Icahn School of Medicine at Mount Sinai

Prescient Design
A Genentech Accelerator

A guided design framework for the optimization of therapeutic-like antibodies

Amy Wang, Zhe Sang, Samuel D. Stanton, Jennifer L. Hofmann, Saeed Izadi, Eliott Park, Jan Ludwiczak, Matthieu Kirchmeyer, Darcy Davidson, Andrew Maier, Tom Pritsky, Nathan C. Frey, Andrew M. Watkins, Franziska Seeger

Main idea

Antibodies must meet stringent criteria for safety and stability
Experimental validation is very low-throughput and costly

Inspiration from **Lipinski's rule** for oral small molecules:
Biophysical definitions to ***filter*** possibly problematic candidates

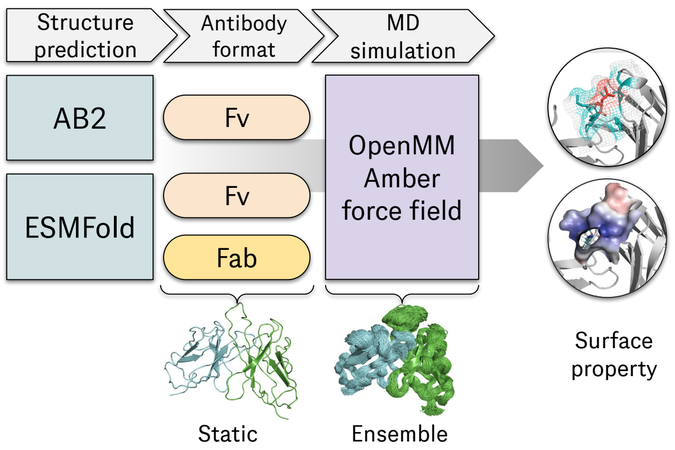
Main contributions

1. Evaluate biophysical filters on experimental viscosity datasets
2. Introduce a **guided design method** which:
   - Predicts biophysical properties **directly from sequence**
   - Optimizes molecules for therapeutic similarity

Biophysical definitions of therapeutic similarity

Therapeutic Antibody Profiler (TAP)[1] and **MolDesk**[2] both consider electrostatics and hydrophobicity

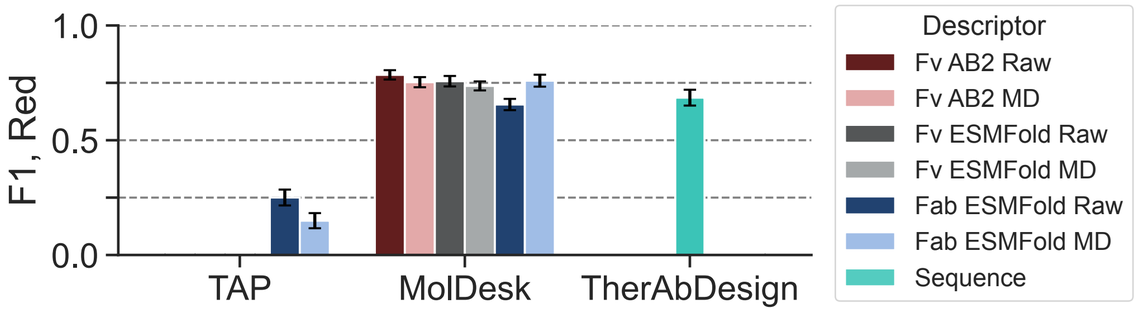
	TAP	MolDesk
Structure prediction	AB2	ESMFold
Reference structure	Fv	Fab
Surface definition	Surface exposed (custom metrics)	Detailed mesh (APBS, SAP)
Region considered	CDR	Fv
Molecular dynamics	✗	✔



We answer: How do different biophysical definitions affect filtering capabilities?

Benchmark filters on viscosity measurements

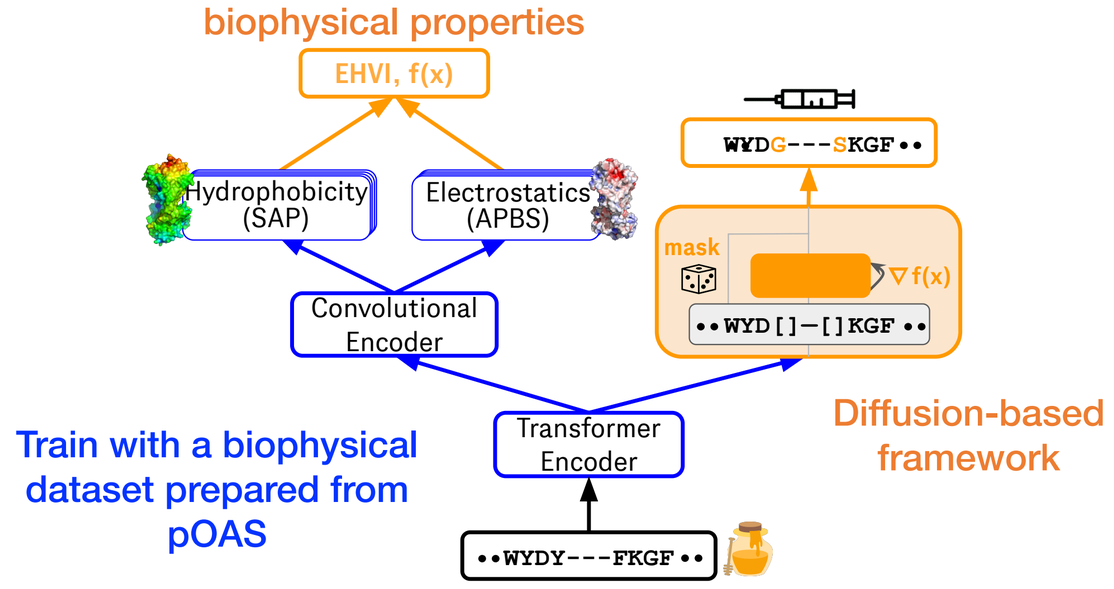
High risk defined by 5% tails in biophysical property distribution of clinical candidates



- Detailed surface definitions (APBS, SAP) appear beneficial
- Computing over MD ensemble mean does not improve filtering on Ab21[3], PDGF38[4], and GCGR[5] viscosity datasets
- TherAbDesign is an effective screening filter compared to structure baselines

TherAbDesign

We **predict** SAP and APBS properties directly from sequence
LaMBO-2 algorithm[6] to **optimize** for therapeutic similarity



Sequence-based predictions strongly correlate with structure-derived physical calculations, demonstrating robust generalization

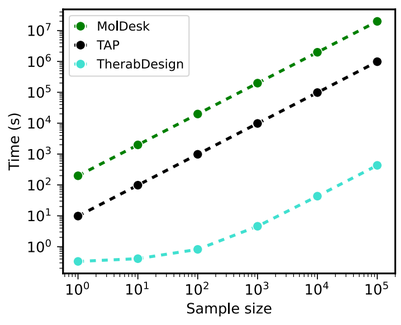
	Fv APBS neg	Fv APBS	Fv CAP	Fv SAP BM	Fv SAP WW
pOAS, IID	0.88 ± 0.03	0.90 ± 0.01	0.91 ± 0.03	0.84 ± 0.04	0.88 ± 0.02
Ab21	0.86 ± 0.03	0.83 ± 0.03	0.85 ± 0.03	0.89 ± 0.02	0.84 ± 0.07
PDGF38	0.86 ± 0.03	0.88 ± 0.02	0.63 ± 0.08	0.69 ± 0.07	0.50 ± 0.05
GCGR	0.52 ± 0.18	0.52 ± 0.07	0.82 ± 0.01	0.86 ± 0.01	0.88 ± 0.01

PDGF38 and GCGR datasets include local variants around seed where viscosity liability has electronegativity and hydrophobicity mechanistic origins, respectively

Computationally efficient compared to structure based approaches

Scoring 10^5 sequences takes **7 minutes** with TherAbDesign on an A100 GPU

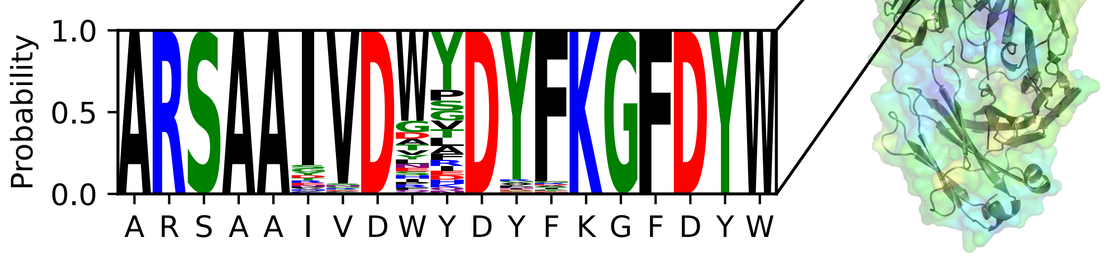
Compare to:
TAP: 10 CPU days
MolDesk: 230 CPU days
No dynamics, single Fab structure



Guided Design

TherAbDesign can directly address underlying liabilities without requiring mechanistic understanding of their biophysical origins

GCGR viscosity liability has known hydrophobicity origins
→**Design modify aromatic residues in CDRH3**



14 designs overlap with experimental valuation dataset
12 decrease viscosity relative to parental molecule

Related work

[1] Raybould et al. Five computational developability guidelines for therapeutic antibody profiling. PNAS 2019.
[2] Park et al. Molecular surface descriptors to predict antibody developability: sensitivity to parameters, structure models, and conformational sampling. mAbs 2024.
[3] Lai, et al. Machine learning applied to determine the molecular descriptors responsible for the viscosity behavior of concentrated therapeutic antibodies. Molecular Pharmaceutics, 2021.
[4] Apgar, et al. Modeling and mitigation of high-concentration antibody viscosity through structure-based computer-aided protein design. PLOS ONE 2020.
[5] Dai et al. Variable domain mutational analysis to probe the molecular mechanisms of high viscosity of an IgG1 antibody. mAbs 2024.
[6] Gruver et al. Protein Design with Guided Discrete Diffusion. NeurIPS 2023.

read the paper!