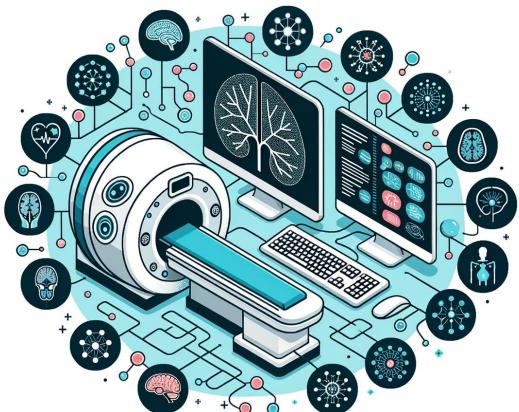


Applied Deep Learning and Generative Models in Healthcare



Session 1: Introduction
Date: Jan 11 2025

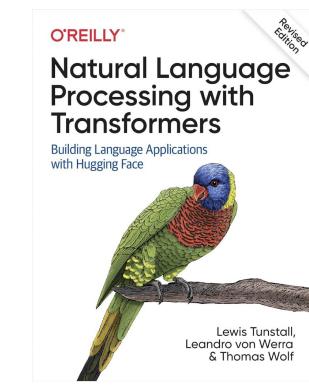
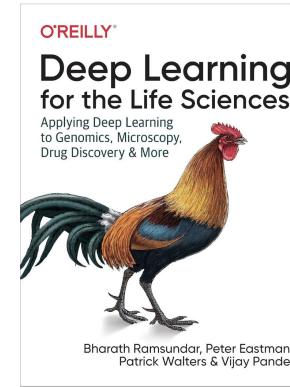
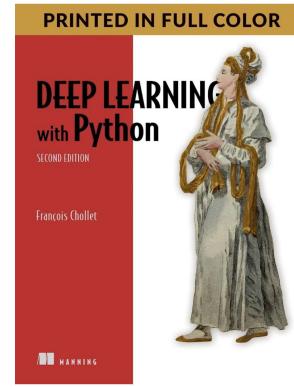
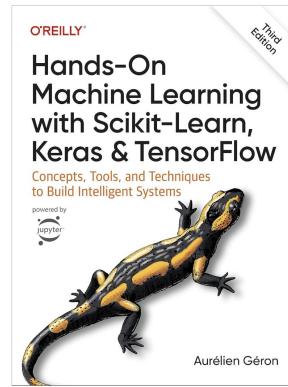
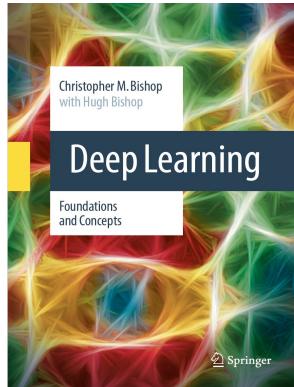


Instructor: Mahmoud E. Khani, Ph.D.

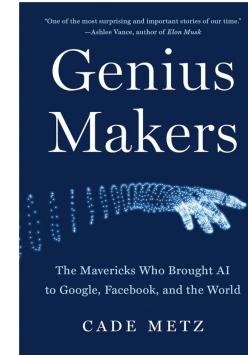
Course structure and objectives

- **Class format:** Lecture + Lab (Jupyter notebooks for hands-on coding)
- **Course material:** Canvas, GitHub
- **Assessments:** Homework assignments, Final project
- **Learning outcomes**
 - Build deep learning models for medical imaging, drug discovery, etc.
 - Understand and apply generative models (e.g., GANs) in a healthcare context
 - Critically evaluate AI models for safety, bias, and regulatory considerations
- **Prerequisites**
 - Familiar with Python
 - Familiarity with basic ML concepts
 - Familiarity with Deep Learning libraries such as PyTorch and Tensorflow.

Some useful resources



- [Stanford CS230 \(Deep Learning\)](#)
- [MIT's 6.S191 \(Introduction to Deep Learning\)](#)
- [fast.ai](#)



Overview of upcoming sessions

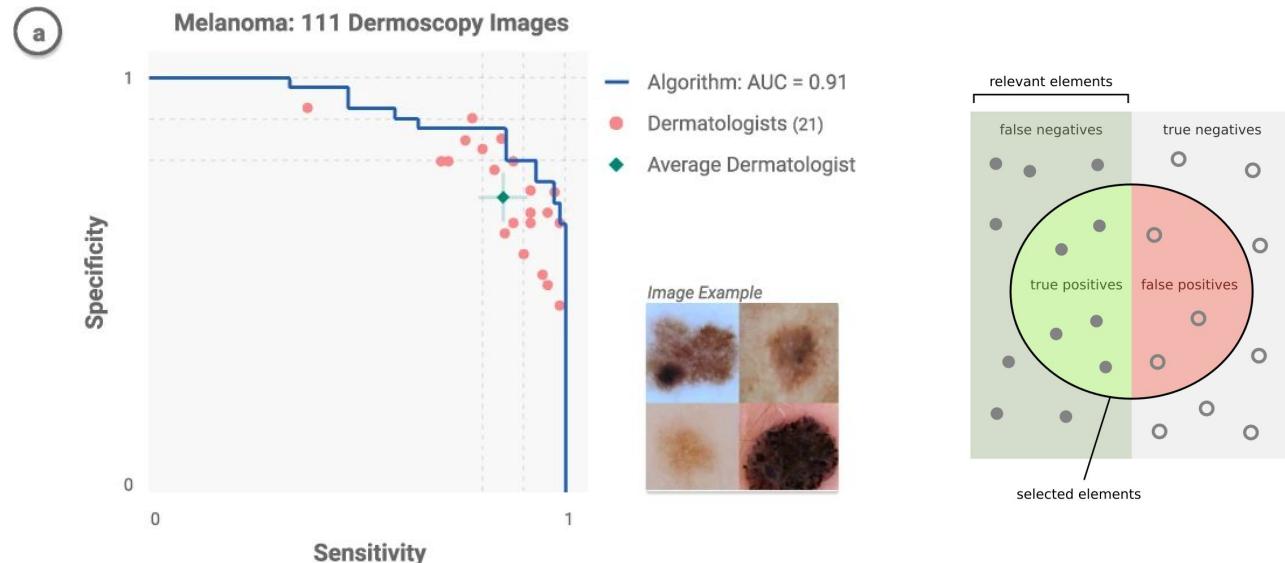
Session 1 (Today): Introduction to Deep Learning in Healthcare — high-level overview of the field, course logistics, Q&A.

Session 2: Convolutional Neural Networks (CNNs) in Medical Imaging — typical imaging tasks (e.g., classification, detection, segmentation) and a hands-on notebook using CNN architectures (ResNet, VGG, etc.).

Session 3: Graph Neural Networks (GNNs) in Drug Discovery — how GNNs can model molecular graphs, predict protein-ligand interactions, and accelerate drug discovery pipelines.

Why Deep Learning in Healthcare?

Transformation Potential: From diagnostics to drug discovery, deep learning is driving innovation.

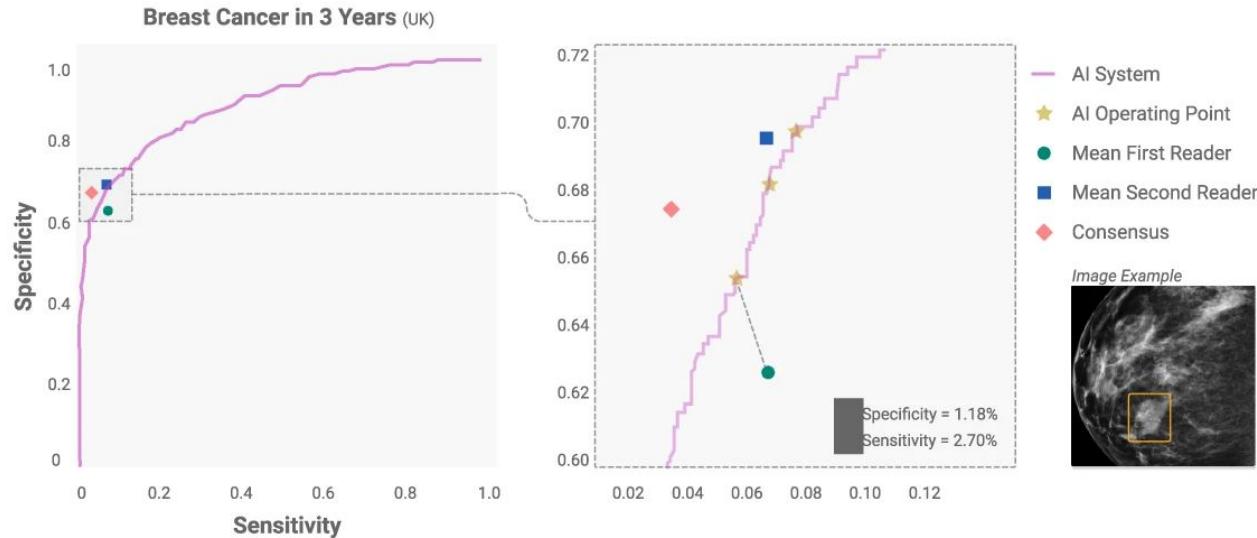


* Esteva, A. et al. npj Digit. Med. 4 (2021)

* Wikipedia

Why Deep Learning in Healthcare?

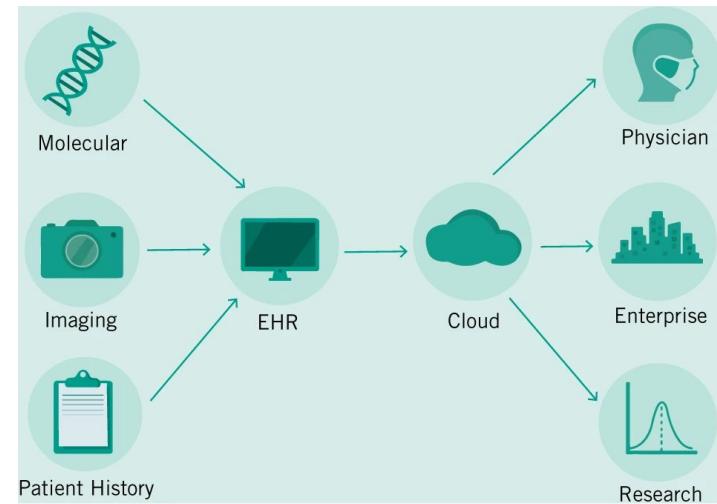
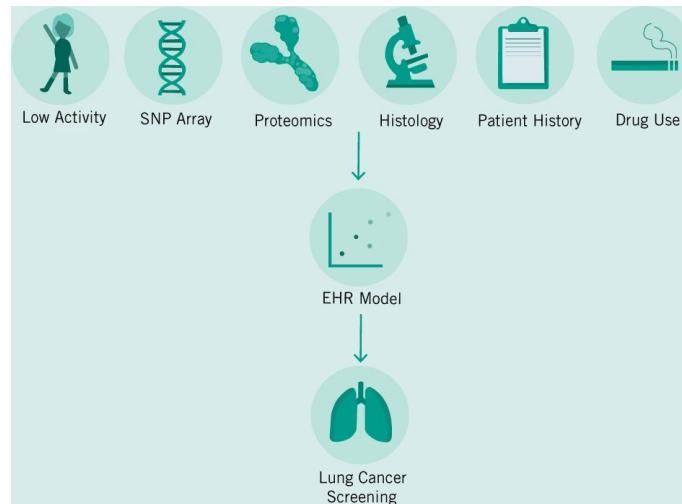
Transformation Potential: From diagnostics to drug discovery, deep learning is driving innovation.



* Esteva, A. et al. npj Digit. Med. 4 (2021)

Why Deep Learning in Healthcare?

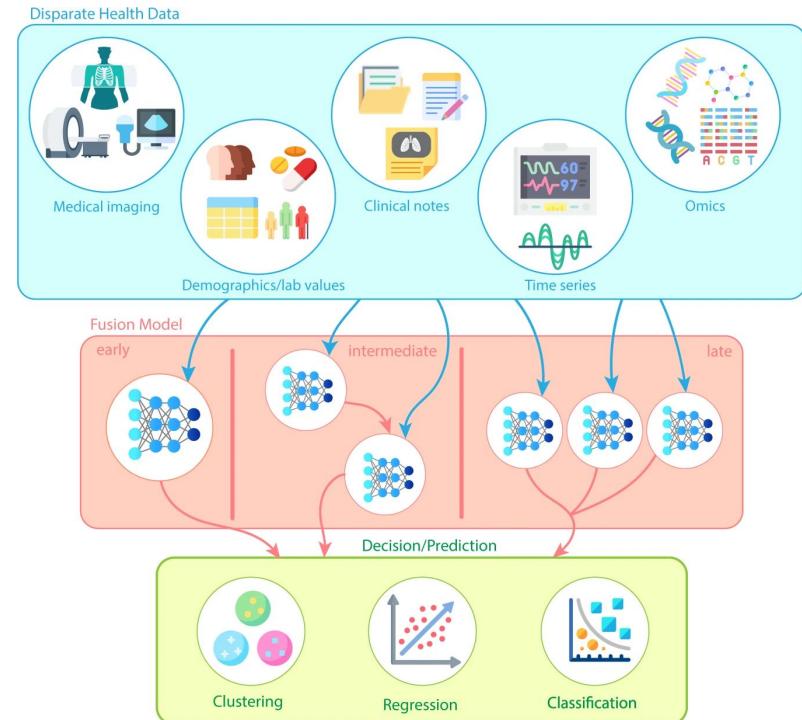
Data Availability: Electronic Health Records (EHRs), medical imaging repositories, genomics data.



Why Deep Learning in Healthcare?

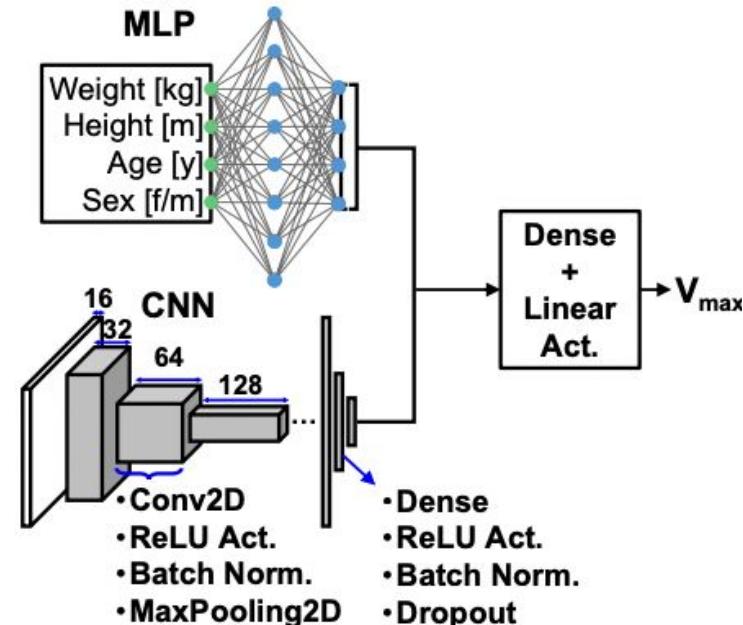
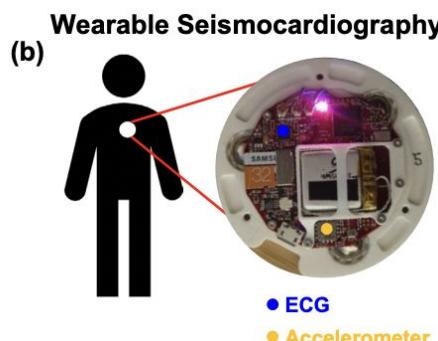
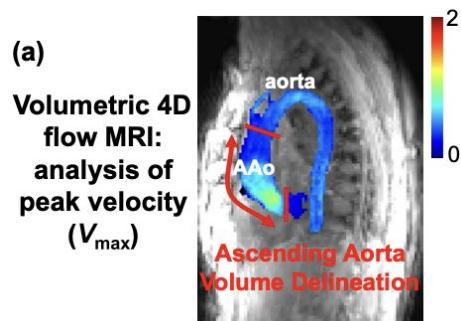
Complexity of Healthcare Data:

Structured (EHRs, lab results),
unstructured (clinical notes), image data
(X-ray, MRI), multimodal data, etc.



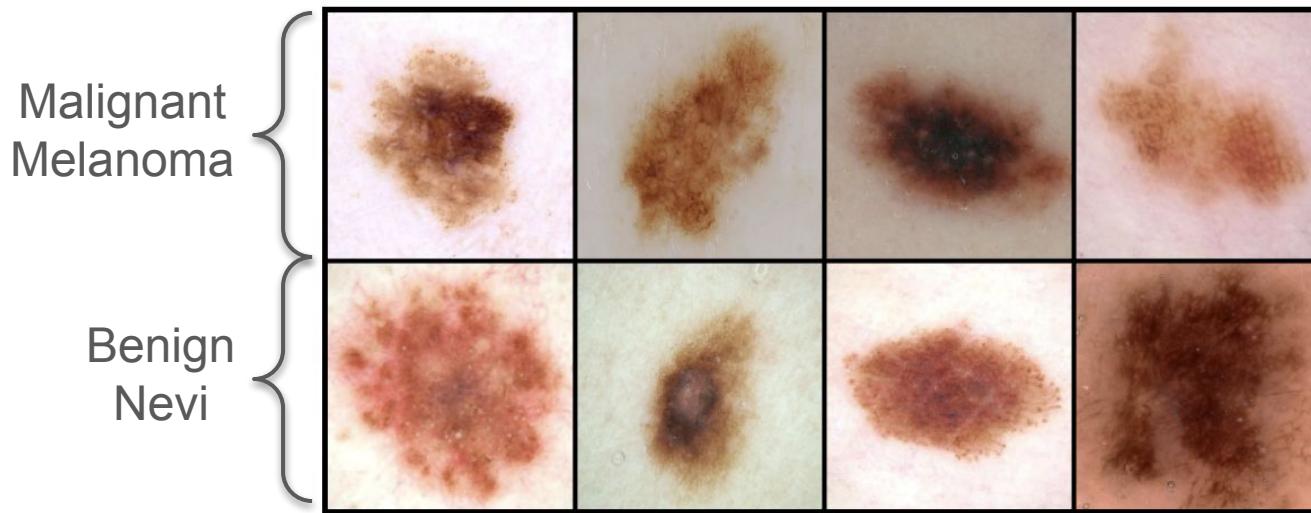
Why Deep Learning in Healthcare?

Complexity of Healthcare Data: Structured (EHRs, lab results), unstructured (clinical notes), image data (X-ray, MRI), multimodal data, etc.



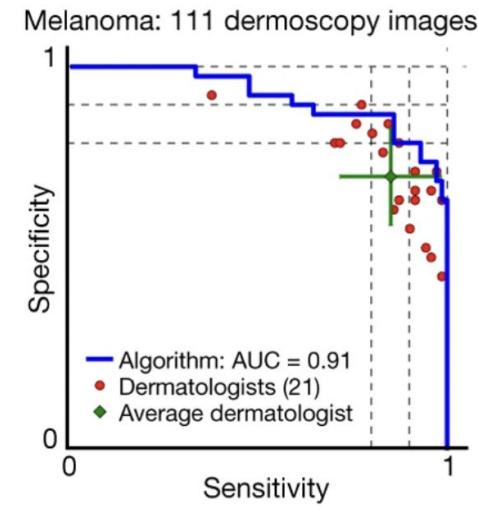
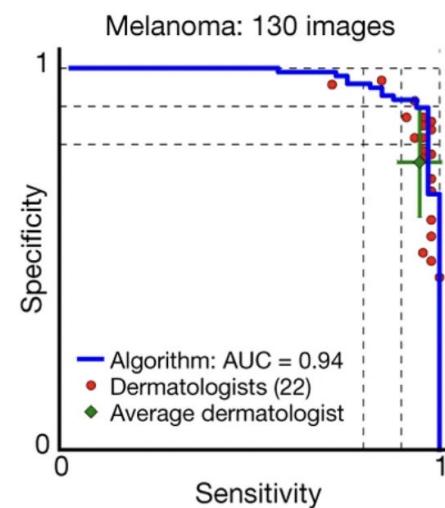
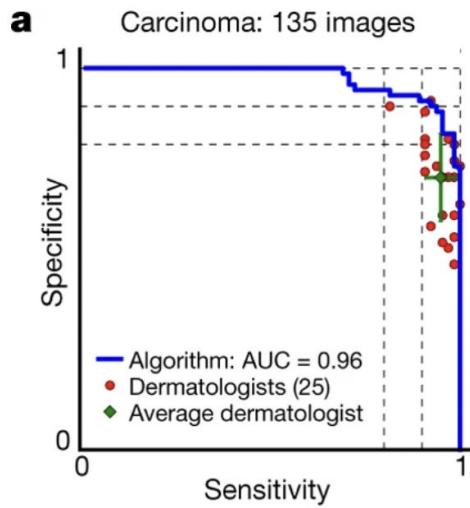
Why Deep Learning in Healthcare?

Growing Need: Address physician shortages, reduce medical errors, accelerate drug discovery, personalized medicine.



Why Deep Learning in Healthcare?

Growing Need: Address physician shortages, reduce medical errors, accelerate drug discovery, personalized medicine.



Techniques used to solve this problem

Training set A large set of lesion images each labelled as *malignant* or *benign* (from biopsy)

Training Adjustment of 25 million parameters in *deep neural network* using the training set

Supervised learning For each training example, the network is told the correct label

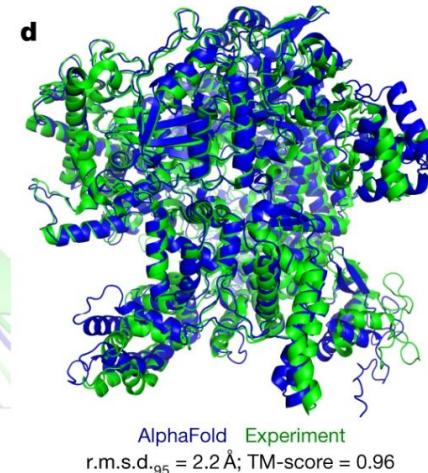
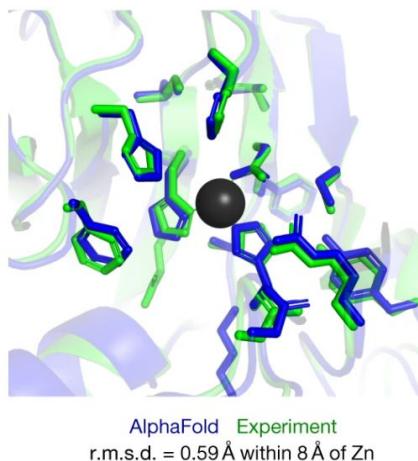
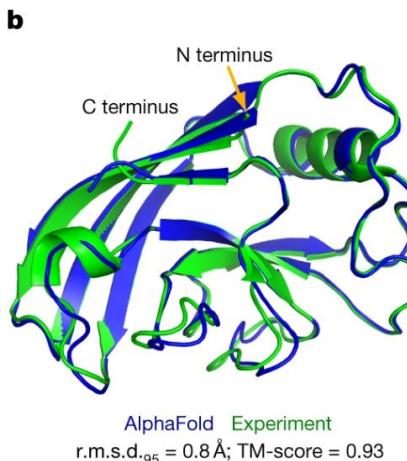
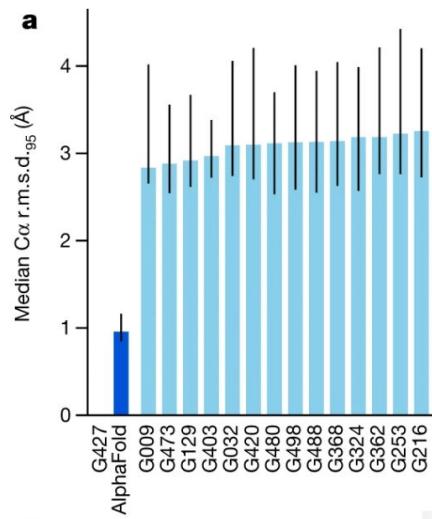
Classification Each input is assigned to a discrete set of classes (benign or malignant)

Transfer learning The deep neural network was first trained on a much larger data set of 1.28 million images of everyday objects (such as dogs, buildings, and mushrooms) and then fine-tuned on the 129,000 data set of lesion images

Evaluation metrics Accuracy, sensitivity, specificity, ROCAUC, confusion matrices, recall, precision, etc.

Why Deep Learning in Healthcare?

Growing Need: Address physician shortages, reduce medical errors, accelerate drug discovery, personalized medicine.



GenAI in Medical Image Synthesis

Medical image acquisition is challenging:

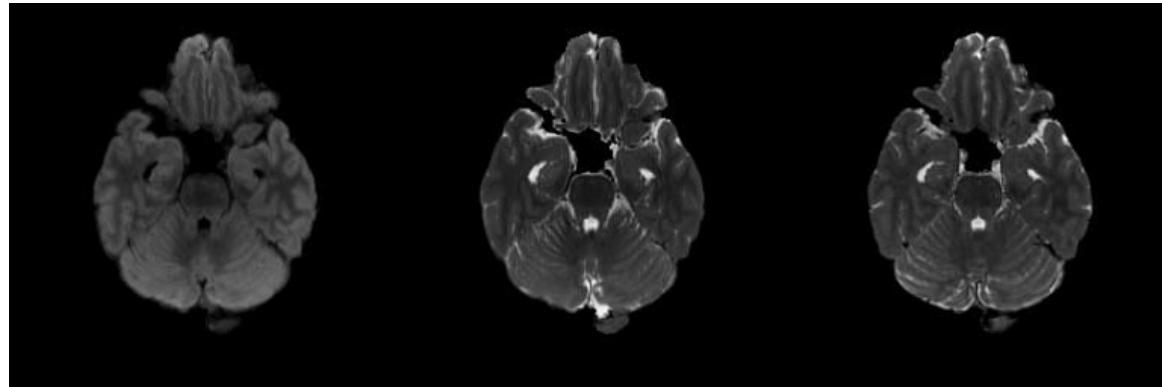
- High operational costs (technical fees, professional fees, facility fee)
- High radiation exposure (PET/CT scans expose patient to high radiation)
- Long acquisition times (motion artifacts due to patient movements)



GenAI in Medical Image Synthesis

Low-field MRI cuts equipment and operational costs, and **low-dose PET** reduces patient radiation exposure.

Both methods face difficulties with **image quality, diagnostic accuracy, and practical implementation.**

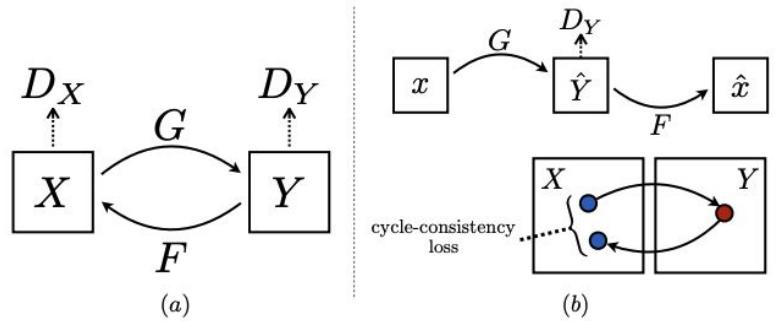
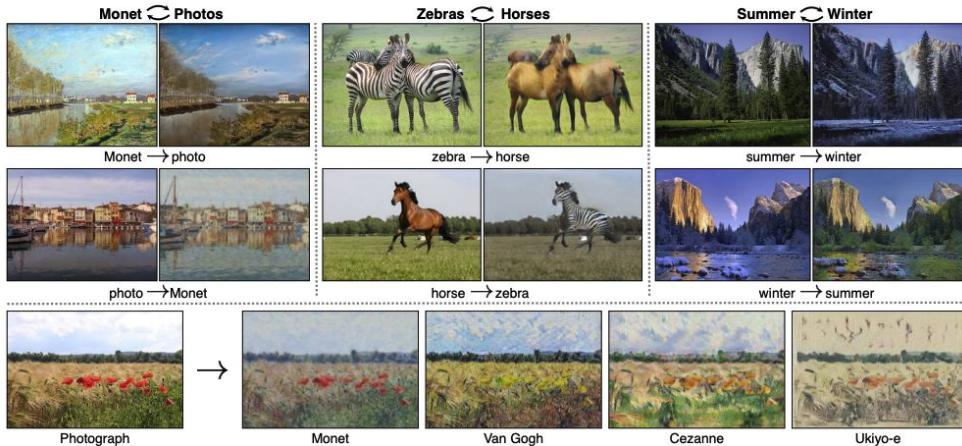


* <https://github.com/sanuwanihewa/MRSyn.git>

CycleGANs for unpaired image-to-image translation

Unpaired Image-to-Image Translation using Cycle-Consistent Adversarial Networks

Jun-Yan Zhu* Taesung Park* Phillip Isola Alexei A. Efros
Berkeley AI Research (BAIR) laboratory, UC Berkeley



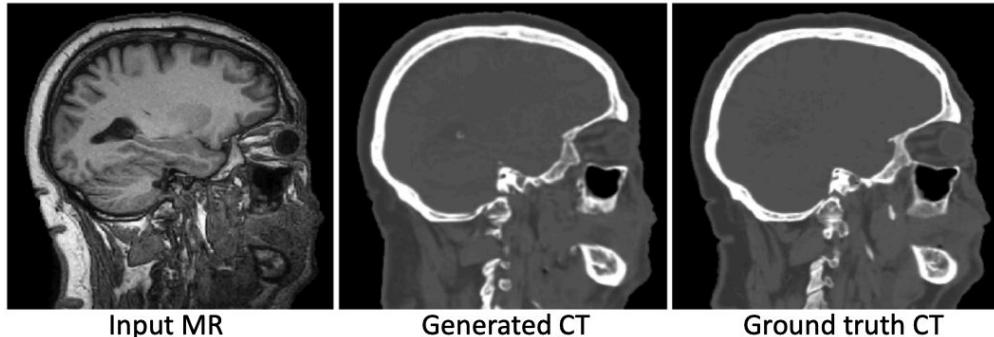
MR to CT synthesis using CycleGANs

Deep MR to CT Synthesis using Unpaired Data

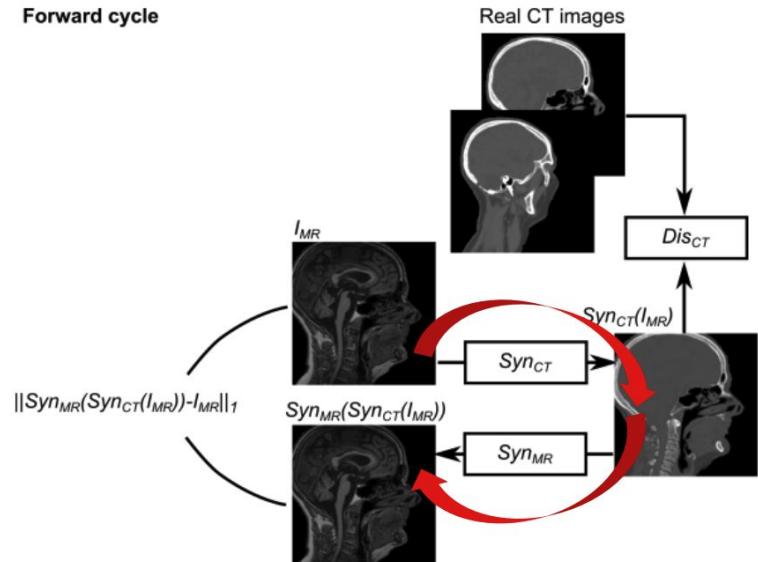
Jelmer M. Wolterink¹✉, Anna M. Dinkla², Mark H.F. Savenije²,
Peter R. Seevinck¹, Cornelis A.T. van den Berg², Ivana Išgum¹

¹ Image Sciences Institute, University Medical Center Utrecht, The Netherlands
j.m.wolterink@umcutrecht.nl

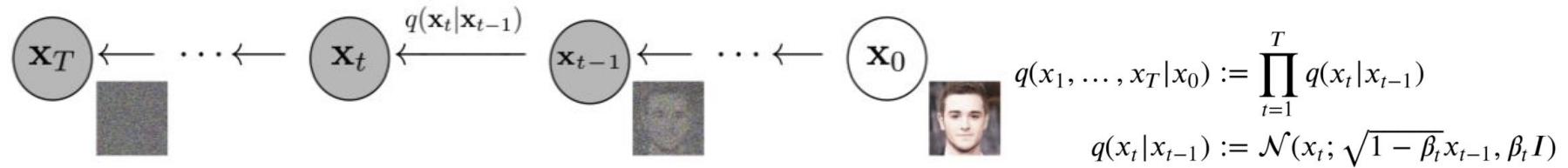
² Department of Radiotherapy, University Medical Center Utrecht, The Netherlands



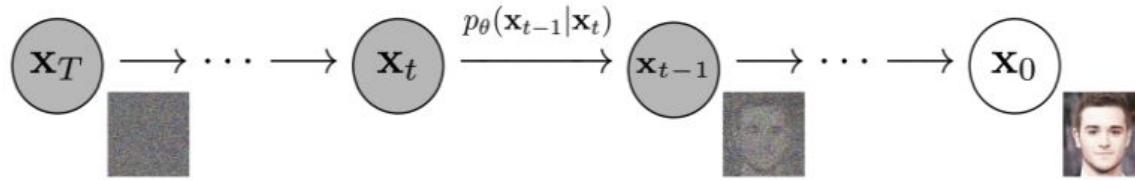
Forward cycle



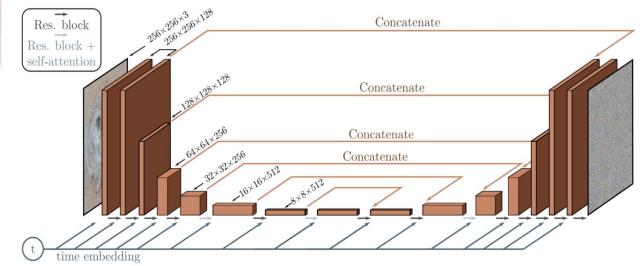
Diffusion models for image-to-image translation



$$q(x_1, \dots, x_T | x_0) := \prod_{t=1}^T q(x_t | x_{t-1})$$
$$q(x_t | x_{t-1}) := \mathcal{N}(x_t; \sqrt{1 - \beta_t} x_{t-1}, \beta_t I)$$

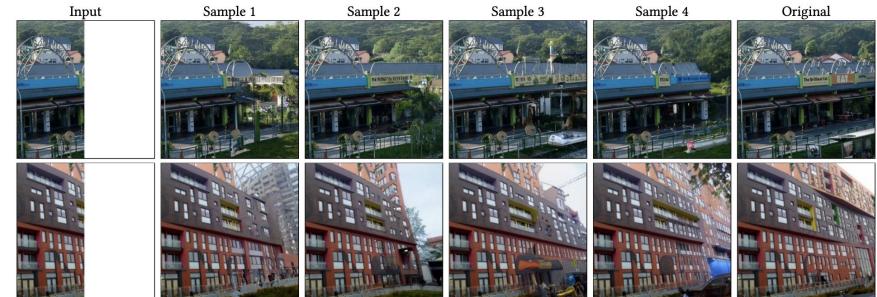
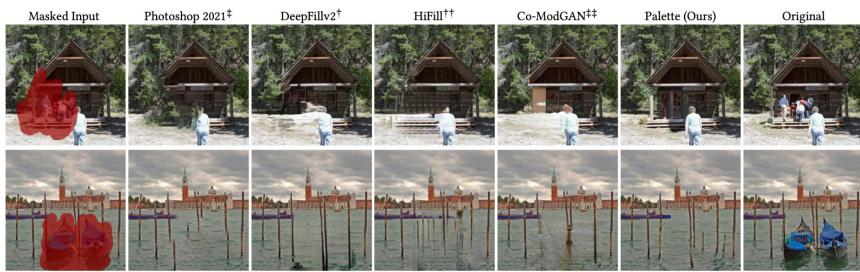
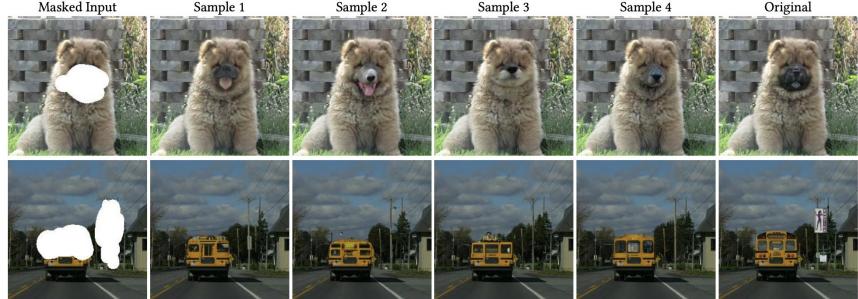


$$p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t) := \mathcal{N}(\mathbf{x}_{t-1}; \boldsymbol{\mu}_\theta(\mathbf{x}_t, t), \boldsymbol{\Sigma}_\theta(\mathbf{x}_t, t))$$



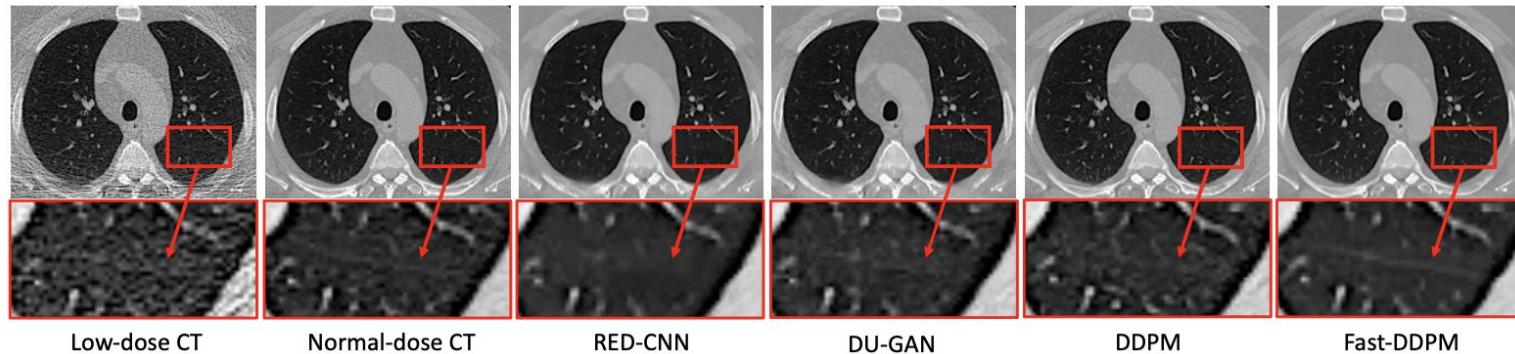
The U-Net architecture used in DDPMs

Diffusion models for image-to-image translation



DDPMs for medical image generation/translation

Image denoising for conversion of low-dose (10% of normal) to full-dose lung CT

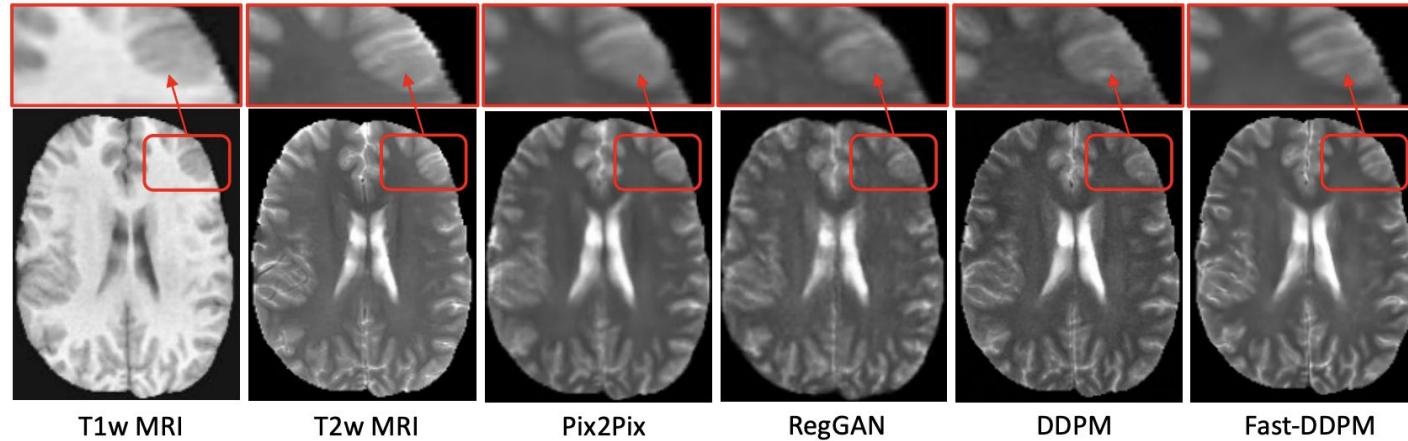


Low-dose CT Normal-dose CT RED-CNN DU-GAN DDPM Fast-DDPM

Method	PSNR	SSIM	Training time	Inference Time
REDCNN [2]	36.4	0.91	3 h	0.5 s
DU-GAN [12]	36.3	0.90	20 h	3.8 s
DDPM [9]	35.4	0.87	141 h	21.4 m
Fast-DDPM	37.5	0.92	26 h	12.5 s

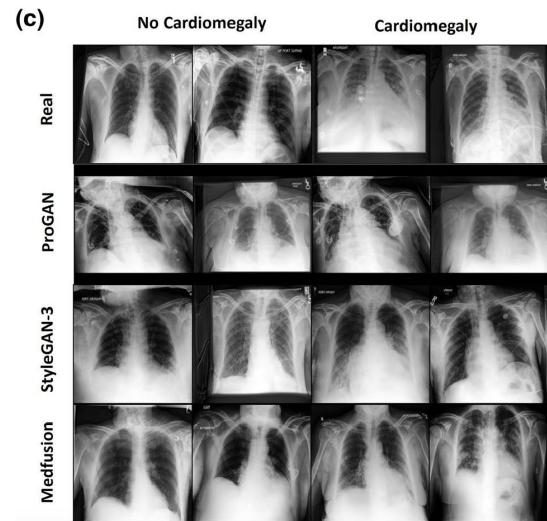
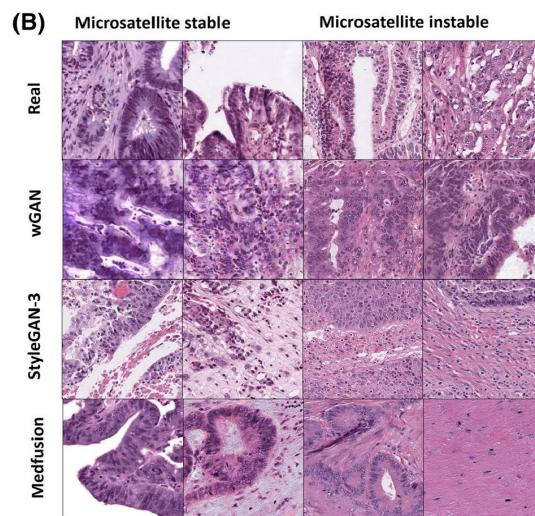
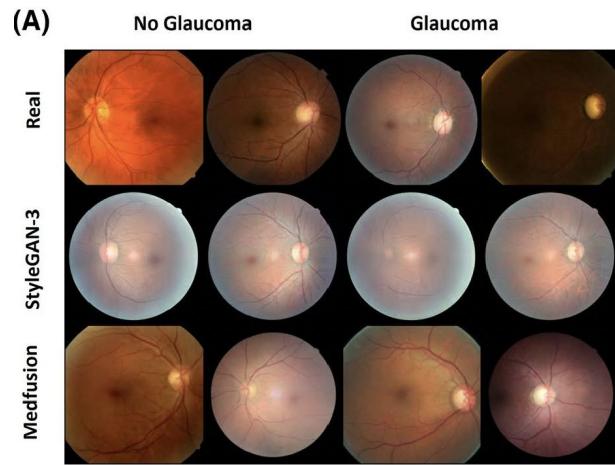
DDPMs for medical image generation/translation

Image-to-image translation for T1w MRI to T2w MRI conversion



Method	PSNR	SSIM	Training time	Inference Time
Pix2Pix [14]	25.6	0.85	6 h	3.3 s
RegGAN [19]	26.0	0.86	9 h	3.1 s
DDPM [9]	26.3	0.89	135 h	22.2 m
Fast-DDPM	26.3	0.89	27 h	13.2 s

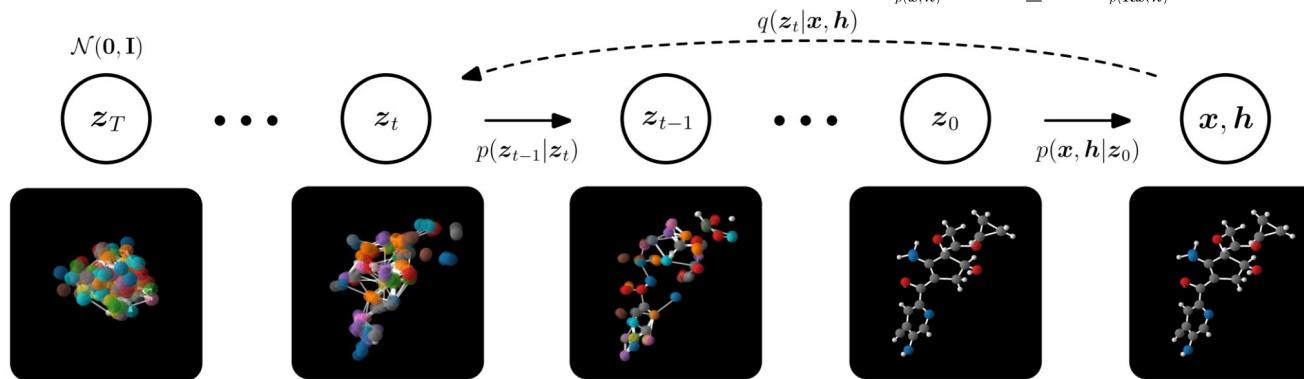
Latent diffusion models for medical image synthesis



Equivariant diffusion for small molecule generation

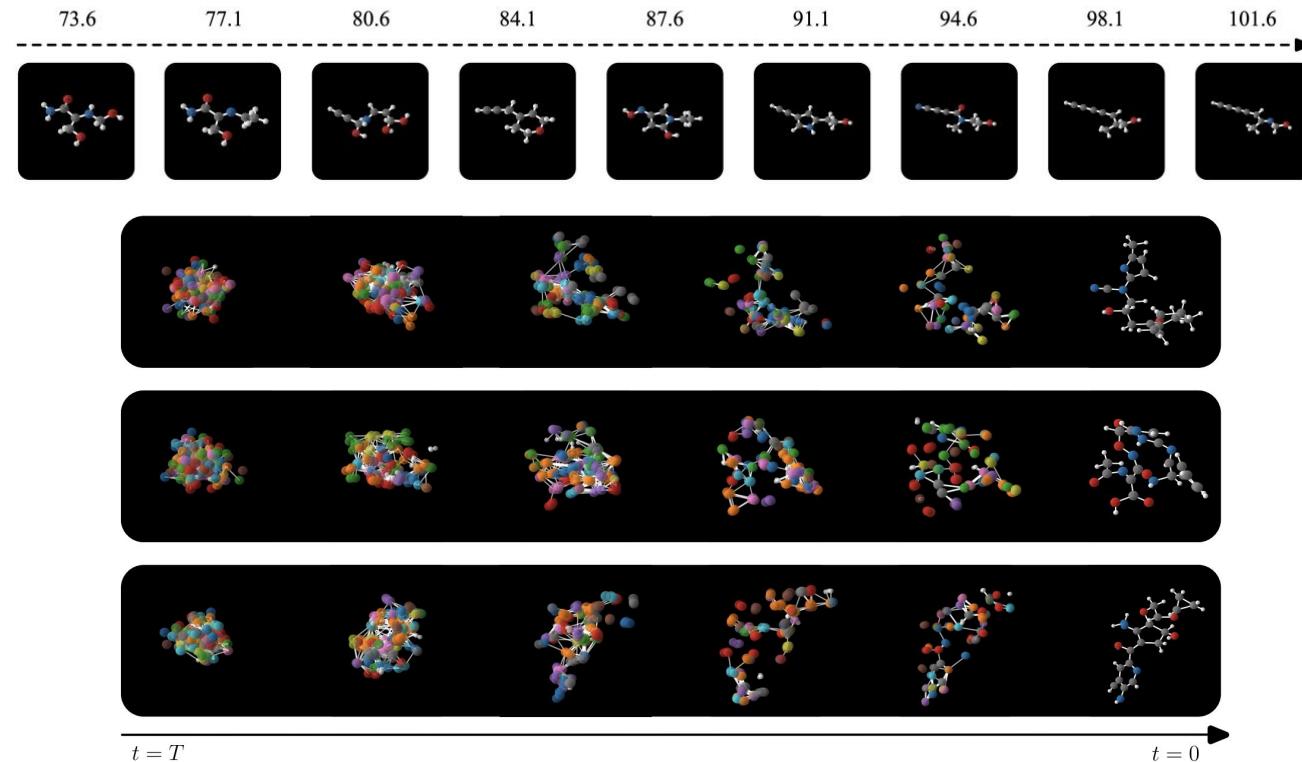
Equivariant Diffusion for Molecule Generation in 3D

Emiel Hoogeboom^{* 1} Victor Garcia Satorras^{* 1} Clément Vignac^{* 2} Max Welling¹



* Hoogeboom, E. et al., arXiv:2203.17003v2(2022)

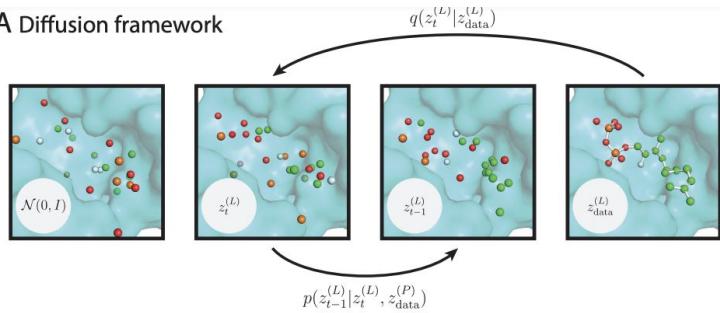
Equivariant diffusion for small molecule generation



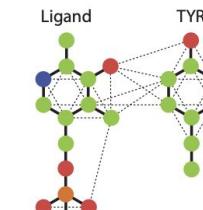
* Hoogeboom, E. et al., arXiv:2203.17003v2(2022)

Conditional diffusion for structure-based drug discovery

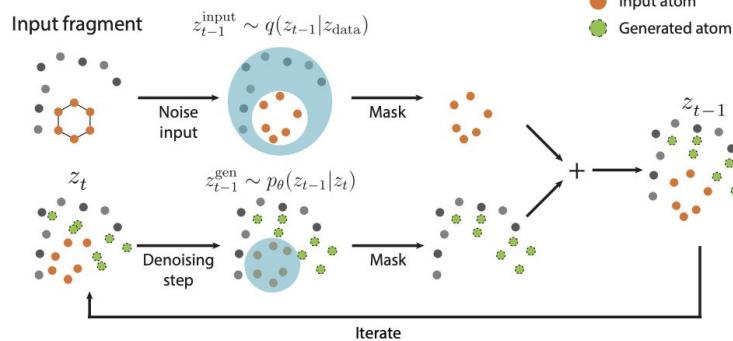
A Diffusion framework



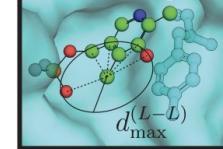
B Graph modeling



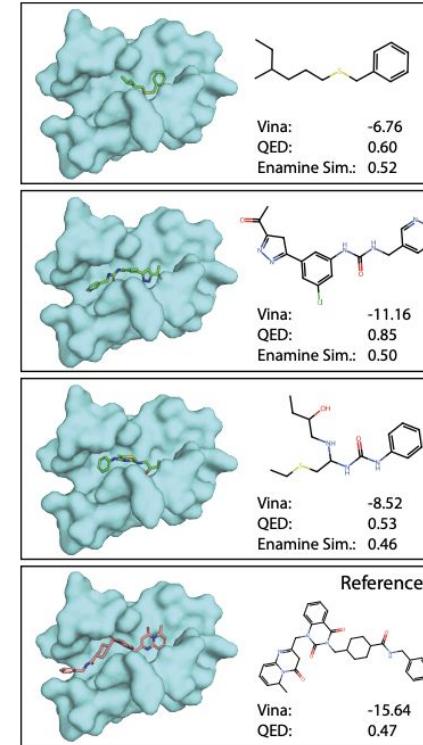
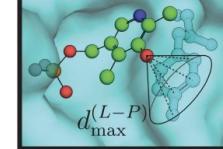
C Fixing known substructures



Intramolecular edges



Intermolecular edges



Diffusion models for designing protein therapeutics

nature

Explore content ▾ About the journal ▾ Publish with us ▾

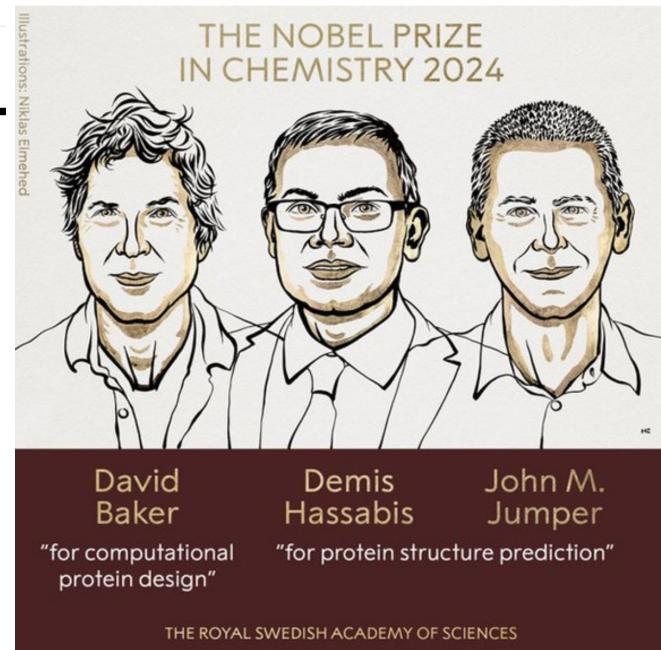
[nature](#) > [articles](#) > [article](#)

Article | [Open access](#) | Published: 11 July 2023

De novo design of protein structure and function with RFdiffusion

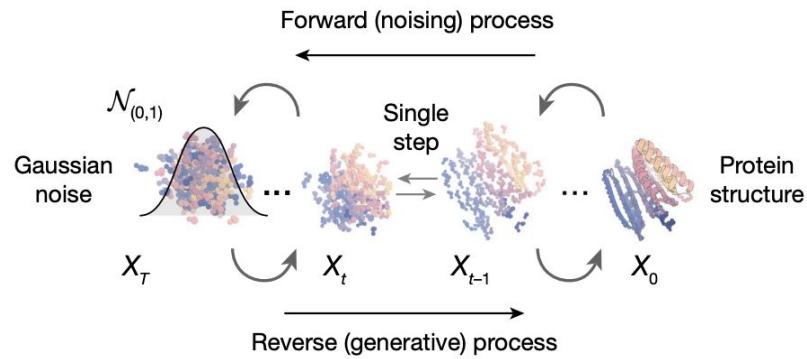
[Joseph L. Watson](#), [David Juergens](#), [Nathaniel R. Bennett](#), [Brian L. Trippe](#), [Jason Yim](#), [Helen E. Eisenach](#),
[Woody Ahern](#), [Andrew J. Borst](#), [Robert J. Ragotte](#), [Lukas F. Milles](#), [Basile I. M. Wicky](#), [Nikita Hanikel](#),
[Samuel J. Pellock](#), [Alexis Courbet](#), [William Sheffler](#), [Jue Wang](#), [Preetham Venkatesh](#), [Isaac Sappington](#),
[Susana Vázquez Torres](#), [Anna Lauko](#), [Valentin De Bortoli](#), [Emile Mathieu](#), [Sergey Ovchinnikov](#), [Regina Barzilay](#), ... [David Baker](#)  [+ Show authors](#)

[Nature](#) **620**, 1089–1100 (2023) | [Cite this article](#)

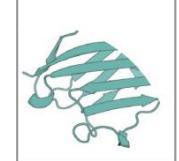


De novo design of proteins using RFDiffusion

Diffusion model



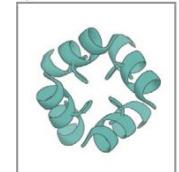
Binding target



Functional motif



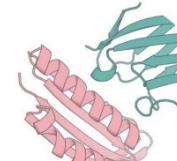
Symmetric motif



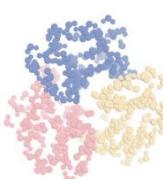
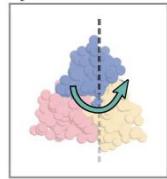
Binder design



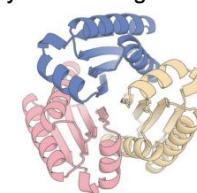
Motif scaffolding



Symmetric noise



Symmetric oligomers

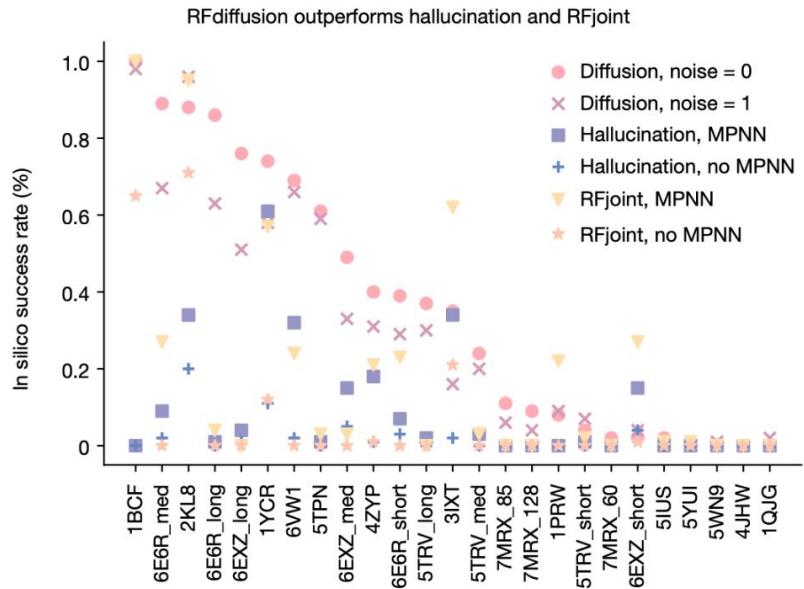


Symmetric scaffolding

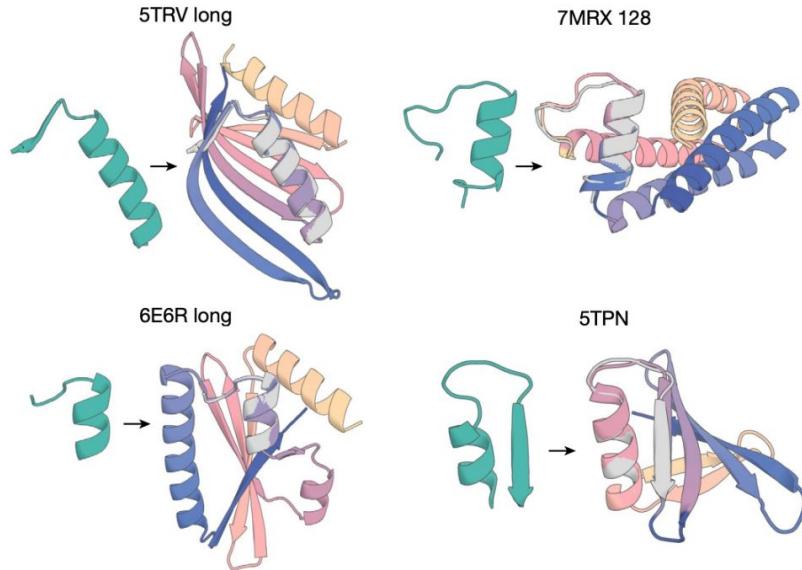


De novo design of proteins using RFDiffusion

a



b

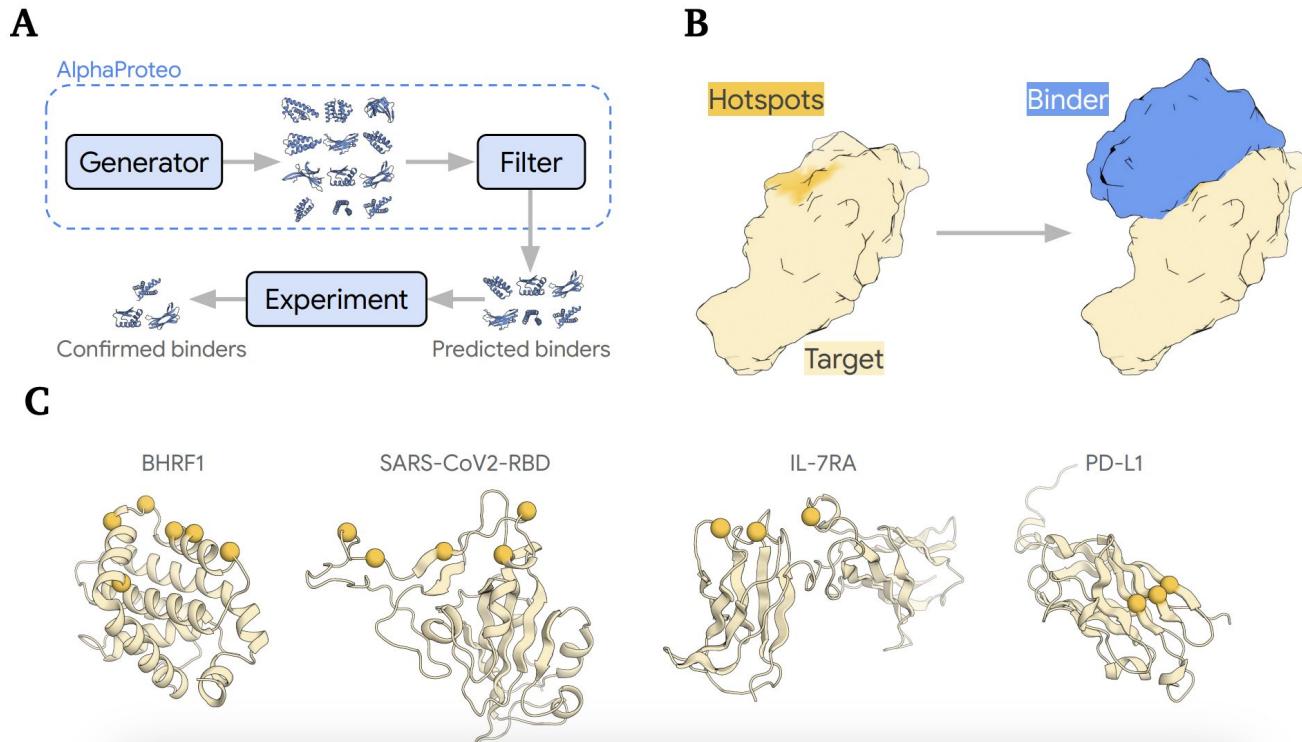


De novo design of high-affinity protein binders with AlphaProteo

Vinicio Zambaldi^{*,1}, David La^{*,1}, Alexander E. Chu^{*,1}, Harshnira Patani^{*,1}, Amy E. Danson^{*,1}, Tristan O. C. Kwan^{*,1}, Thomas Frerix^{*,1}, Rosalia G. Schneider^{*,1}, David Saxton^{*,1}, Ashok Thillaisundaram^{*,1}, Zachary Wu^{*,1}, Isabel Moraes², Oskar Lange², Eliseo Papa¹, Gabriella Stanton¹, Victor Martin¹, Sukhdeep Singh¹, Lai H. Wong¹, Russ Bates², Simon A. Kohl², Josh Abramson¹, Andrew W. Senior¹, Yilmaz Alguel³, Mary Y. Wu⁴, Irene M. Aspalter⁵, Katie Bentley^{5,6}, David L.V. Bauer⁷, Peter Cherepanov³, Demis Hassabis¹, Pushmeet Kohli¹, Rob Fergus^{1,†} and Jue Wang^{1,‡}

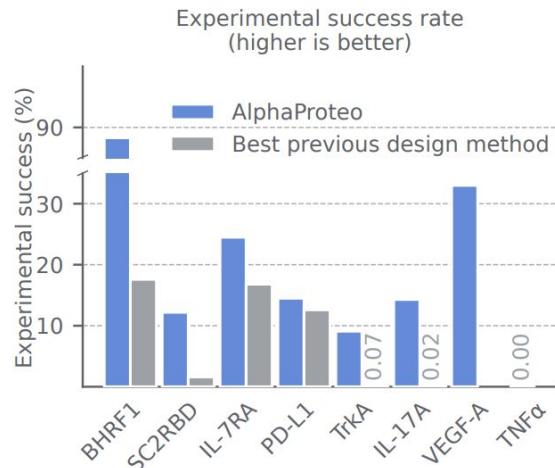
*Equal contributions, †Equal supervision, ¹Google DeepMind, ²Work performed while at Google DeepMind, ³The Chromatin Structure and Mobile DNA Laboratory, The Francis Crick Institute, London, UK, ⁴COVID Surveillance Unit, The Francis Crick Institute, London, UK, ⁵Cellular Adaptive Behaviour Laboratory, The Francis Crick Institute, London, UK., ⁶Department of Informatics, King's College London, London, UK. K.B. performed the work at the Cellular Adaptive Behaviour Laboratory, The Francis Crick Institute, London, UK, ⁷RNA Virus Replication Laboratory, The Francis Crick Institute, London, UK

AlphaProteo: DeepMind model for protein therapeutics

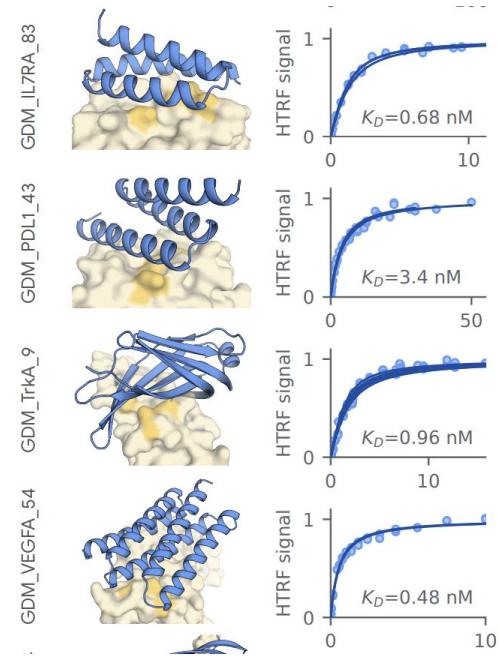
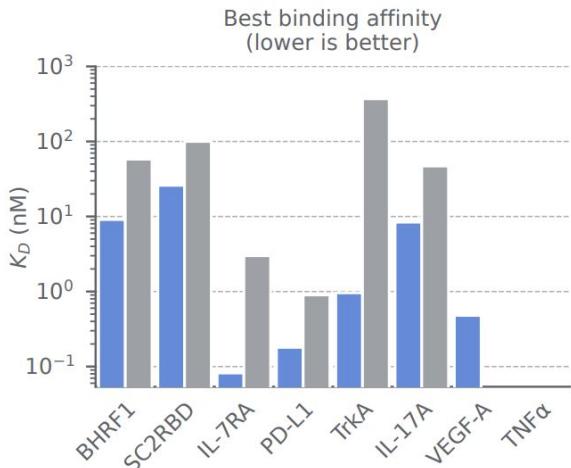


AlphaProteo: DeepMind model for protein therapeutics

D



E



Graph neural networks for molecular dynamics simulations



Explore content ▾ About the journal ▾ Publish with us ▾

nature > articles > article

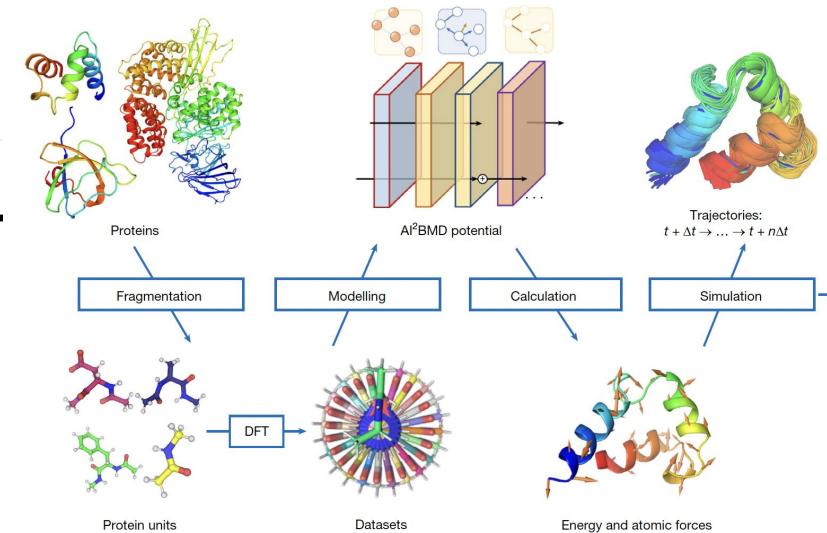
Article | Open access | Published: 06 November 2024

Ab initio characterization of protein molecular dynamics with AI²BMD

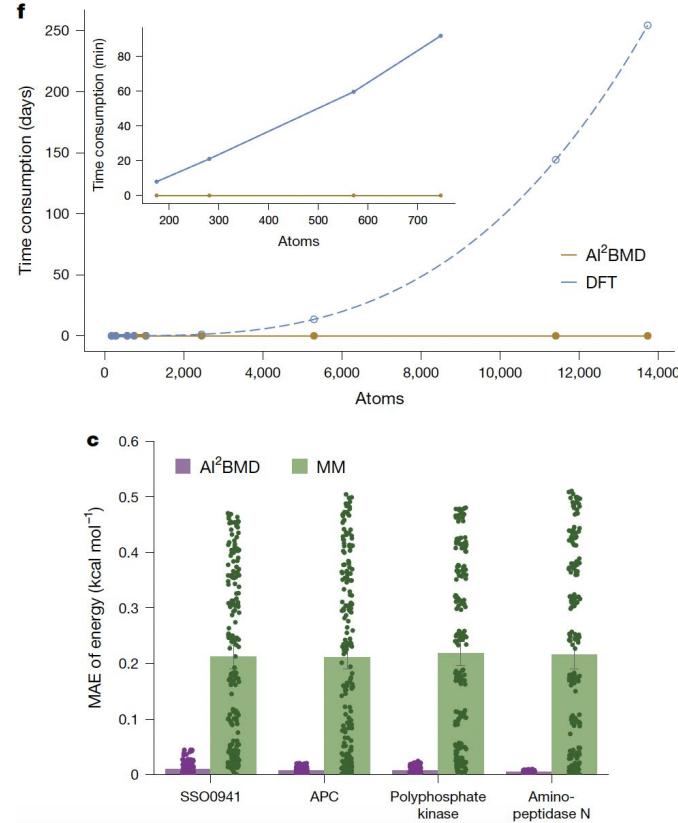
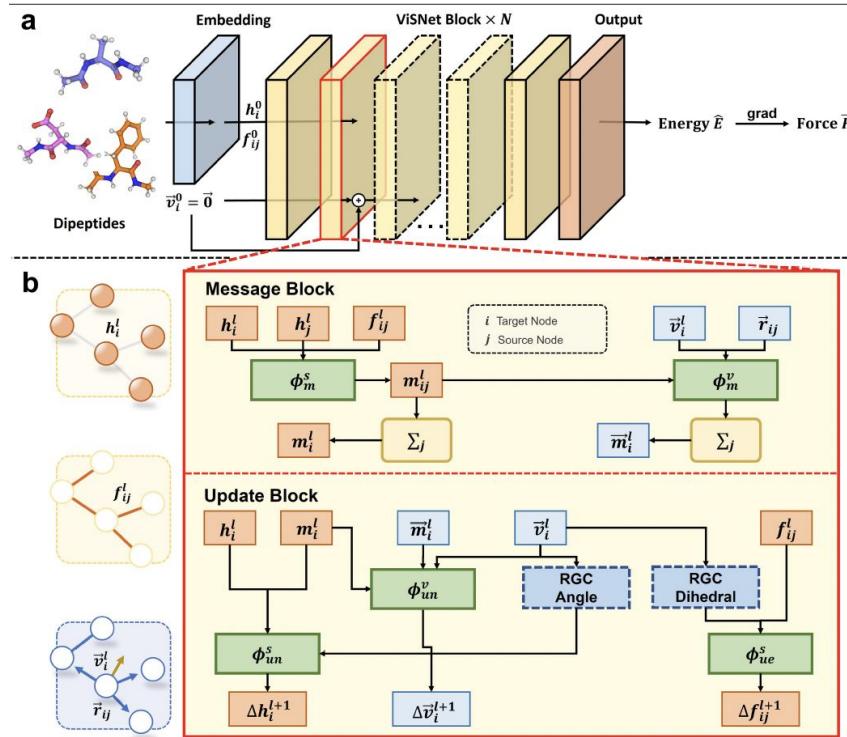
Tong Wang , Xinheng He, Mingyu Li, Yatao Li, Ran Bi, Yusong Wang, Chaoran Cheng, Xiangzhen Shen, Jiawei Meng, He Zhang, Haiguang Liu, Zun Wang, Shaoning Li, Bin Shao  & Tie-Yan Liu

Nature 635, 1019–1027 (2024) | Cite this article

* Wang, T. et al., Nature 635 (2024)



AI²BMD - Ab Initio Accurate Molecular Dynamics



Biomedical Chatbots

Initialized with open-sourced LLM (GPT-4, LLaMA, etc.) and fine-tuned on customized sets of biomedical instruction-following data

- ChatDoctor
- Med-Alpaca
- PMC-LLaMA
- Clinical Camel
- DoctorGLM
- Huatuo
- Visual Med-Alpaca (multimodal: text + vision)

Question	Answer
What is the relationship between very low Mg ²⁺ levels, PTH levels, and Ca ²⁺ levels?	Very low Mg ²⁺ levels correspond to low PTH levels which in turn results in low Ca ²⁺ levels.
What are the cautionary considerations and contraindications for the use of β -blockers?	β -blockers must be used cautiously in decompensated heart failure and are contraindicated in cardiogenic shock.
What is the recommended next step in management for a stable child who is suspected of having intussusception and has a "target sign" on ultrasound?	The recommended next step in management for a stable child with suspected intussusception and a "target sign" on ultrasound is to undergo an ultrasound-guided air contrast enema. This procedure involves using a small amount of air and contrast material to inflate the colon and push the telescoped intestine back into place. It is a non-invasive and effective method for both diagnosing and treating intussusception in children. In some cases, the procedure may need to be repeated or followed by surgery if the intussusception cannot be reduced. It is important to treat intussusception promptly to avoid complications such as bowel obstruction, bowel perforation, or sepsis.
What condition should be suspected in a young infant who is healthy and active and has blood-tinged stools? What is the cause of this condition and how is it managed?	The presence of blood-tinged stools in a young infant who is healthy and active should raise suspicion of protein-induced proctocolitis. This condition is caused by an intolerance to milk or soy protein, which can cause inflammation in the lining of the rectum. The management of protein-induced proctocolitis involves continuing breastfeeding and advising the mother to avoid dairy and soy products in her diet. In most cases, this will lead to resolution of the symptoms within a few days to a few weeks. If the symptoms persist, further evaluation may be necessary to rule out other causes of gastrointestinal bleeding.

United States Medical Licensing Examination (USMLE)

MEDALPACA - AN OPEN-SOURCE COLLECTION OF MEDICAL CONVERSATIONAL AI MODELS AND TRAINING DATA

A PREPRINT

Tianyu Han^{1,+}, Lisa C. Adams^{2,+}, Jens-Michalis Papaioannou⁴, Paul Grundmann⁴, Tom Oberhauser⁴, Alexei Figueroa⁴, Alexander Löser⁴, Daniel Truhn^{1,+}, and Keno K. Bressem^{5,6,+}

¹Department of Radiology, University Hospital Aachen, Aachen, Germany
Email: {tianyu.han, dtruhn}@ukaachen.de

²Department of Diagnostic and Interventional Radiology, Technical University of Munich, Munich, Germany
Email: lisa.adams@tum.de

⁴Berliner Hochschule für Technik (BHT), Berlin, Germany
Email: {michalis.papaioannou, pgrundmann, tom.oberhauser, alexei.figueroa, aloeser}@bht-berlin.de

⁵Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute for Radiology, Berlin, Germany
Email: keno-kyrill.bressem@charite.de

Table 2: Zero shot performance on the USMLE self assessment

Model	Step1	Step2	Step3
LLaMA 7b [15]	0.198	0.202	0.203
Alpaca 7b naive [11]	0.275	0.266	0.293
Alpaca 7b LoRA	0.220	0.138	0.252
MedAlpaca 7b	0.297	0.312	0.398
MedAlpaca 7b LoRA	0.231	0.202	0.179
MedAlpaca 7b LoRA 8bit	0.231	0.241	0.211
ChatDoctor (7b) [10]	0.187	0.185	0.148
LLaMA 13b [15]	0.222	0.248	0.276
Alpaca 13b naive	0.319	0.312	0.301
MedAlpaca 13b	0.473	0.477	0.602
MedAlpaca 13b LoRA	0.250	0.255	0.255
MedAlpaca 13b LoRA 8bit	0.189	0.303	0.289

Attention Is All You Need

Ashish Vaswani*
Google Brain
avaswani@google.com

Noam Shazeer*
Google Brain
noam@google.com

Niki Parmar*
Google Research
nikip@google.com

Jakob Uszkoreit*
Google Research
usz@google.com

Llion Jones*
Google Research
llion@google.com

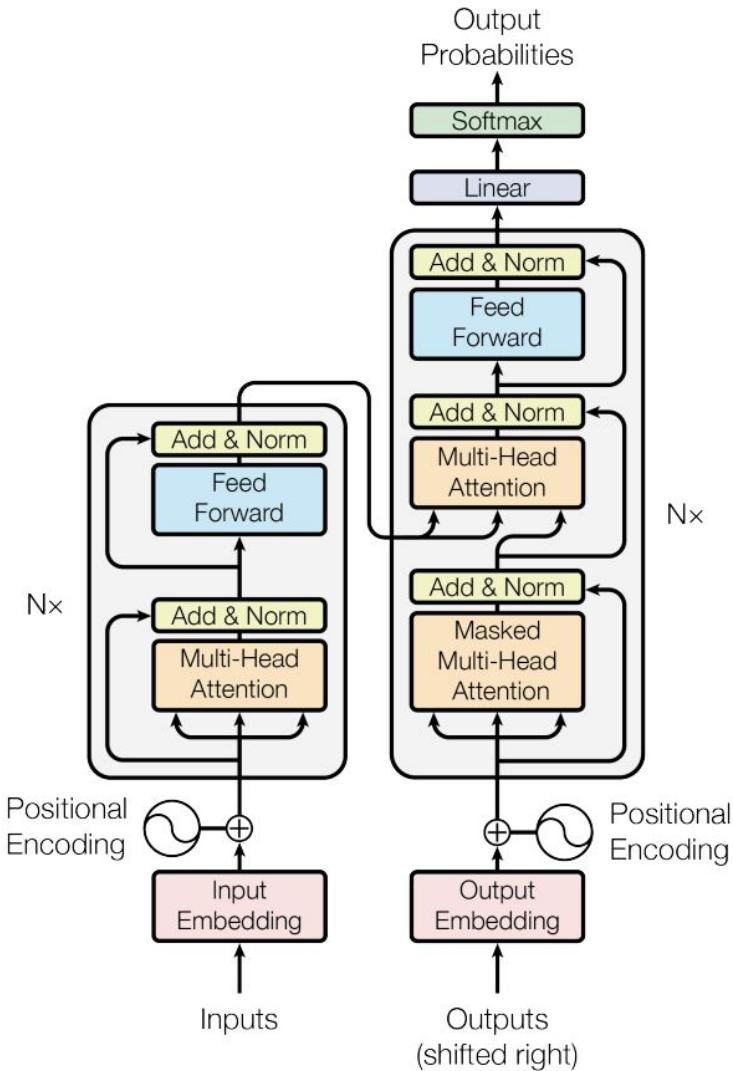
Aidan N. Gomez* †
University of Toronto
aidan@cs.toronto.edu

Lukasz Kaiser*
Google Brain
lukaszkaiser@google.com

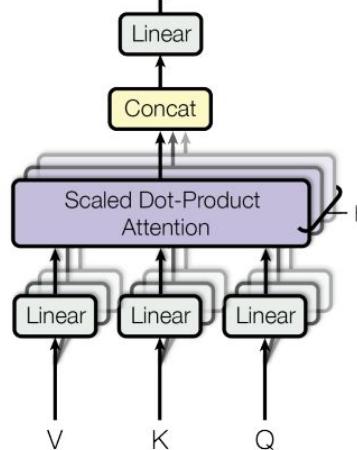
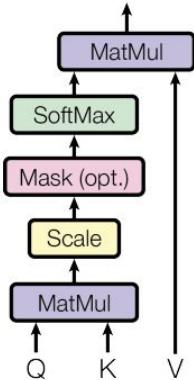
Illia Polosukhin* ‡
illia.polosukhin@gmail.com

Abstract

The dominant sequence transduction models are based on complex recurrent or convolutional neural networks that include an encoder and a decoder. The best performing models also connect the encoder and decoder through an attention mechanism. We propose a new simple network architecture, the Transformer, based solely on attention mechanisms, dispensing with recurrence and convolutions entirely. Experiments on two machine translation tasks show these models to be superior in quality while being more parallelizable and requiring significantly less time to train. Our model achieves 28.4 BLEU on the WMT 2014 English-to-German translation task, improving over the existing best results, including ensembles, by over 2 BLEU. On the WMT 2014 English-to-French translation task, our model establishes a new single-model state-of-the-art BLEU score of 41.8 after training for 3.5 days on eight GPUs, a small fraction of the training costs of the best models from the literature. We show that the Transformer generalizes well to other tasks by applying it successfully to English constituency parsing both with large and limited training data.

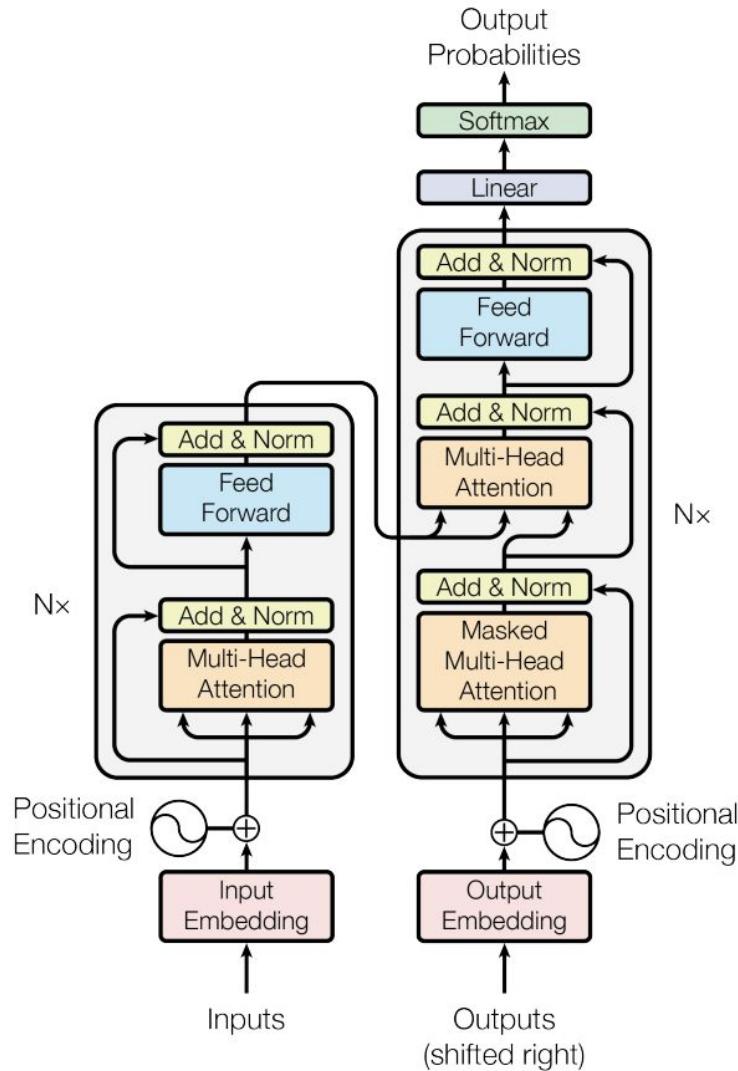


Attention please!

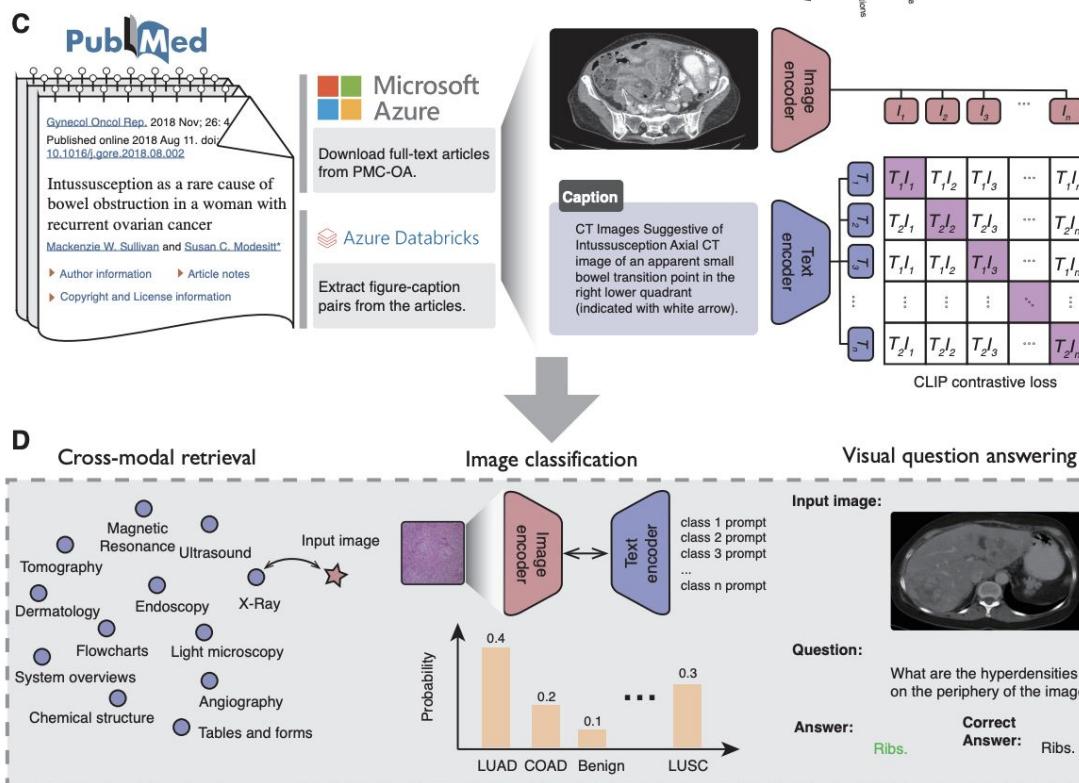


$$\sigma(\vec{z})_i = \frac{e^{z_i}}{\sum_{j=1}^K e^{z_j}}$$

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V$$

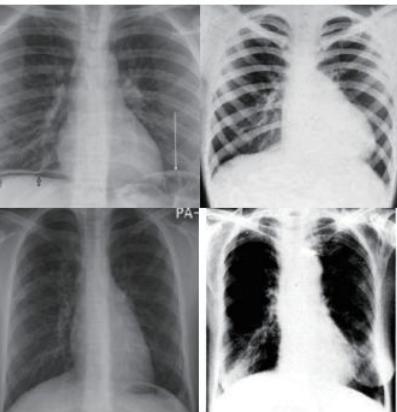


BiomedCLIP: a multimodal biomedical foundation model



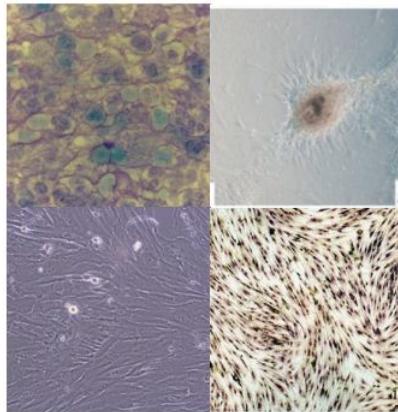
CLIP

BiomedCLIP



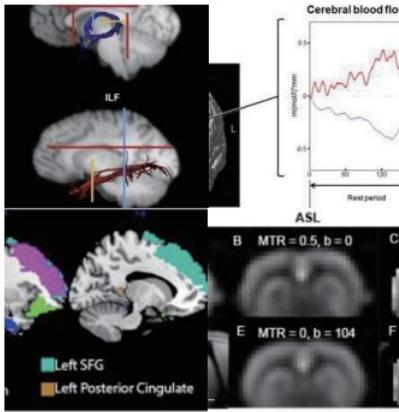
Caption

Chest X-ray on admission showing a large pleural effusion on the right.



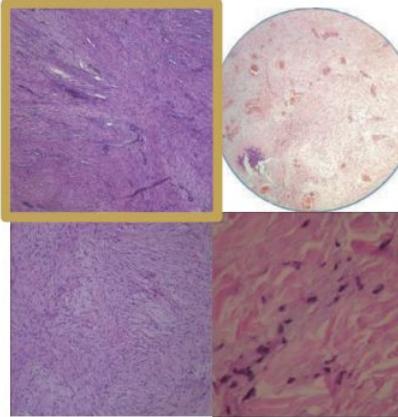
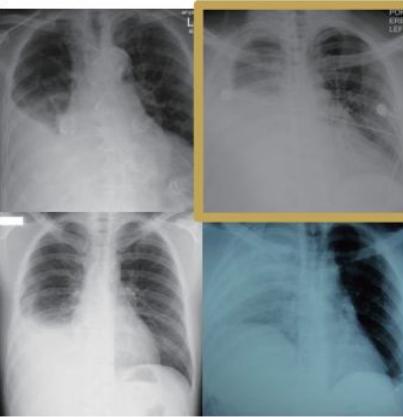
Caption

Photomicrograph showing proliferation of spindle cells with wavy nuclei in collagenous to myxoid stroma (Hematoxylin and Eosin staining, 40x).



Caption

ASL image shows increased cerebral blood flow (CBF) in left fronto-parieto-temporal region.



The Virtual Lab: AI Agents Design New SARS-CoV-2 Nanobodies with Experimental Validation

Kyle Swanson¹, Wesley Wu², Nash L. Bulaong², John E. Pak^{2,4}, James Zou^{1,2,3,4}

¹ Department of Computer Science, Stanford University

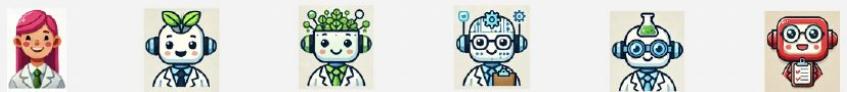
² Chan Zuckerberg Biohub - San Francisco

³ Department of Biomedical Data Science, Stanford University

⁴ Correspondence: jamesz@stanford.edu, john.pak@czbiohub.org

AI Agents propose strategy for nanobody design

(a) Phase 1: Team selection



Human Researcher Principal Investigator Immunologist
Machine Learning Specialist Computational Biologist Scientific Critic

(b) Phase 2: Project specification

Team Meeting



Summary

Modify nanobodies Ty1, H11-D4, Nb21, and VHH-72 to improve binding to KP3.

(c) Phase 3: Tools selection

Team Meeting



Summary

ESM, AlphaFold-Multimer, and Rosetta to design improved nanobodies.

(d) Phase 4: Tools implementation

ESM

DVQLVE... → DVQLVE...
ESM LLR = 3.65

Individual Meeting



Summary

Python script to compute ESM log-likelihood ratios for single point mutations.

AlphaFold-Multimer

DVQLVE... →
AF ipLDDT = 76.52

Individual Meeting



Summary

Python script to extract AlphaFold-Multimer interface pLDDT.

Rosetta

→
RS ΔG = -37.91

Individual Meeting



Summary

Python and XML scripts to compute binding energies with Rosetta.

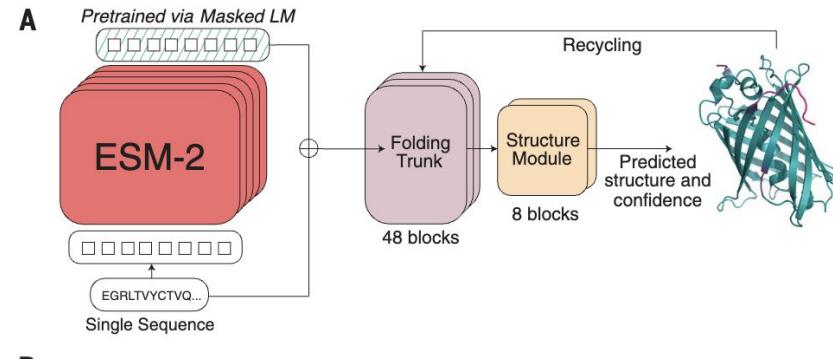
ESM (from Meta AI)

STRUCTURE PREDICTION

Evolutionary-scale prediction of atomic-level protein structure with a language model

Zeming Lin^{1,2†}, Halil Akin^{1†}, Roshan Rao^{1†}, Brian Hie^{1,3†}, Zhongkai Zhu¹, Wenting Lu¹, Nikita Smetanin¹, Robert Verkuij¹, Ori Kabeli¹, Yaniv Shmueli¹, Allan dos Santos Costa⁴, Maryam Fazel-Zarandi¹, Tom Sercu¹, Salvatore Candido¹, Alexander Rives^{1,2*}

Recent advances in machine learning have leveraged evolutionary information in multiple sequence alignments to predict protein structure. We demonstrate direct inference of full atomic-level protein structure from primary sequence using a large language model. As language models of protein sequences are scaled up to 15 billion parameters, an atomic-resolution picture of protein structure emerges in the learned representations. This results in an order-of-magnitude acceleration of high-resolution structure prediction, which enables large-scale structural characterization of metagenomic proteins. We apply this capability to construct the ESM Metagenomic Atlas by predicting structures for >617 million metagenomic protein sequences, including >225 million that are predicted with high confidence, which gives a view into the vast breadth and diversity of natural proteins.



Conclusions

- **Enhanced Diagnostic Accuracy:** Deep learning models excel in medical imaging, detecting anomalies with precision, often surpassing human performance.
- **Accelerated Drug Discovery:** Generative AI speeds up the design of novel drugs, **reducing time and cost** in the development pipeline.
- **Personalized Medicine:** AI enables **tailored treatments** by predicting patient-specific responses, improving outcomes, and minimizing side effects.
- **Scalable and Equitable Healthcare:** AI-powered solutions improve access to care in under-resourced areas through **telemedicine** and **predictive analytics**.
- **Data-Driven Insights:** Unlocks patterns in large-scale health data, **supporting evidence-based decisions** and advancing medical research.