NanoGPT2: De novo nanobody sequence generation using a fine-tuned protein language model

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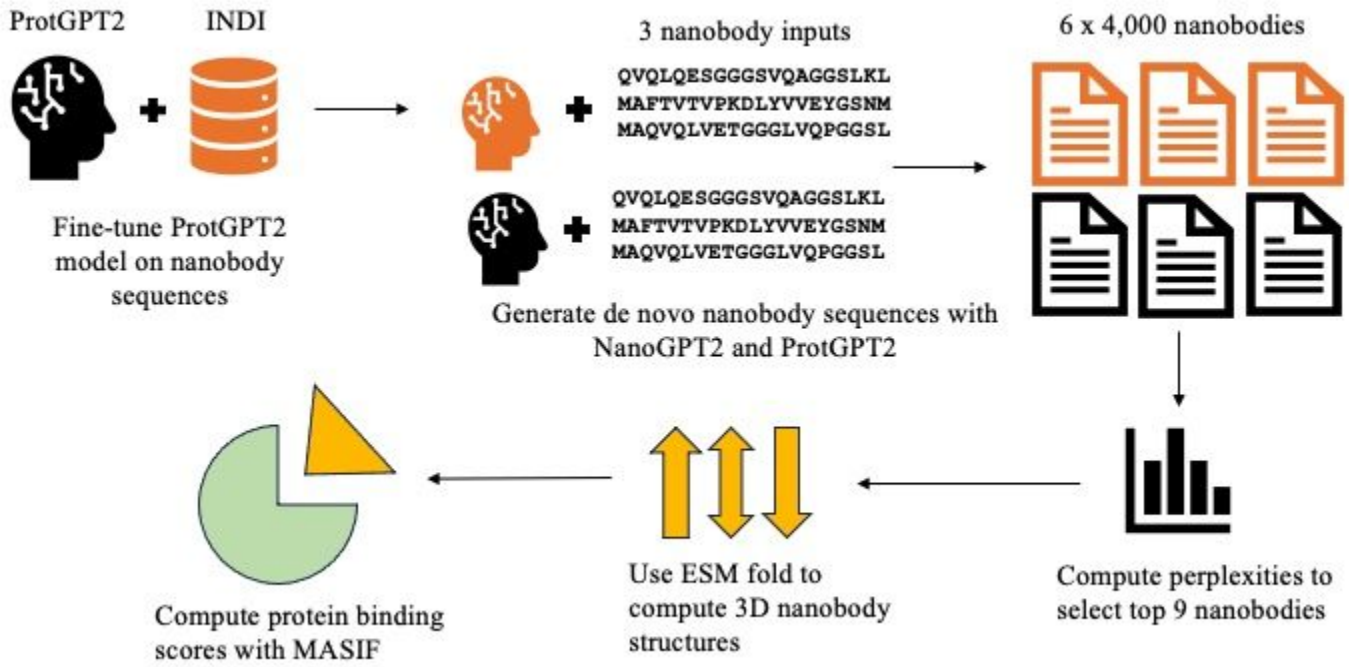
Introduction & Purpose

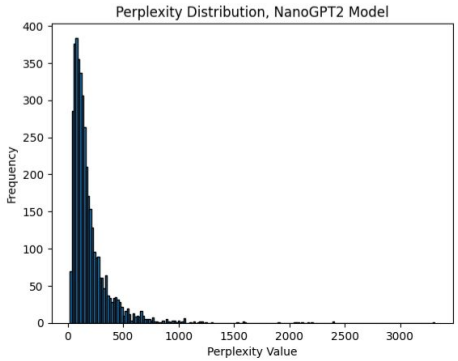
- Within the past few years, **deep learning** has been applied to **de novo protein generation tasks** with much success.
- Last year, **ProtGPT2**, a large-language model (LLM) built on the GPT2 architecture, was able to produce de novo protein sequences with **striking similarity to those found in nature**
- **Nanobodies**, a class of proteins that are **similar to antibodies but more simple**, are known for having many **therapeutic effects** due to their size and properties. However, effective **de novo synthesis of nanobodies remains challenging**.
- In this project, we successfully **fine-tuned ProtGPT2 to create NanoGPT2, a new LLM intended to facilitate de novo nanobody synthesis**.
- Additionally, we assess the **structural integrity** and **predicted protein-protein interaction affinities** of our **best nanobody sequences** using **ESMFold** and **MaSIF** to demonstrate the potential downstream **clinical relevance** of our approach.

Methods & Data



Results: Fine-tuned vs. Base Model

a)



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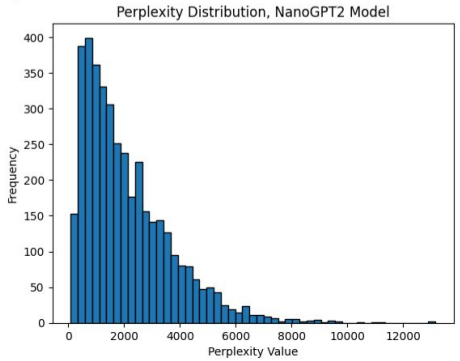

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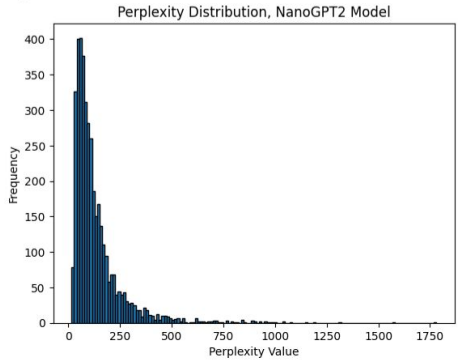

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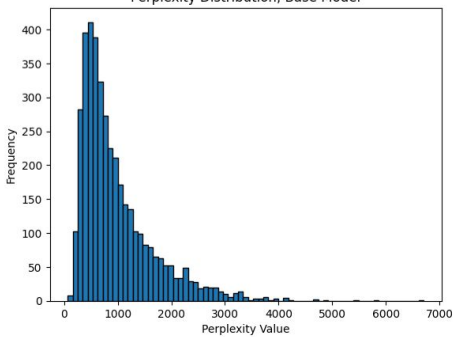

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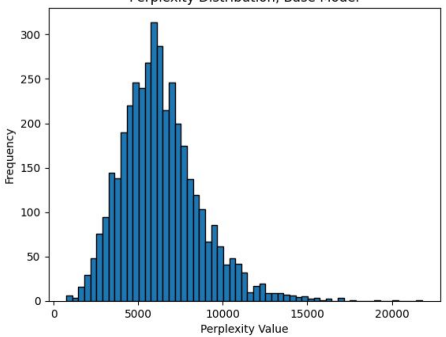
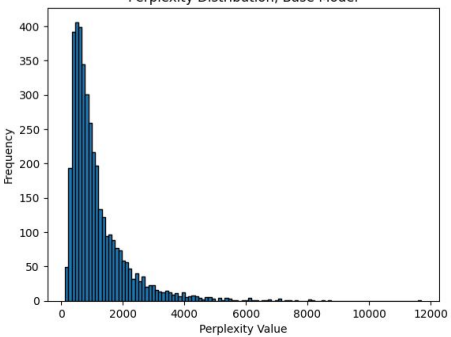
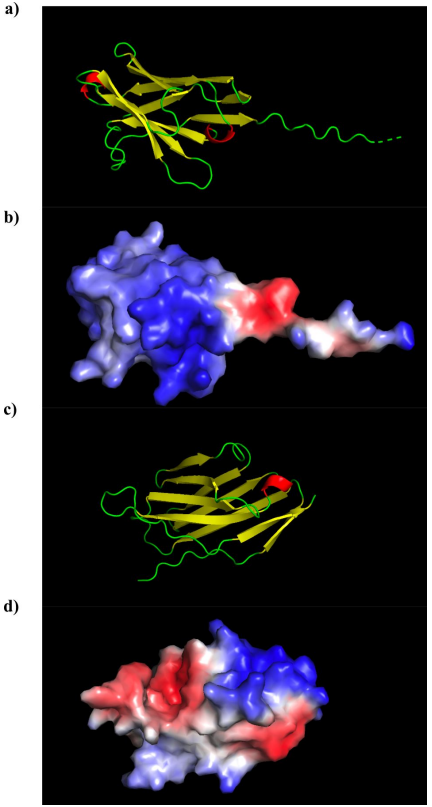


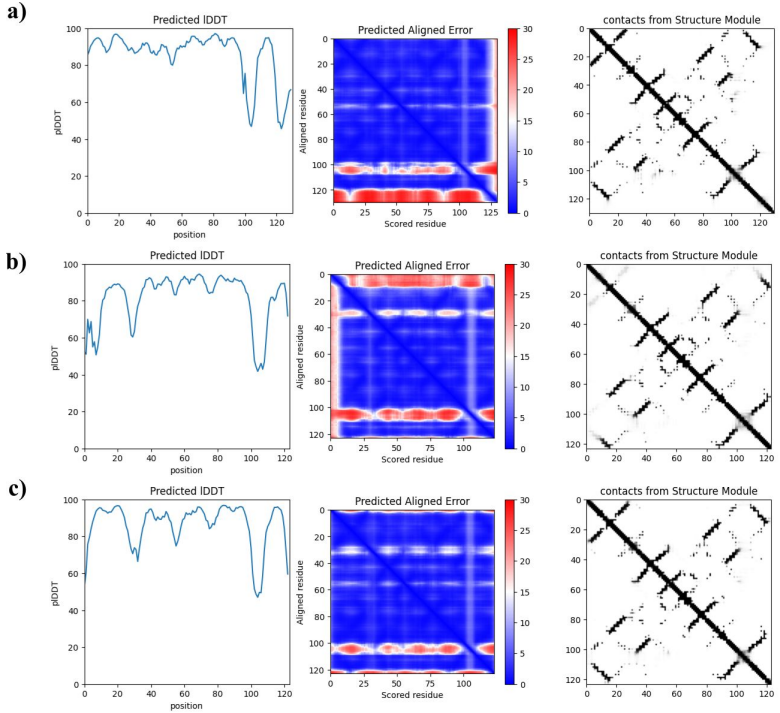
c)



Nanobody ID	Perplexity Score
7OM4, 1	18.7
7OM4, 2	19.6
7OM4, 3	20.4
5JDS, 1	82.5
5JDS, 2	100.2
5JDS, 3	100.6
5DWX, 1	14.6
5DWX, 2	15.0
5DWX, 3	15.6

Results: ESM and MaSIF predictions





Nanobody ID	Top Score	Protein ID	Chemical Function
7OM4, 1	0.9830	3F8H	Unknown
7OM4, 2	0.9630	2J6X	Oxidoreductase
7OM4, 3	0.8446	3EQX	DNA binding
5JDS, 1	0.9868	1NJJ	Lyase
5JDS, 2	0.9969	2EJ0	Transferase
5JDS, 3	0.9896	1FL6	Immune system
5DWX, 1	0.9587	1VJL	Unknown
5DWX, 2	0.9841	2FU5	Signaling
5DWX, 3	0.9816	2QUY	Hydrolase

Discussion: NanoGPT2 was successful

- Based on our results, we concluded that **NanoGPT2** was **far superior** at the de **novo nanobody generation tasks** compared to the baseline model, **ProtGPT2**.
- For each of the three reference nanobody groups selected, we noted **statistically significant perplexity scores against the baseline (p-value=0.00)**, with a substantial separation in means.
- We found a notable **clinically relevant partner protein** was associated with **African Sleeping Sickness**
- Furthermore, our **top scoring sequences** were found to be structurally viable
- **Future work** could **involve attempting to express these these nanobodies in a wetlab setting**

References

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