Protein Design and Engineering with Multi-Modal Generative AI Models

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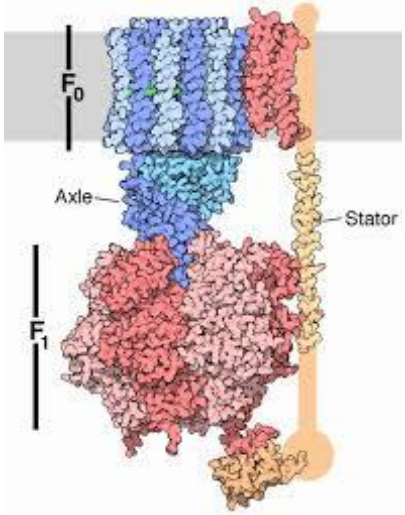
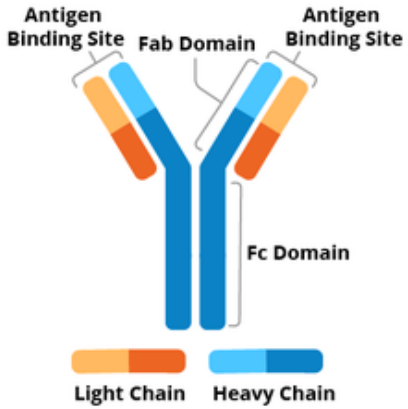
Proteins perform diverse biological functions



ATP Synthase

Producing energy currency (ATP) of life

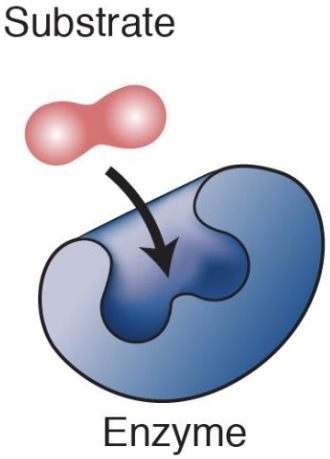


Antibody

Detecting and neutralizing viruses

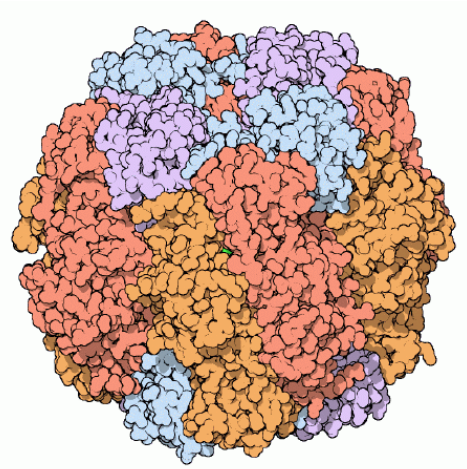
Insulin

Regulating blood sugar



Enzyme

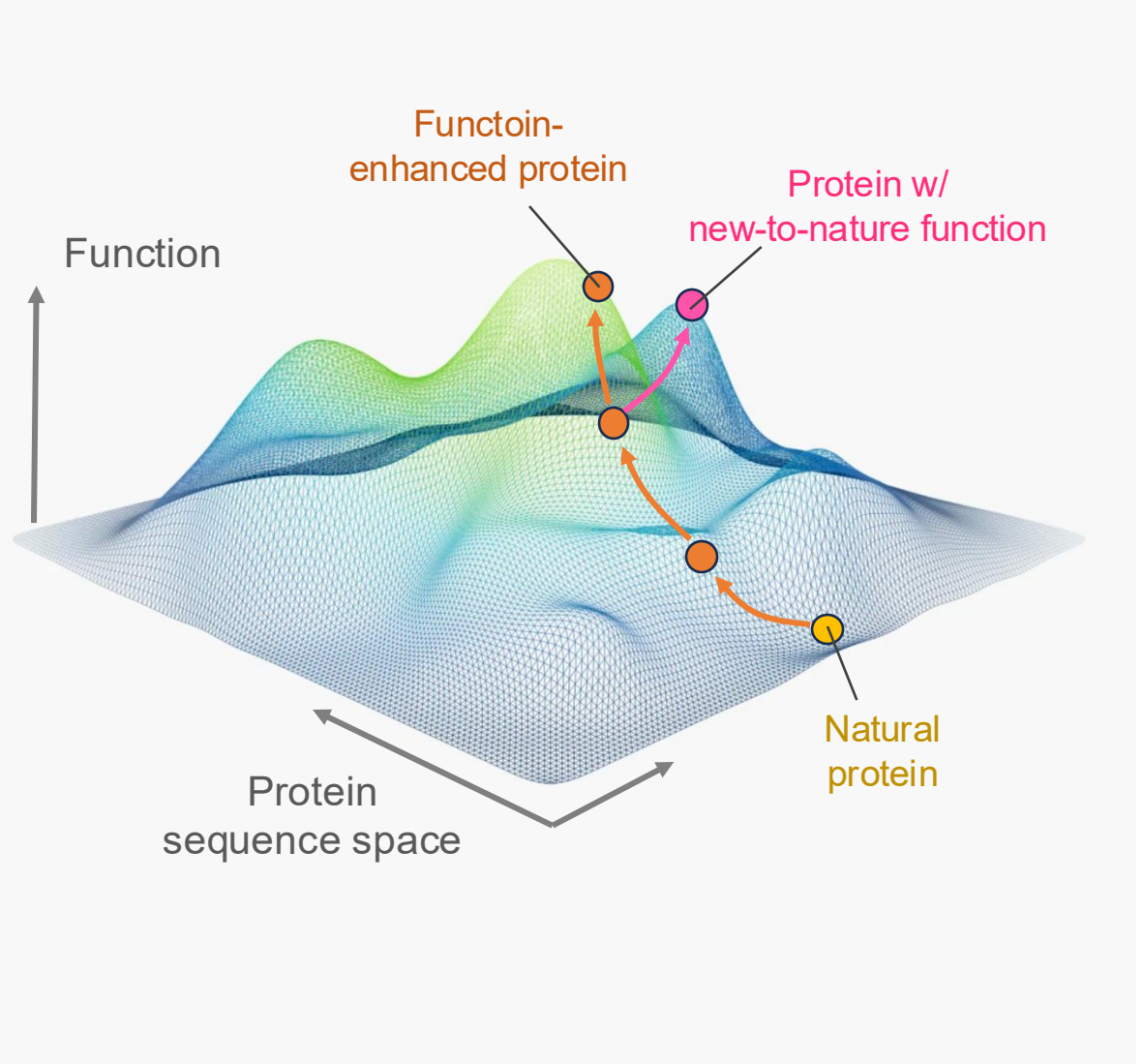
Speeding up chemical reactions



Rubisco

Capturing CO_2 in photosynthesis

Protein design and engineering

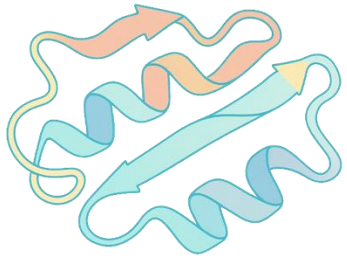


How is a protein's function determined?

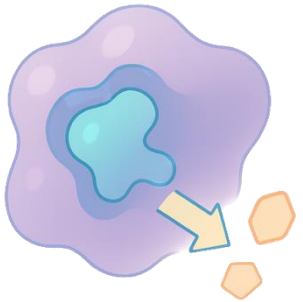
Protein's sequence-structure-function relationship

Protein sequence

Protein structure



Protein function



Nobel Prize in Chemistry 2024
for protein structure prediction (AlphaFold)

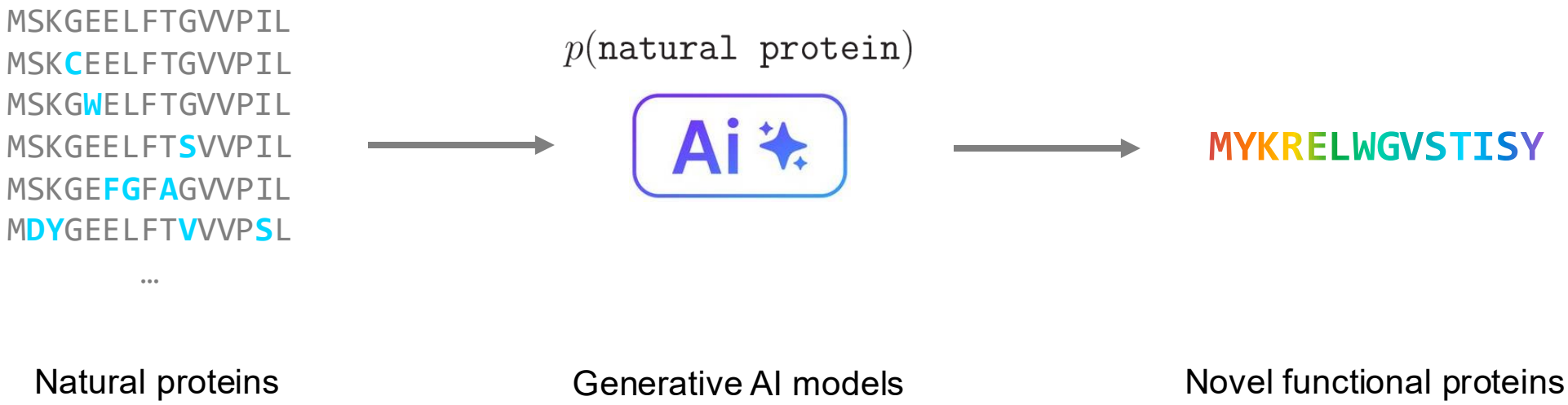
Demis Hassabis John Jumper

This project: *functional protein design*

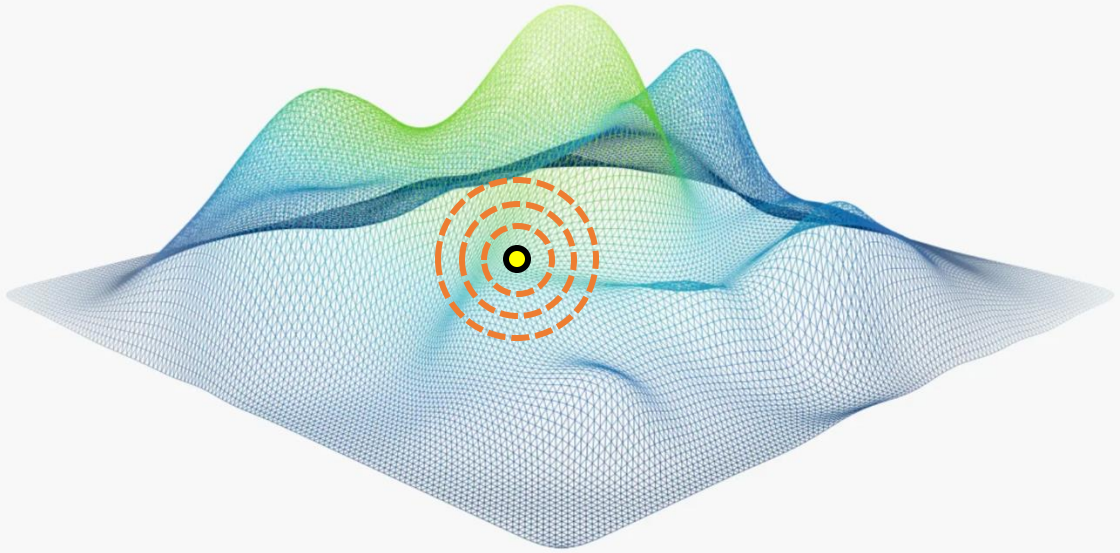
How to design functional proteins?

- Learning from natural protein evolution using GenAI

$$p(\texttt{functional protein}) \approx p(\texttt{natural protein})$$



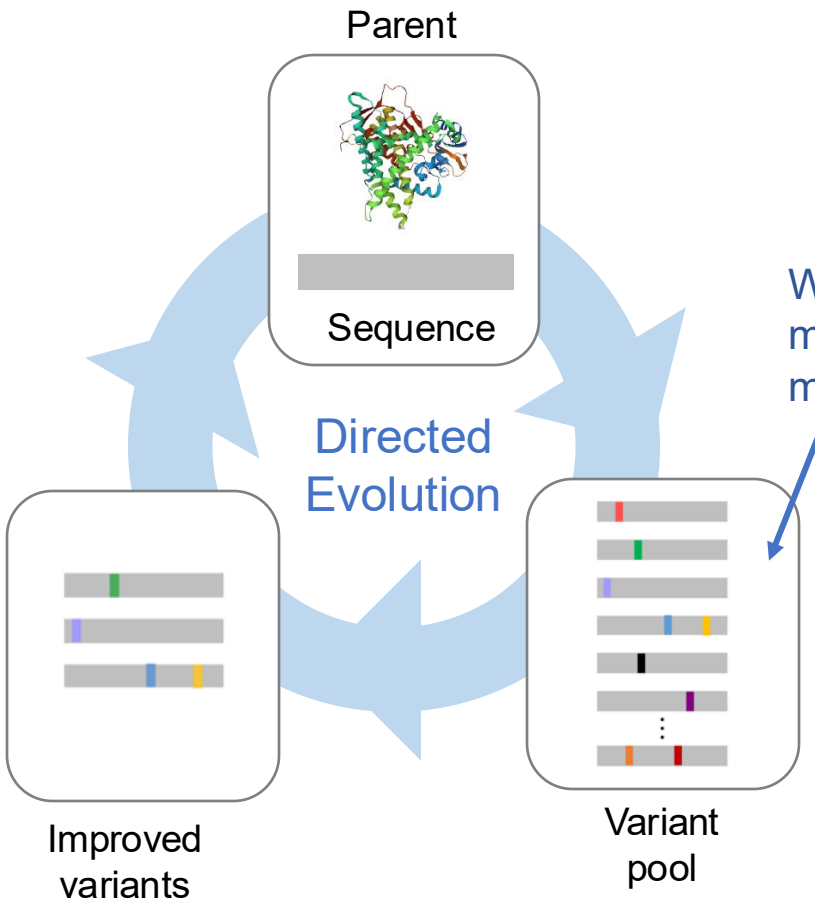
Protein fitness landscape



How to find functional proteins?

Directed evolution for protein engineering
(2018 Nobel Prize in Chemistry)

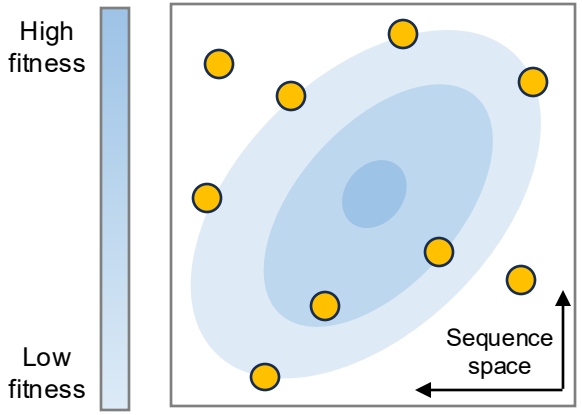
Frances Arnold
(Caltech)



Protein engineering for new-to-nature function

- **Task**: Design functional and diverse proteins
- **Challenge**: No existing fitness data (e.g., because the function is new-to-nature)

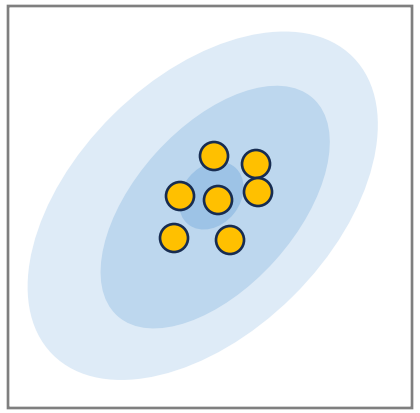
Conventional starting library design
(e.g., NNK library)



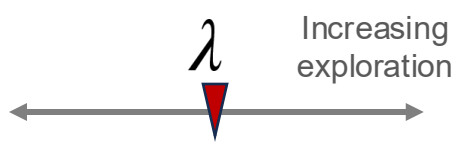
(random search, many are non-functional)

Our approach: Pareto-optimal library design (MODIFY)

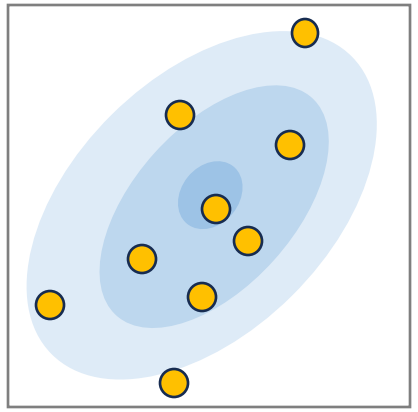
Goal 1: High ***fitness***



(most variants in the library are functional)



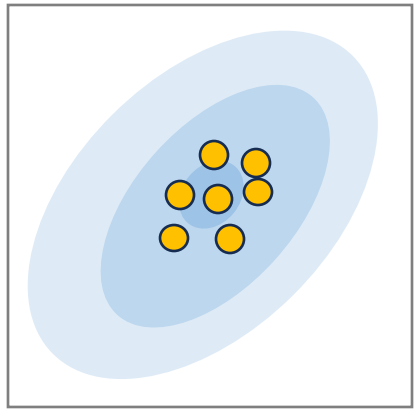
Goal 2: High ***diversity***



(the library contains novel protein variants)

Zero-Shot Fitness Prediction using Foundation Models

Goal 1: High ***fitness***



Q: Cold-start problem. No data to train a supervised fitness predictor.

A: Use pre-trained protein language models to make zero-shot fitness prediction

- ***Natural language model (LM):***

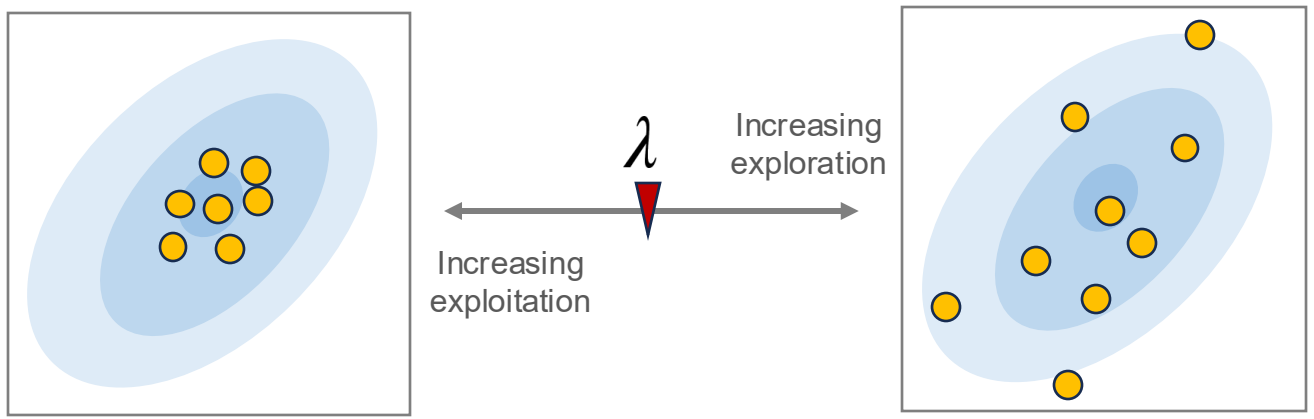
- ***Protein language model (PLM):***

- PLMs are trained on protein sequences we observed in nature
- Evolutionary plausibility correlates with fitness

Characterizing the library diversity

Goal 1: High ***fitness***

Goal 2: High ***diversity***



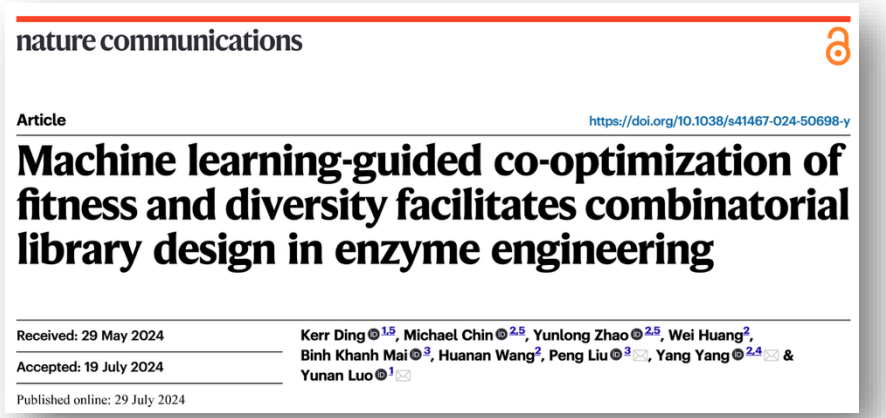
- **Goal:**

$$\max_{p \in \mathcal{P}} \mathbb{E}_{\boldsymbol{x} \sim p(\boldsymbol{x})} \, \text{fitness}\,(\boldsymbol{x}) + \lambda \cdot \, \text{diversity}\,(p)$$

Predicted by protein language model

Quantified by sequence entropy

- A Pareto optimization problem
- Learned a probability distribution over protein sequence


nature communications

Article

https://doi.org/10.1038/s41467-024-50698-y

Machine learning-guided co-optimization of fitness and diversity facilitates combinatorial library design in enzyme engineering

Received: 29 May 2024

Accepted: 19 July 2024

Published online: 29 July 2024

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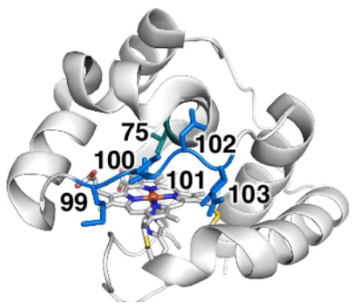
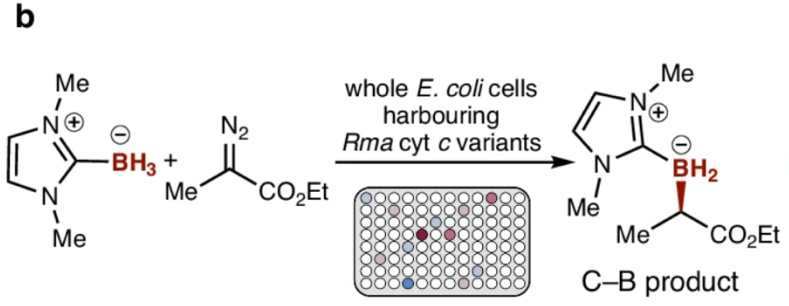
Ding, K., Chin, M., Zhao, Y. et al. "Machine learning-guided co-optimization of fitness and diversity facilitates combinatorial library design in enzyme engineering," *Nature Communications*, 2024

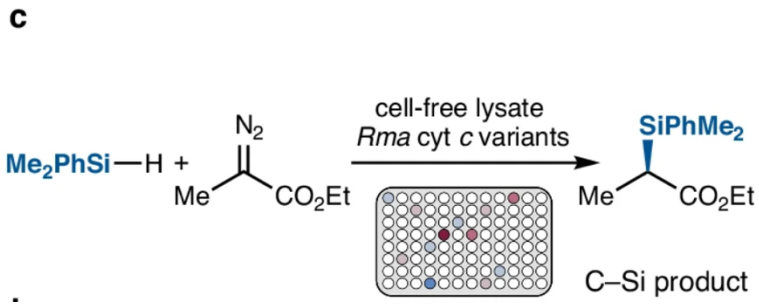
Using AI to Engineer generalist new-to-nature biocatalysts



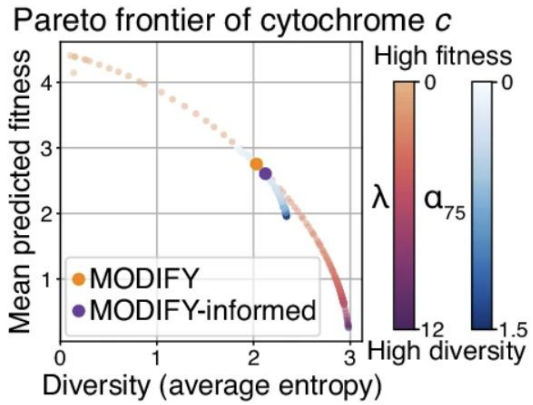
Rma cytochrome *c*

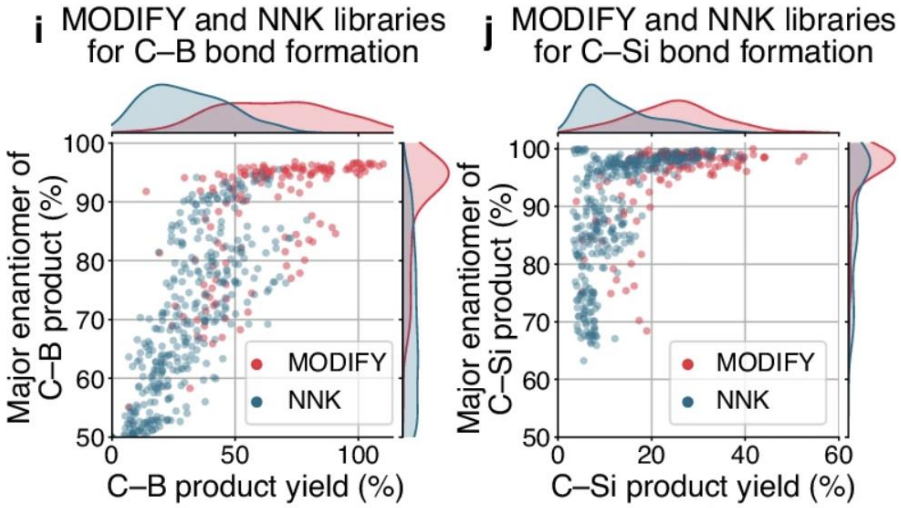


Carbon-boron (C-B) bond formation

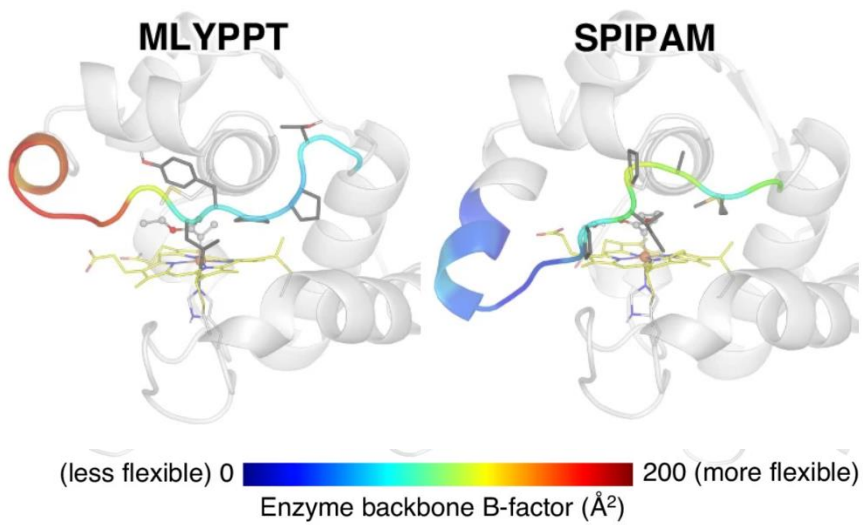


Carbon-silicon (C-Si) bond formation

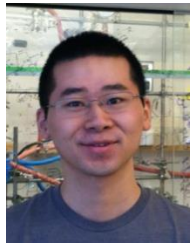




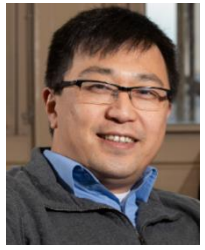
Improved two objectives: yield and selectivity



GenAI designed novel proteins 6-mutation away from human-designed proteins



Yang Yang (UCSB Chemistry)



Peng Liu (U of Pitt Chemistry)

Ding, K., Chin, M., Zhao, Y. et al. "Machine learning-guided co-optimization of fitness and diversity facilitates combinatorial library design in enzyme engineering," *Nature Communications*, 2024

How to design functional proteins?

- Learning from natural protein evolution using GenAI

$$p(\texttt{functional protein}) \approx p(\texttt{natural protein})$$

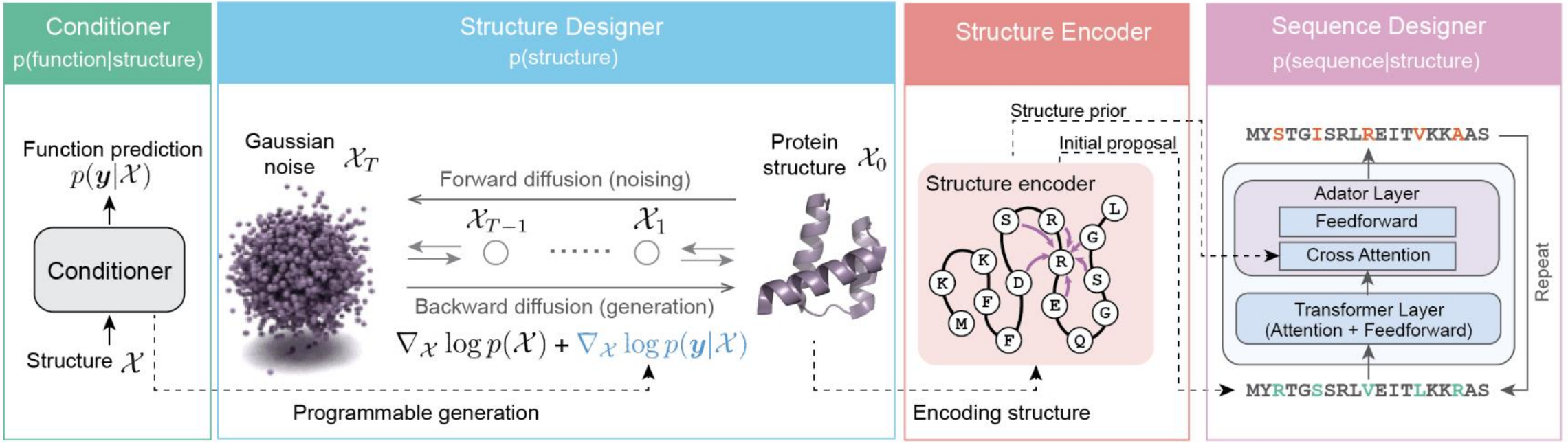
- Function-guided protein design with GenAI

$$p(\texttt{protein}|\texttt{function}) \propto p(\texttt{protein}) \times p(\texttt{function}|\texttt{protein})$$

Protein sequence/structure GenAI model

Protein function prediction model

Programmable multi-modal protein design



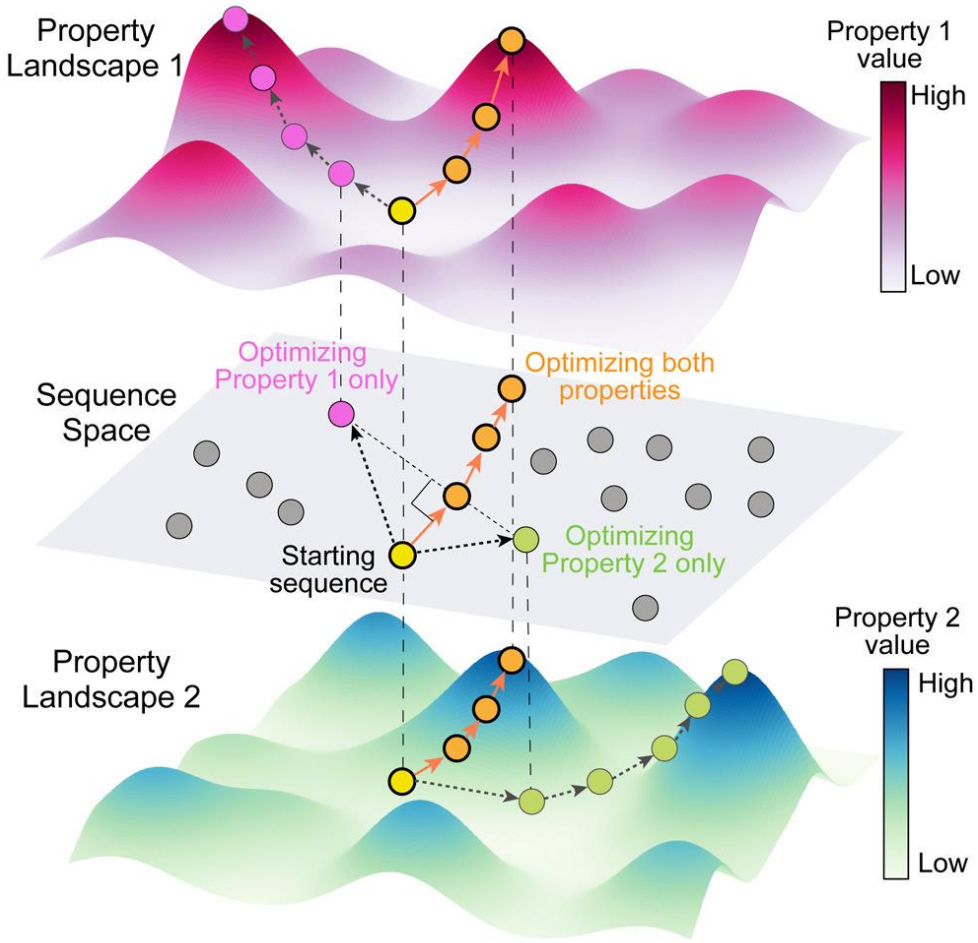
Protein function prediction model

Protein structure generative model

Protein sequence generative model

Multi-objective protein design

Recent results



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Article

Pareto-optimal sampling for multi-objective protein sequence design

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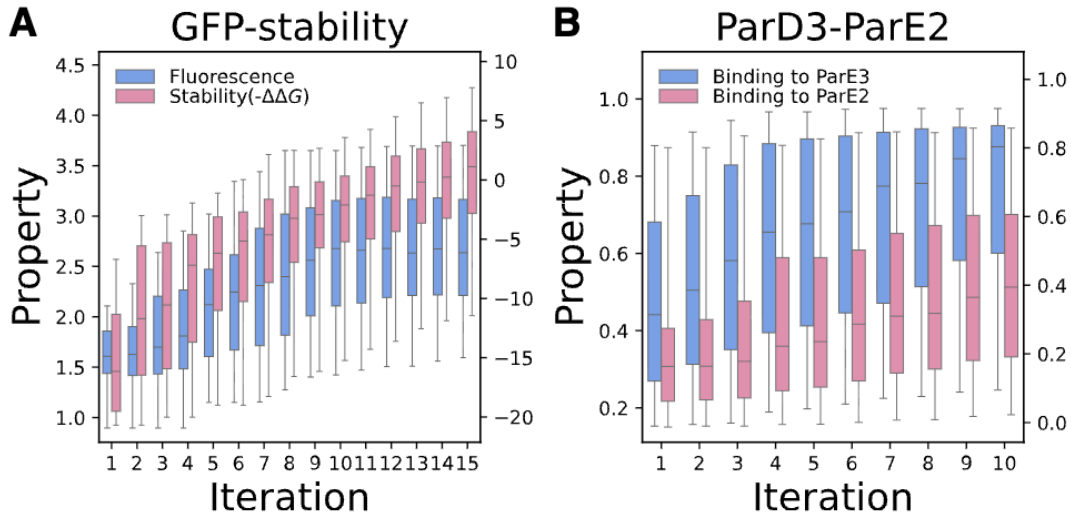
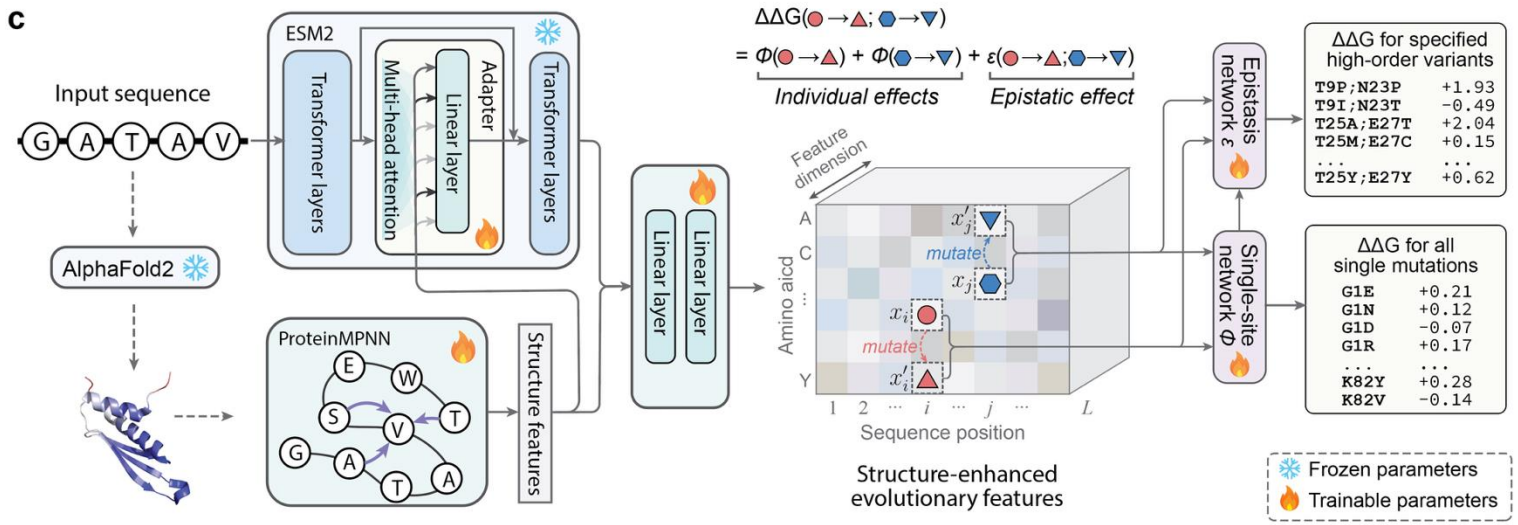
https://doi.org/10.1016/j.isci.2025.112119

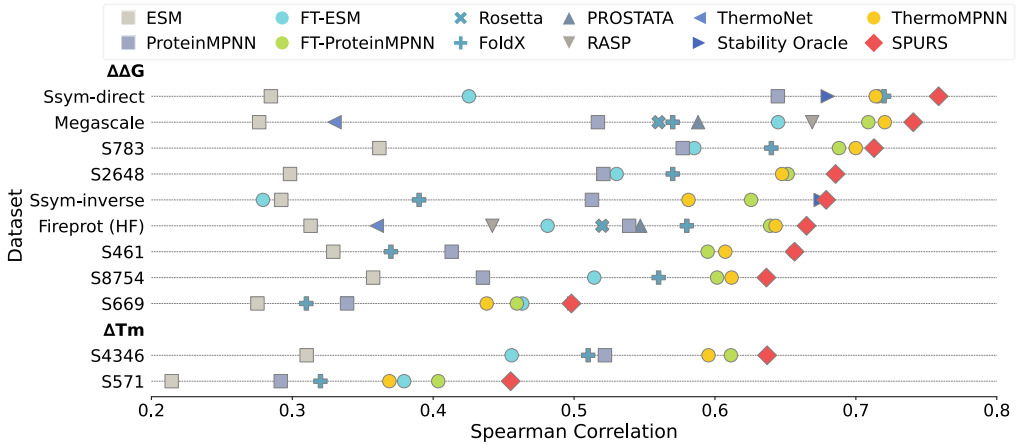


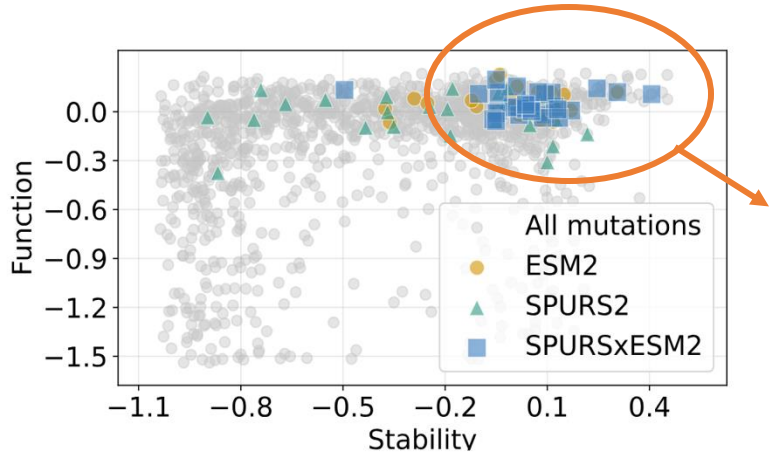
Supported by GaTech IDEaS x Microsoft CloudHub Seed Grant 2024

Multi-modal, multi-objective protein design

Preliminary results







Functional and stable proteins

Li, Ziang, and Yunan Luo. "Rewiring protein sequence and structure generative models to enhance protein stability prediction." *RECOMB*, 2025.

Conclusion

- Protein generative AI models capture evolutionary patterns of functional proteins
- Function-guided protein design improves hits rate
- Enables the design of novel, diverse functional proteins

Acknowledgements

- **Group:** Kerr Ding, Ziang Li, Jiaqi Luo, Tony Tu, Shitong Dai
- **Collaborators:** Huimin Zhao, Yang Yang, Peng Liu, Tianhao Yu, Junming Zhao, Liupeng Zhao, Michael Chin, Yunlong Zhao, Wei Huang, Binh Khanh Mai, Huanan Wang, et al.
- **Fundings:** GaTech IDEaS x Microsoft CloudHub Seed Grant, NIH MIRA (R35GM150890), NSF CAREER (2442063)

Georgia Tech Institute for Data Engineering and Science

Microsoft Azure

NIH National Institutes of Health

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