Advancing Fragment-Based Drug Discovery in the ASAP Consortium with Fragmenstein

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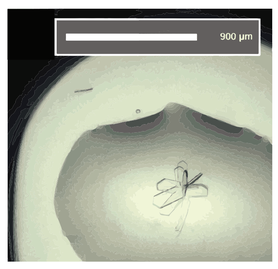
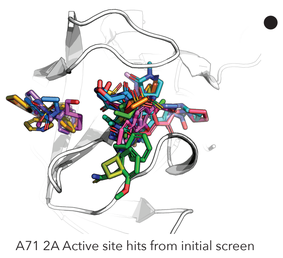
(1. University of Oxford; 2. MSKCC; 3. Diamond Light Source)

ASAP

Accessible Antivirals to Prevent Pandemics

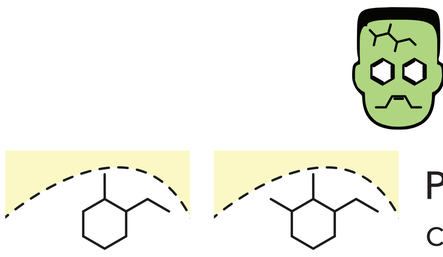


- **Collaborative** global effort
- Accelerate **drug development** against overlooked viral pathogens
- Born from the **COVID Moonshot** project
- Diverse combined expertise
- High-throughput crystallographic **fragment screening**: >1,000 fragments screened per target; data analysed with XChem Explorer and PanDDA and uploaded to Fragalysis



A71 2A Active site hits from initial screen

Fragmenstein



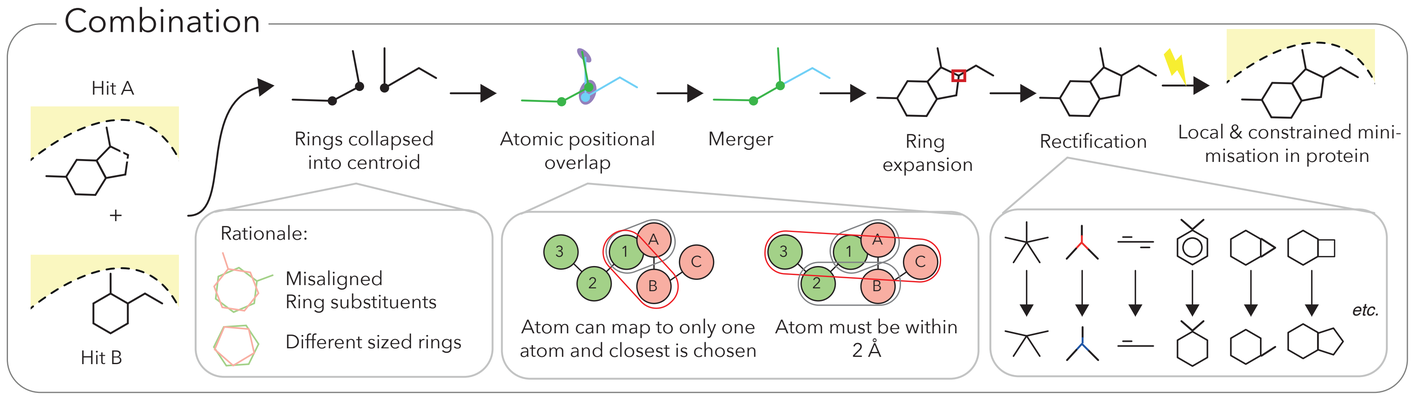
Principle: structural analogues generally conserve binding mode and atom positions

Problem: This is not strictly obeyed by docking and merging software

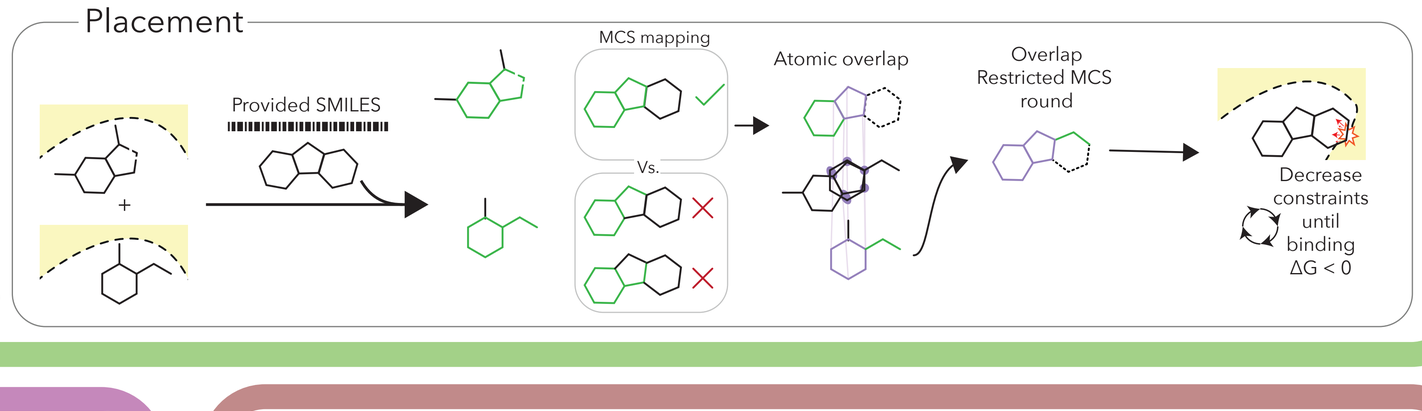
Solution: Fragmenstein

- Generate conformers by stitching together atomic positions of parent hits and minimising in the protein
- Performs combinations (linking + merging) or Placements

Combination

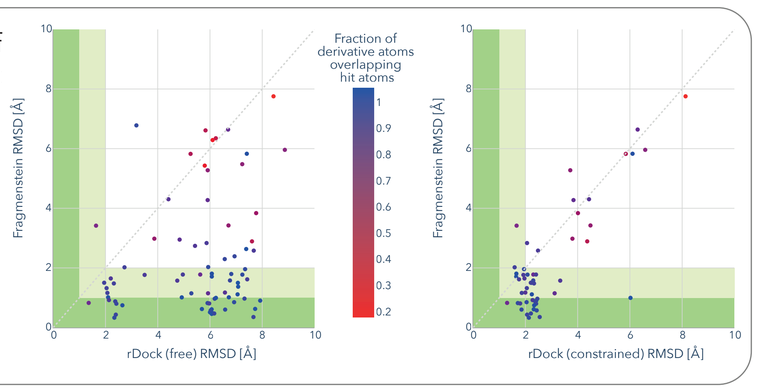


Placement



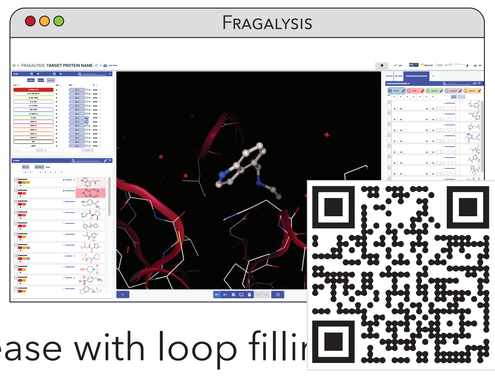
Accuracy

Accuracy of placement of COVID19 MPro Moonshot compounds

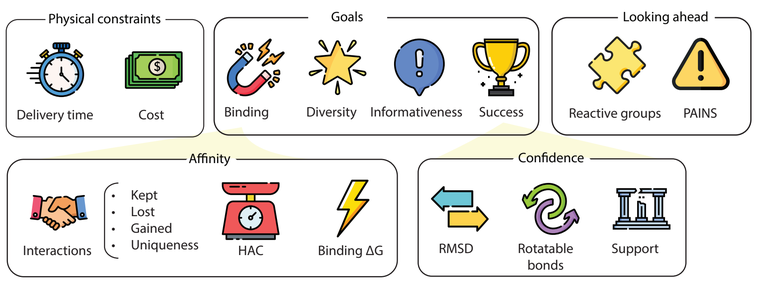


Fragmenstein in ASAP

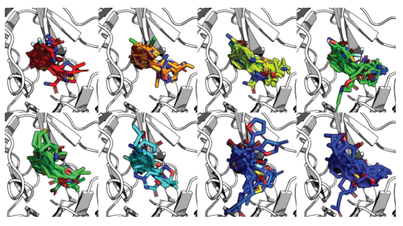
Within ASAP at the **hit discovery** stage, Fragmenstein is used in many pipelines to place derivatives faithfully against parents hits ready for external review in Fragalysis. Three hit discovery stage targets elaborated as of February 2024:



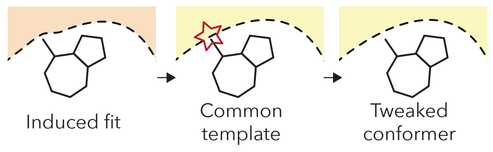
- **Enterovirus A71 2A** – cysteine protease with loop fillin hydrophobic P2 pocket when shut
- **Enterovirus D68 3C** – cysteine protease with P1 pocket for glutamine and large P2 for hydrophobics
- **Zika NS2B/3** – serine protease (NS3) with P1 pocket for arginine held thanks to NS2B activator



Predicted binding energy is a poor metric for selection: **multiple terms** are used in **scoring**, such as penalty for number of unconstrained atoms



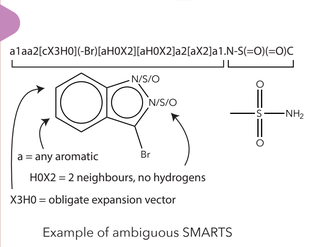
Diversity is key in exploration: **interaction fingerprint clustering** (binary or probability scaled) is often performed



Tweaking conformers generated by induced fit, but to be shown within a common template

Virtual screening

OpenEye ROCS refinement – Conformers refined by minimising in the pocket with Fragmenstein



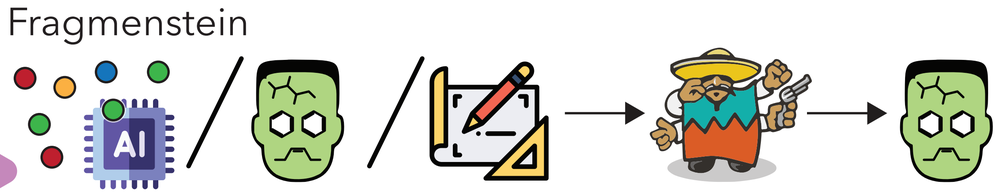
Example of ambiguous SMARTS

Arthorian Quest – Targeted ambiguous SMARTS patterns are easily created for querying in NextMove Software Arthor and placement with Fragmenstein against parent compounds

Fragment Knitwork – Substructures or shape-and-colour analogues of two parent hits are linked by catalogue enumeration

De novo + analogue search

Given generated compounds, catalogue analogues are sought with NextMove Software SmallWorld and then placed and ranked with Fragmenstein



Generated compounds created via:

- **Fragmenstein combination route**
- **SILVR**, a deep-learning method utilising constrained denoising diffusion), combined with the chemistry-correction of Fragmenstein's Rectifier
- **Strife**, a hotspot-driven deep learning method
- Manual sketches and other approaches

See also

Poster P17. Development of antiviral toolbox compounds targeting the Nsp3 Macrodomain 1 of SARS-CoV-2
Poster P18. The AI-driven Structure-enabled Antiviral Platform (ASAP): Accelerating drug discovery and development through crystallographic fragment screening
Poster P38. A Formulaic Approach to Rapid Fragment Progression

GitHub: Tools | YouTube: Presentation | Fragmenstein preprint | Mac1 paper | Moonshot paper

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