Multi-Objective Active Learning for Nanobody Development

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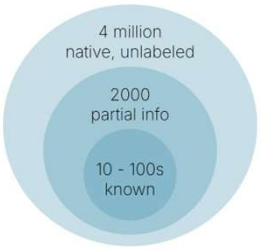
Motivation

Nanobodies:
- small "**keys**" that match specific sites on cells, proteins
- can bind to **block or modulate specific functions**
- can **carry payload** (e.g., drug, fluorescent marker)

Advantages:
- **Small size** → reach hidden epitopes that classical antibodies cannot reach
- **Stable & robust** → more tolerant to harsh conditions
- **Versatile** → can be engineered for therapy, diagnostics, research

Dataset



Small dataset (10 - 100s): in-house nanobodies with measured yields & developability (high-quality labels).
Medium dataset (~2,000): nanobodies with partial annotations (literature/structural).
Largest dataset (4 million): non-redundant native repertoire sequences (**no experimental data, unlabeled**).

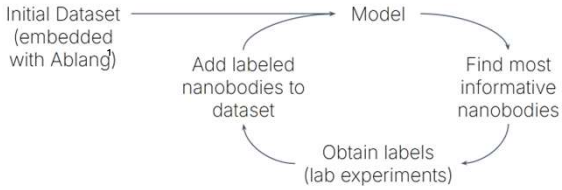
Research Question

Obtaining experimental data is **costly**. A great ML model could guide discovery as it can point to potential candidates for a task, ensuring **developability** in the wet lab. A great model needs **data** to learn from.

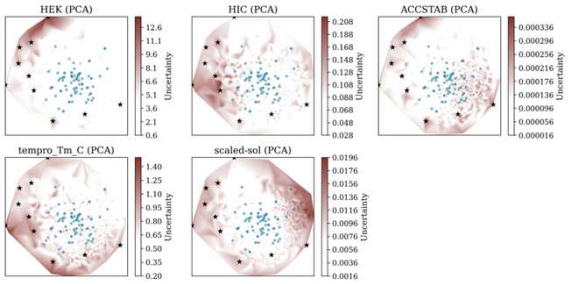
Which experiments (= labeled data) would help to train such a model?

Active Learning

Big-Picture Idea



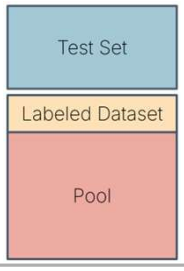
Uncertainty



Uncertainty Map highlighting areas with uncertain predictions per target in Ablang embedding space (dimensionality reduced with PCA). Blue = initial nanobodies; black = selected batch of nanobodies.

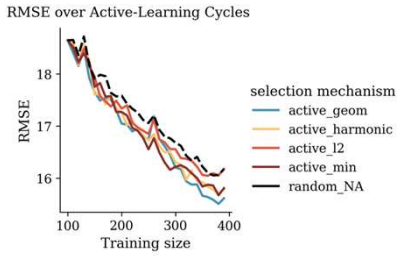
Active Learning Cycle

In each AL cycle, to select **batch of nanobodies (e.g., 10):**
- filter based on **constraints** for yield, thermal stability, solubility (as predicted)
- drop **outliers**
- select **top X** nanobodies that **maximize uncertainty** in predicting yield, polyreactivity, accelerated & thermal stability, solubility
- greedily select **diverse subset**



Simulation

- Simulation on **3000 nanobodies** from our native library
- **Labels** were obtained using Abpred[2], TEMPRO[3] and Protein-Sol[4]
- Per-target models with per-target uncertainties; different **aggregation strategies**



Conclusion

Summary:
- Multi-objective active nanobody selection strategy for better property predictions

Next Steps:
- Model catering to distribution shift
- Refined multi-objective optimization techniques
- Tests on complete native library
- Real AL cycle + tags

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References

[1] https://github.com/oxpig/AbLang2
[2] https://github.com/maxhebditch/abpred
[3] https://github.com/Jerome-Alvarez/TEMPRO
[4] https://protein-sol.manchester.ac.uk/

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