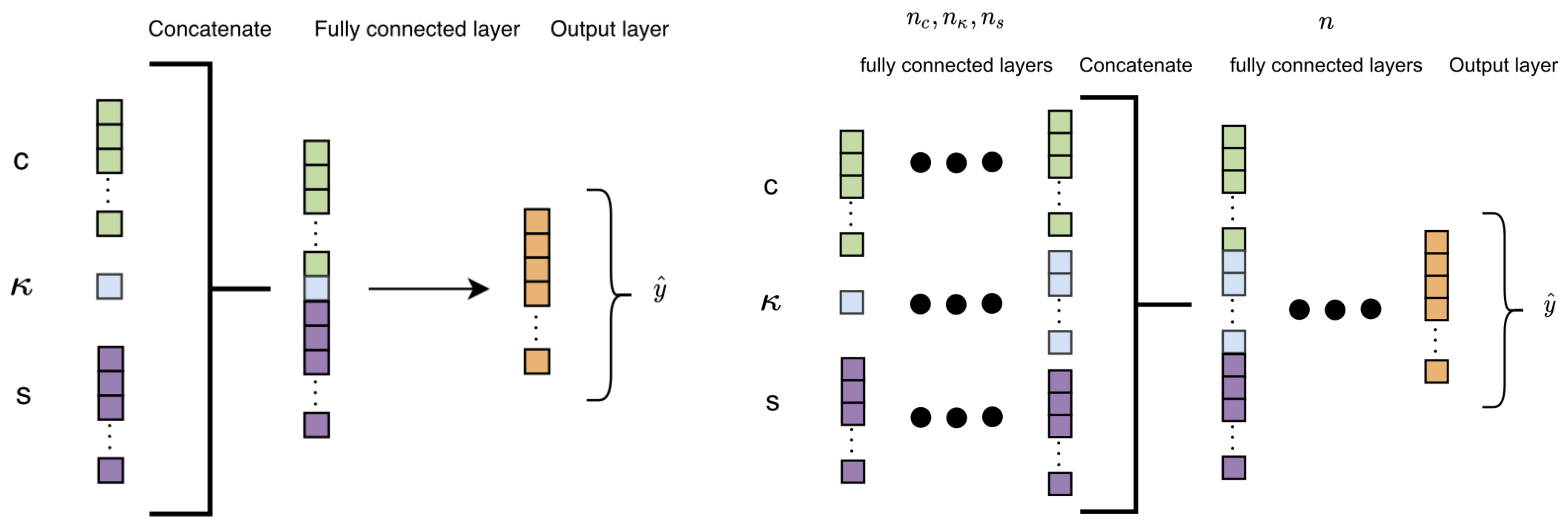
subject	predicate	object
	Effects sub-KG	
et:test/1147366	et:compound	et:chemical/134623
et:test/1147366	et:species	et:taxon/1
et:test/1147366	et:hasResult	et:result/102570
et:result/102570	et:endpoint	et:endpoint/LC50
et:result/102570	et:effect	et:effect/Mortality
	Entity Mappings	
et:taxon/1	owl:sameAs	ncbi:taxon/90988
ncbi:taxon/90988	owl:sameAs	wd:Q2700010
wd:Q2700010	owl:sameAs	eol:211492
	Taxonomy sub-KG	
ncbi:taxon/90988	rdf:type	ncbi:taxon/51137[2]
ncbi:taxon/90988	rdf:type	ncbi:division/10
ncbi:taxon/90988	ncbi:scientific_name	"Pimephales promelas"
ncbi:taxon/90988	ncbi:rank	ncbi:species
ncbi:taxon/51137	rdfs:subClassOf	ncbi:taxon/7953[3]
	Chemical sub-KG	
mesh:D003671	mesh:broaderDescriptor	mesh:D001549[5]
mesh:D003671	mesh:pharmacologicalAction	mesh:D007302[6]
chembl_m:CHEMBL1453317	chembl:hasTarget	chembl_t:CHEMBL1907594[7]
chembl_t:CHEMBL1907594	chembl:relSubsetOf	chembl_t:CHEMBL3137273[8]

TERA: Toxicological Effect and Risk Assessment KG



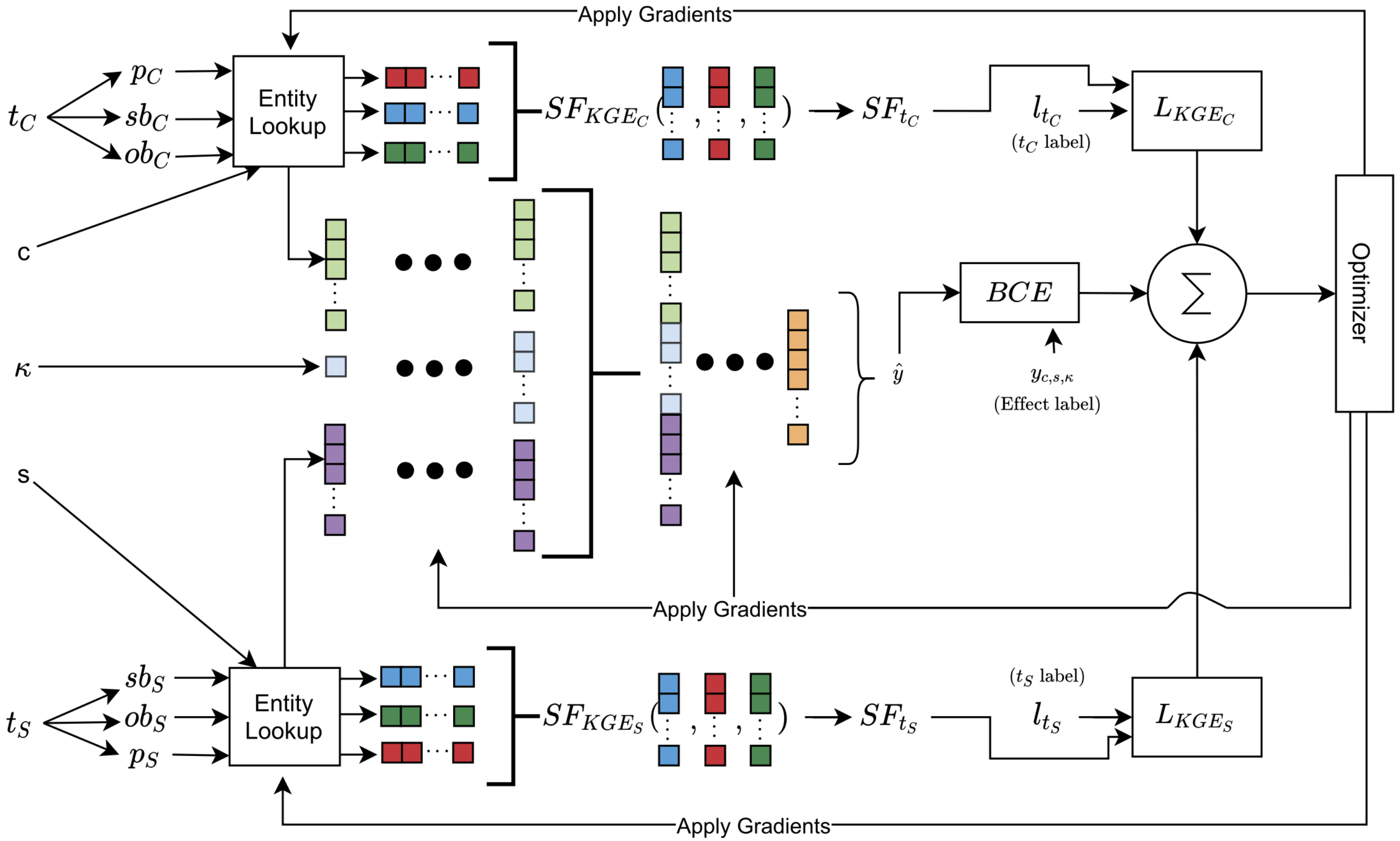
Example of an ECOTOX test and related triples

Link Prediction with TERA



Baselines: Simple (left) and complex (right) **MLP**s, with the input of **pre-trained KG embeddings** of the species and chemical

Link Prediction with TERA



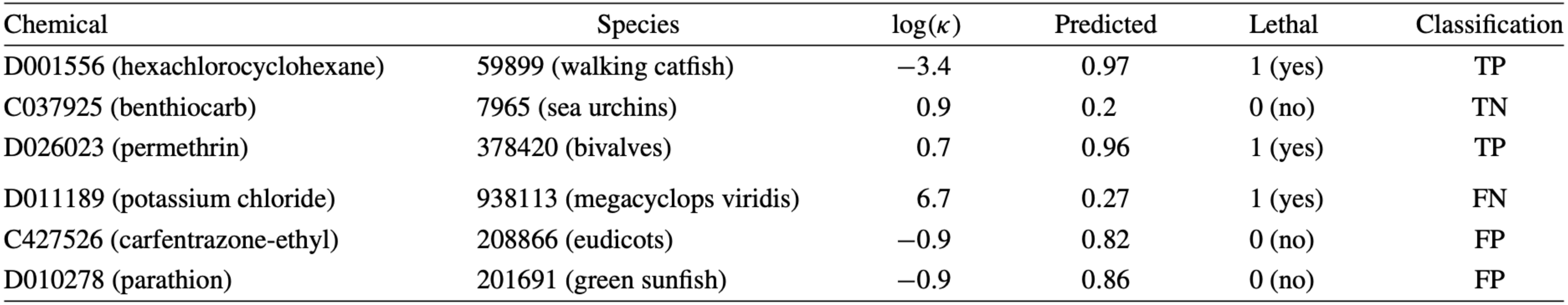
Method: **Simultaneously** train the KG embeddings and the MLP

$$L = \alpha_C L_{KGE_C} + \alpha_S L_{KGE_S} + \alpha_{\text{MLP}} L_{\text{MLP}}$$

Link Prediction with TERA

- Tested TransE, HolE, DistMult, HAKE, ConvE, ConvKB, RotatE, pRotatE, and three different sampling strategies
- Result summary:

  in the majority of the settings, Sensitivity (TP/TP+FN) > 0.9, Specificity (TN/FP+TN) > 0.75)



Chemical	Species	$\log(\kappa)$	Predicted	Lethal	Classification
D001556 (hexachlorocyclohexane)	59899 (walking catfish)	−3.4	0.97	1 (yes)	TP
C037925 (benthiocarb)	7965 (sea urchins)	0.9	0.2	0 (no)	TN
D026023 (permethrin)	378420 (bivalves)	0.7	0.96	1 (yes)	TP
D011189 (potassium chloride)	938113 (megacyclops viridis)	6.7	0.27	1 (yes)	FN
C427526 (carfentrazone-ethyl)	208866 (eudicots)	−0.9	0.82	0 (no)	FP
D010278 (parathion)	201691 (green sunfish)	−0.9	0.86	0 (no)	FP

Example predictions by the **simultaneously training method** with the best combination of **HolE-DistMult**

Discussion from a KG Perspective

- KG construction with more data sources?
  - Literatures & reports
  - Data of specific scientific/experimental systems (e.g., in AnIML)
  - Multi-modal data

- Link prediction
  - Accuracy & explanation
  - Multi-modal semantic embedding
  - + symbolic reasoning

Outline

1 KG Definitions and Core Concepts

2 Ecotoxicological Effect Assessment: A Simple Case

3 **KG for Life Science: Review and Challenges**

KG for Life Science

Knowledge Graph Construction and Management (Sect. 3)

- Alignment for Knowledge Validation
- Knowledge Integration
- Repositories of Ontologies and Mappings
- Ontology Extension
- Instance Matching

Life Science Knowledge Discovery (Sect. 4)

- Therapeutics and Drug Discovery
- Protein Function Prediction
- Predictions for Healthcare

Knowledge Graph for Explainable AI (Sect. 5)

- Explainable AI for Healthcare Practice
- Explainable AI for Knowledge Discovery
- Explainable AI for KG Construction

KG in Life Sciences (Sect. 2)

❖ Schema-less KGs: Facts in RDF triples
❖ Schema-based KGs: RDFS, OWL, SHACL, etc.
❖ Simple ontologies: Taxonomies
❖ Expressive OWL ontologies

Challenges for Life Science KGs (Sect. 6)

❖ Scalability
❖ Evolution & Quality Assurance
❖ Heterogeneity: Multi-domain & Multi-modality
❖ Human Interaction & Explainability
❖ Personalized & Customized KGs
❖ Distributed KGs
❖ Representation Learning: Symbolic & Sub-symbolic Integration

Chen, Jiaoyan, et al. "Knowledge Graphs for the Life Sciences: Recent Developments, Challenges and Opportunities." ***Transactions On Graph Data and Knowledge*** (2024). (**New, open access journal in the KG community)**

Part II: Scientific Large Language Models

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About Me

Dr. Qiang Zhang

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https://github.com/HICAI-ZJU

https://scimind.ai/resource/

- I'm an Assistant Professor under the Hundred Talents Program at Zhejiang University, since 2021.9.
- Before that, I was a postdoctoral research fellow in the Centre for Artificial Intelligence in University College London (UCL) in UK.
  I studied for the Ph.D. degree at UCL from 2017-2020.
- Prior to that, I obtained M.Sc. from Chinese Academy of Sciences in 2017 and B.Sc. from Shandong University in 2014.

❖ AI theory: data-efficient machine learning, foundation model.

❖ Applications: natural language processing, knowledge graphs, **AI for Science**.

❖ Publications: nature portfolio * 5， top-tier conference papers * 52， patents *4, Google Scholar citations: 5000+.

❖ Research projects: national/provincial funding * 5, corporate sponsorship * 4, in total 8M+ RMB.

Outline

1 **Introduction and Preliminary**

2 **Scientific Large Language Models**

3 **Challenges and Perspective**

Outline

1 **Introduction and Preliminary**

2 Scientific Large Language Models

3 Challenges and Perspective

LLMs Revolutionize AGI

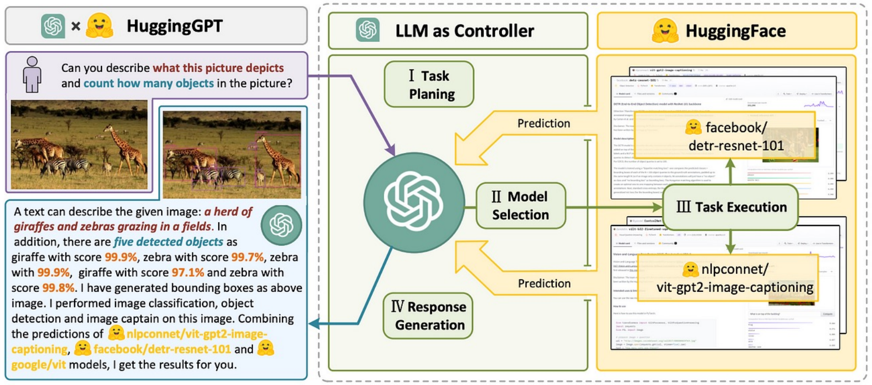
Upstream Techniques

Pre-trained
Large Language Model,
e.g., GPT, GLM, LLaMA

Computational Linguistics:
Understanding human language
through computational models!

Downstream Tasks

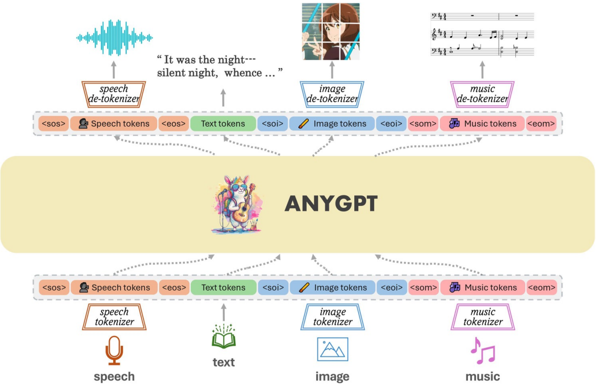
- Question Answering
- Knowledge Extraction
- Complex Reasoning



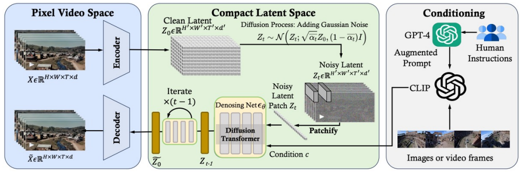
Can you describe **what this picture depicts** and **count how many objects** in the picture?

A text can describe the given image: ***a herd of giraffes and zebras grazing in a fields***. In addition, there are ***five detected objects*** as giraffe with score **99.9%**, zebra with score **99.7%**, zebra with **99.9%**, giraffe with score **97.1%** and zebra with score **99.8%**. I have generated bounding boxes as above image. I performed image classification, object detection and image captain on this image. Combining the predictions of **nlpconnet/vit-gpt2-image-captioning**, **facebook/detr-resnet-101** and **google/vit** models, I get the results for you.

HuggingGPT: Solving AI Tasks with ChatGPT and its Friends in Hugging Face, https://arxiv.org/pdf/2303.17580, 2023.



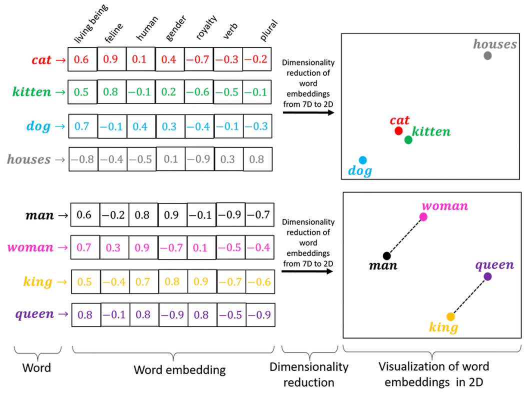
AnyGPT: Unified Multimodal LLM with Discrete Sequence Modeling, https://arxiv.org/abs/2402.12226, 2024



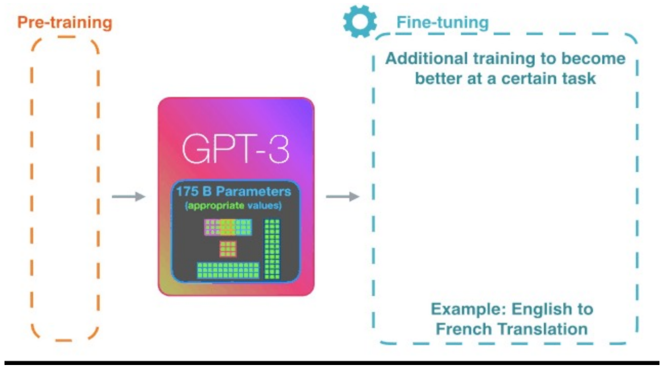
A stylish woman walks down a Tokyo street filled with warm glowing neon andanimated city signage. She wears a black leather jacket, a long red dress, and black boots, and carries a black purse. She wears sunglasses and red lipstick. She walks confidently and casually. The street is damp and reflective, creating a mirror effect of the colorful lights.Many pedestrians walk about.

Sora, https://openai.com/index/sora/
OpenAI, 2024

LLMs Limited to Human Language

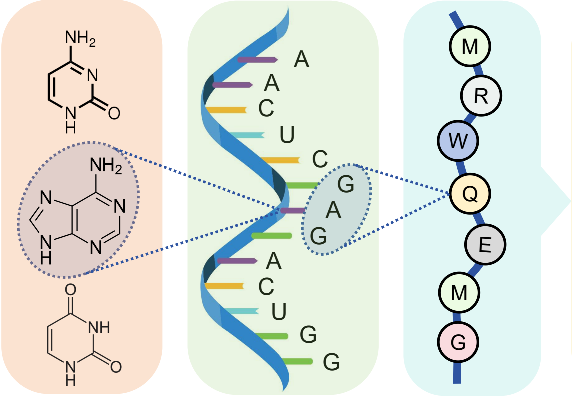


	living being	feline	human	gender	royalty	verb	plural
cat →	0.6	0.9	0.1	0.4	−0.7	−0.3	−0.2
kitten →	0.5	0.8	−0.1	0.2	−0.6	−0.5	−0.1
dog →	0.7	−0.1	0.4	0.3	−0.4	−0.1	−0.3
houses →	−0.8	−0.4	−0.5	0.1	−0.9	0.3	0.8
man →	0.6	−0.2	0.8	0.9	−0.1	−0.9	−0.7
woman →	0.7	0.3	0.9	−0.7	0.1	−0.5	−0.4
king →	0.5	−0.4	0.7	0.8	0.9	−0.7	−0.6
queen →	0.8	−0.1	0.8	−0.9	0.8	−0.5	−0.9



What can GPTs do?

1. Chatbots talking to historical figures
2. Code generation based on text descriptions
3. Answer medical questions
4. Stylistic transfer of text
5. Write creative novels
6. .....

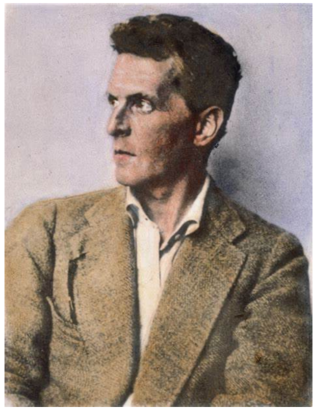


- **Protein**: MOTS-c
- **Gene**: MT-RNR1
- **Organism**: Homo sapiens
- **Sequences**: MRWQEMGYIFYPRKLR

Question: What is the solubility of this protein?

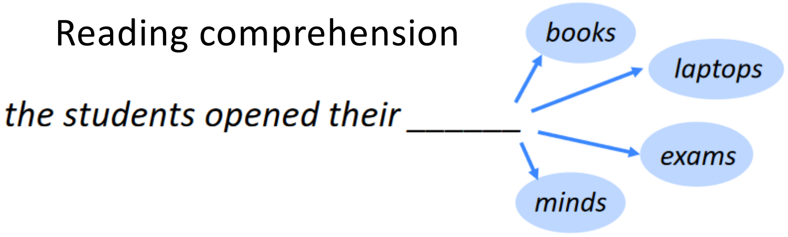
General LLMs

The solubility of a specific protein, such as MOTS-c, isn't typically available as a standard piece of information. Protein solubility can depend on various factors, including pH, temperature, ...



"The limits of my language mean the limits of my world."
--Ludwig Wittgenstein, 1921

Scientific Language Understanding



Reading comprehension

the students opened their ______

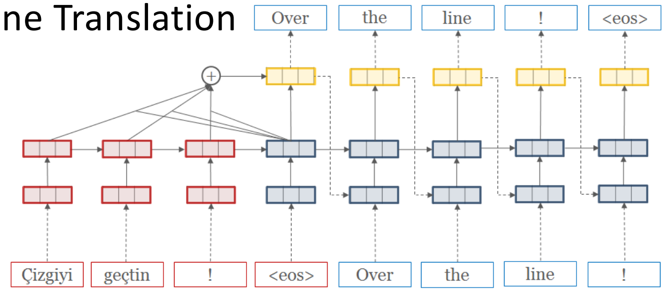
books

laptops

exams

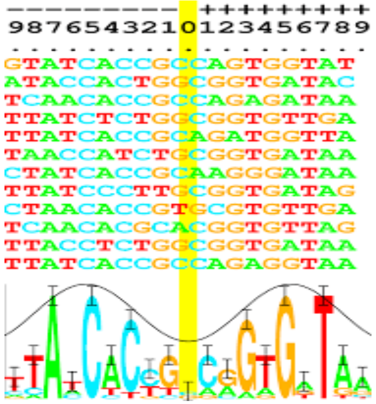
minds

Machine Translation

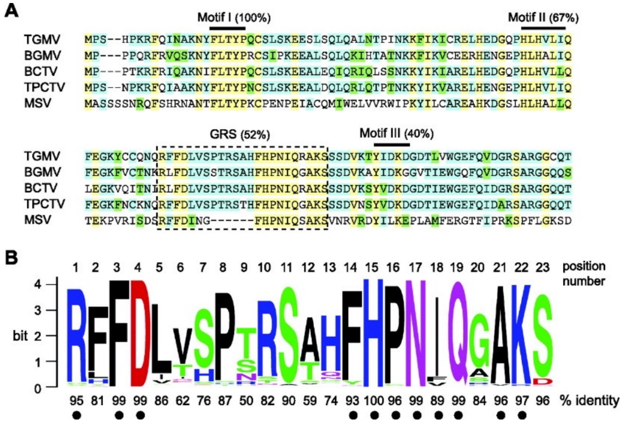


Symbolized human language ⇨ Natural language Models

Symbolized biological language ⇨ Genomic/Protein language Models



Gene

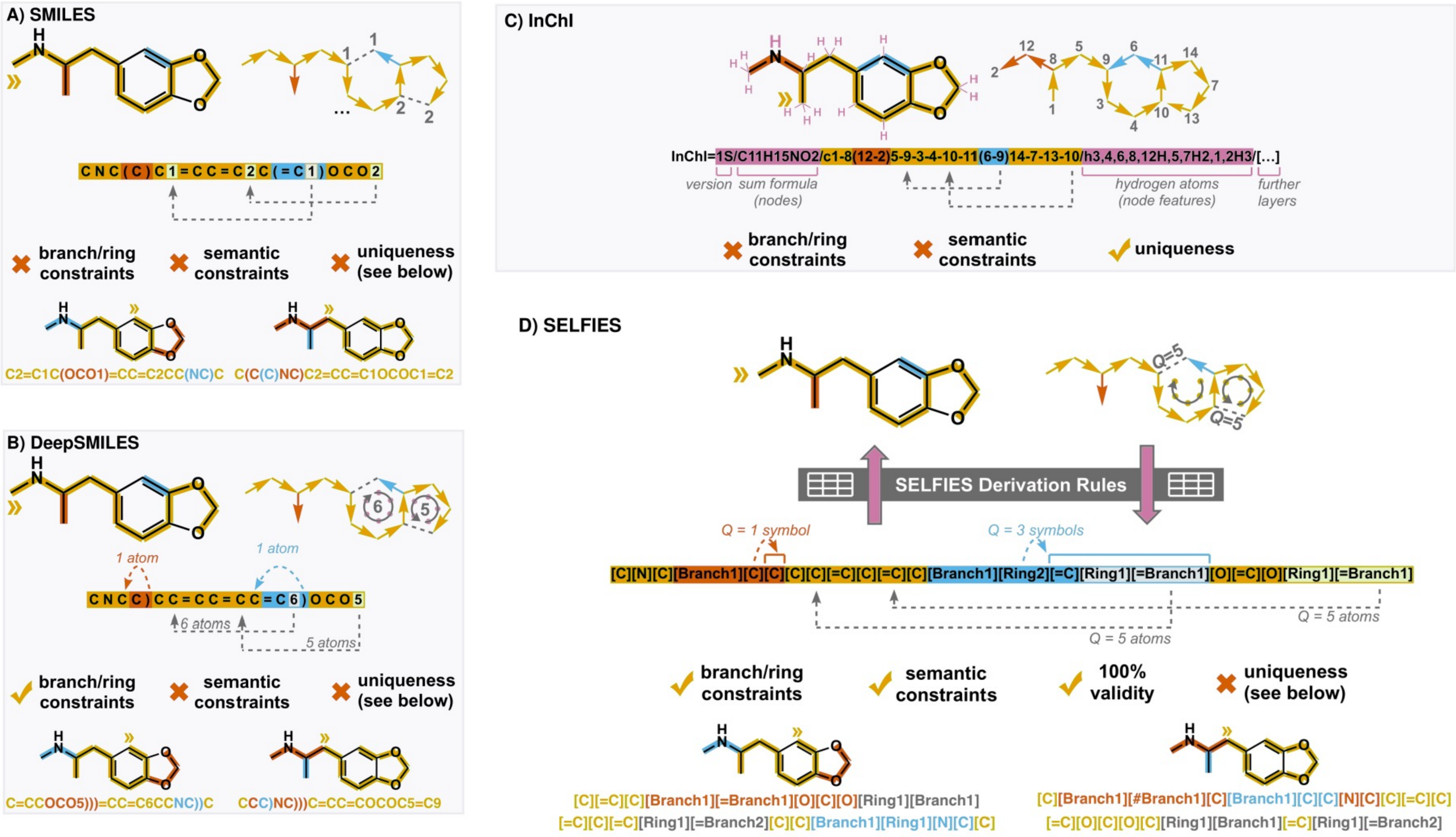


Protein

Central Law

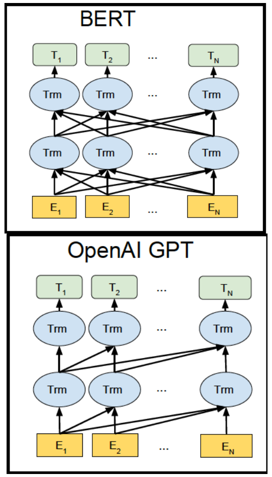
Scientific Language Understanding

Symbolized molecule language ⇨ Molecular language Models



LLMs for Scientific Language?

NLP → Learning the General Rules of Human Languages → $P(w_1, w_2, \cdots, w_n)$ →



Distributional Semantics

- *You shall know a word by the company it keeps* — Firth, 1957
- Document co-occurrence indicative of topic (**document** as context)
  - E.g. *voting* and *politics*
- Local context reflects its meaning (**word window** as context)
  - E.g. *eat a pizza* vs. *eat a burger*

Mol/ Protein → Learning the General Rules of Scientific Symbols → ? → ?

Fundamental Question: Does the Distributional Semantics Hypothesis Hold?

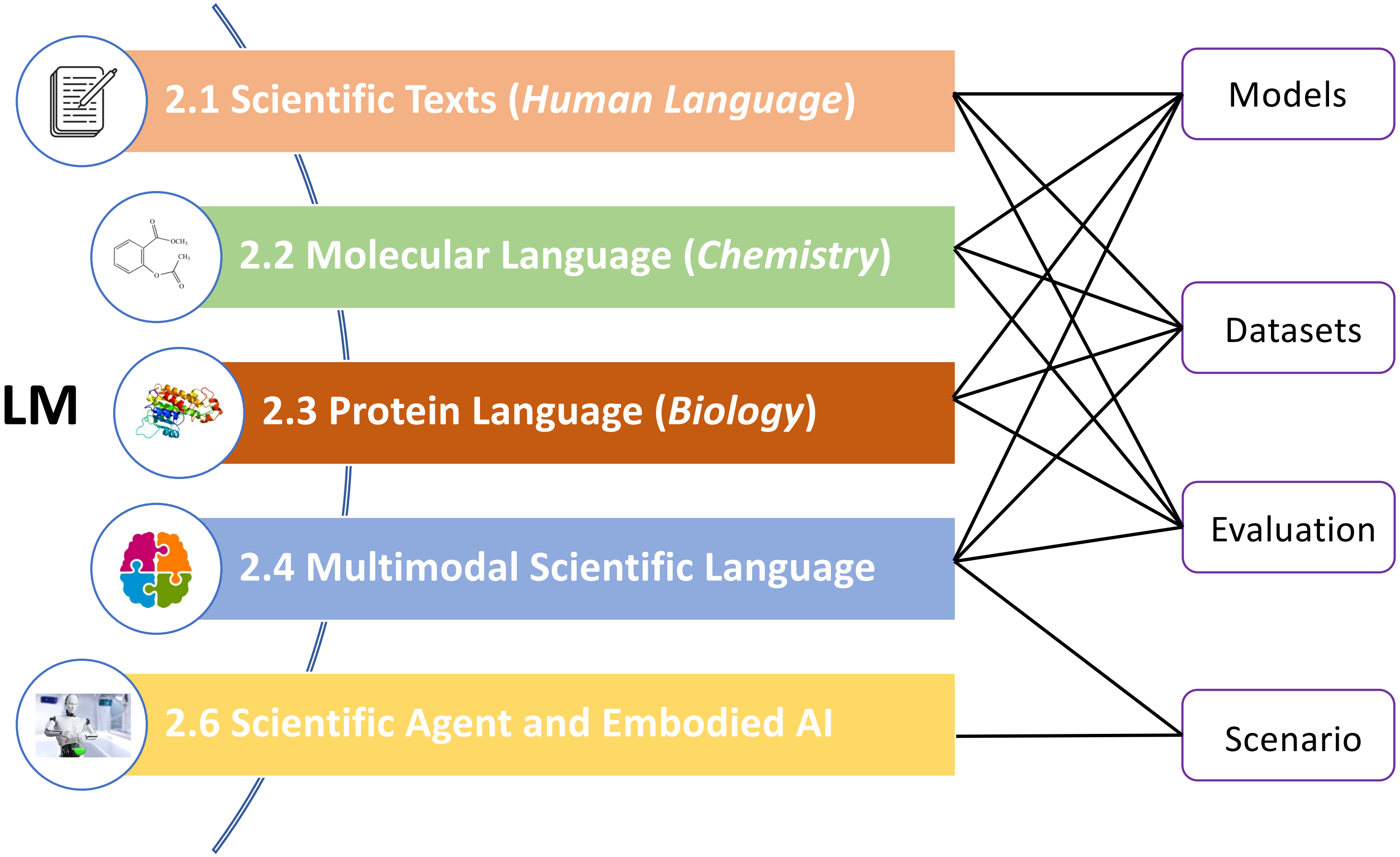
Outline

1 Introduction and Preliminary

2 Scientific Large Language Models

3 Challenges and Perspective

Scope of Scientific LLM



Sci-LLM

2.1 Scientific Texts (*Human Language*)

2.2 Molecular Language (*Chemistry*)

2.3 Protein Language (*Biology*)

2.4 Multimodal Scientific Language

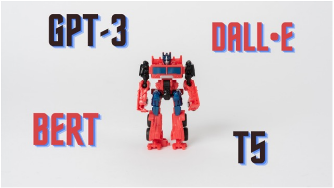
2.6 Scientific Agent and Embodied AI

Models

Datasets

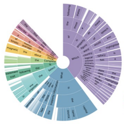
Evaluation

Scenario



PubMed UniProt

ATOM3D



MoleculeNet

A Benchmark for Molecular Machine Learning

TorchProtein

Outline

1 Introduction and Preliminary

2 Scientific Large Language Models

- 2.1 Scientific Texts

3 Challenges and Perspective

Text-Sci-LLM: Models & Datasets

❖ Biology + Chemistry + Comprehensive LLM
  - Architecture: **BERT**-based (BioBERT, ChemBERT), **GPT**-based (BioGPT, PharmLLM) and **GLM**-based (SciGLM)
  - Corpus: Initially trained on broad corpora like Wikipedia and papers and then fine-tuned on specific tasks

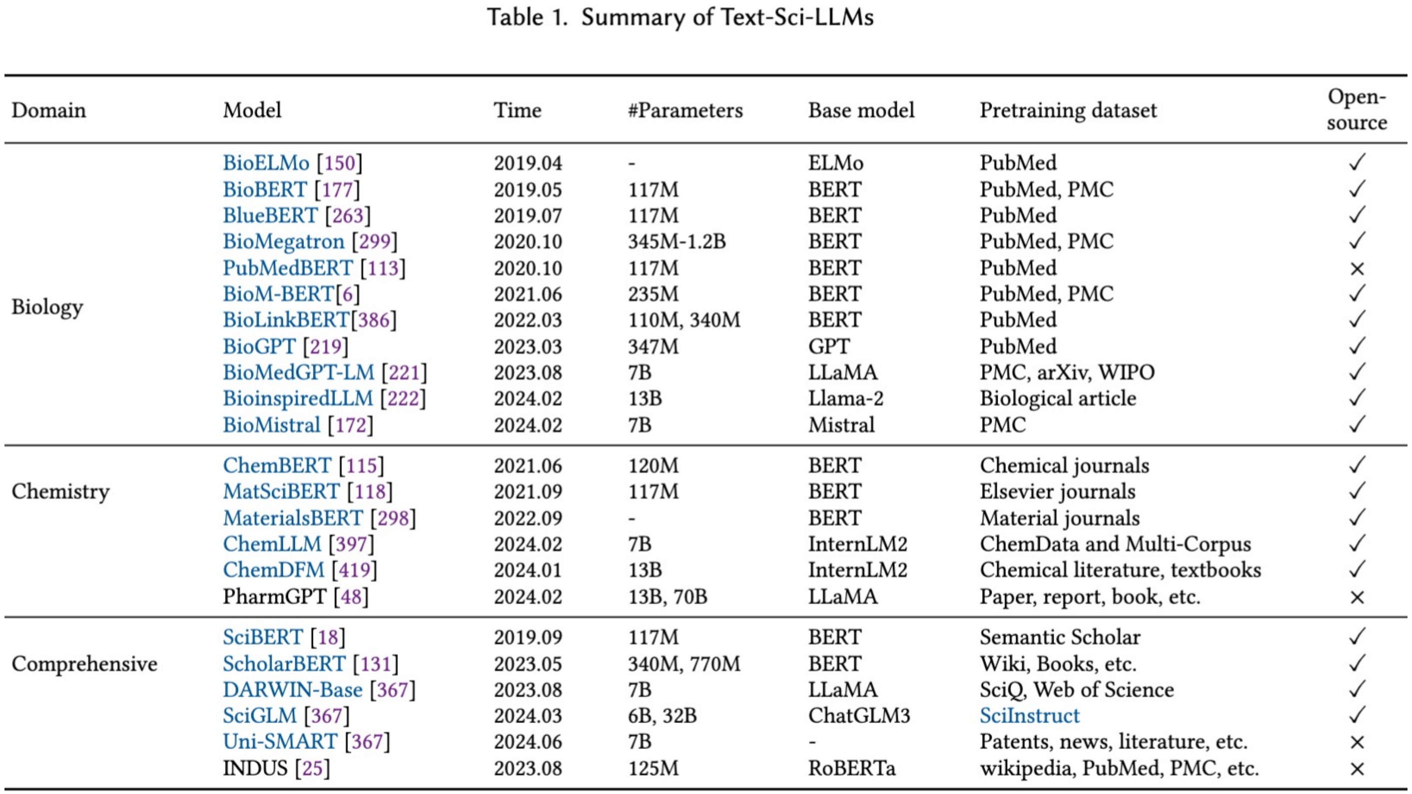
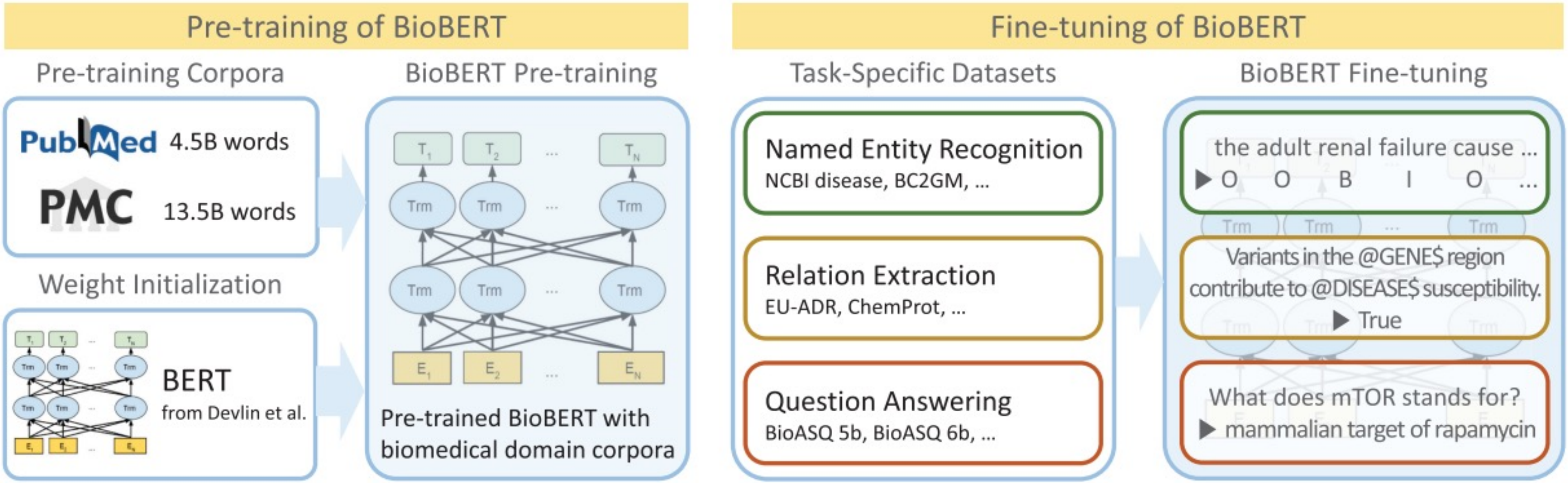


Table 1. Summary of Text-Sci-LLMs

Domain	Model	Time	#Parameters	Base model	Pretraining dataset	Open-source
Biology	BioELMo [150]	2019.04	-	ELMo	PubMed	✓
	BioBERT [177]	2019.05	117M	BERT	PubMed, PMC	✓
	BlueBERT [263]	2019.07	117M	BERT	PubMed	✓
	BioMegatron [299]	2020.10	345M-1.2B	BERT	PubMed, PMC	✓
	PubMedBERT [113]	2020.10	117M	BERT	PubMed	×
	BioM-BERT[6]	2021.06	235M	BERT	PubMed, PMC	✓
	BioLinkBERT[386]	2022.03	110M, 340M	BERT	PubMed	✓
	BioGPT [219]	2023.03	347M	GPT	PubMed	✓
	BioMedGPT-LM [221]	2023.08	7B	LLaMA	PMC, arXiv, WIPO	✓
	BioinspiredLLM [222]	2024.02	13B	Llama-2	Biological article	✓
	BioMistral [172]	2024.02	7B	Mistral	PMC	✓
Chemistry	ChemBERT [115]	2021.06	120M	BERT	Chemical journals	✓
	MatSciBERT [118]	2021.09	117M	BERT	Elsevier journals	✓
	MaterialsBERT [298]	2022.09	-	BERT	Material journals	✓
	ChemLLM [397]	2024.02	7B	InternLM2	ChemData and Multi-Corpus	✓
	ChemDFM [419]	2024.01	13B	InternLM2	Chemical literature, textbooks	✓
	PharmGPT [48]	2024.02	13B, 70B	LLaMA	Paper, report, book, etc.	×
Comprehensive	SciBERT [18]	2019.09	117M	BERT	Semantic Scholar	✓
	ScholarBERT [131]	2023.05	340M, 770M	BERT	Wiki, Books, etc.	✓
	DARWIN-Base [367]	2023.08	7B	LLaMA	SciQ, Web of Science	✓
	SciGLM [367]	2024.03	6B, 32B	ChatGLM3	SciInstruct	✓
	Uni-SMART [367]	2024.06	7B	-	Patents, news, literature, etc.	×
	INDUS [25]	2023.08	125M	RoBERTa	wikipedia, PubMed, PMC, etc.	×

Text-Sci-LLM: Encoder-only



Pre-training of BioBERT

Pre-training Corpora

PubMed 4.5B words

PMC 13.5B words

Weight Initialization

BERT
from Devlin et al.

BioBERT Pre-training

Pre-trained BioBERT with biomedical domain corpora

Fine-tuning of BioBERT

Task-Specific Datasets

Named Entity Recognition
NCBI disease, BC2GM, ...

Relation Extraction
EU-ADR, ChemProt, ...

Question Answering
BioASQ 5b, BioASQ 6b, ...

BioBERT Fine-tuning

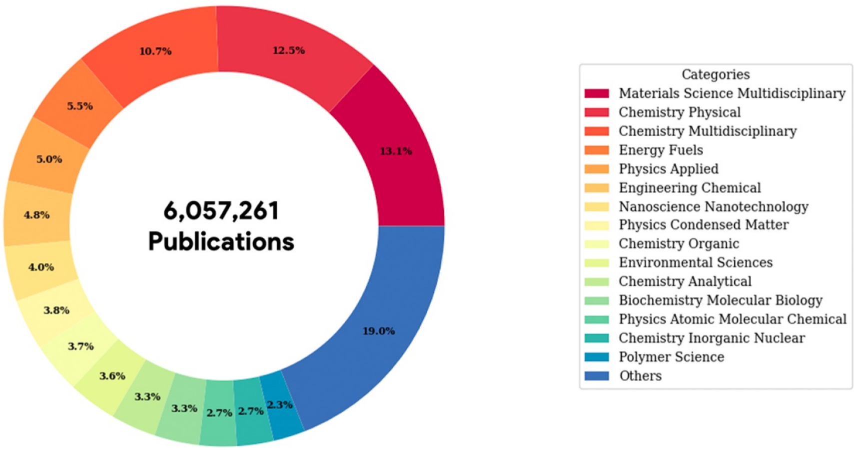
the adult renal failure cause ...
▶ O O B I O ...

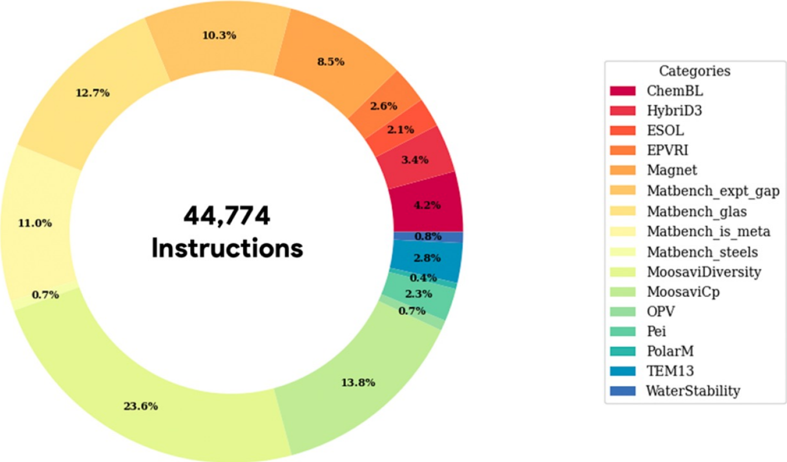
Variants in the @GENE$ region contribute to @DISEASE$ susceptibility.
▶ True

What does mTOR stands for?
▶ mammalian target of rapamycin

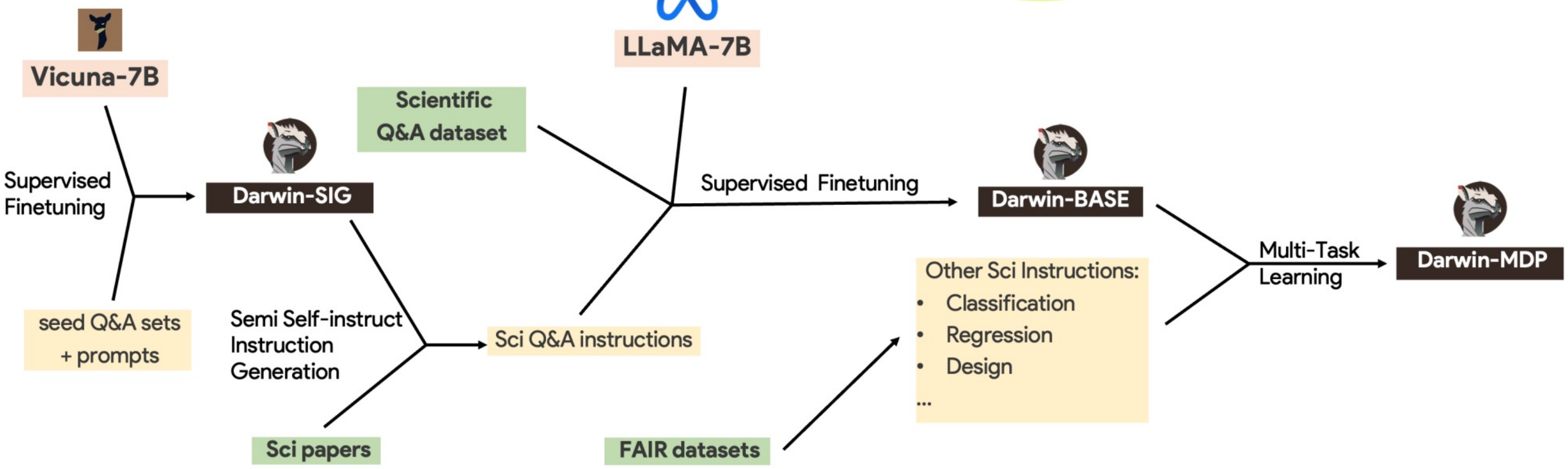
BioBERT: A pre-trained biomedical language representation model for biomedical text mining, **Bioinformatics**, 2019

Text-Sci-LLM: Decoder-only





DARWIN



Vicuna-7B

Supervised Finetuning

seed Q&A sets + prompts

Darwin-SIG

Semi Self-instruct Instruction Generation

Sci papers

Sci Q&A instructions

Scientific Q&A dataset

LLaMA-7B

Supervised Finetuning

Darwin-BASE

FAIR datasets

Other Sci Instructions:
- Classification
- Regression
- Design

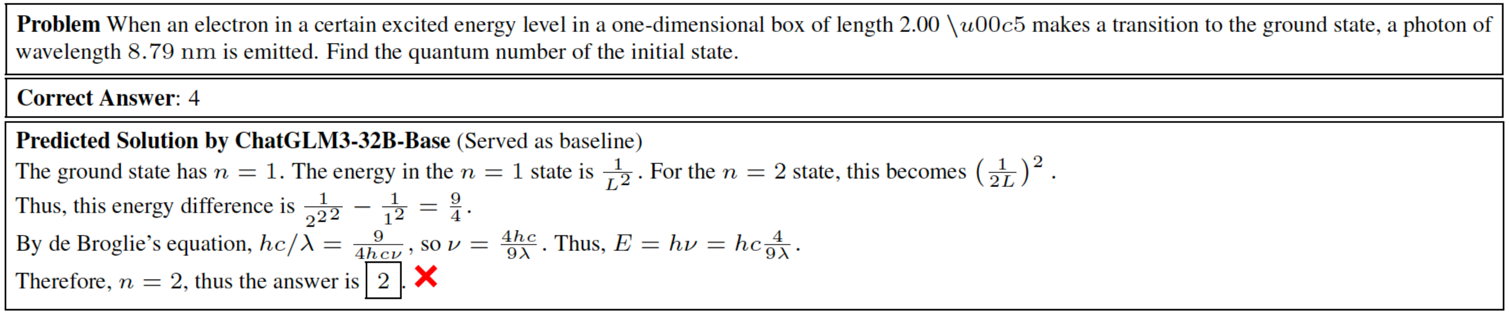
…

Multi-Task Learning

Darwin-MDP

DARWIN Series: Domain Specific Large Language Models for Natural Science, https://arxiv.org/pdf/2308.13565, 2023

Text-Sci-LLM: Encoder-decoder



Problem When an electron in a certain excited energy level in a one-dimensional box of length $2.00\ \backslash u00c5$ makes a transition to the ground state, a photon of wavelength $8.79\ \mathrm{nm}$ is emitted. Find the quantum number of the initial state.

Correct Answer: 4

Predicted Solution by ChatGLM3-32B-Base (Served as baseline)

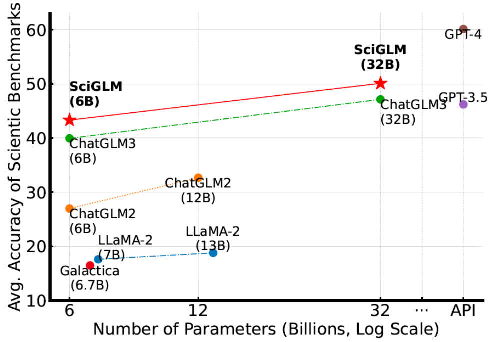
The ground state has $n = 1$. The energy in the $n = 1$ state is $\frac{1}{L^2}$. For the $n = 2$ state, this becomes $\left(\frac{1}{2L}\right)^2$.

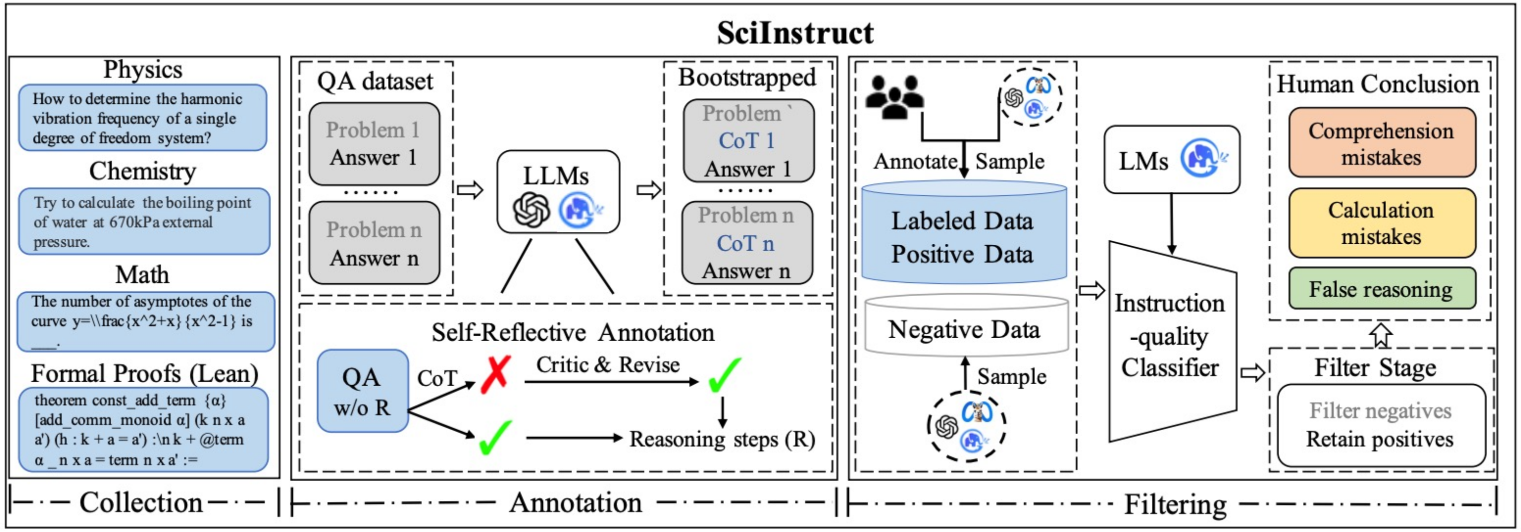
Thus, this energy difference is $\frac{1}{2^{22}} - \frac{1}{1^2} = \frac{9}{4}$.

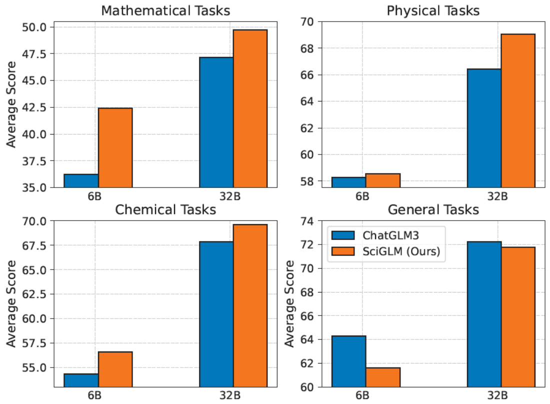
By de Broglie's equation, $hc/\lambda = \frac{9}{4hc\nu}$, so $\nu = \frac{4hc}{9\lambda}$. Thus, $E = h\nu = hc\frac{4}{9\lambda}$.

Therefore, $n = 2$, thus the answer is $\boxed{2}$. ✗

SciGLM







SciGLM: Training Scientific Language Models with Self-Reflective Instruction Annotation and Tuning, https://arxiv.org/pdf/2401.07950, 2024

Text-Sci-LLM: Evaluation

Table 2. Summary of the benchmarks for Text-Sci-LLMs

Dataset	Last updated	Subset	#Item	Domain	Type	Capability	Language
MMLU [127]	2020.09	High-school-biology	344	Biology	Multiple choice	Pre-college	English
		High-school-chemistry	227	Chemistry		Pre-college	
		College-biology	162	Biology		College	
		College-chemistry	110	Chemistry		College	
C-Eval [138]	2023.05	Mid-school-biology	218	Biology	Multiple choice	Pre-college	Chinese
		Mid-school-chemistry	210	Chemistry		Pre-college	
		High-school-biology	199	Biology		Pre-college	
		High-school-chemistry	196	Chemistry		Pre-college	
		College-chemistry	253	Chemistry		College	
AGIEval [424]	2023.04	Gaokao-biology	210	Biology	Multiple choice	Pre-college	Chinese
		Gaokao-chemistry	207	Chemistry			
ScienceQA [216]	2022.09	Natural-science-biology	4098	Biology	Multiple choice / QA	Pre-college	English
		Natural-science-chemistry	1194	Chemistry			
XieZhi [114]	2023.06	Science-biology	2831	Biology	Multiple choice	Mixed	Both
		Science-chemistry	399	Chemistry			
SciEval [313]	2023.08	Basic-biology	2142	Biology	Multiple choice / QA	Mixed	English
		Knowledge-biology	1369	Biology			
		Calculation-biology	299	Biology			
		Research-biology	995	Biology			
		Basic-chemistry	2909	Chemistry			
		Knowledge-chemistry	1700	Chemistry			
		Calculation-chemistry	3396	Chemistry			
GAOKAO-Bench [406]	2023.11	Biology	266	Biology	Multiple choice / QA	Mixed	Chinese
		Chemistry	133	Chemistry			
SciKnowEval [98]	2024.06	Biology	27730	Biology	Multiple choice / QA / True or flase	Mixed	English
		Chemistry	22250	Chemistry			
Bioinfo-Bench-QA [49]	2023.10	-	150	Biology	Multiple choice	Post-college	English
BLURB [113]	2020.07	-	648k	Biology	Multiple NLP tasks	Mixed	
PubMedQA [151]	2019.09	-	273.2k	Biology	True or false	College	
SciBench [345]	2023.07	-	272	Chemistry	QA	College	
ARC [64]	2018.03	-	7.78k	Natural Science	Multiple choice	Pre-college	
SciQ [152]	2017.07	-	13.7k	Natural Science	Multiple choice	Mixed	
ChemData [397]	2024.02	-	727k	Chemistry	QA	Mixed	

❖ Evaluation Benchmarks

- **MMLU**: 57 subjects, including STEM humanities, social sciences
- **C-Eval**: 13,948 multi-choice questions spanning 52 diverse disciplines
- **AGIEval**: 20 qualification exams, e.g., Gaokao and American SAT, law school admission tests
- **ScienceQA**: 21,208 multimodal multiple-choice questions, involving elementary and high school science curricula
- **Xiezhi**: 249,587 multi-choice questions spanning 516 diverse disciplines from the elementary to graduate entrance tests
- **SciEval**: 18,000 scientific questions across chemistry, physics, and biology
- **SciQ**: 13,679 science exam questions on subjects like chemistry and biology
- **SciBench**: 695 problems from textbooks, tailored for college-level problem-solving
- **SciAssess**: 14,721 questions across 29 tasks in five domains, with paper memorization, comprehension, and analysis

Text-Sci-LLM: Evaluation

SciKnowEval

- **L1**: **Studying Extensively** (i.e., knowledge coverage): remember and understand concepts
- **L2**: **Enquiring Earnestly** (i.e., knowledge enquiry and exploration): deep enquiry and exploration
- **L3**: **Thinking Profoundly** (i.e., knowledge reflection and reasoning): reasoning and calculating
- **L4**: **Discerning Clearly** (i.e., knowledge discernment and safety assessment): make secure, ethical decisions
- **L5**: **Practicing Assiduously** (i.e., knowledge practice and application): apply knowledge in real-world

SciKnowEval: Evaluating Multi-level Scientific Knowledge of Large Language Models, https://arxiv.org/abs/2406.09098, 2024

Text-Sci-LLM: Evaluation

Evaluation Tasks and Dataset Statistics

Domain	Ability	Task Name	Task Type	Data Source	Method	#Questions
Biology	L1	Biological Literature QA	MCQ	Literature Corpus	I	14,869
		Protein Property Identification	MCQ	UniProtKB	III	1,500
	L2	Drug-Drug Relation Extraction	RE	Bohrium	II	464
		Biomedical Judgment and Interpretation	T/F	PubMedQA	II	904
		Compound-Disease Relation Extraction	RE	Bohrium	II	867
		Gene-Disease Relation Extraction	RE	Bohrium	II	203
		Detailed Understanding	MCQ	LibreTexts	I	828
		Text Summary	GEN	LibreTexts	I	1,291
		Hypothesis Verification	T/F	LibreTexts	I	619
		Reasoning and Interpretation	MCQ	LibreTexts	I	647
	L3	Solubility Prediction	MCQ	PEER, DeepSol	III	201
		β-lactamase Activity Prediction	MCQ	PEER, Envision	III	209
		Fluorescence Prediction	MCQ	PEER, Sarkisyan's	III	205
		GB1 Fitness Prediction	MCQ	PEER, FLIP	III	201
		Stability Prediction	MCQ	PEER, Rocklin's	III	203
		Protein-Protein Interaction	MCQ	STRING, SHS27K, SHS148K	III	205
		Biological Calculation	MCQ	MedMCQA, SciEval, MMLU	II	60
	L4	Biological Harmful QA	GEN	Self-generated	I	297
		Proteotoxicity Prediction	MCQ, T/F	UniProtKB	III	510
		Biological Laboratory Safety Test	MCQ, T/F	LabExam (ZJU)	II	194
	L5	Biological Protocol Procedure Design	GEN	Protocol Journal	I	591
		Biological Protocol Reagent Design	GEN	Protocol Journal	I	565
		Protein Captioning	GEN	UniProtKB	III	937
		Protein Design	GEN	UniProtKB	III	860
		Single Cell Analysis	GEN	SHARE-seq	III	300
Chemistry	L1	Molecular Name Conversion	MCQ	PubChem	III	1,008
		Molecular Property Identification	MCQ, T/F	MoleculeNet	III	1,625
		Chemical Literature QA	MCQ	Literature Corpus	I	6,316
	L2	Reaction Mechanism Inference	MCQ	LibreTexts	I	269
		Compound Identification and Properties	MCQ	LibreTexts	I	497
		Doping Extraction	RE	NERRE	II	821
		Detailed Understanding	MCQ	LibreTexts	I	626
		Text Summary	GEN	LibreTexts	I	692
		Hypothesis Verification	T/F	LibreTexts	I	544
		Reasoning and Interpretation	MCQ	LibreTexts	I	516
	L3	Molar Weight Calculation	MCQ	PubChem	III	1,042
		Molecular Property Calculation	MCQ	MoleculeNet	II	740
		Molecular Structure Prediction	MCQ	PubChem	III	608
		Reaction Prediction	MCQ	USPTO-Mixed	II	1,122
		Retrosynthesis	MCQ	USPTO-50k	II	1,122
		Balancing Chemical Equation	GEN	WebQC	III	535
		Chemical Calculation	MCQ	XieZhi, SciEval, MMLU	II	269
	L4	Chemical Harmful QA	GEN	Proposition-65, ILO	III	454
		Molecular Toxicity Prediction	MCQ, T/F	Toxric	III	870
		Chemical Laboratory Safety Test	MCQ, T/F	LabExam (ZJU)	II	531
	L5	Molecular Captioning	GEN	ChEBI-20	II	943
		Molecular Generation	GEN	ChEBI-20	II	897
		Chemical Protocol Procedure Design	GEN	Protocol Journal	I	74
		Chemical Protocol Reagent Design	GEN	Protocol Journal	I	129

Zero-shot performance of LLMs on SciKnowEval

Models	Biology						Chemistry						Overall Rank
	L1	L2	L3	L4	L5	All	L1	L2	L3	L4	L5	All	
GPT-4o	**2.00**	**2.25**	**6.00**	4.00	**1.20**	**3.28**	**1.00**	2.29	4.00	7.00	3.75	**3.46**	1
Gemini1.5-Pro	4.50	5.12	6.14	**2.67**	6.60	5.36	2.67	4.00	**3.57**	**1.33**	11.75	4.67	2
GPT-4-Turbo	4.00	5.50	7.86	3.33	4.00	5.48	3.00	**1.57**	7.29	4.67	7.75	4.83	3
Claude3-Sonnet	5.50	4.12	8.43	4.00	2.00	5.00	6.00	4.43	7.86	8.00	6.00	6.33	4
GPT-3.5-Turbo	2.50	7.62	11.86	4.67	7.60	8.04	9.00	7.86	8.29	7.00	8.00	8.04	5
Llama3-8B-Inst	8.50	5.50	11.71	7.67	10.80	8.80	6.00	6.29	8.57	7.33	14.25	8.38	6
Qwen1.5-14B-Chat	5.50	10.38	8.71	9.00	8.40	8.96	9.33	7.14	6.43	8.00	10.50	7.88	7
Qwen1.5-7B-Chat	9.00	10.50	13.71	8.00	10.60	11.00	10.67	9.86	9.29	11.67	13.50	10.62	10
ChatGLM3-6B	12.00	14.25	11.43	10.00	12.00	12.32	15.33	15.00	15.00	12.33	12.75	14.33	12
Gemma1.1-7B-Inst	16.00	16.75	11.71	14.67	12.80	14.24	17.00	15.86	12.57	11.00	7.25	13.00	14
Llama2-13B-Chat	19.00	11.38	17.14	10.67	10.60	13.36	18.67	13.86	15.57	10.33	14.00	14.54	15
Mistral-7B-Inst	11.00	13.12	14.71	12.67	18.20	14.30	14.33	14.14	15.29	7.33	19.00	14.46	16
ChemDFM-13B	6.50	11.12	12.00	9.67	12.40	11.08	6.67	9.43	8.29	8.33	1.75	7.33	8
ChemLLM-20B-Chat	12.50	6.62	10.14	14.67	13.00	10.32	10.00	7.71	11.00	16.33	4.00	9.42	9
MolInst-Llama3-8B	13.50	9.88	7.86	12.00	18.20	11.52	9.33	9.57	7.43	9.33	17.75	10.25	11
Galactica-30B	11.00	13.75	8.43	16.67	16.80	13.00	7.67	16.43	13.00	16.67	16.00	14.29	13
SciGLM-6B	16.00	14.12	11.43	16.00	16.60	14.24	16.00	15.29	13.14	17.67	15.25	15.04	17
ChemLLM-7B-Chat	15.00	15.88	13.86	14.33	16.60	15.20	15.33	14.86	15.43	16.00	7.75	14.04	18
Galactica-6.7B	17.50	16.50	11.86	18.00	19.20	16.00	13.00	17.86	13.00	13.00	18.50	15.33	19
LlaSMol-Mistral-7B	19.50	16.75	14.14	19.67	17.20	16.68	19.33	18.71	16.29	20.00	**1.25**	15.33	20

Outline

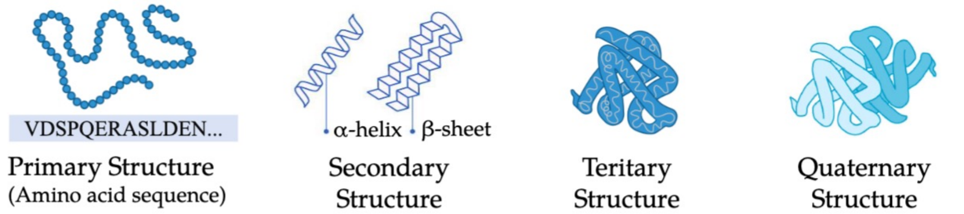
1 Introduction and Preliminary

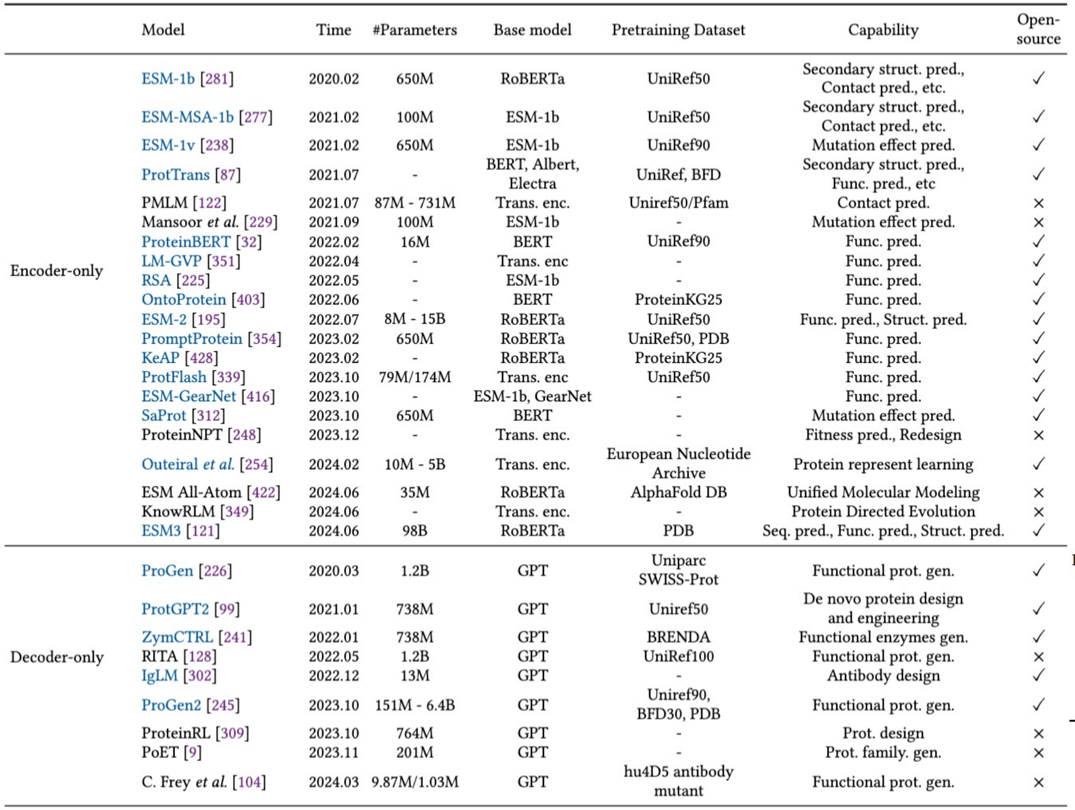
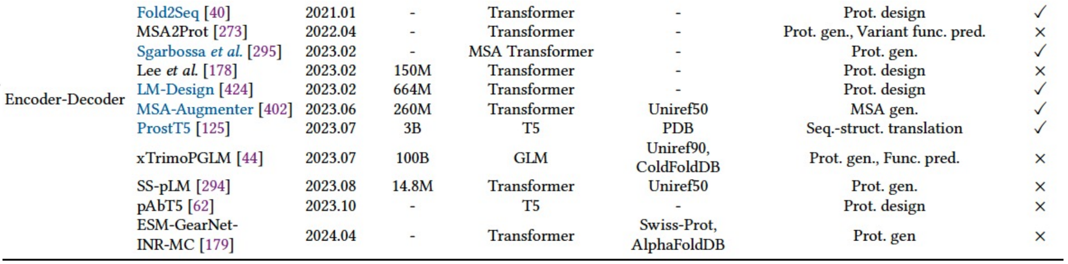
2 **Scientific Large Language Models**

- **2.3 Protein Language**

3 Challenges and Perspective

Prot-LLM: Models



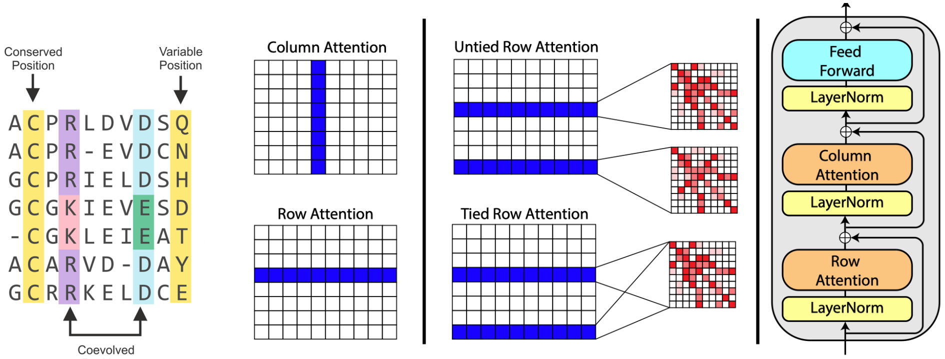
	Model	Time	#Parameters	Base model	Pretraining Dataset	Capability	Open-source
Encoder-only	ESM-1b [281]	2020.02	650M	RoBERTa	UniRef50	Secondary struct. pred., Contact pred., etc.	✓
	ESM-MSA-1b [277]	2021.02	100M	ESM-1b	UniRef50	Secondary struct. pred., Contact pred., etc.	✓
	ESM-1v [238]	2021.02	650M	ESM-1b	UniRef90	Mutation effect pred.	✓
	ProtTrans [87]	2021.07	-	BERT, Albert, Electra	UniRef, BFD	Secondary struct. pred., Func. pred., etc	✓
	PMLM [122]	2021.07	87M - 731M	Trans. enc.	Uniref50/Pfam	Contact pred.	✕
	Mansoor *et al.* [229]	2021.09	100M	ESM-1b	-	Mutation effect pred.	✕
	ProteinBERT [32]	2022.02	16M	BERT	UniRef90	Func. pred.	✓
	LM-GVP [351]	2022.04	-	Trans. enc	-	Func. pred.	✓
	RSA [225]	2022.05	-	ESM-1b	-	Func. pred.	✓
	OntoProtein [403]	2022.06	-	BERT	ProteinKG25	Func. pred.	✓
	ESM-2 [195]	2022.07	8M - 15B	RoBERTa	UniRef50	Func. pred., Struct. pred.	✓
	PromptProtein [354]	2023.02	650M	RoBERTa	UniRef50, PDB	Func. pred.	✓
	KeAP [428]	2023.02	-	RoBERTa	ProteinKG25	Func. pred.	✓
	ProtFlash [339]	2023.10	79M/174M	Trans. enc	UniRef50	Func. pred.	✓
	ESM-GearNet [416]	2023.10	-	ESM-1b, GearNet	-	Func. pred.	✓
	SaProt [312]	2023.10	650M	BERT	-	Mutation effect pred.	✓
	ProteinNPT [248]	2023.12	-	Trans. enc.	-	Fitness pred., Redesign	✕
	Outeiral *et al.* [254]	2024.02	10M - 5B	Trans. enc.	European Nucleotide Archive	Protein represent learning	✓
	ESM All-Atom [422]	2024.06	35M	RoBERTa	AlphaFold DB	Unified Molecular Modeling	✕
	KnowRLM [349]	2024.06	-	Trans. enc.	-	Protein Directed Evolution	✕
	ESM3 [121]	2024.06	98B	RoBERTa	PDB	Seq. pred., Func. pred., Struct. pred.	✓
Decoder-only	ProGen [226]	2020.03	1.2B	GPT	Uniparc SWISS-Prot	Functional prot. gen.	✓
	ProtGPT2 [99]	2021.01	738M	GPT	Uniref50	De novo protein design and engineering	✓
	ZymCTRL [241]	2022.01	738M	GPT	BRENDA	Functional enzymes gen.	✓
	RITA [128]	2022.05	1.2B	GPT	UniRef100	Functional prot. gen.	✕
	IgLM [302]	2022.12	13M	GPT	-	Antibody design	✓
	ProGen2 [245]	2023.10	151M - 6.4B	GPT	Uniref90, BFD30, PDB	Functional prot. gen.	✓
	ProteinRL [309]	2023.10	764M	GPT	-	Prot. design	✕
	PoET [9]	2023.11	201M	GPT	-	Prot. family. gen.	✕
	C. Frey *et al.* [104]	2024.03	9.87M/1.03M	GPT	hu4D5 antibody mutant	Functional prot. gen.	✕
Encoder-Decoder	Fold2Seq [40]	2021.01	-	Transformer	-	Prot. design	✓
	MSA2Prot [273]	2022.04	-	Transformer	-	Prot. gen., Variant func. pred.	✕
	Sgarbossa *et al.* [295]	2023.02	-	MSA Transformer	-	Prot. gen.	✓
	Lee *et al.* [178]	2023.02	150M	Transformer	-	Prot. design	✕
	LM-Design [424]	2023.02	664M	Transformer	-	Prot. design	✓
	MSA-Augmenter [402]	2023.06	260M	Transformer	Uniref50	MSA gen.	✓
	ProstT5 [125]	2023.07	3B	T5	PDB	Seq.-struct. translation	✓
	xTrimoPGLM [44]	2023.07	100B	GLM	Uniref90, ColdFoldDB	Prot. gen., Func. pred.	✕
	SS-pLM [294]	2023.08	14.8M	Transformer	Uniref50	Prot. gen.	✕
	pAbT5 [62]	2023.10	-	T5	-	Prot. design	✕
	ESM-GearNet-INR-MC [179]	2024.04	-	Transformer	Swiss-Prot, AlphaFoldDB	Prot. gen	✕

(Continued)

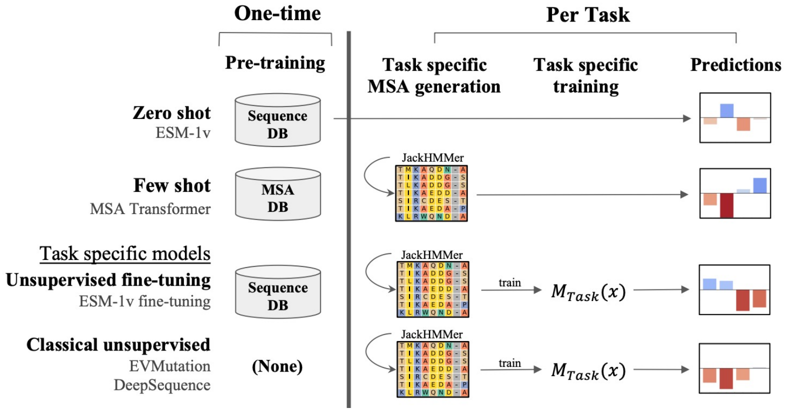
❖ Protein LLMs
- **Protein vocabulary**: 20 amino acids in nature, special tokens like <BOS> and <EOS>
- **Architectures**: BERT, RoBERTa, GPT, GLM, T5, Transformer
- **Sizes**: 100M, 1B, 10B, 100B
- **Datasets**: Uniref, Pfam, SwissProt, PDB, BFD30, AlphaFoldDB, ColdFoldDB
- **Tasks**: function prediction, family prediction, protein-protein interaction, contact prediction, mutation effect prediction, structure prediction, sequence optimization, protein de novo design, inverse folding

Prot-LLM: Encoder-only

ESM series

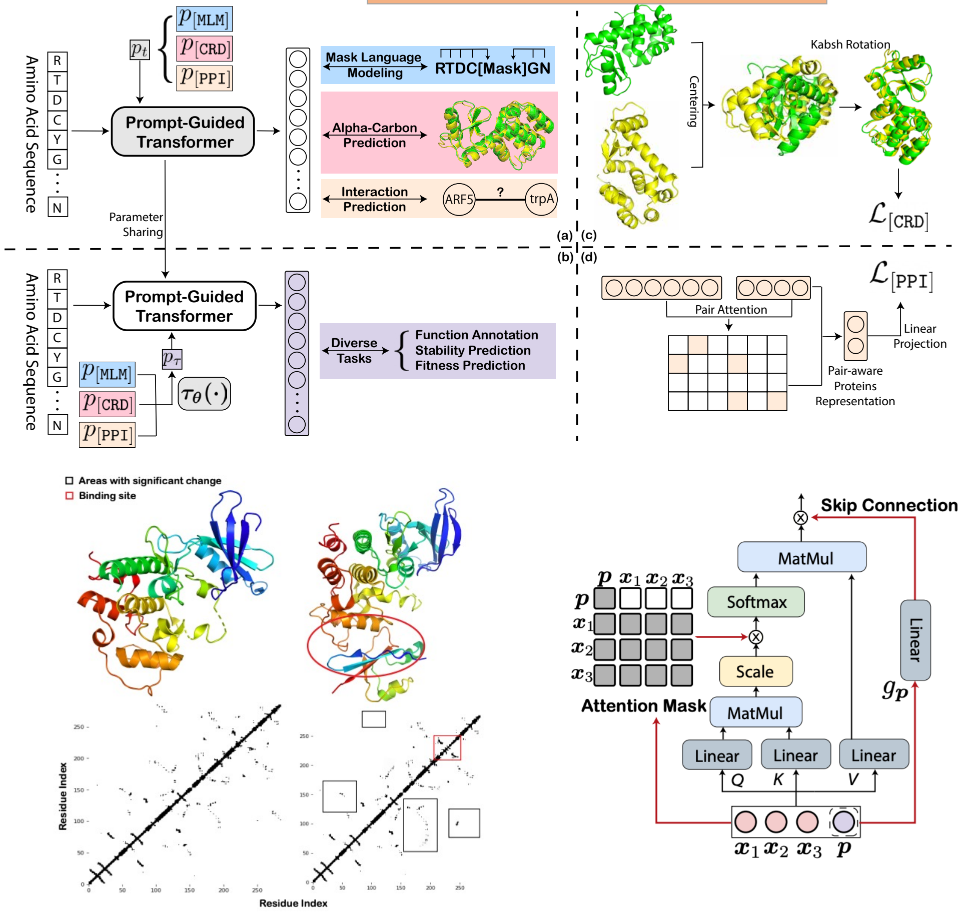


MSA Transformer, **ICML**, 2021.



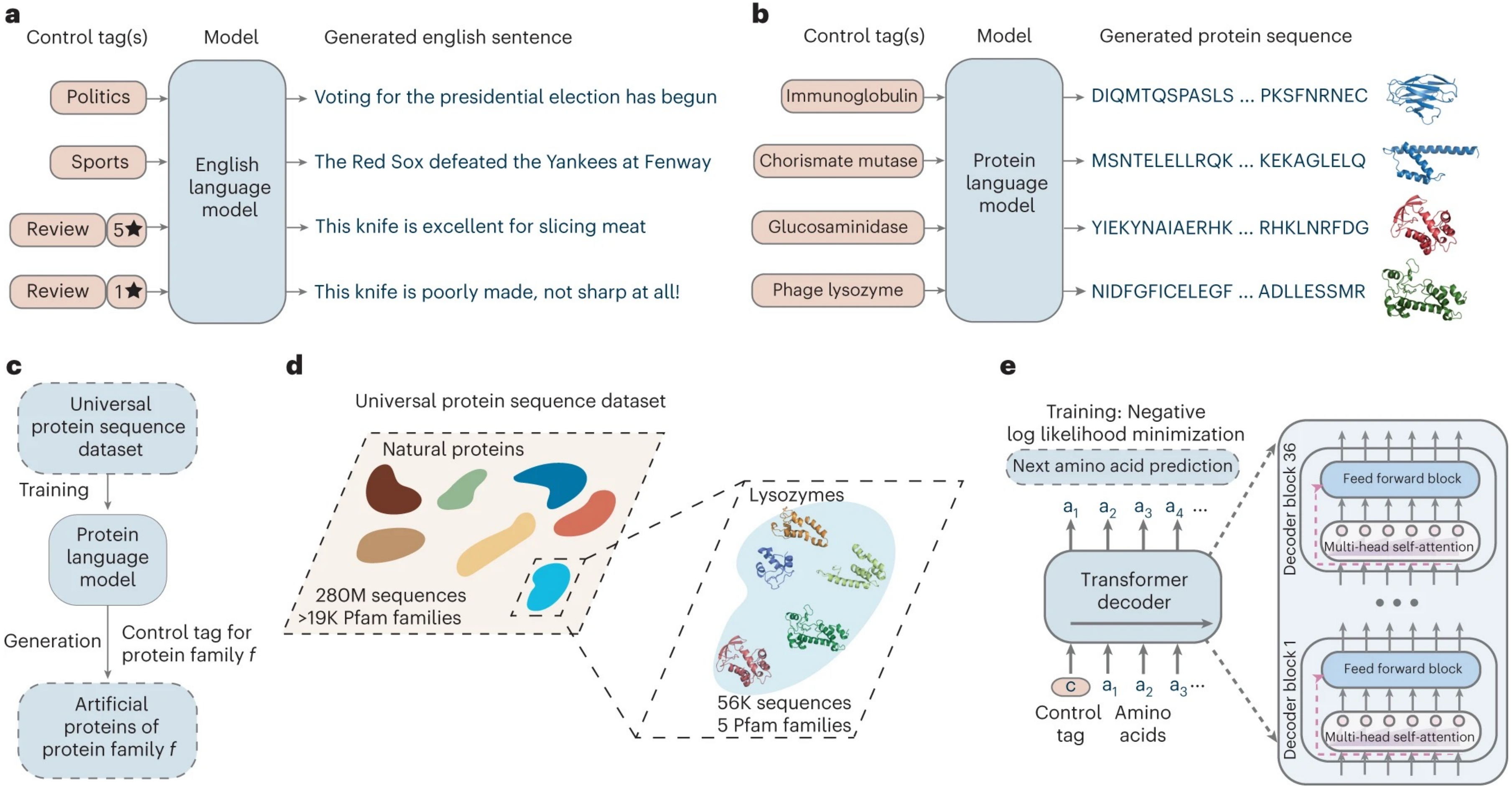
Language models enable zero-shot prediction of the effects of mutations on protein function, www.biorxiv.org/content/10.1101/2021.07.09.450648v2, 2021

PromptProtein



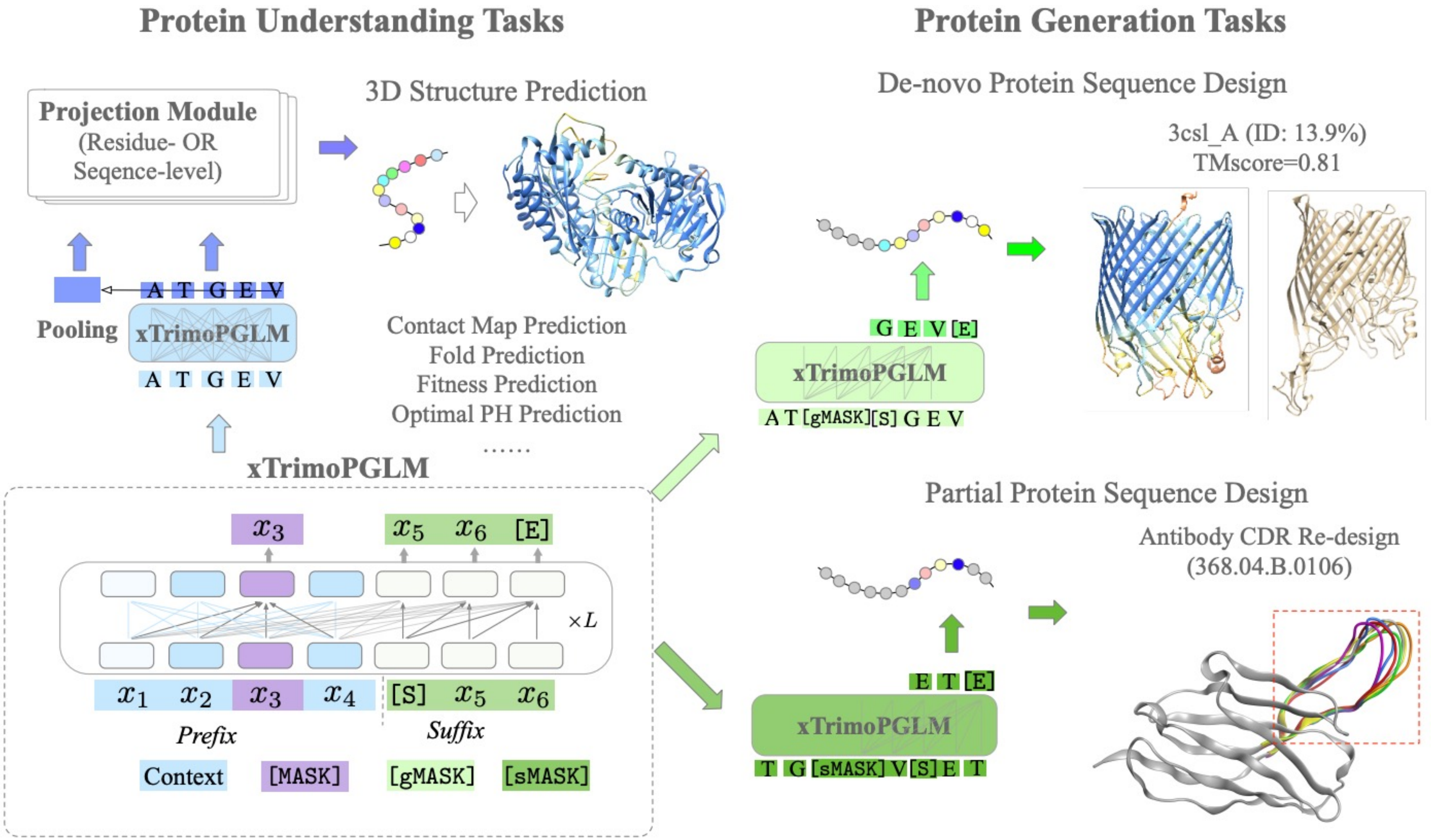
Multi-level Protein Structure Pre-training with Prompt Learning, **ICLR**, 2022

Prot-LLM: Decoder-only



ProGen: Large language models generate functional protein sequences across diverse families, **Nature Biotechnology**, 2023

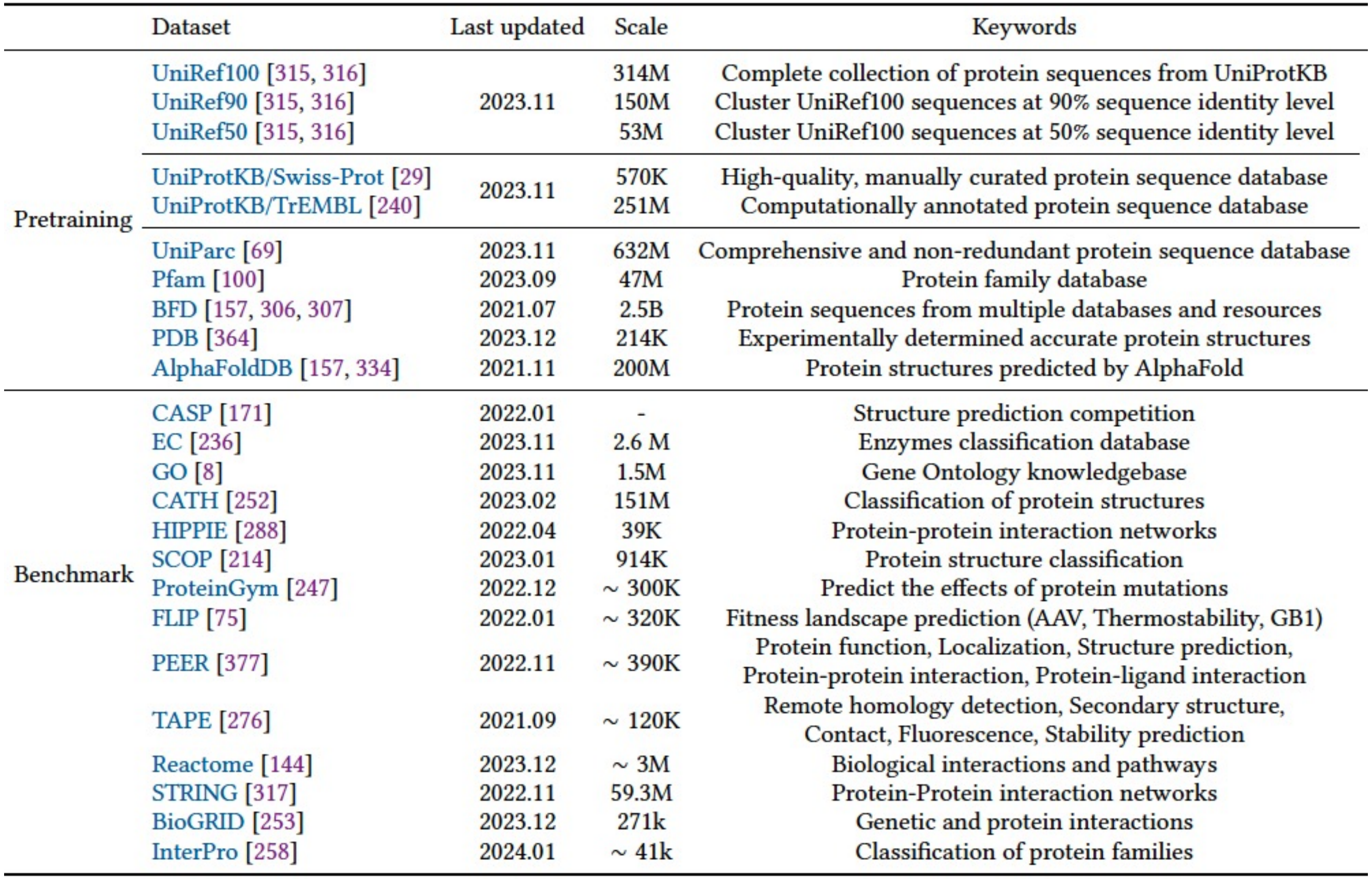
Prot-LLM: Encoder-decoder



xTrimoPGLM: Unified 100B-Scale Pre-trained Transformer for Deciphering the Language of Protein, https://arxiv.org/pdf/2401.06199, 2024

Prot-LLM: Datasets

Table 6. Summary of datasets for Prot-LLMs



	Dataset	Last updated	Scale	Keywords
Pretraining	UniRef100 [315, 316]	2023.11	314M	Complete collection of protein sequences from UniProtKB
	UniRef90 [315, 316]		150M	Cluster UniRef100 sequences at 90% sequence identity level
	UniRef50 [315, 316]		53M	Cluster UniRef100 sequences at 50% sequence identity level
	UniProtKB/Swiss-Prot [29]	2023.11	570K	High-quality, manually curated protein sequence database
	UniProtKB/TrEMBL [240]		251M	Computationally annotated protein sequence database
	UniParc [69]	2023.11	632M	Comprehensive and non-redundant protein sequence database
	Pfam [100]	2023.09	47M	Protein family database
	BFD [157, 306, 307]	2021.07	2.5B	Protein sequences from multiple databases and resources
	PDB [364]	2023.12	214K	Experimentally determined accurate protein structures
	AlphaFoldDB [157, 334]	2021.11	200M	Protein structures predicted by AlphaFold
Benchmark	CASP [171]	2022.01	-	Structure prediction competition
	EC [236]	2023.11	2.6 M	Enzymes classification database
	GO [8]	2023.11	1.5M	Gene Ontology knowledgebase
	CATH [252]	2023.02	151M	Classification of protein structures
	HIPPIE [288]	2022.04	39K	Protein-protein interaction networks
	SCOP [214]	2023.01	914K	Protein structure classification
	ProteinGym [247]	2022.12	∼ 300K	Predict the effects of protein mutations
	FLIP [75]	2022.01	∼ 320K	Fitness landscape prediction (AAV, Thermostability, GB1)
	PEER [377]	2022.11	∼ 390K	Protein function, Localization, Structure prediction, Protein-protein interaction, Protein-ligand interaction
	TAPE [276]	2021.09	∼ 120K	Remote homology detection, Secondary structure, Contact, Fluorescence, Stability prediction
	Reactome [144]	2023.12	∼ 3M	Biological interactions and pathways
	STRING [317]	2022.11	59.3M	Protein-Protein interaction networks
	BioGRID [253]	2023.12	271k	Genetic and protein interactions
	InterPro [258]	2024.01	∼ 41k	Classification of protein families

Prot-LLM: Evaluation

Evaluation Metric

- **Novelty**: the fraction of the generated proteins that are not present in the training set
- **Frechet Protein Distance**: the similarity between a set of generated proteins (G) and a reference set (R)

$$\mathrm{FPD} = ||\mu_G - \mu_R||^2 + \mathrm{Tr}(\Sigma_G + \Sigma_R - 2\sqrt{\Sigma_G \Sigma_R})$$

- **Diversity**: analyzing the variety of the generated proteins against known protein databases with BLAST, metrics such as sequence similarity, percentage of unique sequences, and alignment scores

- **Foldability**: the average per-residue confidence score, denoted as **pLDDT**, across the entire protein sequence, being an indicator of the model's confidence in its predictions for individual residues

- **Recovery**: the success or accuracy in predicting the correct amino acid sequence that corresponds to a given 3D structure. A high recovery rate indicates that the designed sequences are likely to fold the desired structures.

Outline

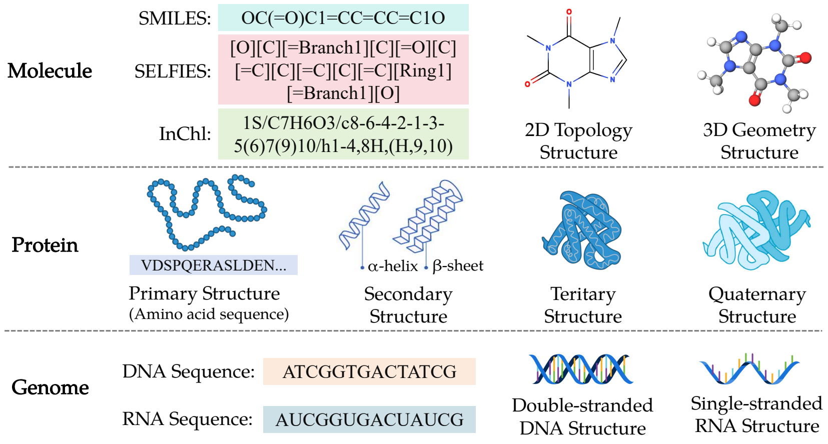
1 Introduction and Preliminary

2 Scientific Large Language Models

3 Challenges and Perspective

Sci-LLM: Summary

Scientific Symbols & Language



Molecule

SMILES: OC(=O)C1=CC=CC=C1O

SELFIES: [O][C][=Branch1][C][=O][C][=C][C][=C][C][=C][Ring1][=Branch1][O]

InChl: 1S/C7H6O3/c8-6-4-2-1-3-5(6)7(9)10/h1-4,8H,(H,9,10)

2D Topology Structure

3D Geometry Structure

Protein

VDSPQERASLDEN...

Primary Structure (Amino acid sequence)

α-helix β-sheet

Secondary Structure

Teritary Structure

Quaternary Structure

Genome

DNA Sequence: ATCGGTGACTATCG

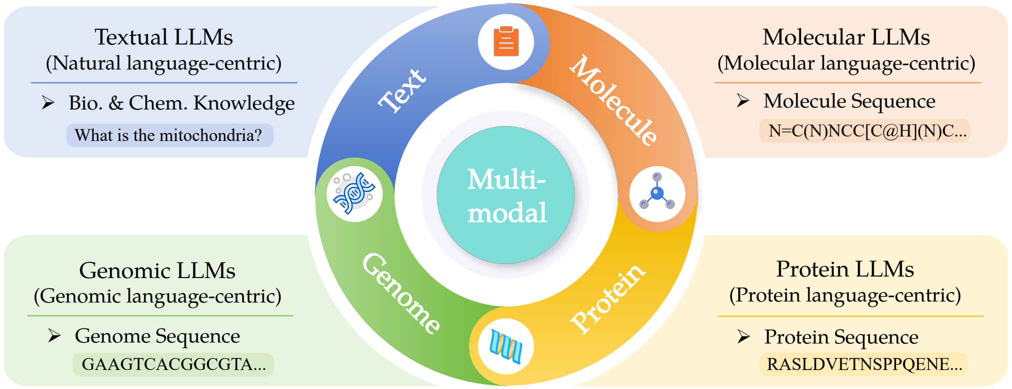
RNA Sequence: AUCGGUGACUAUCG

Double-stranded DNA Structure

Single-stranded RNA Structure

Modeling

Scientific Language Models



Textual LLMs (Natural language-centric)
- Bio. & Chem. Knowledge
  What is the mitochondria?

Molecular LLMs (Molecular language-centric)
- Molecule Sequence
  N=C(N)NCC[C@H](N)C...

Genomic LLMs (Genomic language-centric)
- Genome Sequence
  GAAGTCACGGCGTA...

Protein LLMs (Protein language-centric)
- Protein Sequence
  RASLDVETNSPPQENE...

Perspective

- **Training Data**:
  - Scale of Pre-training Datasets
  - Quality of Finetuning Datasets
  - Lack of Cross-modal Datasets
- **Model Evaluation**:
  - Computational vs wet-lab
- **Architectures and Learning Objectives**:
  - Handling Longer Sequences
  - Incorporating 3D Structural Information
  - Autoregressive Learning Objective
- **Security and Ethics**:
  - Data Privacy, Model Bias, Equal Access

Relevant Materials

- Accompanying survey of this tutorial:
  - Scientific Large Language Models: A Survey on Biological & Chemical Domains, https://arxiv.org/pdf/2401.14656
  - Github Repository: https://github.com/HICAI-ZJU/Scientific-LLM-Survey
- Surveys for related topics:
  - Comprehensive
    - Artificial Intelligence for Science in Quantum, Atomistic, and Continuum Systems, https://arxiv.org/pdf/2307.08423
    - A Comprehensive Survey of Scientific Large Language Models and Their Applications in Scientific Discovery, https://arxiv.org/abs/2406.10833
  - Chemical molecules
    - MolGenSurvey: A systematic survey in machine learning models for molecule design, https://arxiv.org/abs/2203.14500
    - A Systematic Survey of Chemical Pre-trained Models, https://www.ijcai.org/proceedings/2023/0760.pdf
  - Biological proteins
    - Learning the protein language: Evolution, structure, and function, https://www.cell.com/cell-systems/pdf/S2405-4712(21)00203-9.pdf
    - Protein language models and structure prediction: Connection and progression, https://arxiv.org/pdf/2211.16742
    - Learning functional properties of proteins with language models, https://www.nature.com/articles/s42256-022-00457-9

Resources
Available

Thank You!

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Part III: Integrating KGs and LLMs for Scientific Applications

Zaiqiao Meng
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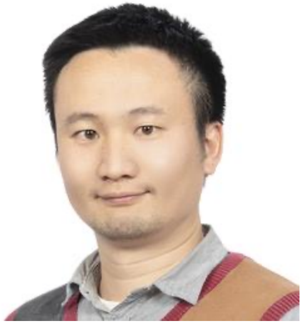
Tutorial at Learning on Graph Conference (LoG)
26th November, 2024

About Me



Dr. Zaiqiao Meng

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⚗ https://www.ai4biomed.org

- UK Lecturer (Assistant Professor) at the School of Computing Science, **University of Glasgow** (2022.01 – now)
- Postdoctoral Researcher at the Language Technology Lab (LTL) of the **University of Cambridge** (2020.07 – 2022.01)
- Postdoctoral Researcher at the IR Group of the **University of Glasgow** (2019.03 – 2020.07)
- Ph.D. degree in Computer Science from **Sun Yat-sen University** (2018)

Research Topic

- AI for BioMedicine
- Information Retrieval
- Knowledge Graphs
- Large Language Models
- LLM-based Agents
- AI for Scientific Discovery

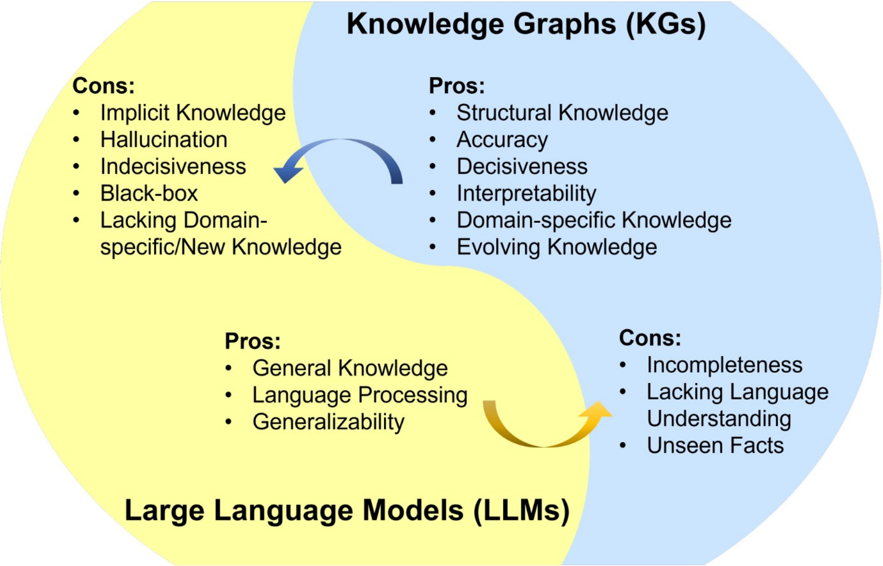
Outline

1. Knowledge Incorporation Frameworks
2. KG Integration for Scientific NLP Tasks
3. KG Integration for Scientific Prediction Tasks

Outline

1. **Knowledge Incorporation Frameworks**
2. KG Integration for Scientific NLP Tasks
3. KG Integration for Scientific Prediction Tasks

KG-enhanced LLMs



Knowledge Graphs (KGs)

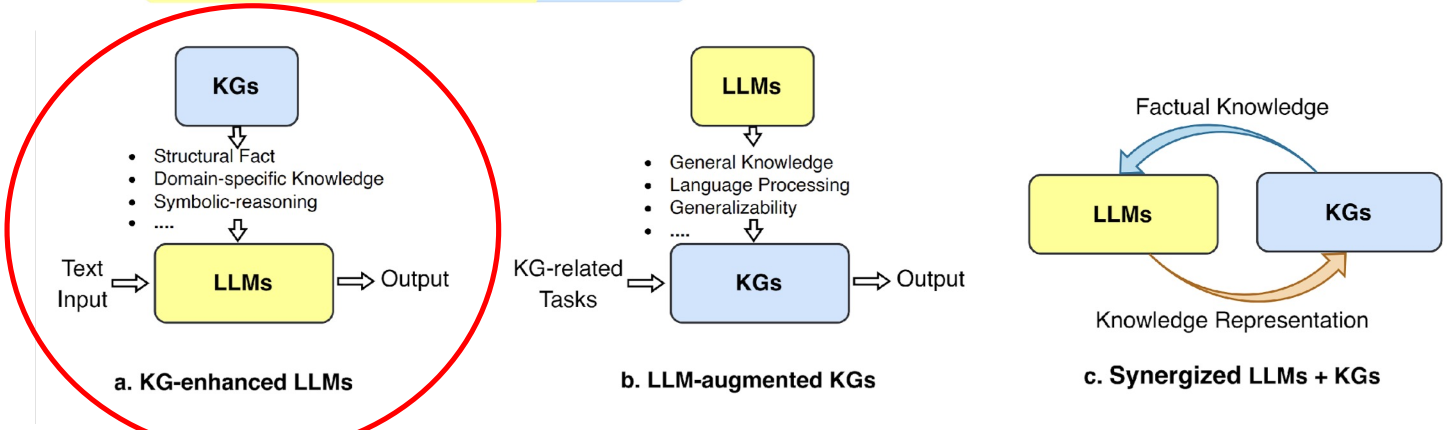
Cons:
- Implicit Knowledge
- Hallucination
- Indecisiveness
- Black-box
- Lacking Domain-specific/New Knowledge

Pros:
- Structural Knowledge
- Accuracy
- Decisiveness
- Interpretability
- Domain-specific Knowledge
- Evolving Knowledge

Pros:
- General Knowledge
- Language Processing
- Generalizability

Cons:
- Incompleteness
- Lacking Language Understanding
- Unseen Facts

Large Language Models (LLMs)



a. KG-enhanced LLMs

b. LLM-augmented KGs

c. Synergized LLMs + KGs

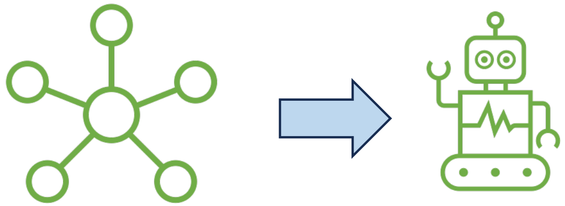
KG-enhanced LLMs, which incorporate KGs during different phases of LLMs, or for the purpose of enhancing understanding of the knowledge learned by LLMs;

- Knowledge aware pretraining
- Knowledge integration finetuning
- Knowledge editing
- Knowledge unlearning

Unifying Large Language Models and Knowledge Graphs: A Roadmap. (2024) Link

Categorization over different stages

- Integrating scientific knowledge can occur at any stage in the development of LLMs



pre-training

- Pretrain-KGEs [1]
- ERNIE [2]
- MolXPT [3]

post-training

- SapBERT [3]
- MoP [4]
- OntoProtein [5]
- Bridge [6]
- MedLaSA [10]

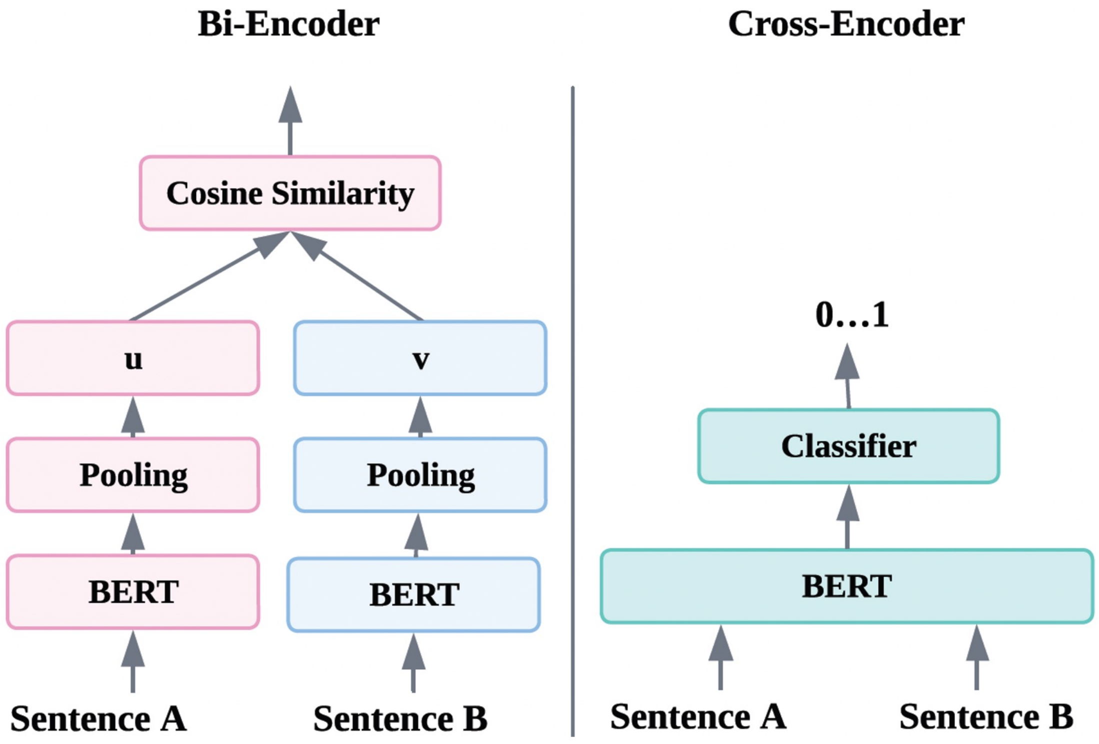
finetuning

- FusionDTI [8]
- FusionGDA [9]
- Saprot-based applications [13]

inference

- MKRAG [10]
- KRAGEN [11]
- BioRAG [12]

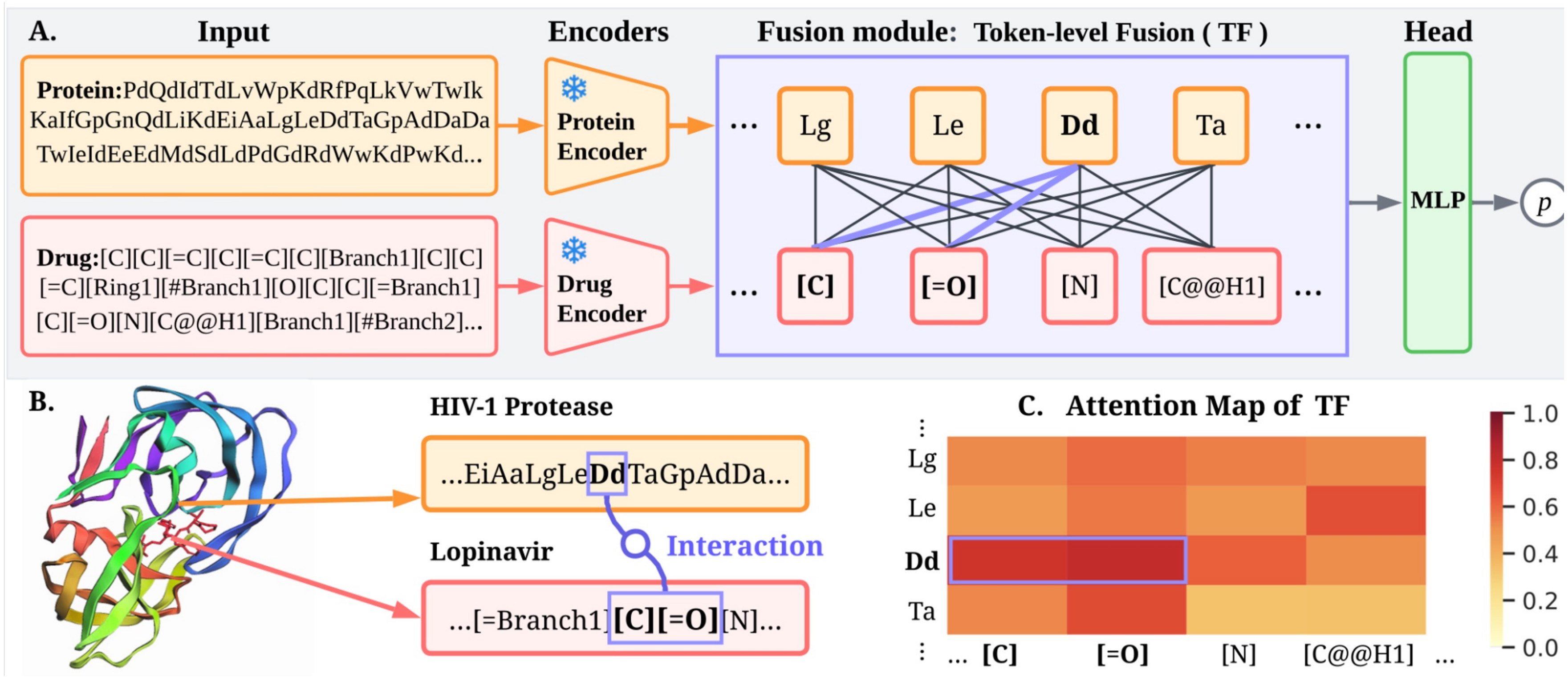
Bi-Encoder vs. Cross-Encoder



Bi-Encoder: Efficient encoding of individual entities can speed up retrieval and computation, but may sacrifice finer-grained interactions between different encoders.
High efficiency.

Cross-Encoder: Encodes entities jointly, capturing more detailed interactions, but at the cost of greater computational resources and time.
High effectiveness.

Bi-Encoder for Drug-Target Prediction

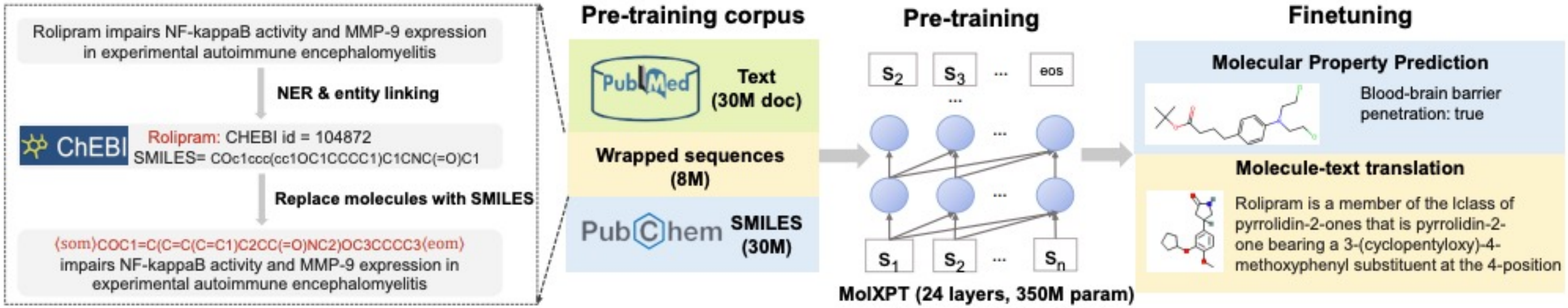


FusionDTI uses a token-level fusion module to effectively learn fine-grained information for drug-target interaction.

FusionDTI: Fine-grained Binding Discovery with Token-level Fusion for Drug-Target Interaction. Link

Cross-Encoder for molecular property prediction

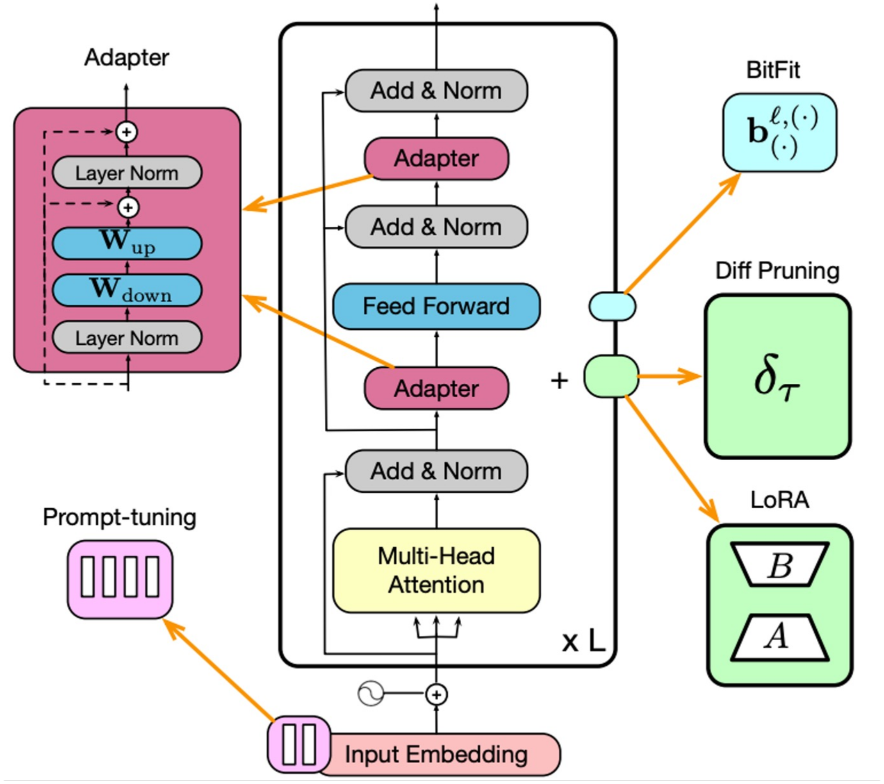
MolXPT: Wrapping Molecules with Text for Generative Pre-training



- A unified language model of text and molecules pre-trained on SMILES (a sequence representation of molecules) wrapped by text
- Text and SMILES are tokenized separately (molecular are encoded)

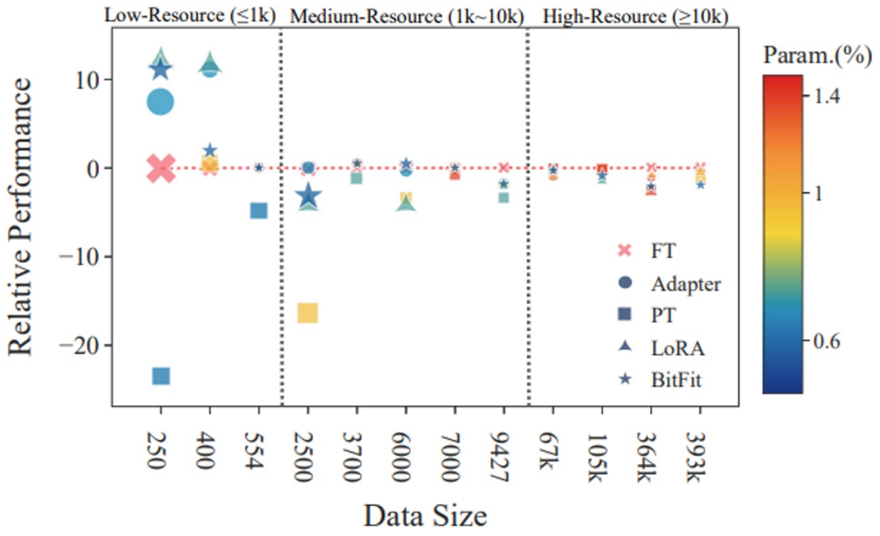
MolXPT: Wrapping Molecules with Text for Generative Pre-training (ACL 2023). Link

Integration Techniques of LLMs



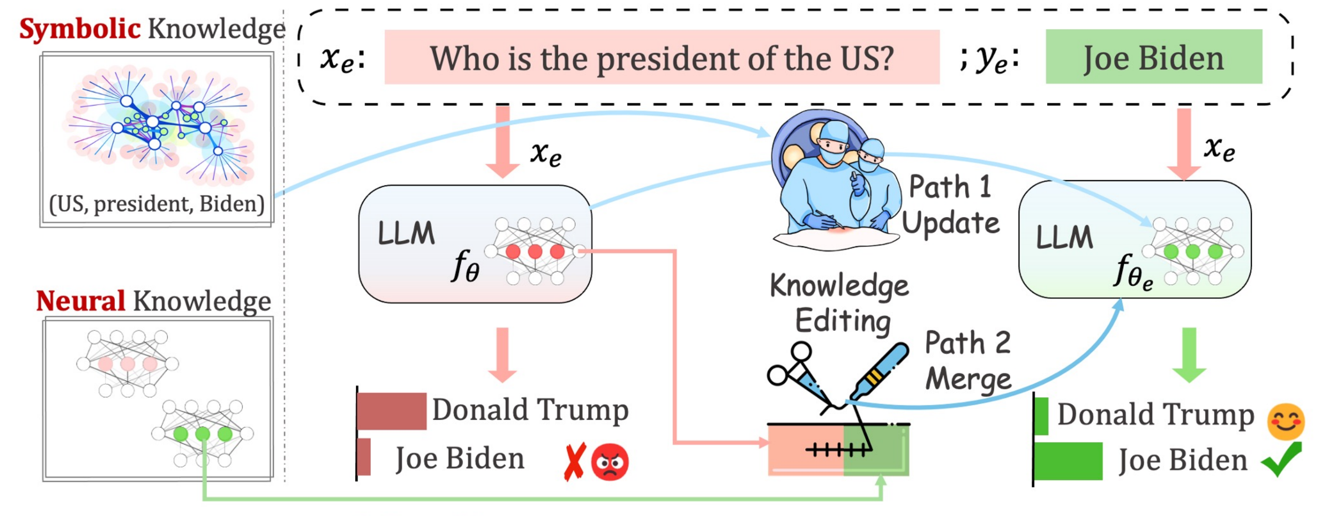
Parameter-Efficient Fine-Tuning (PEFT):

Techniques like **Adapters**, **Prefix Tuning, LoRA, Diff Pruning, BitFit or Prompt-tuning** that fine-tune only a small subset of model parameters, reducing computational costs while maintaining performance.



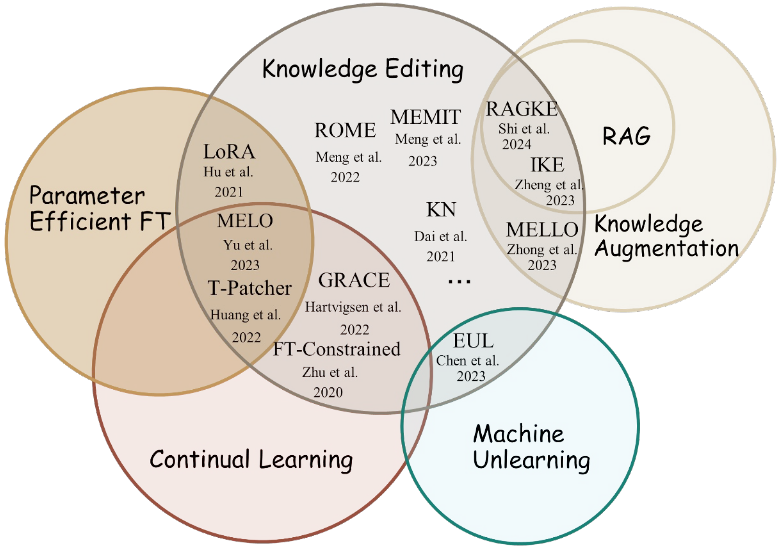
Revisiting Parameter-Efficient Tuning: Are We Really There Yet? (EMNLP 2022) Link

Knowledge Editing



Knowledge Editing Types: Insertion Modification Erasure

post-training



Comparison of different technologies

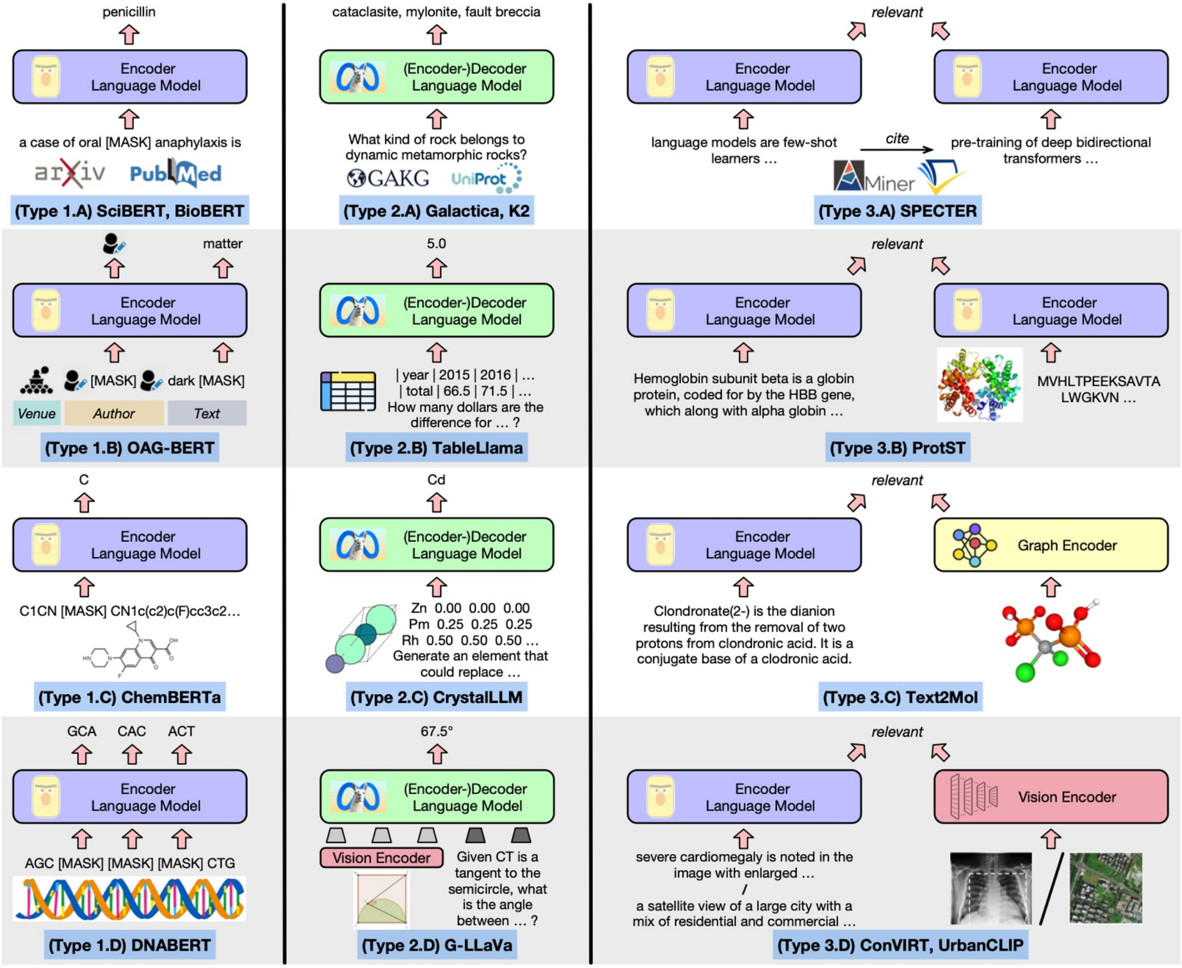
LLMs notoriously *hallucinate*, *perpetuate bias*, and *factually decay*, so we should be able to adjust specific behaviors of pre-trained models.

Easyedit: An easy-to-use knowledge editing framework for large language models: https://github.com/zjunlp/EasyEdit

Outline

1. Knowledge Incorporation Frameworks
2. **KG Integration for Scientific NLP Tasks**
3. KG Integration for Scientific Prediction Tasks

KG Integration for Scientific NLP Tasks



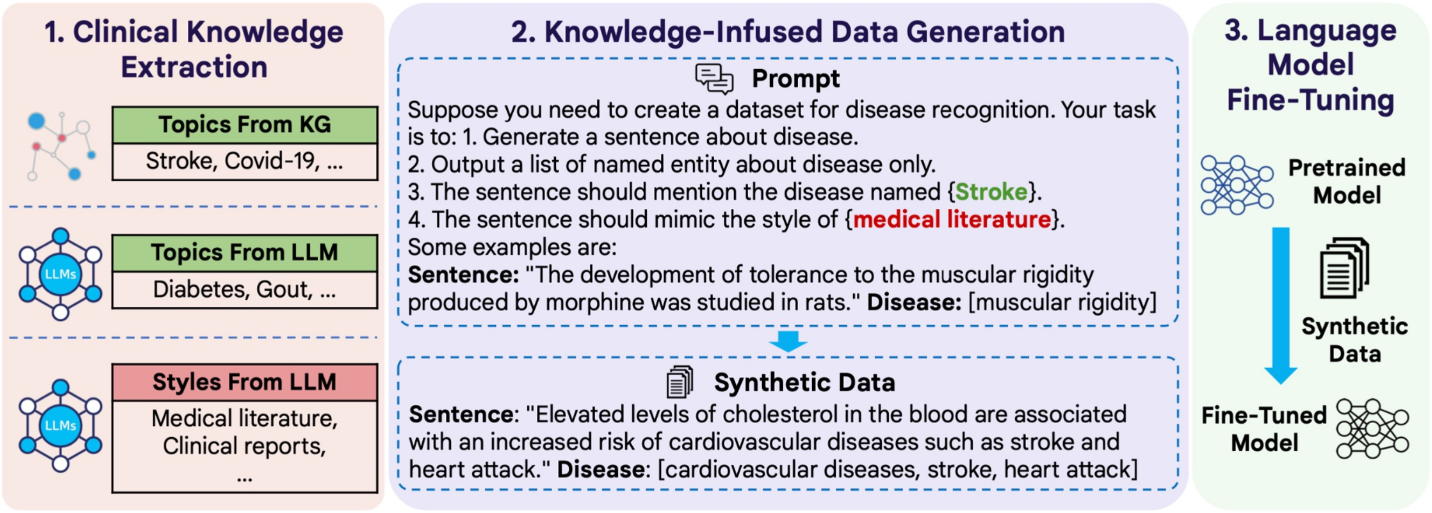
- Question Answering [5]
- Entity Linking [4]
- Document Classification [5]
- Summarisation/Note Generation [14]
- Hypothesis Generation [15]
- Knowledge Graph Construction and Completion [1]
- Reasoning [12, 15]

A Comprehensive Survey of Scientific Large Language Models and Their Applications in Scientific Discovery, Arxiv 2024

KG Integration for Clinical Text Data Generation

Clinical Text Data Generation

fine-tune



1. Clinical Knowledge Extraction

Topics From KG
Stroke, Covid-19, ...

Topics From LLM
Diabetes, Gout, ...

Styles From LLM
Medical literature,
Clinical reports,
...

2. Knowledge-Infused Data Generation

Prompt

Suppose you need to create a dataset for disease recognition. Your task is to: 1. Generate a sentence about disease.
2. Output a list of named entity about disease only.
3. The sentence should mention the disease named {**Stroke**}.
4. The sentence should mimic the style of {**medical literature**}.
Some examples are:
Sentence: "The development of tolerance to the muscular rigidity produced by morphine was studied in rats." **Disease:** [muscular rigidity]

Synthetic Data

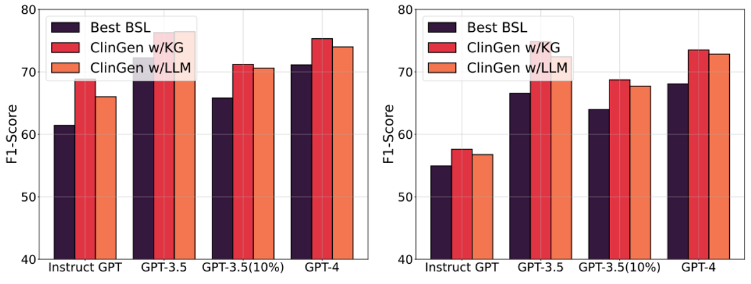
Sentence: "Elevated levels of cholesterol in the blood are associated with an increased risk of cardiovascular diseases such as stroke and heart attack." **Disease**: [cardiovascular diseases, stroke, heart attack]

3. Language Model Fine-Tuning

Pretrained Model

Synthetic Data

Fine-Tuned Model

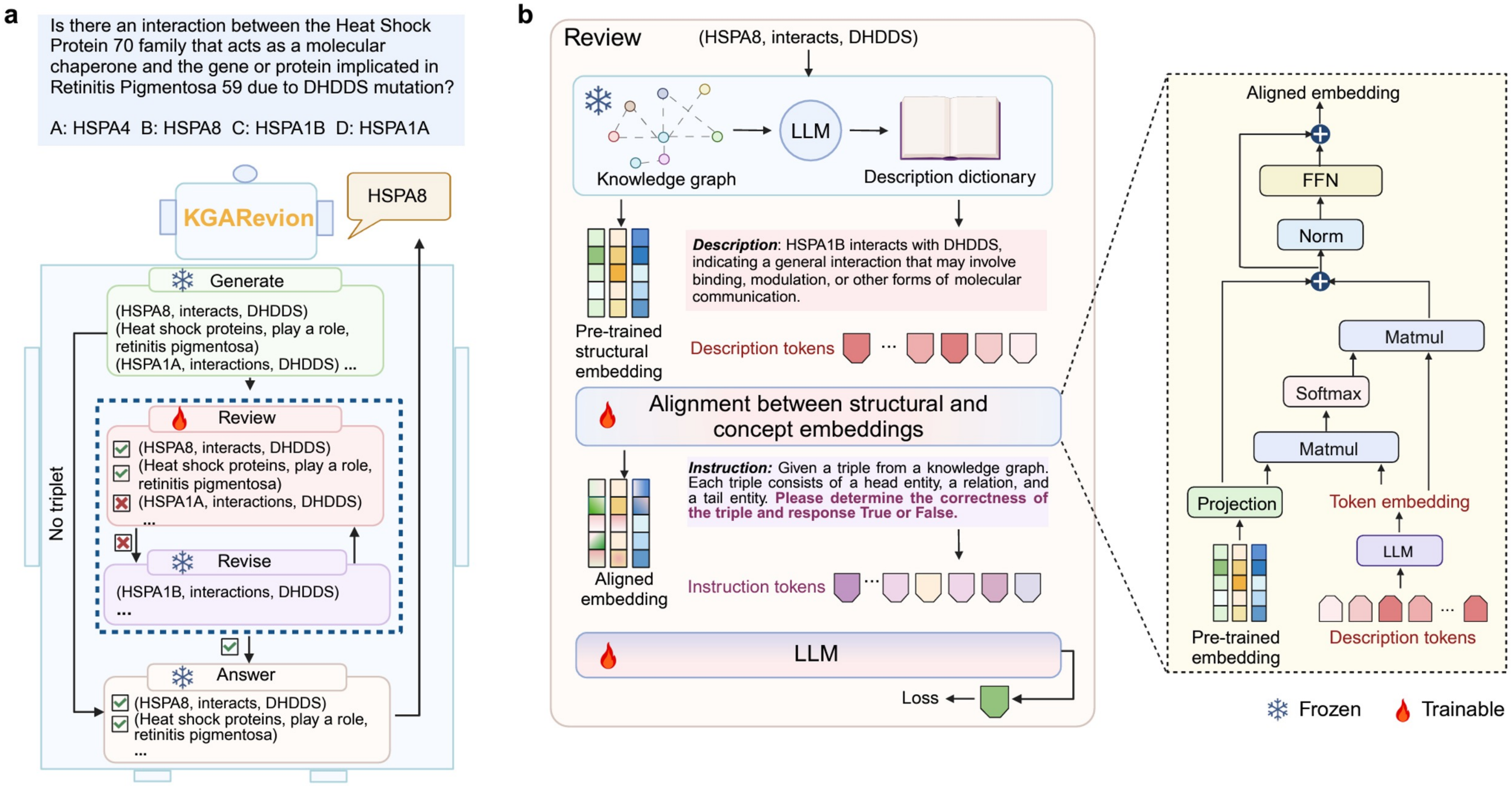


(a) HOC (b) MEDIQA-RQE

CLINGEN is a knowledge-informed framework for clinical data generation. This two-step methodology harnesses the emergent capabilities of LLMs and external knowledge from KGs to facilitate the synthesis of clinical data, even with few-shot examples only.

Knowledge-Infused Prompting: Assessing and Advancing Clinical Text Data Generation with Large Language Models. (ACL 2024) Link

KG Integration for QA Tasks



Question Answering (QA)

KG: Heterogeneous (primeKG)

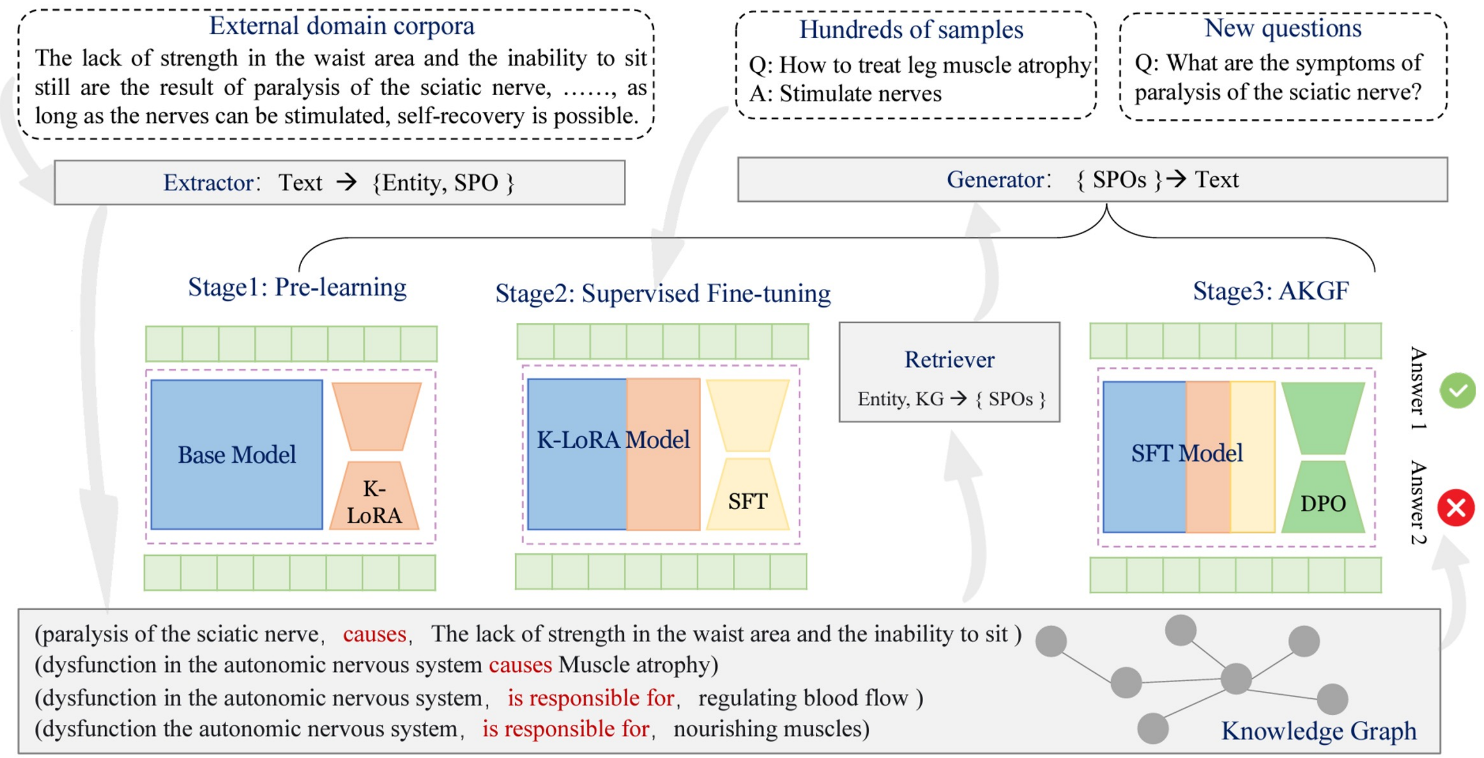
KGAREVION a KG-based LLM agent for complex medical QA that leverages non-codified knowledge of LLMs and structured, codified knowledge of medical concepts within KGs.

fine-tune

LORA *

Knowledge Graph Based Agent for Complex, Knowledge-Intensive QA in Medicine. (2024) Link

KG Integration for QA Tasks



The lack of strength in the waist area and the inability to sit still are the result of paralysis of the sciatic nerve, ……, as long as the nerves can be stimulated, self-recovery is possible.

Q: How to treat leg muscle atrophy
A: Stimulate nerves

Q: What are the symptoms of paralysis of the sciatic nerve?

(paralysis of the sciatic nerve, causes, The lack of strength in the waist area and the inability to sit)
(dysfunction in the autonomic nervous system causes Muscle atrophy)
(dysfunction in the autonomic nervous system, is responsible for, regulating blood flow)
(dysfunction the autonomic nervous system, is responsible for, nourishing muscles)

Efficient Knowledge Infusion via KG-LLM Alignment. (ACL 2024) Link

Question Answering (QA)

The Enhanced LLM with Knowledge Pre-learning and Feedback (ELPF) framework can be divided into four main stages.

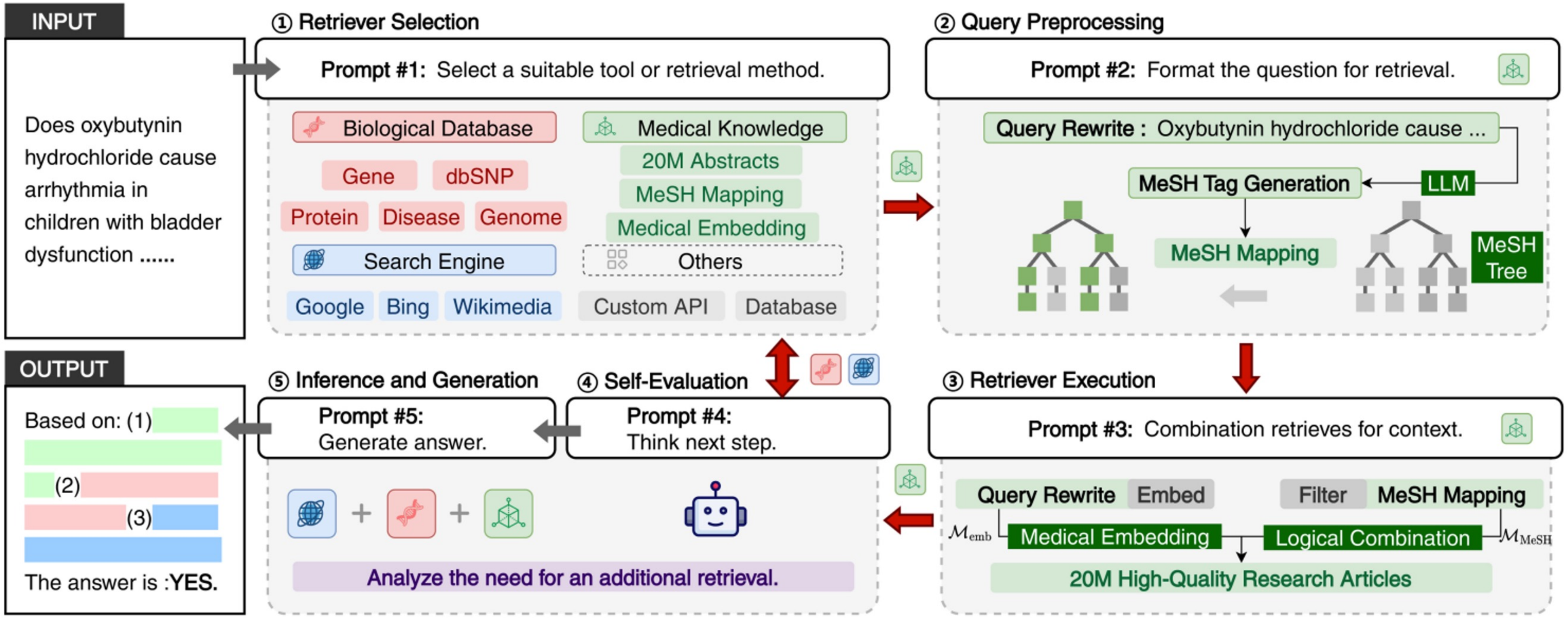
1) Efficient construction of domain KGs
2) Pre-learning with K-LoRA
3) SFT with KG retrieval
4) AKGF: KG acts as an evaluator

post-train+fine-tune

LORA *

RAG for Biological Question Reasoning

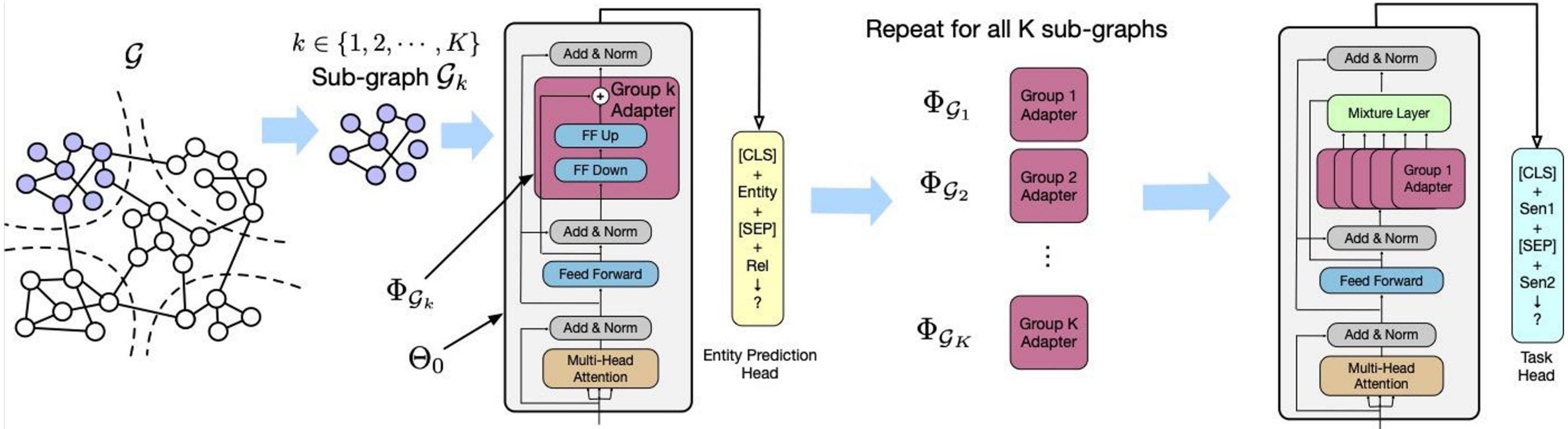
- BIORAG adaptively select knowledge source and domain-specific tools to advance the biology question-reasoning task.



Inference

BIORAG: A RAG-LLM Framework for Biological Question Reasoning, Arxiv 2024

Dealing with large scale knowledge graphs



(a) Graph Partitioning (b) Infuse Knowledge with Adapter (c) Collect Pretrained Adapters (d) Mixture of Adapters

- Partitioning it into smaller sub-graphs, e.g. METIS
- Infusing their specific knowledge into LLMs using lightweight adapters

post-train

adapter *

Mixture-of-Partitions: Infusing Large Biomedical Knowledge Graphs into BERT. (EMNLP 2021) Link

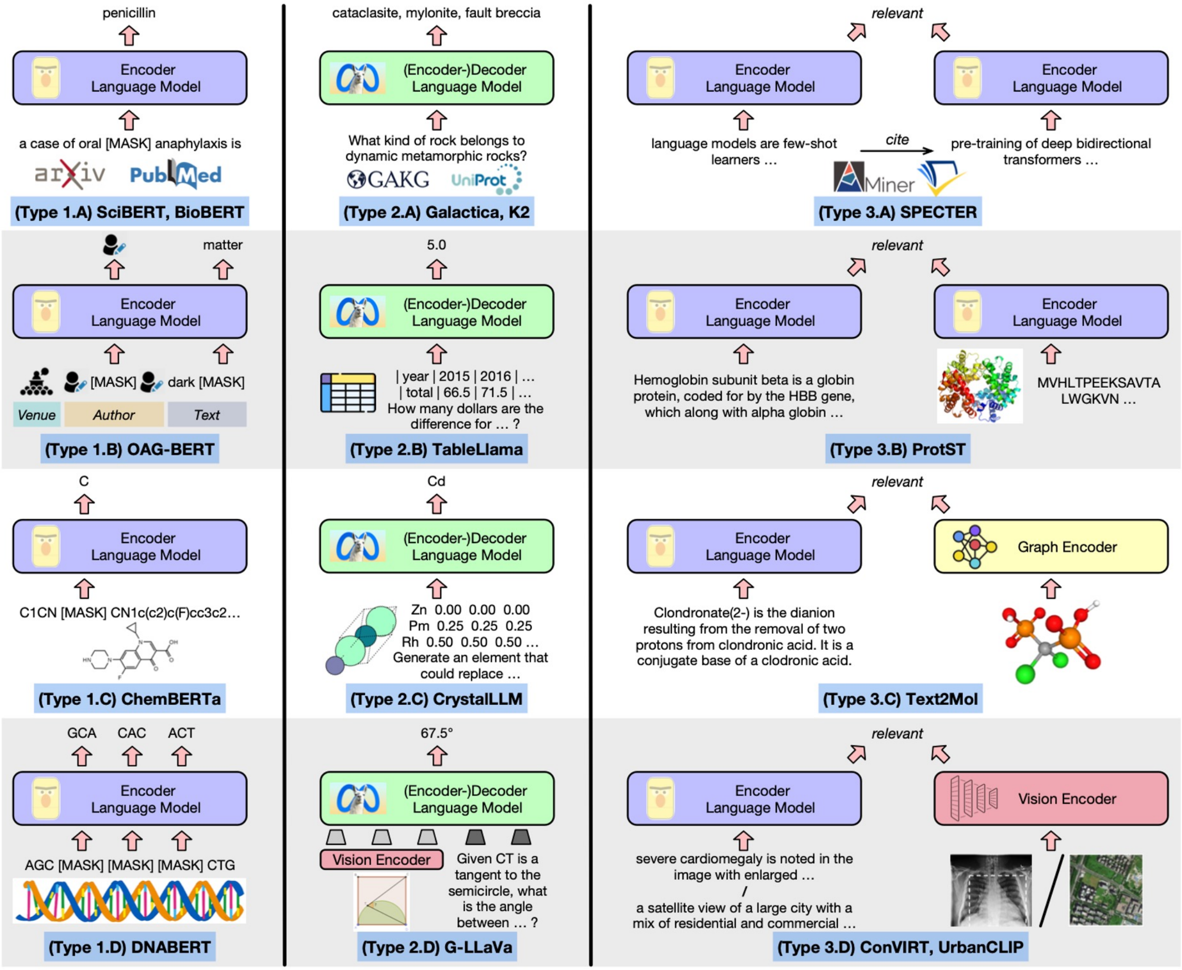
Outline

1 Knowledge Incorporation Frameworks

2 KG Integration for Scientific NLP Tasks

3 **KG Integration for Scientific Prediction Tasks**

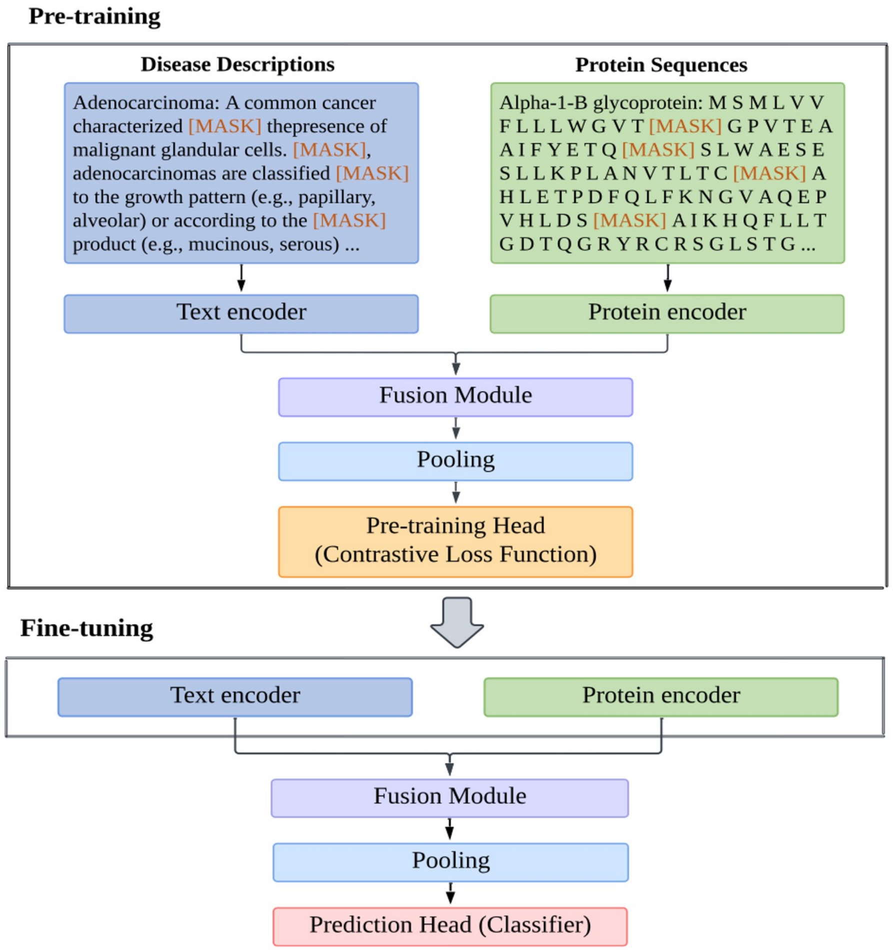
KG Integration for Scientific Prediction Tasks



- **Gene-Disease Association (GDA)** [19]
- **Protein Function Prediction** [18]
- **Drug Repurposing** [18]
- **Drug-Target Interaction (DTI)** [8,17]
- **Text2Mol** [3]
- **Amino acid contact prediction**
- **…**

A Comprehensive Survey of Scientific Large Language Models and Their Applications in Scientific Discovery, Arxiv 2024

Gene-Disease Association (GDA)



Pre-training

Disease Descriptions

Adenocarcinoma: A common cancer characterized [MASK] thepresence of malignant glandular cells. [MASK], adenocarcinomas are classified [MASK] to the growth pattern (e.g., papillary, alveolar) or according to the [MASK] product (e.g., mucinous, serous) ...

Protein Sequences

Alpha-1-B glycoprotein: M S M L V V F L L L W G V T [MASK] G P V T E A A I F Y E T Q [MASK] S L W A E S E S L L K P L A N V T L T C [MASK] A H L E T P D F Q L F K N G V A Q E P V H L D S [MASK] A I K H Q F L L T G D T Q G R Y R C R S G L S T G ...

Text encoder

Protein encoder

Fusion Module

Pooling

Pre-training Head (Contrastive Loss Function)

Fine-tuning

Text encoder

Protein encoder

Fusion Module

Pooling

Prediction Head (Classifier)

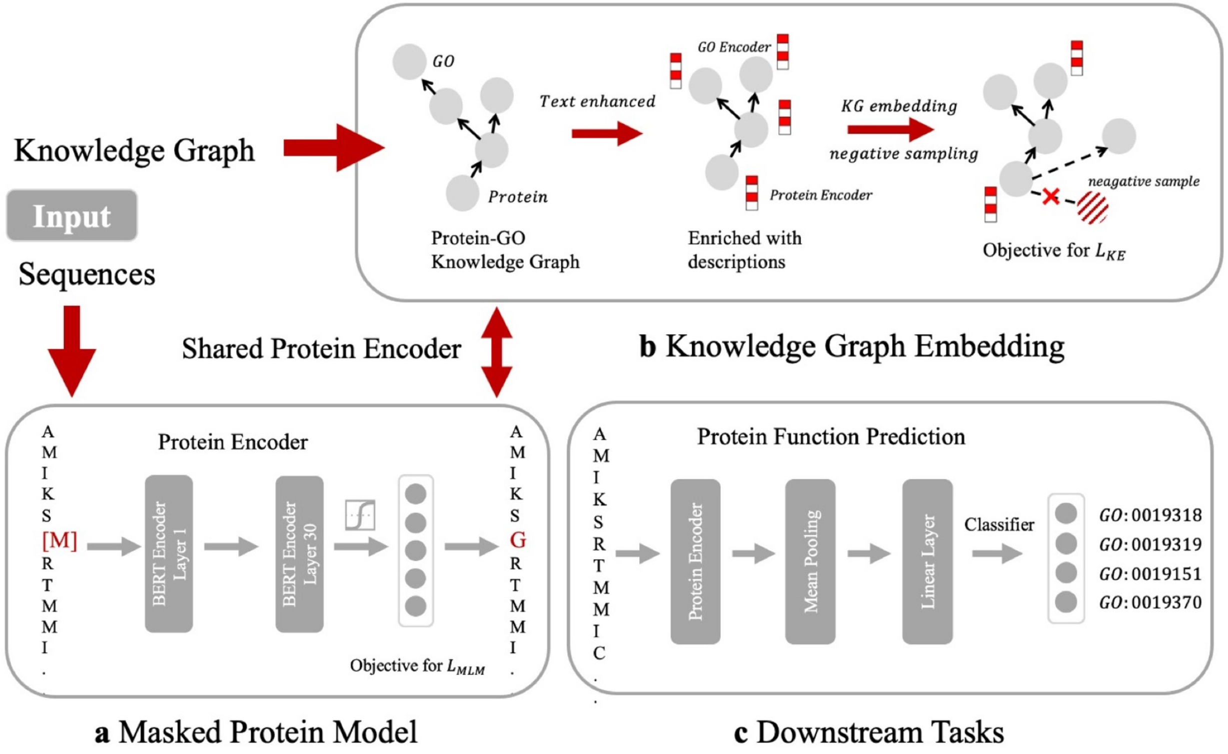
FusionGDA utilises bi-encoder with a fusion module to enrich the gene and disease semantic representations encoded by PLMs.

KG: Heterogeneous GDA
Encoder method: Bi-Encoder

post-train + fine-tune

Heterogeneous biomedical entity representation learning for gene–disease association prediction. Briefings in Bioinformatics (2024) Link

Protein Function Prediction

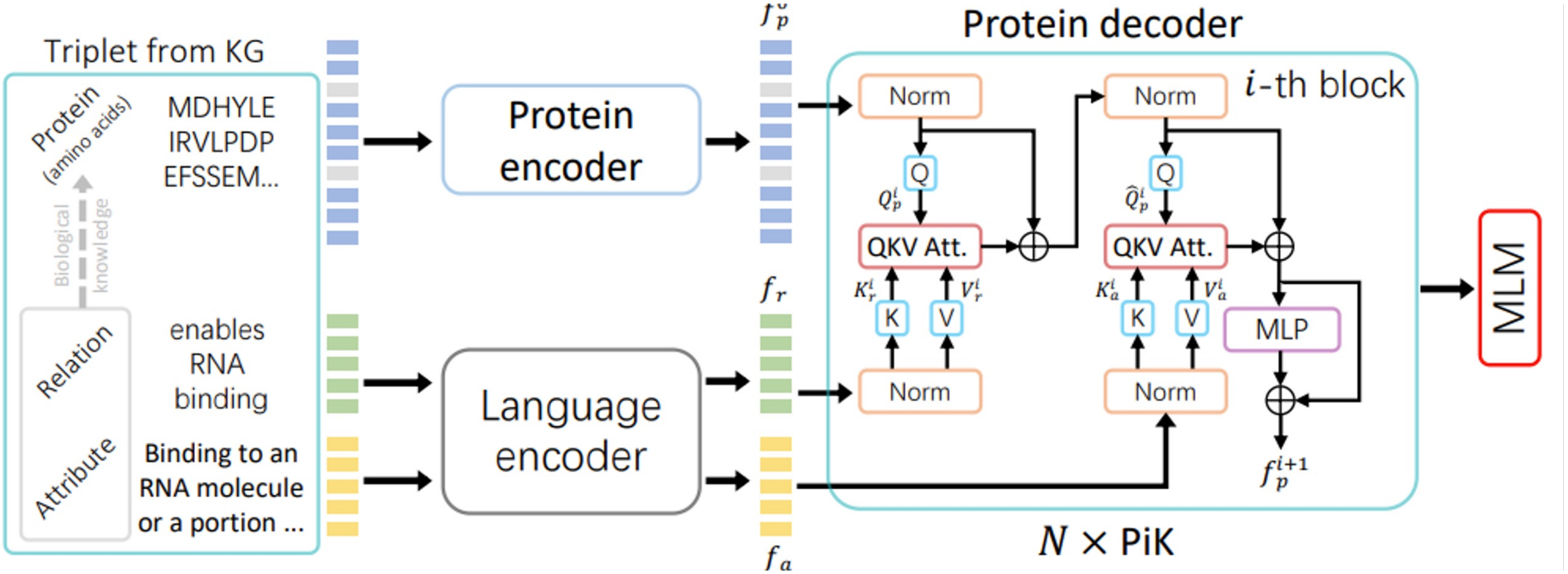


post-train + fine-tune

1. **OntoProtein** constructs a novel large-scale knowledge graph that consists of GO (Gene Ontology) and its related proteins, and gene annotation texts or protein sequences describe all nodes in the graph.
2. This KG was integrated by a novel contrastive learning with knowledge-aware negative sampling to jointly optimize the knowledge graph and protein embedding during pre-training

Ontoprotein: Protein pretraining with gene ontology embedding.(ICLR 2022) Link

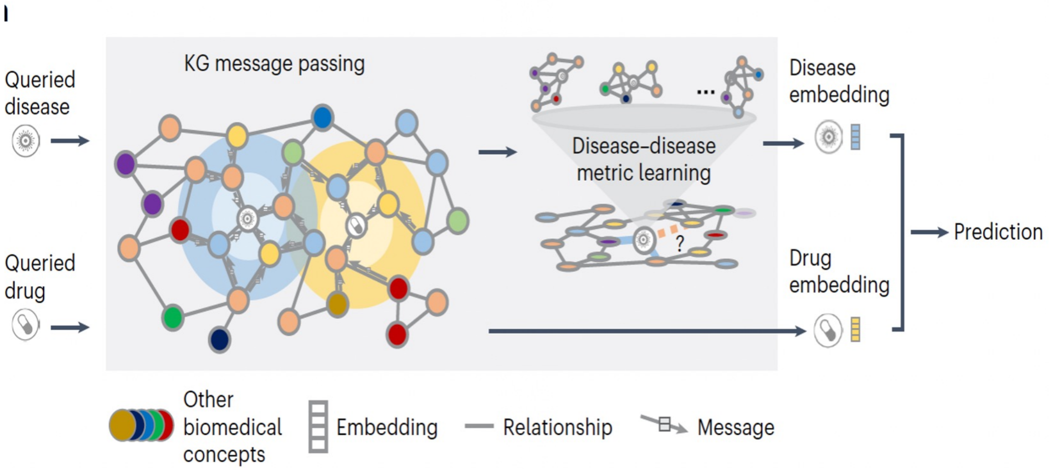
Amino acid contact prediction

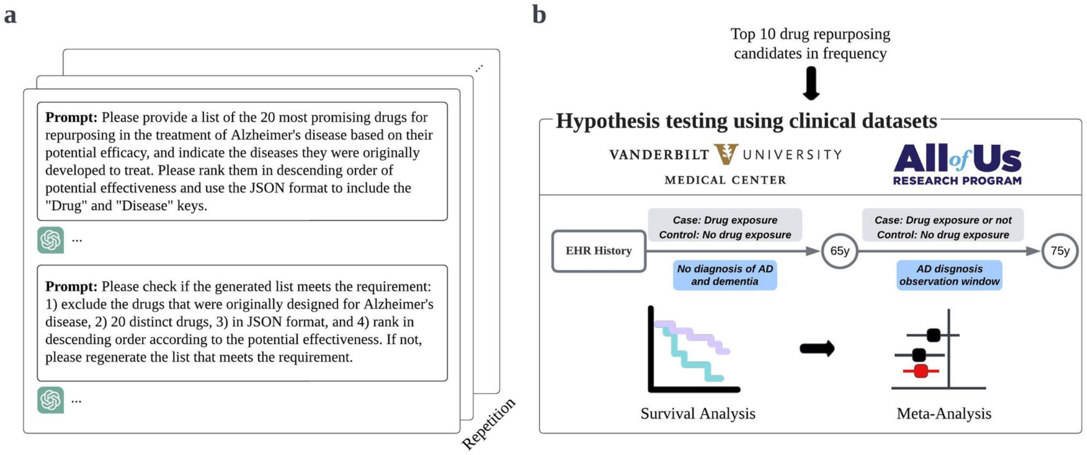


- KeAP is trained on a knowledge graph that consists of about five million triplets from ProteinKG25
- KeAP explores knowledge graphs at a more granular level by applying cross-attention to sequences of amino acids and words from relation and attributes.
- KeAP can be trained using the MLM objective only (both contrastive loss and MLM are used in OntoProtein)

Protein Representation Learning via Knowledge Enhanced Primary Structure Modeling, ICLR 2023

Drug repurposing





Prompt: Please provide a list of the 20 most promising drugs for repurposing in the treatment of Alzheimer's disease based on their potential efficacy, and indicate the diseases they were originally developed to treat. Please rank them in descending order of potential effectiveness and use the JSON format to include the "Drug" and "Disease" keys.

...

Prompt: Please check if the generated list meets the requirement: 1) exclude the drugs that were originally designed for Alzheimer's disease, 2) 20 distinct drugs, 3) in JSON format, and 4) rank in descending order according to the potential effectiveness. If not, please regenerate the list that meets the requirement.

...

TxGNN, a graph foundation model for zero-shot drug repurposing, identifying therapeutic candidates even for diseases with limited treatment options or no existing drugs. Trained on a medical knowledge graph, TxGNN uses a ***graph neural network*** and ***metric learning module*** to rank drugs as potential indications and contraindications for 17,080 diseases.

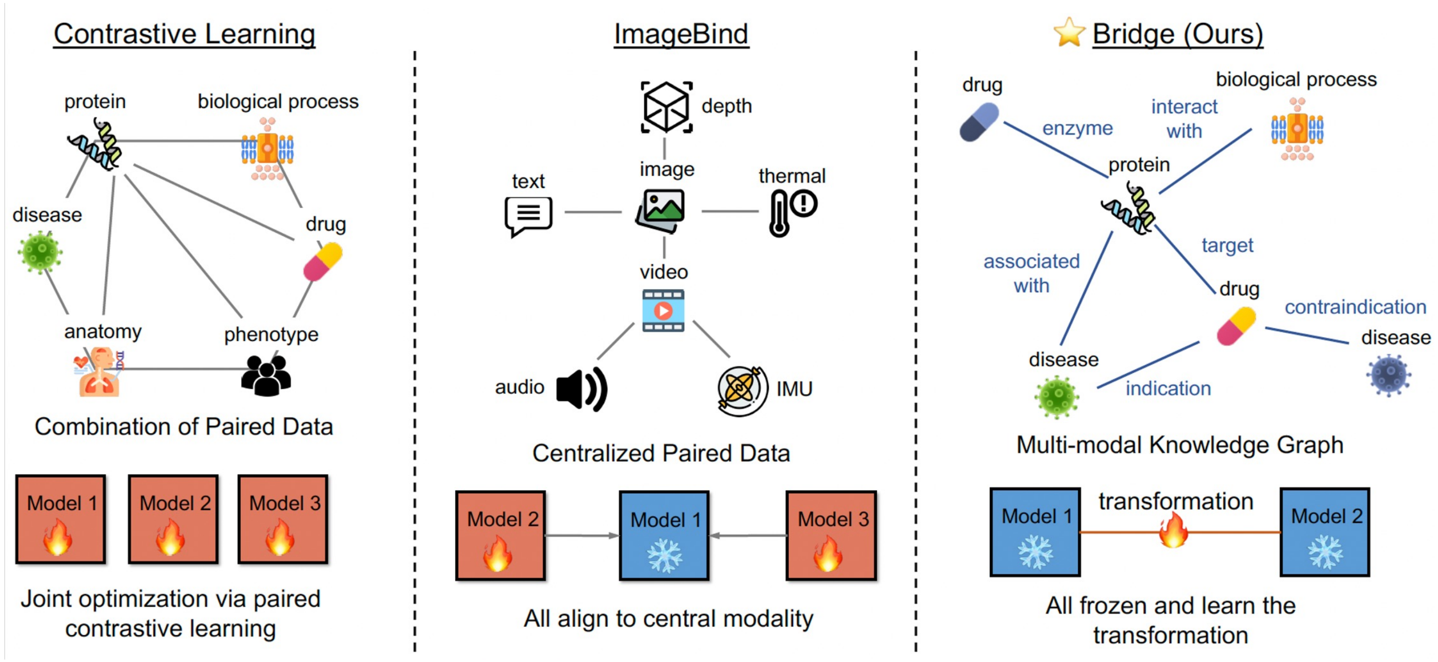
a Employing iterative queries of ChatGPT to recommend twenty drugs for AD repurposing.

b Evaluating the potential efficacy of the ten most frequently suggested drugs using electronic health records (EHR) data from two large clinical databases.

Leveraging generative AI to prioritize drug repurposing candidates for Alzheimer's disease with real-world clinical validation. **Nature, 2024**

A foundation model for clinician-centered drug repurposing. Nature Medicine, 2024. Link

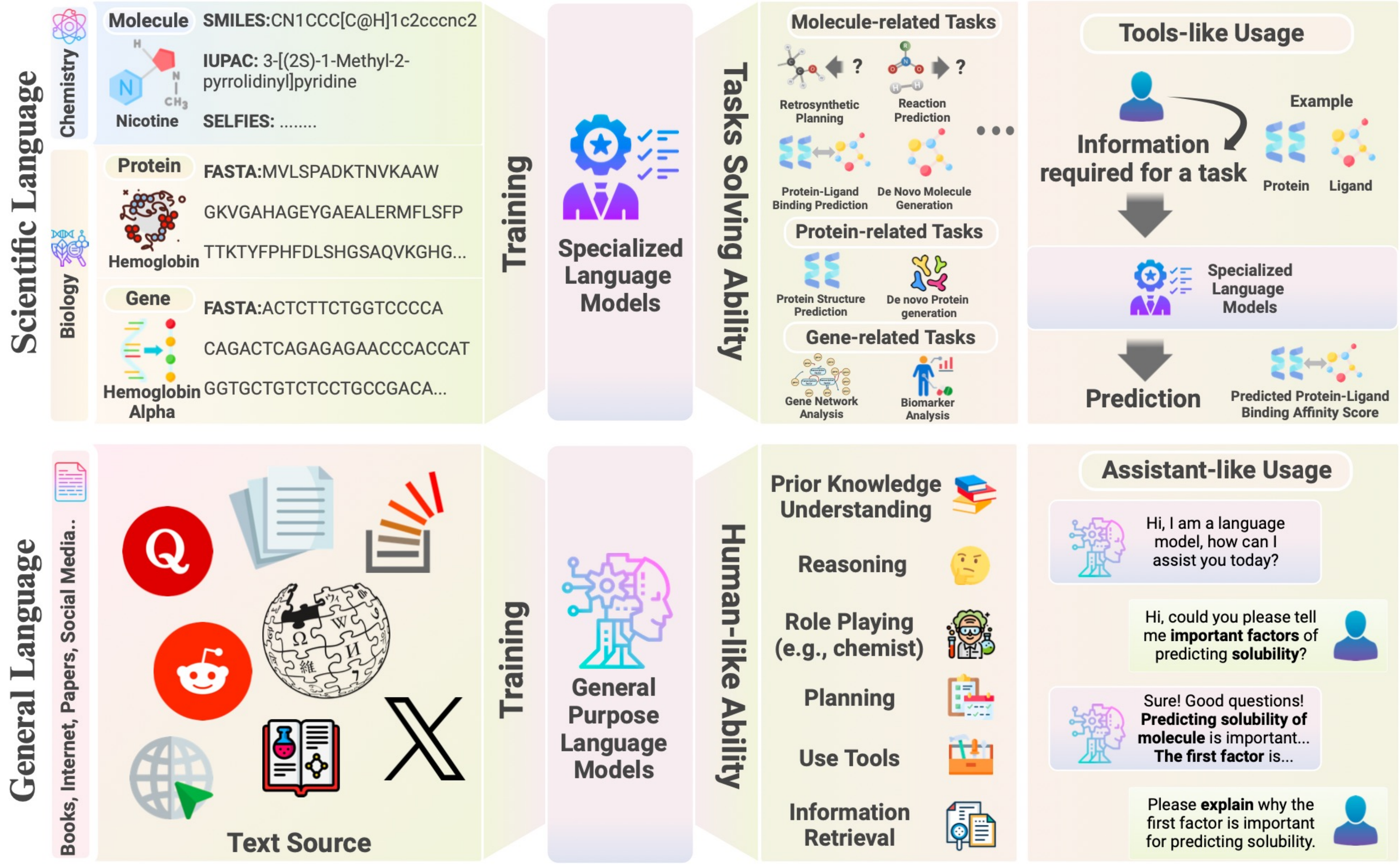
The comparison of cross-modality methods



1. **Multimodal contrastive learning**, e.g., CLIP, learns from a combination of paired data, updating all unimodal encoders.
1. **ImageBind** aligns all modalities with the central modality, with only the central model frozen.
1. **BioBRIDGE** (ICLR 2024) learns the transformation across modalities (Bridge Module) from a multi-modal KG, keeping all FMs frozen.

Imagebind: One embedding space to bind them all. (CVPR 2023) Link
Biobridge: Bridging biomedical foundation models via knowledge graph.(ICLR 2024) Link

Scientific Discovery Agent: Unifying Scientific NLP and Predictions



Hi, I am a language model, how can I assist you today?

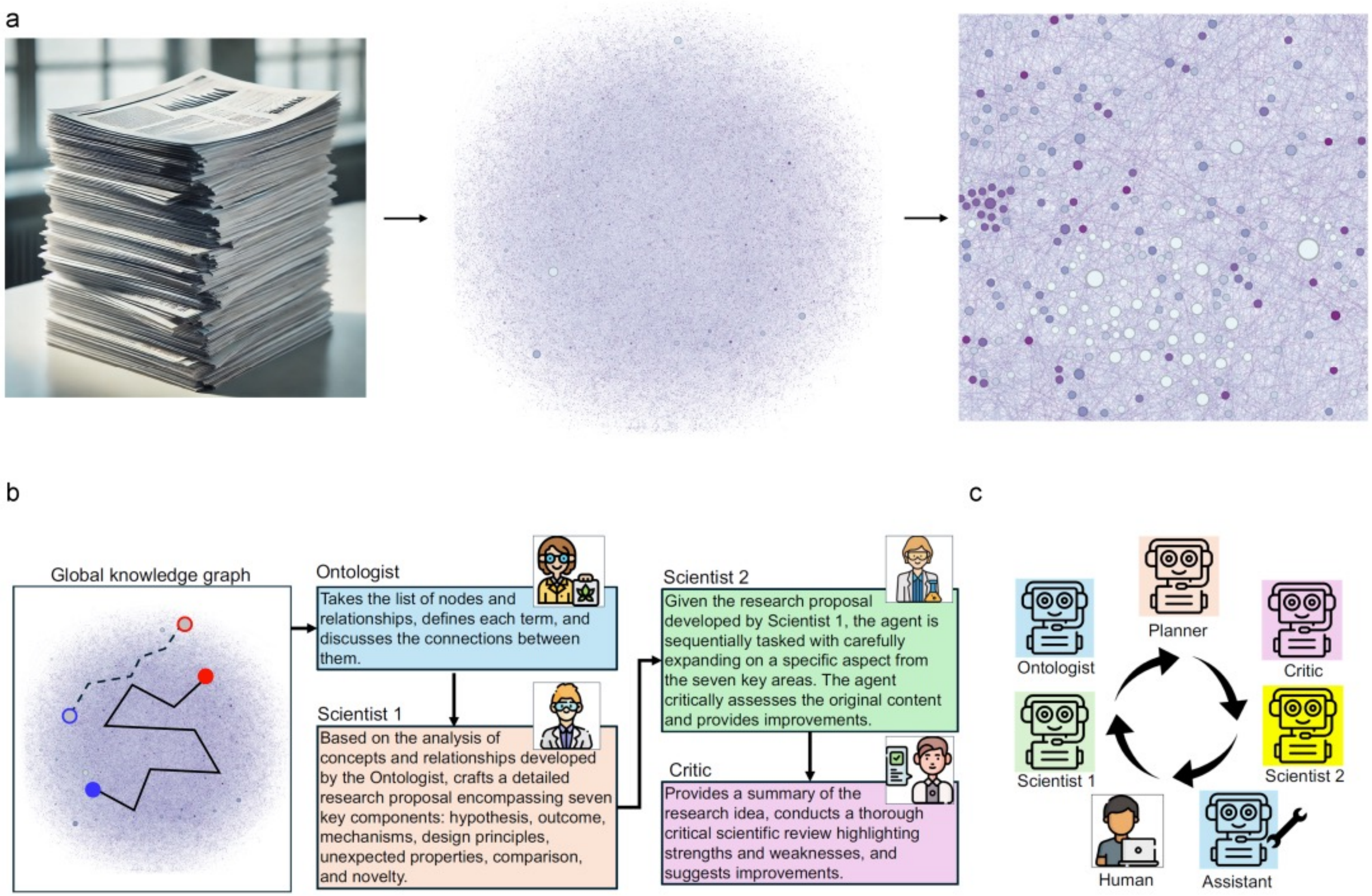
Hi, could you please tell me **important factors** of predicting **solubility**?

Sure! Good questions! **Predicting solubility of molecule** is important... **The first factor** is...

Please **explain** why the first factor is important for predicting solubility.

Large Language Models in Drug Discovery and Development: From Disease Mechanisms to Clinical Trials, link

Multiple Agents with KGs for Scientific Discovery



Ontologist

Takes the list of nodes and relationships, defines each term, and discusses the connections between them.

Scientist 1

Based on the analysis of concepts and relationships developed by the Ontologist, crafts a detailed research proposal encompassing seven key components: hypothesis, outcome, mechanisms, design principles, unexpected properties, comparison, and novelty.

Scientist 2

Given the research proposal developed by Scientist 1, the agent is sequentially tasked with carefully expanding on a specific aspect from the seven key areas. The agent critically assesses the original content and provides improvements.

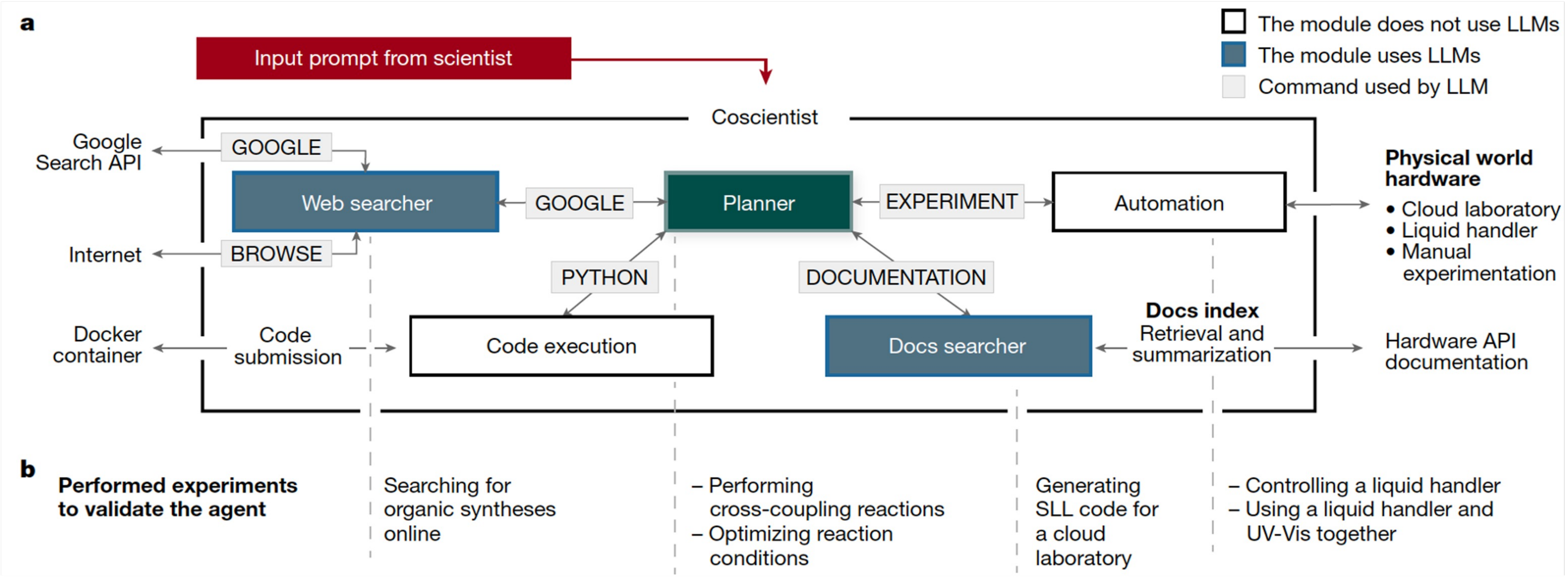
Critic

Provides a summary of the research idea, conducts a thorough critical scientific review highlighting strengths and weaknesses, and suggests improvements.

SciAgents: Automating scientific discovery through multi-agent intelligent graph reasoning, link

Coscientist: Chemistry - Unifying Physical World

CoScientist



Autonomous chemical research with large language models, **Nature**, 2023

Summary

Part I: KG Definitions and Core Concepts

- Introduction to KGs: why we need to integrate KG into LLMs?
- A Simple Case of KGs: Ecotoxicological Effect Assessment
- KGs in Life Sciences: Challenges and Opportunities

Part II: Scientific Large Language Models (LLMs)

- Overview of Scientific LLMs: Bi-encoder, Cross-encoders
- Challenges and Perspectives

Part III: Integrating KGs and LLMs for Scientific Applications

- Knowledge Incorporation Frameworks
- KG Integration for Scientific NLP Tasks
- KG Integration for Scientific Prediction Tasks

Take-away

What KG brings to LLMs?

- Enhanced Knowledge Representation
- Improved Explainability, Reasoning and Inference
- Increased Accuracy and Reduced Hallucination

How to effectively incorporate KGs into LLMs?

- Backbone Model (protein, molecular, text, visual)
- Encoder Method (bi-encoder, cross-encoder)
- Integration Stages (pretrain, post-train, fine-tune, inference)
- Integration Techniques (adapter, lora, ICL, RAG, LLM Agent)

References

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[2] ERNIE: Enhanced Language Representation with Informative Entities, ACL 2019

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[4] Self-Alignment Pretraining for Biomedical Entity Representations, NAACL 2021

[5] Mixture-of-partitions: Infusing large biomedical knowledge graphs into BERT, EMNLP 2021

[7] BioBRIDGE: Biobridge: Bridging biomedical foundation models via knowledge graph, ICLR 2024

[8] FusionDTI: Fine-grained Binding Discovery with Token-level Fusion for Drug-Target Interaction, AI4Science 2024

[9] MKRAG: Medical Knowledge Retrieval Augmented Generation for Medical Question Answering, AMIA 2024

[10] Editing Factual Knowledge and Explanatory Ability of Medical Large Language Models CIKM 2024

[11] KRAGEN: a knowledge graph-enhanced RAG framework for biomedical problem solving using large language models, bioinformatics

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[13] SaprotHub: Making Protein Modeling Accessible to All Biologists

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[15] SciAgent: Tool-augmented Language Models for Scientific Reasoning

[16] Imagebind: One embedding space to bind them all. (CVPR 2023)

[17] Knowledge Enhanced Representation Learning for Drug Discovery (AAAI 2024). Link

[18] Ontoprotein: Protein pretraining with gene ontology embedding.(ICLR 2022)

[19] Heterogeneous biomedical entity representation learning for gene–disease association prediction. Briefings in Bioinformatics (2024) Link

[20] Leveraging generative AI to prioritize drug repurposing candidates for Alzheimer’s disease with real-world clinical validation, Nature

Thank you!

Q & A