PROTEIN EMBEDDING MODELS:

LEARNING THE LANGUAGE OF PROTEINS

GHENT UNIVERSITY

LABORATORY OF APPLIED BIOTECHNOLOGY

KERMIT

Dimi Boeckaerts

Overview of this workshop

VHDMCYIRCAHTSIRDSHDRDGG**INTRODUCTION**EYFFNKTTDMEFPWYAPTFTRLESTLPFLVAFWNP

D

V

W

PNFISGDQWAVCGHFWSPQPFFMI**HISTORY**FTLGMGEEKIDDG

M

L

P

DMW**STATE-OF-THE-ART**VWEHGPNFISGDQWYRSVHRGQDQHRHMIIY

P

H

IRCAHTSIRDSHDRDGGESIDNFTLPFLVAFWNPQTWLFKY**OUTLOOK**LHEIADCVYWRVLDIWH

W

N

RYASEYFFNKTTD**PRACTICE**TFTRLESGDQWAVCGHFWSPQPFFMIRIFHQWCFTLTNGTKFAFFVFFYVWEHGPN

The rapid progress in natural language processing

Natural language processing: the field of computer science that is concerned with automated text and language analysis.

Thought experiment generation

10 Thought experiments

Humor

500+ Openers for Tinder wri...

Deepfakes

AI Eminem

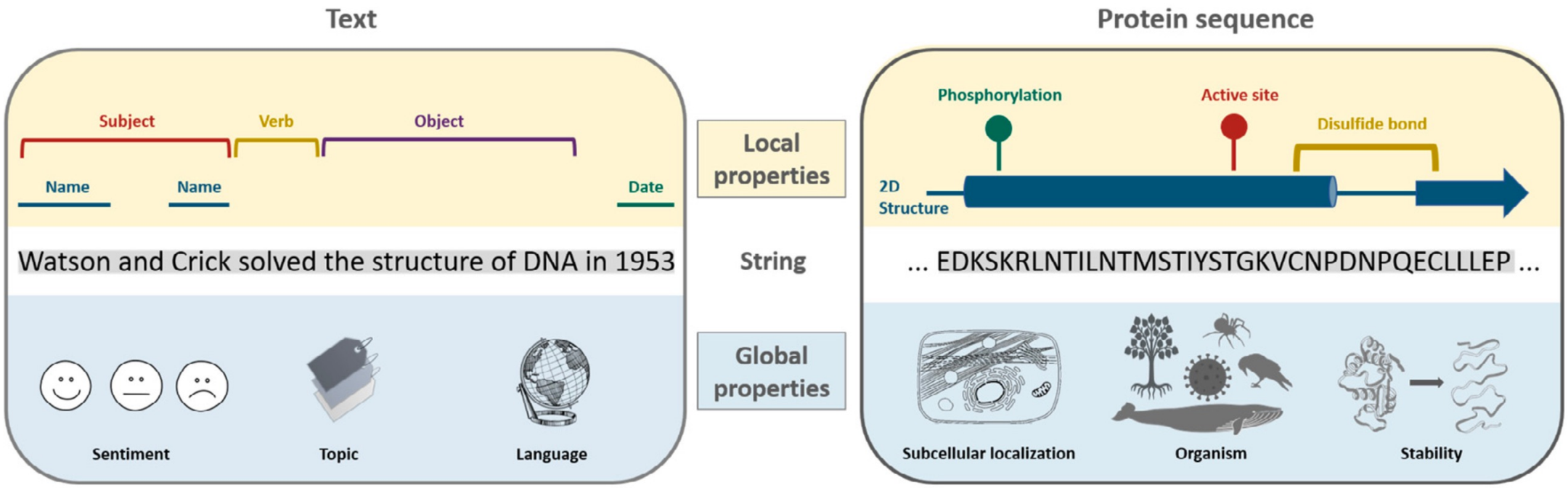
View details

Image Generation

DALL·E by OpenAI

OpenAI's GPT-3 examples

Proteins are similar to natural language…



Ofer et al. (2021). The language of proteins: NLP, machine learning & protein sequences.

… but not entirely similar

- We cannot ‘read’ proteins
- I love you vs. I loved you
- Protein 3D structure -> distant interactions
- Sequencing bias

Are proteins learnable?

The linguistic hypothesis

The space of naturally occurring proteins occupies a learnable manifold. This manifold emerges from evolutionary pressures that heavily encourage the reuse of components at many scales: from short motifs of secondary structure, to entire globular domains.

Mohammed AlQuraishi

Keep it simple: use a bag-of-words

	about	bird	heard	is	the	word	you
About the bird, the bird, bird bird bird	1	5	0	0	2	0	0
You heard about the bird	1	1	1	0	1	0	1
The bird is the word	0	1	0	1	2	1	0

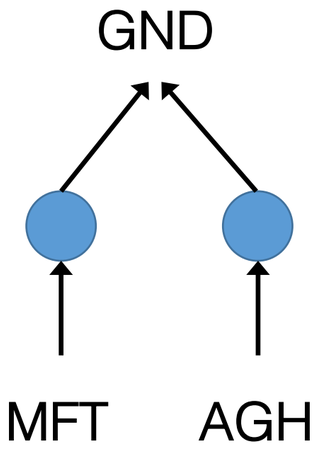
Keep it simple: use a bag-of-words

	DMC	MCY	YIR	HRG	SVH	QDQ	CAH
DMCYIRCAHTSIRD…	1	1	1	0	0	0	0
WYRSVHRGQDQH…	0	0	0	1	1	1	1

- Different k-mer lengths
- Overlapping vs. non-overlapping
- Binary vs. count vs. frequency

Embedding methods for protein language

Word2Vec



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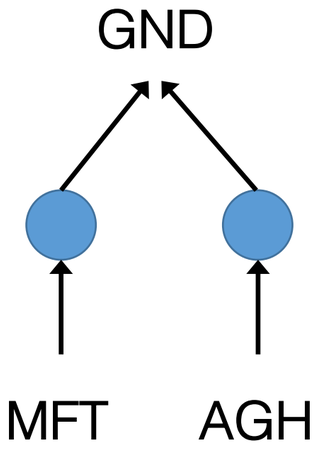
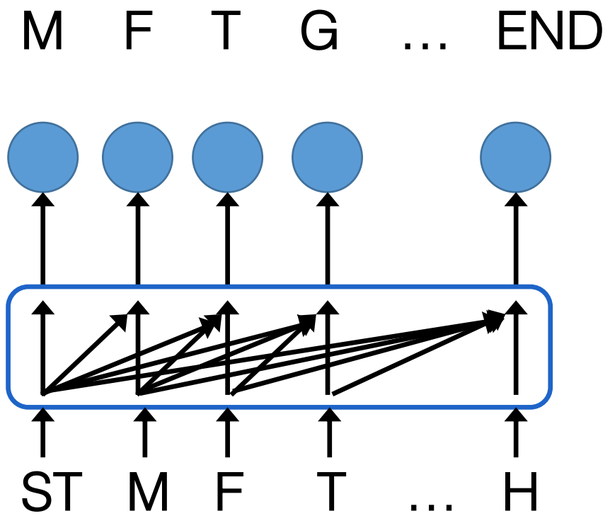
Embedding methods for protein language

Word2Vec



Autoregressive
language model



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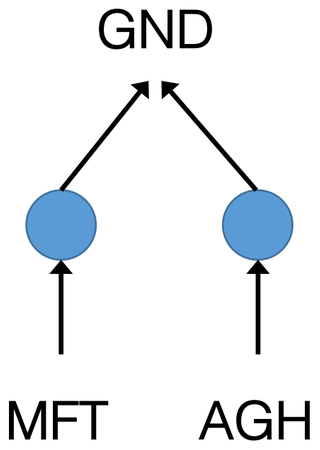
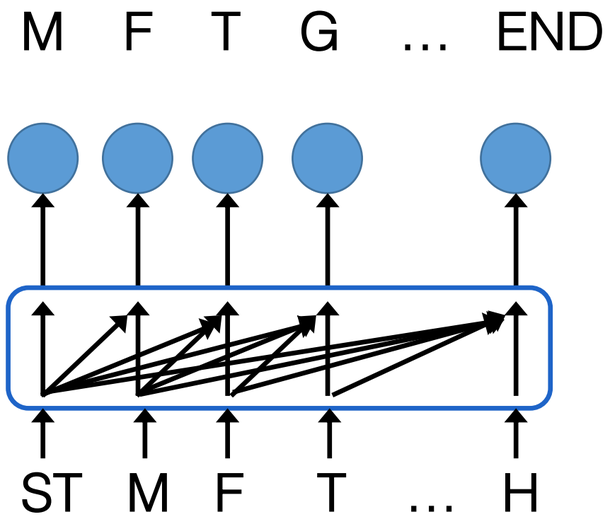
Embedding methods for protein language

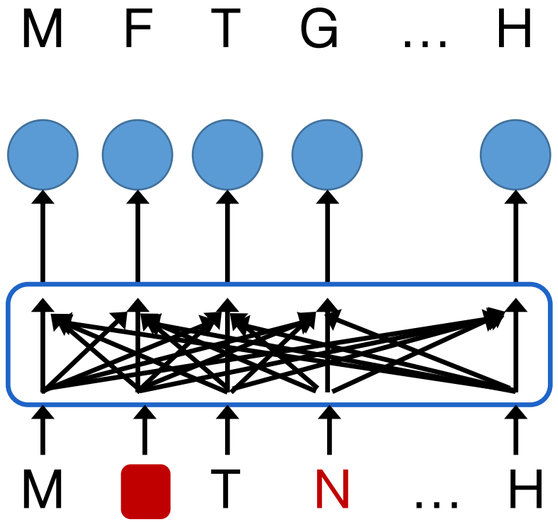
Word2Vec



Autoregressive
language model



Masked
language model



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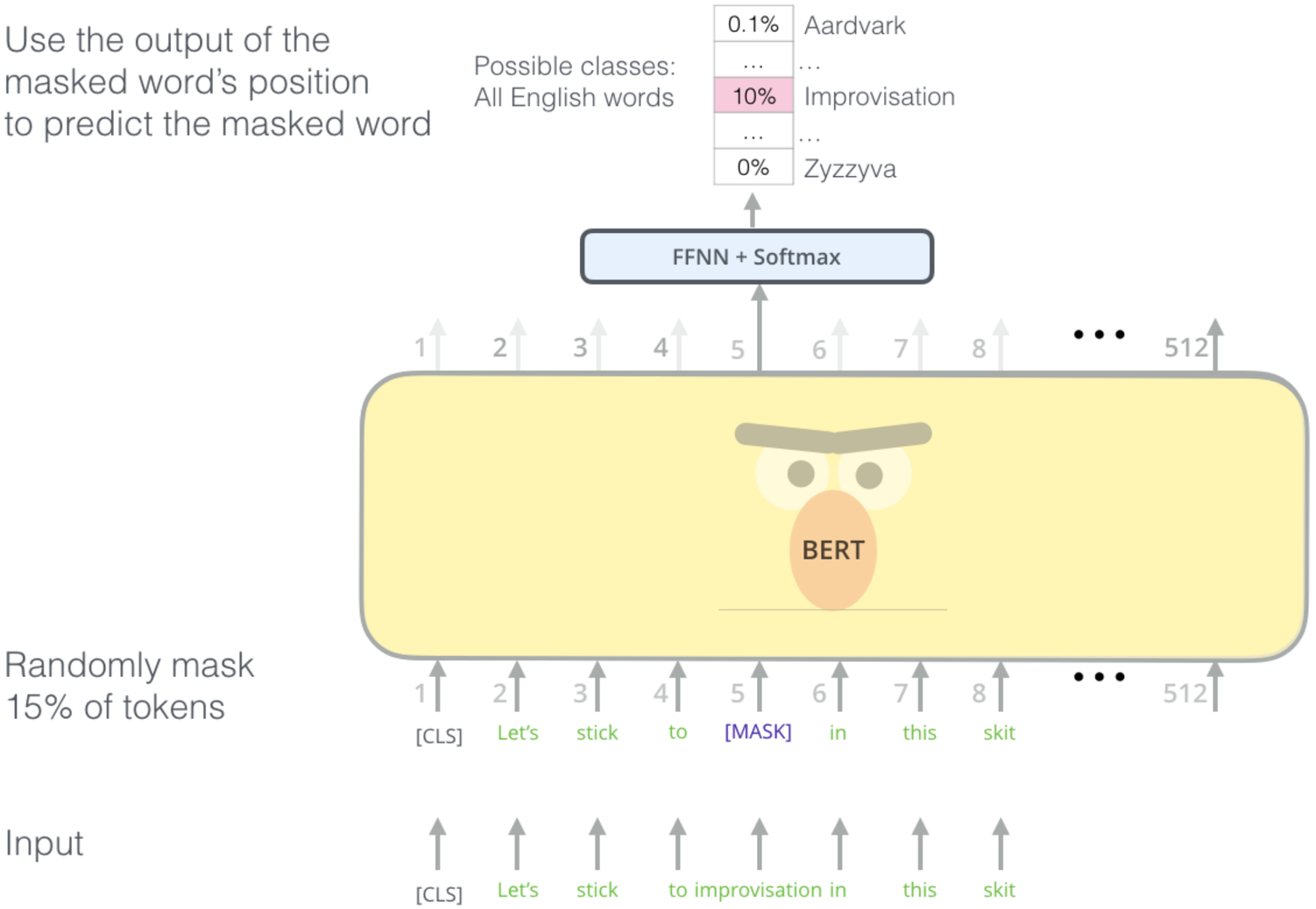
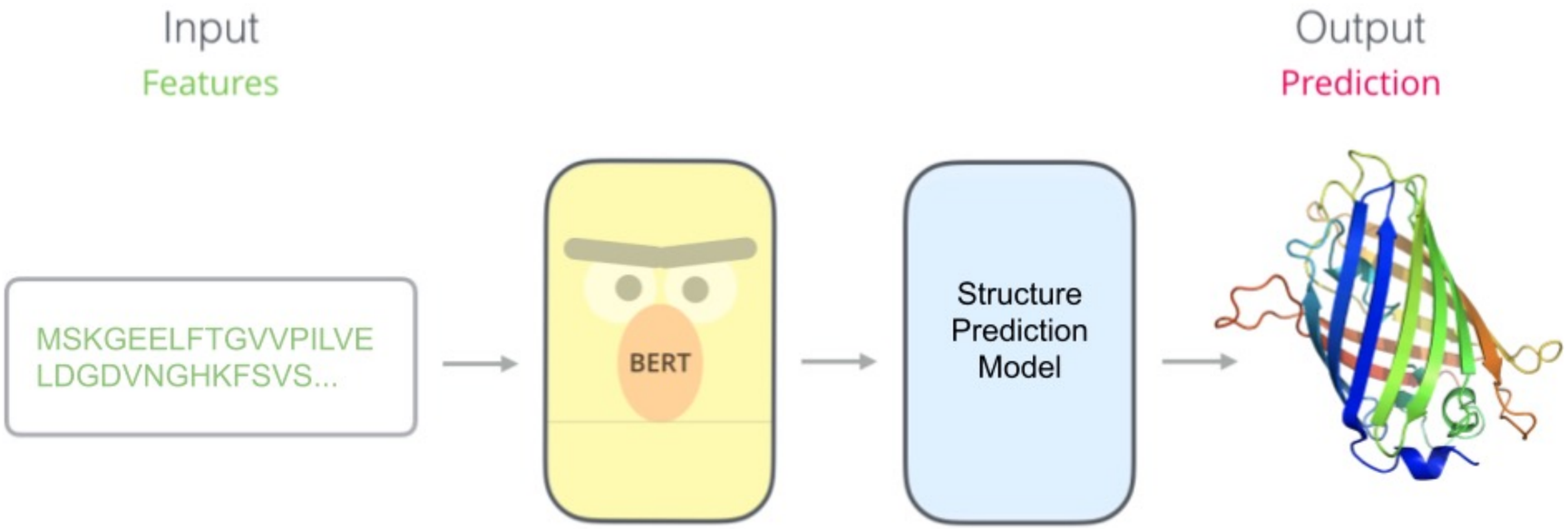
BERT model training



https://jalammar.github.io/illustrated-bert/

Stacking supervised prediction models



https://bair.berkeley.edu

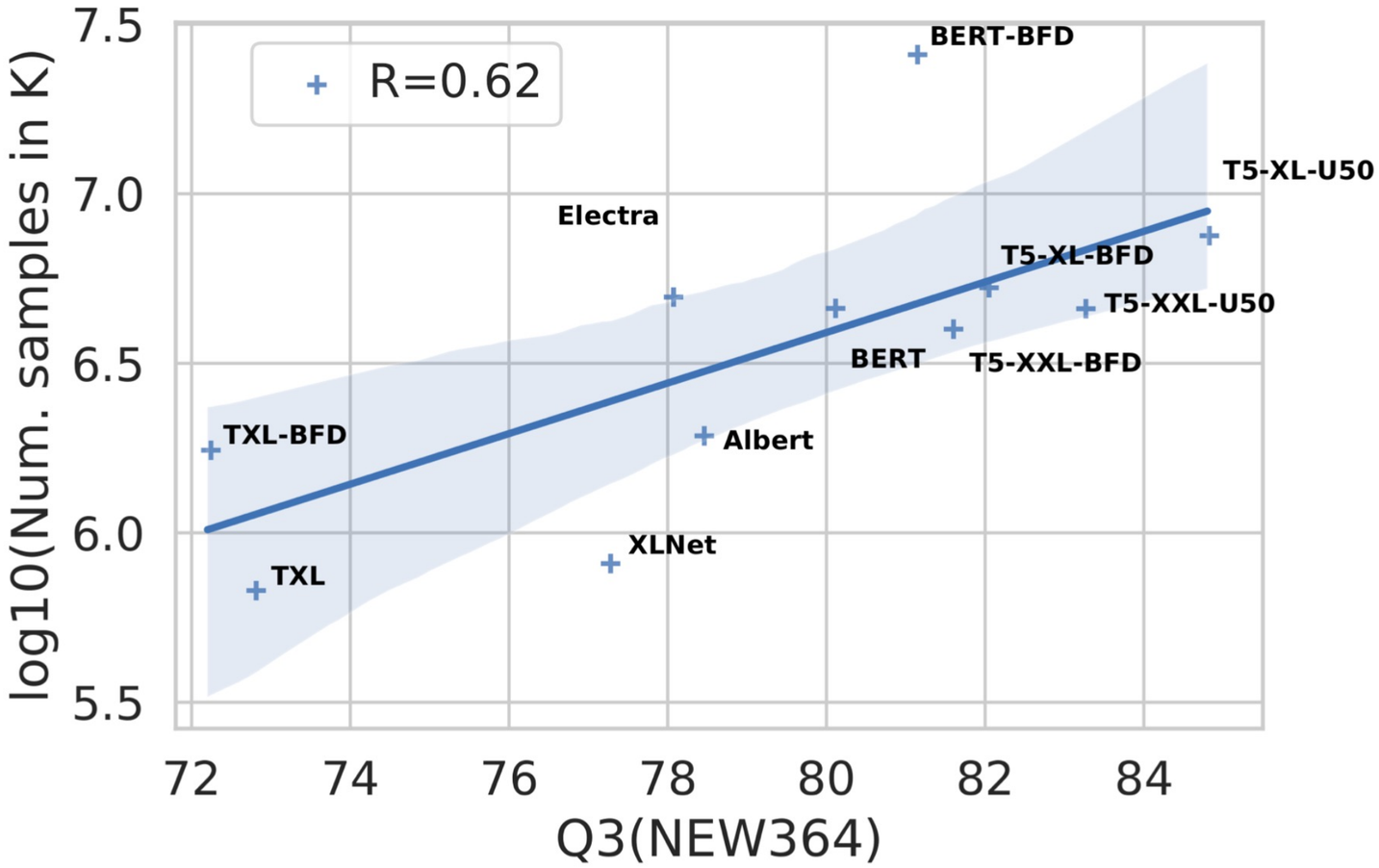
Language models are data hungry

Data LM	*UniRef50*	*UniRef100*	*BFD*
Number proteins [in m]	45	216	2,122
Number of amino acids [in b]	14	88	393
Disk space [in GB]	26	150	572

TABLE 1: Data Protein LM - UniRef50 and UniRef100 cluster the UniProt database at 50% and 100% pairwise sequence identity (100% implying that duplicates are removed) [41]; BFD combines UniProt with metagenomic data keeping only one copy for duplicates [24], [42]. Units: number of proteins in millions (m), of amino acids in billions (b), and of disk space in GB (uncompressed storage as text).

Elnaggar et al. (2021). ProtTrans: towards cracking the language of life's code through self-supervised learning.

Language models are data hungry



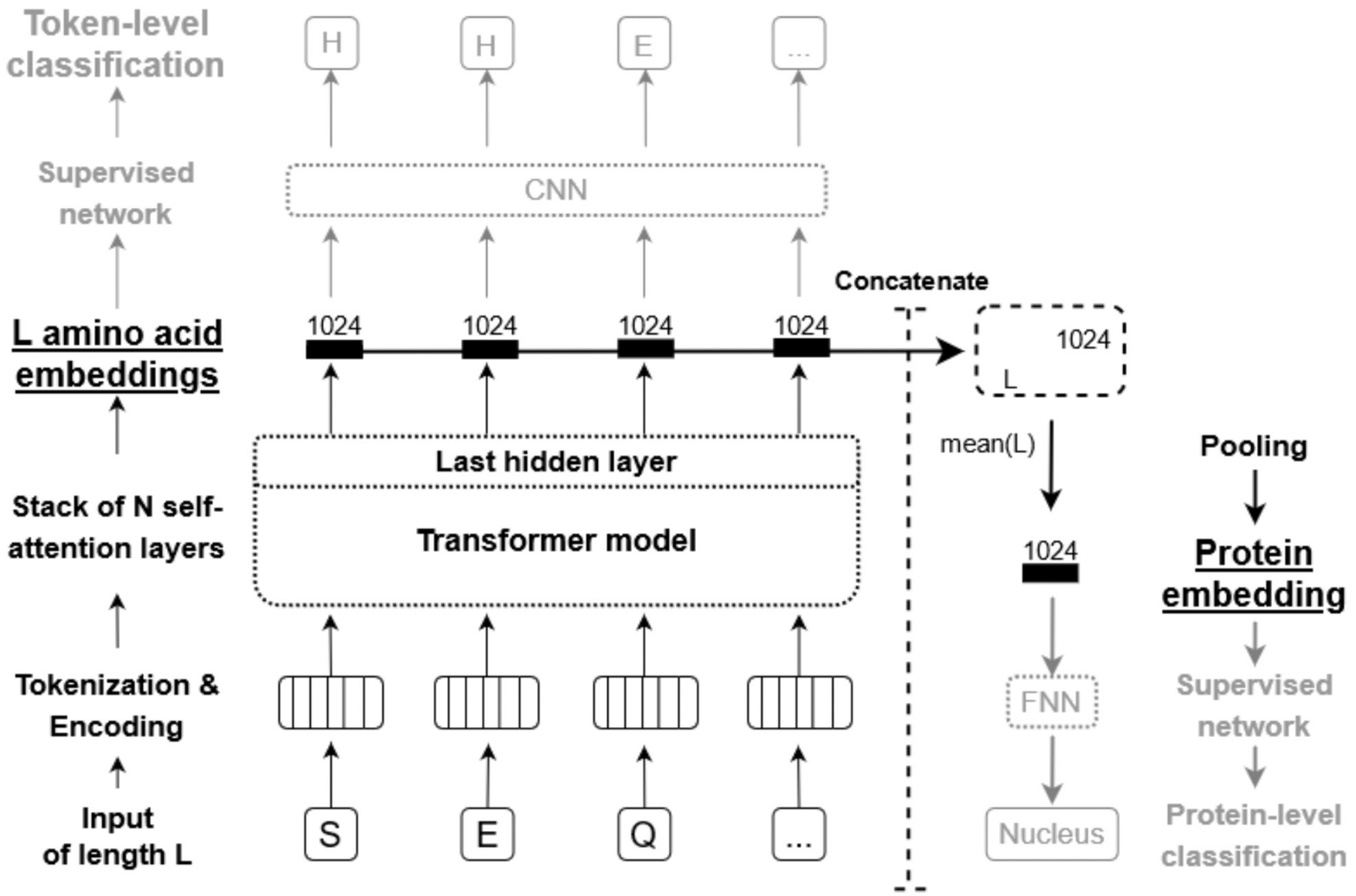
More data during pre-training seems better for downstream performance.

Redundancy and noise

It’s all about abundant and high-quality data!

“Less noisy and less redundant corpora (e.g. UniRef50) improved over larger but more noisy and redundant corpora (e.g. BFD).” (Elnaggar *et al.*, 2021)

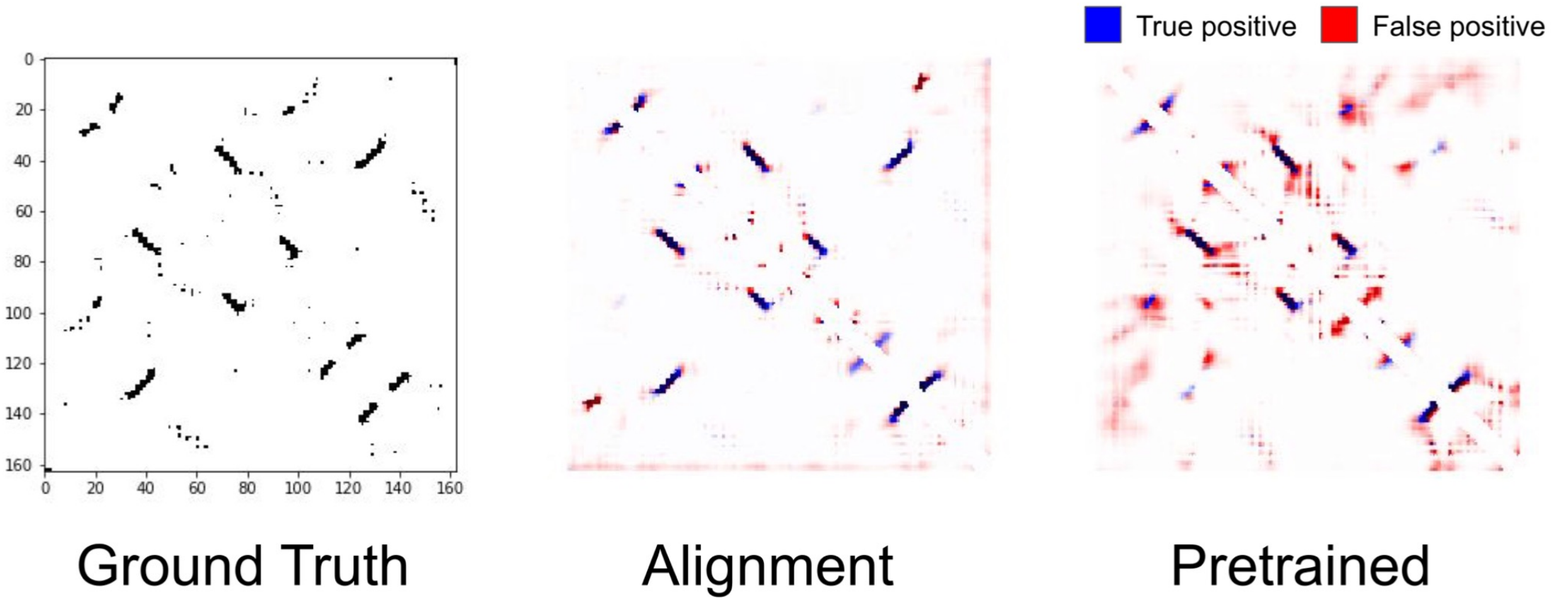
Recent applications



Elnaggar et al. (2021). ProtTrans: towards cracking the language of life's code through self-supervised learning.

Recent applications

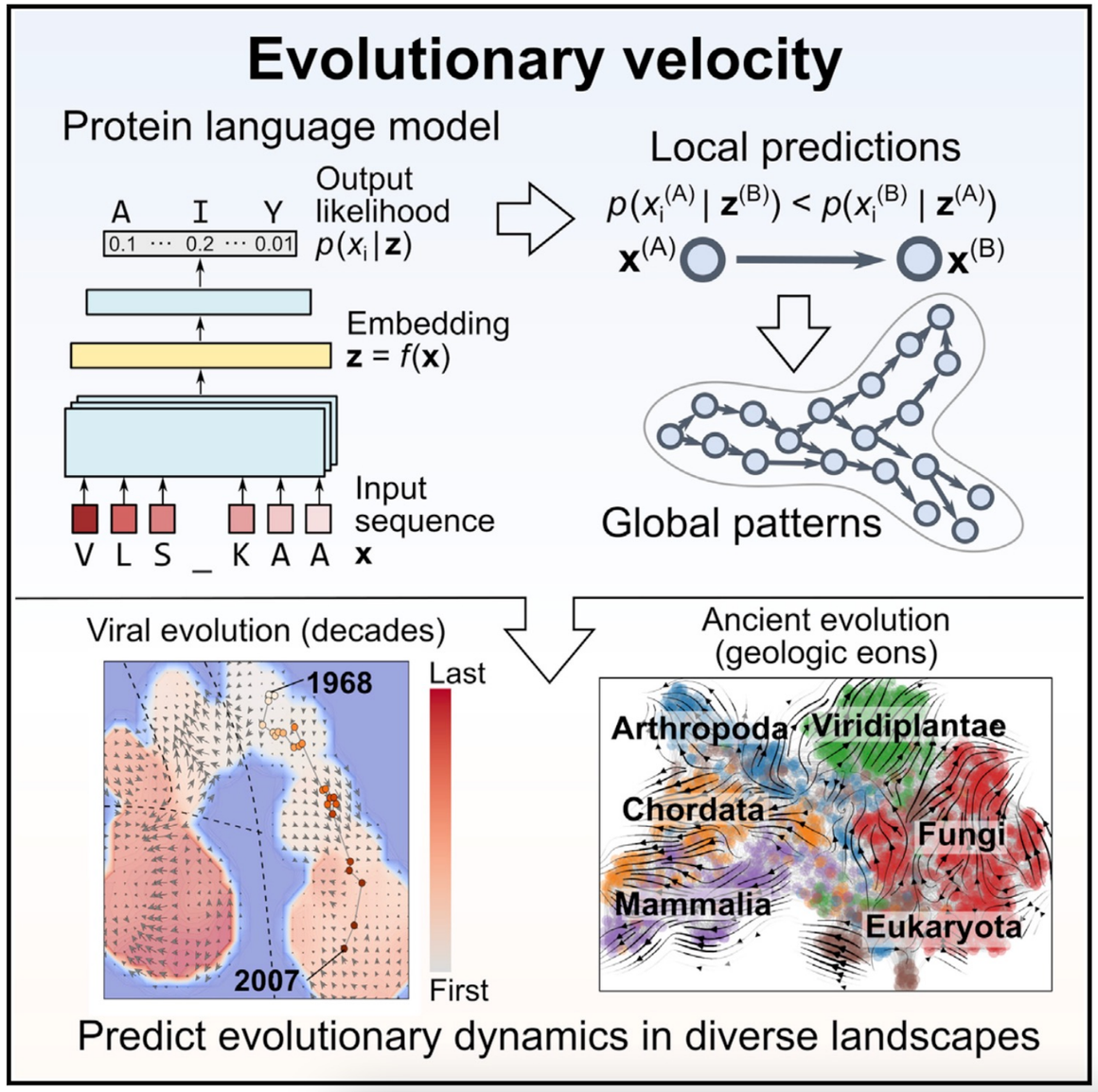
Simpler methods using evolutionary information can (still) outperform DL methods.



The true contact map for the same protein as above (left), predicted contacts from a model with alignment-based features (center), predictions from a ***pretrained*** *LSTM (right).*

https://bair.berkeley.edu

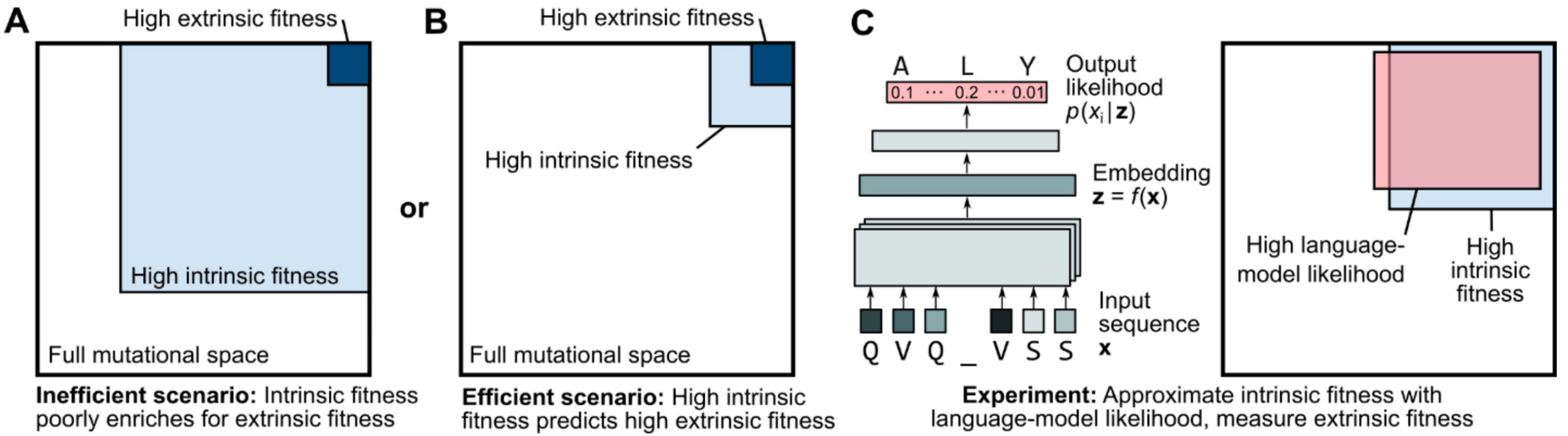
Recent applications



Protein language models can predict mutational effects across diverse proteins.

Hie et al. (2022). Evolutionary velocity with protein language mdels predicts evolutionary dynamics...

Recent applications



Inefficient scenario: Intrinsic fitness poorly enriches for extrinsic fitness

Efficient scenario: High intrinsic fitness predicts high extrinsic fitness

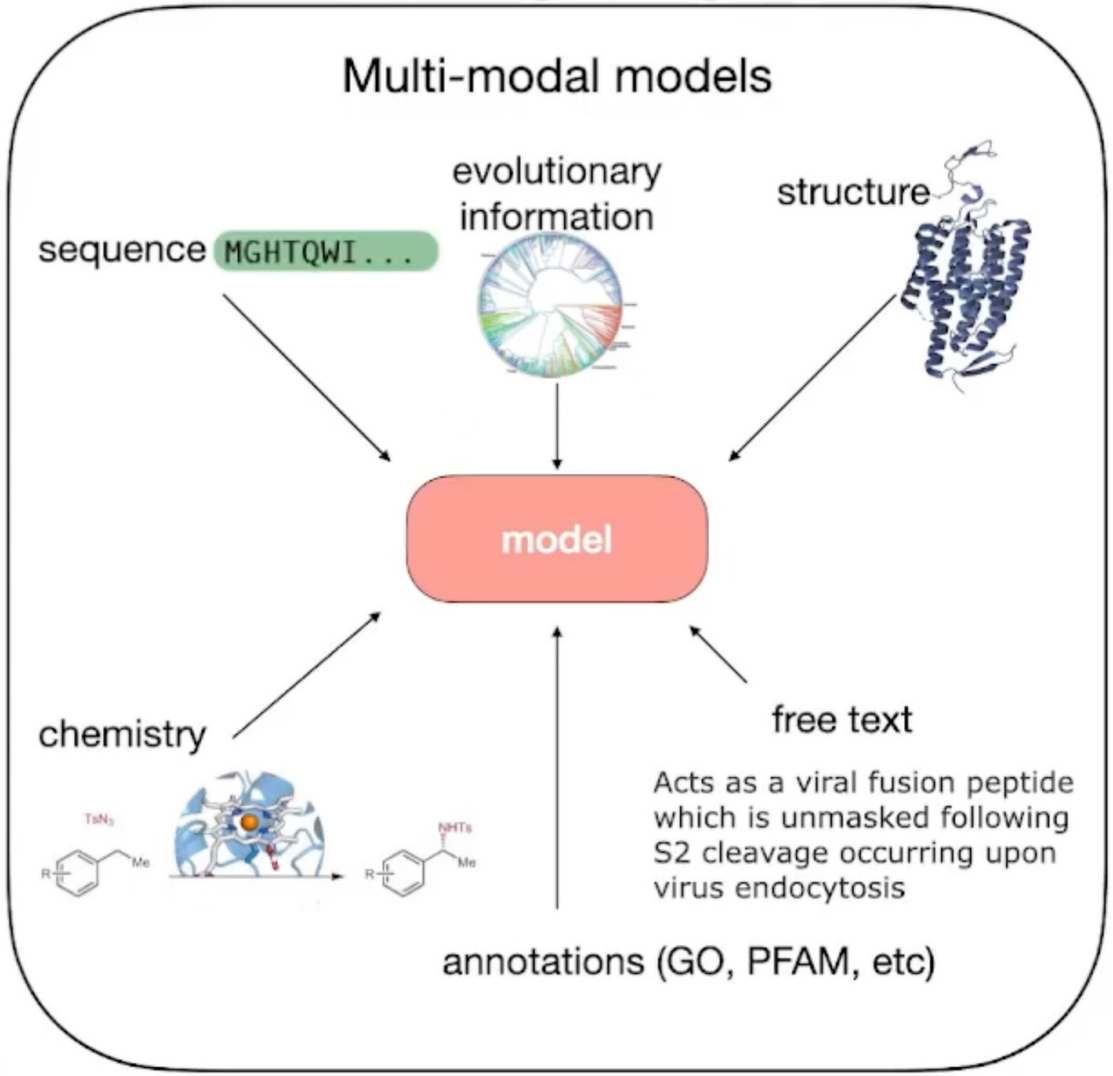
Experiment: Approximate intrinsic fitness with language-model likelihood, measure extrinsic fitness

Hie et al. (2022). Efficient evolution of human antibodies from geneal protein language models…

Outlook: trends and challenges

Big data needs large models need loads of computational resources.

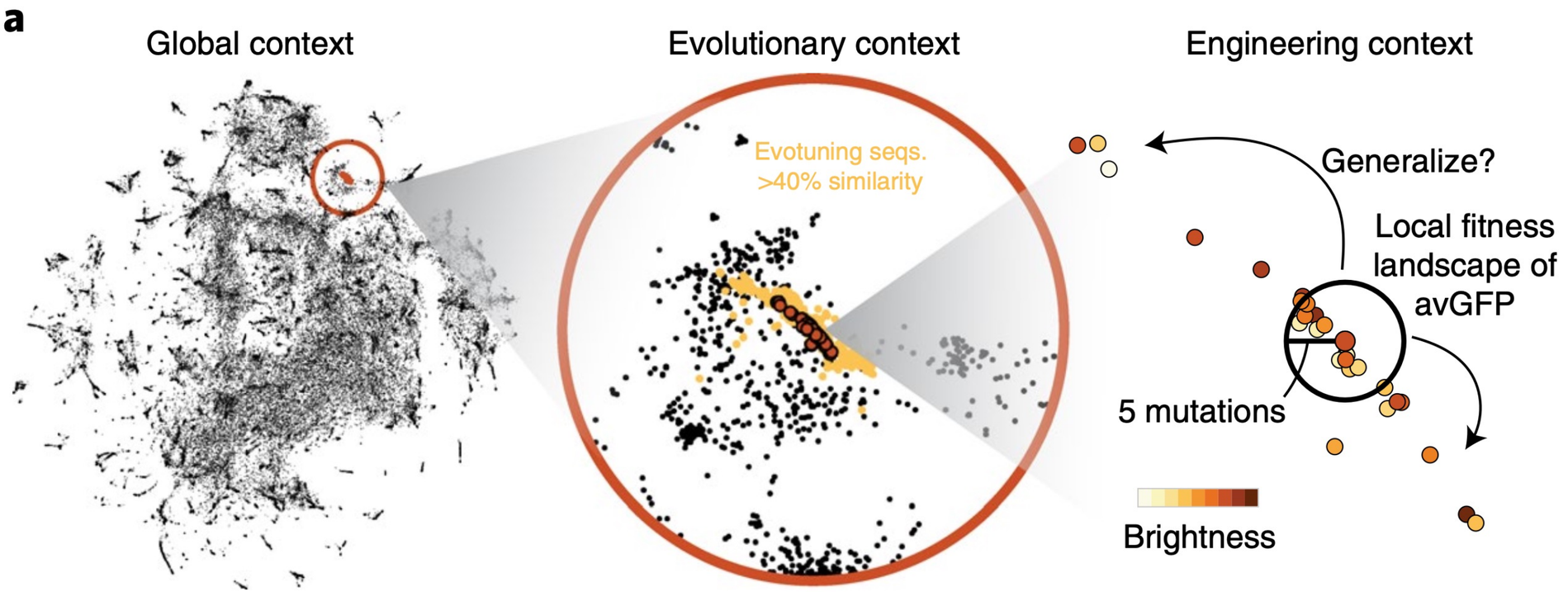
Outlook: trends and challenges



https://www.youtube.com/watch?v=0l2G9_LrY_c

Outlook: trends and challenges

Actual impact in biological applications



Alley et al. (2019). Unified rational protein engineering with sequence-based deep representation learning.

Open questions

Foundation models for biology?

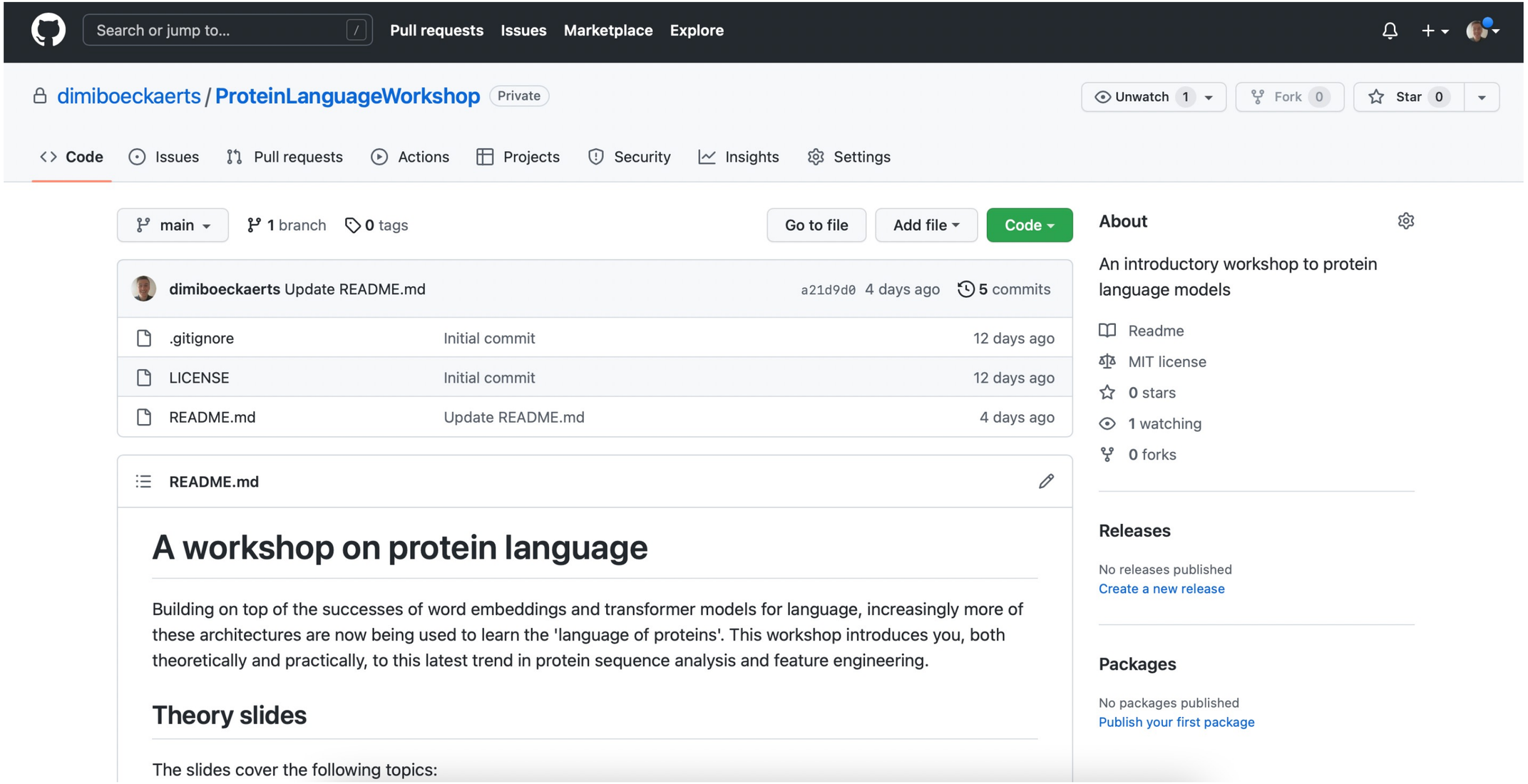
“Bio” DeepMind or OpenAI company?

Deep fake content, deep fake life forms?

Questions?

@dimiboeckaerts
Dimi Boeckaerts

Embeddings in practice!



GPT-3 thought experiments

The Omelet Parable

Imagine that you are on a train. You have always wanted to make the perfect omelet. A genie appears and offers you two options: you can have a delicious omelet, or you can have a device that will let you make unlimited omelets for the rest of your life.

Would you rather have a delicious omelet?
Or the device?

The Red Pill/Blue Pill

Imagine that there is a drug that will cure all diseases. It also has a side effect of making people feel like they are living in a computer simulation. They are in a simulation, and after they take the pill they can see the pixels and their world is filled with triangles.

Would you take it?

https://twitter.com/TomerUllman/status/1363851329463087109