Scripps Research

D3R GC4:

On-the-fly sampling of macrocycle conformations during docking to BACE-1

Diogo Santos-Martins, Jérôme Eberhardt, Giulia Bianco,
Leonardo Solis-Vasquez, Francesca Alessandra Ambrosio, Andreas Koch
Stefano Forli

Department of Integrative Structural and Computational Biology
The Scripps Research Institute, La Jolla, California, USA

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@ForliLab

The team

Diogo
Santos-Martins

Jérôme
Eberhardt

Leonardo
Solis-Vasquez

Andreas
Koch

Stefano
Forli

Giulia
Bianco

Francesca
Ambrosio

Overview

Macrocycle flexibility model for docking

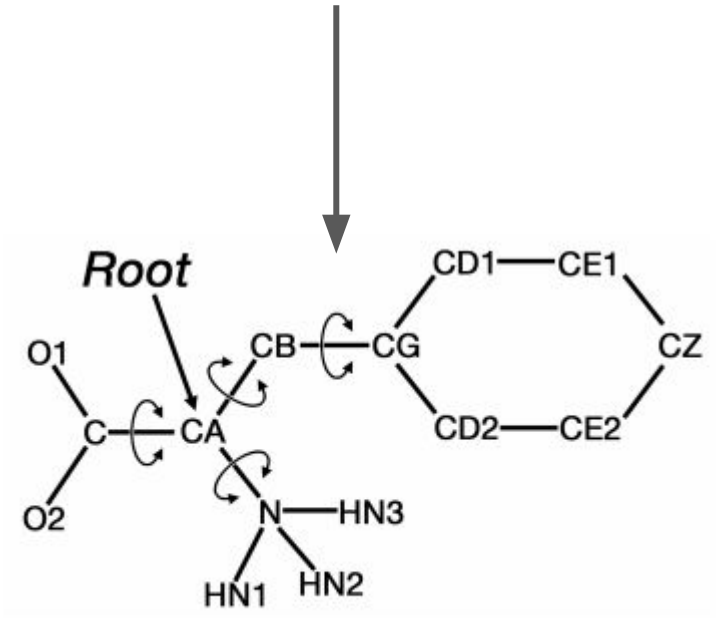
Capture binding pocket variability using multiple receptor conformations

Application of AutoDock-GPU (OpenCL, gradient-based local search)

Limitations of the ligand flexibility representation

Rotatable bonds are independent from each other
and rotate atoms downstream from the “root”

This torsion affects only the ring



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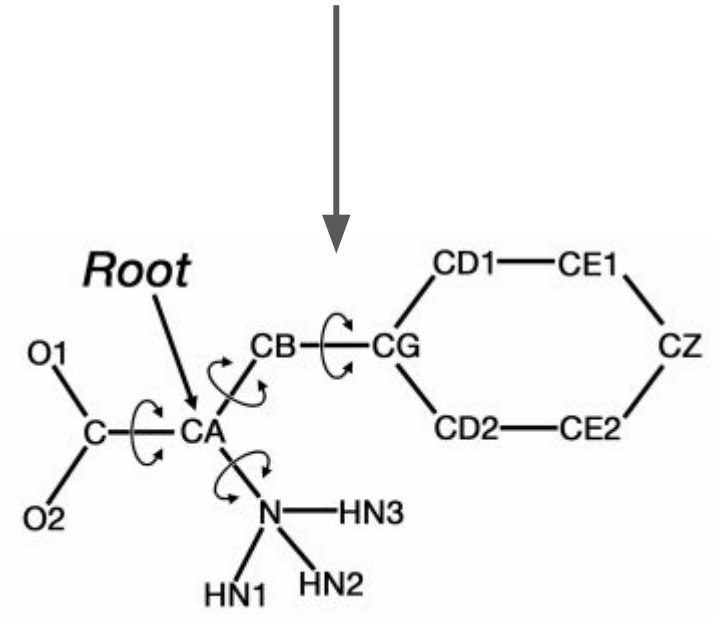
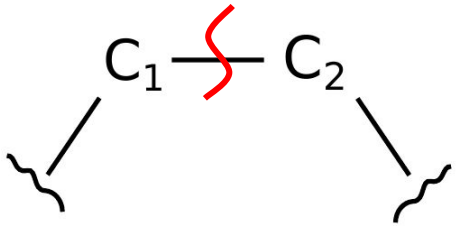


For macrocycles, rotatable bonds
must be perturbed in a concerted way

Macrocycles are modeled in an open state and closed during docking



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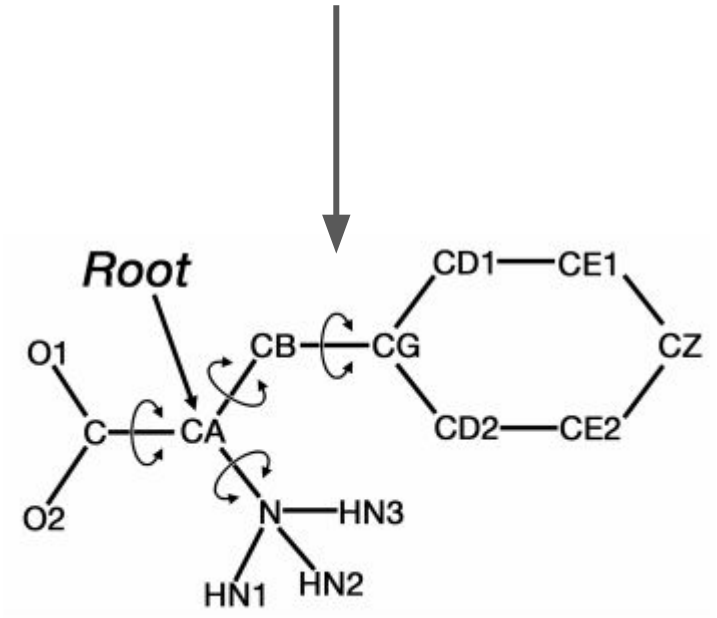
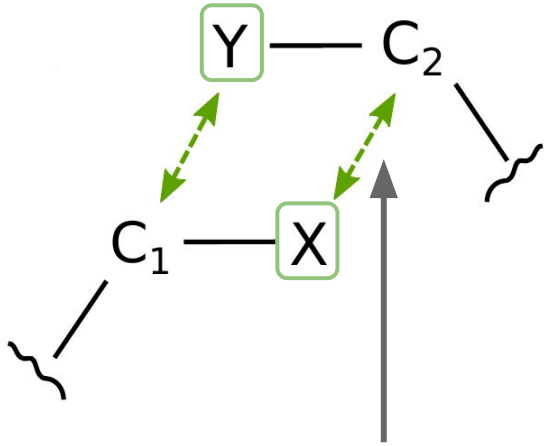


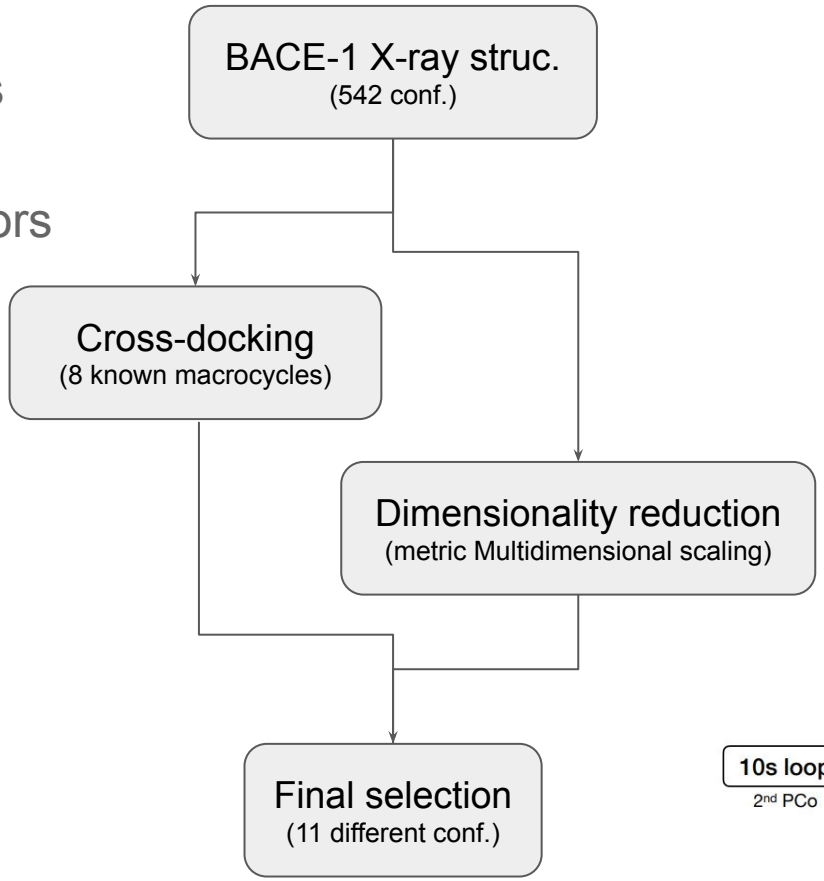


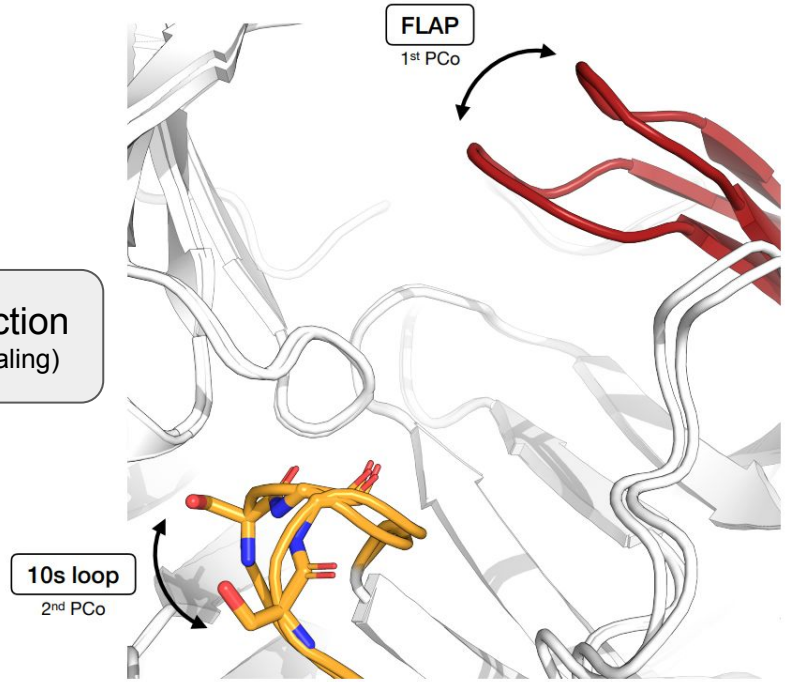
Linear attractive potentials
(50 kcal / mol / Å)

Forli, Botta, *J.Chem.Inf.Mod (2007)*

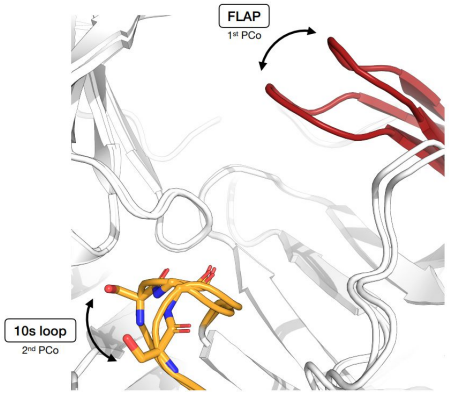
Selection of representative protein conformations

similar ligands
should bind to
similar receptors



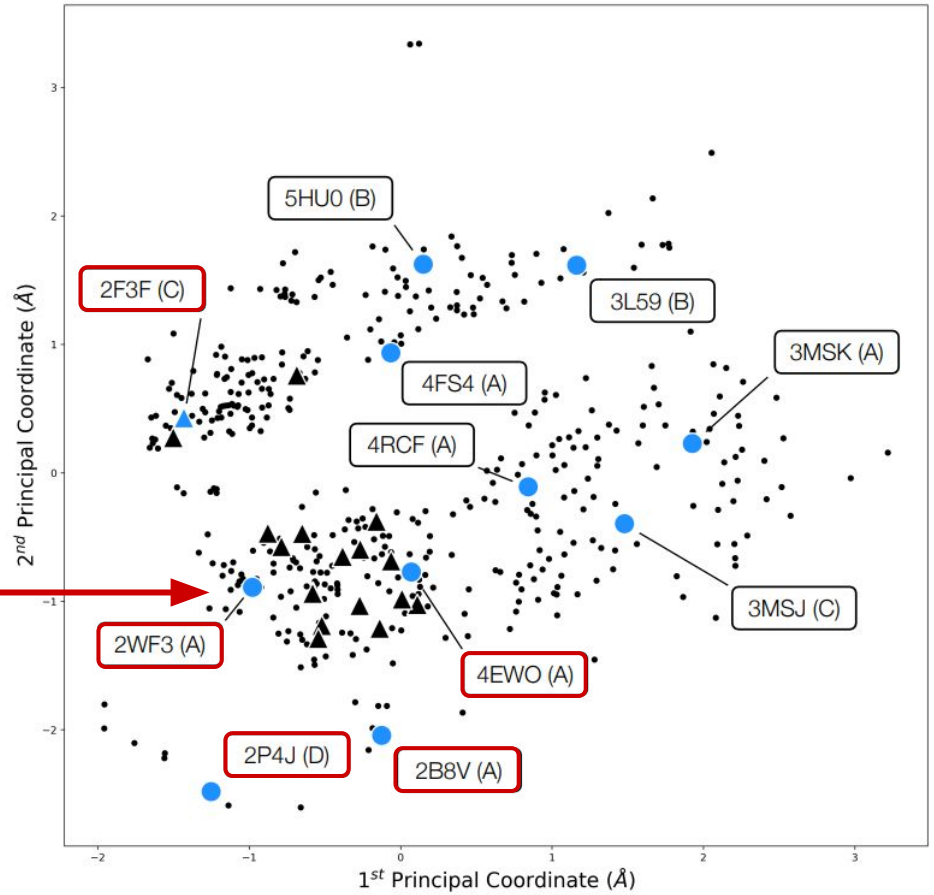


Top poses docked in similar receptor conformations



Metric Multidimensional Scaling using
RMSD of 10s and flap loops

10s loop



11 out of 20 ligands
docked to 2wf3
(does not contain macrocycle)

The rest in 2f3f, 2p4j, 2b8v and 4ewo

FLAP

Accelerating AutoDock4 on GPU

https://github.com/ccsb-scripps/AutoDock-GPU

Scoring function evaluation steps:

50x - 200x faster (Solis-Wets)

10x - 50x faster (ADADELTA gradient-based)
(...but less evals required -> more accurate)

search	mean RMSD (Å)	N < 2 Å
SW	8.49	1 / 20
ADA	1.52	18 / 20

Overall performance comparable to Vina on 8 cores.
(Vina has a simpler scoring function)

In collaboration with
Leonardo Solis-Vasquez and Andreas Koch
from TU Darmstadt, Germany

Each submission focused on a different aspect of docking

Standard dockings

- scoring function only
- post-processing filter & visual inspection
  (based on known ligands)

Modified dockings

- biased docking potential (known interactions)
- hydrated docking

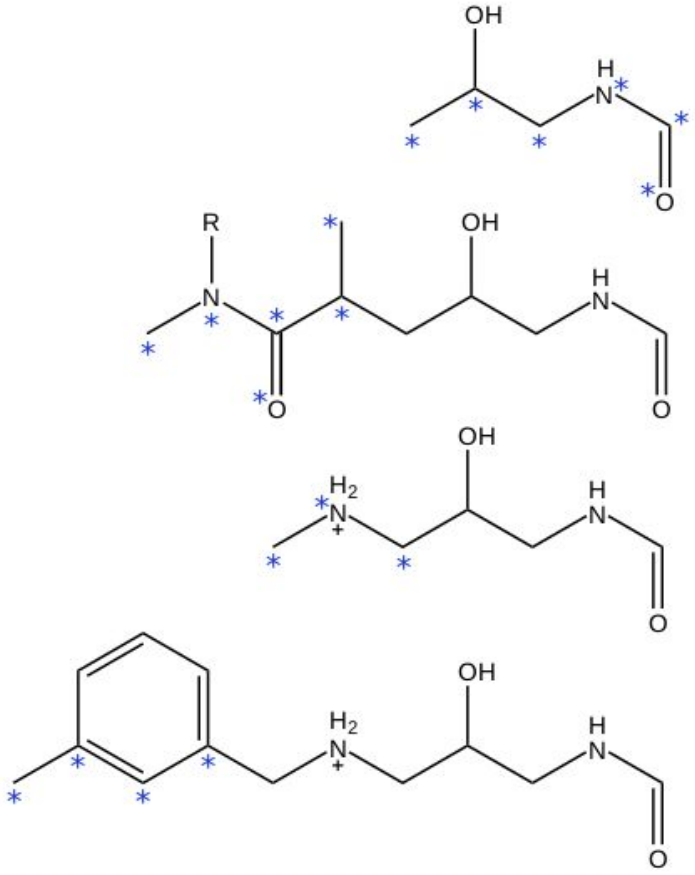
Using existing ligands as templates to filter poses

Dry receptor (Stage 1a)

filters	mean RMSD (Å)	N < 2 Å
No	2.35	12 / 20
Auto	1.56	18 / 20
Visual	1.29	20 / 20

With X-ray water (Stage 1b)

filters	mean RMSD (Å)	N < 2 Å
No	1.52	18 / 20
Auto	1.12	19 / 20



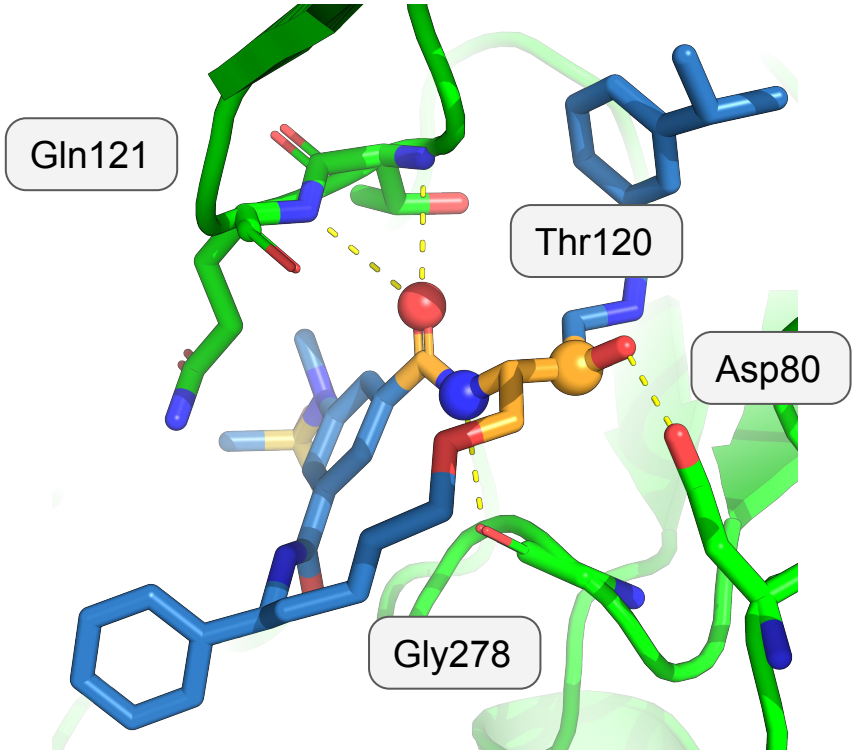
Docked poses that do not overlap with known binding modes are excluded

Using known binding modes to steer ligands to correct position

Distance-dependent penalty:

$$P = \begin{cases} 0, & \text{if } r \leq 1.2 \text{ Å} \\ 10^5 \times r, & \text{otherwise} \end{cases}$$

bias	mean RMSD (Å)	N < 2 Å
No	1.36	19
Yes	1.13	20



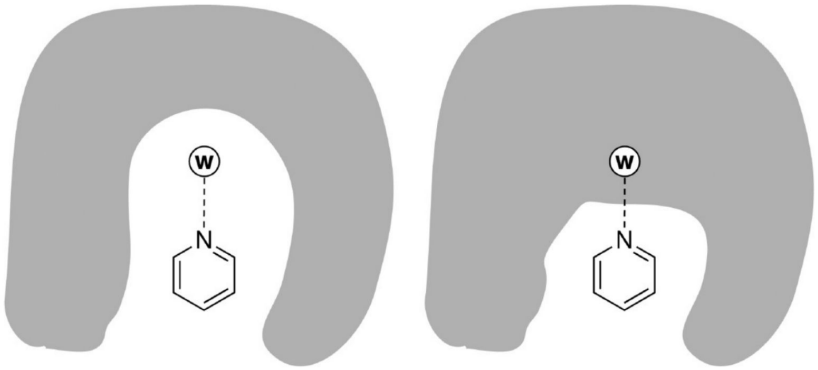
BACE-1 in complex with a macrocycle inhibitor (PDB ID: 4dpf)

X-ray waters were crucial for pose prediction

Ligand hydration

("hydrated docking", predicted on the fly)

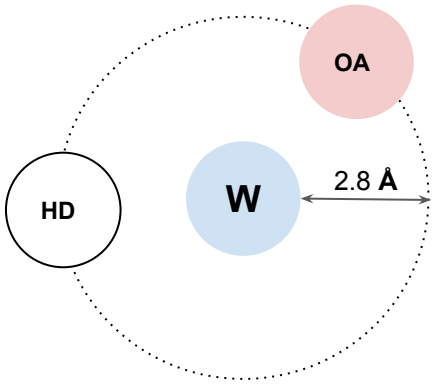
Forli *et al.* J. Med. Chem. 2012



water conserved water displaced

Receptor hydration

(x-ray waters)



spherical HB don/acc water model

X-Ray water	hydrated lig.	mean RMSD (Å)	N < 2 Å
No	No	2.96	8
No	Yes	2.83	7
Yes	No	1.36 (1.52)	19 (18)
Yes	Yes	1.31	19

Ranking 154 ligands by affinity

MM/GBSA performed comparably to docking scores (Kendall Tau ~0.2)

In collaboration with:

Sukanya Sasmal, Léa El Khoury, David Mobley

UC Irvine

There will be a poster by Sukanya

Conclusions

Gradient based local search: much better search performance

X-ray waters: very important (...but hard to model)

Receptor conformation: important but not critical (at least for these ligands)

Pose filters and bias: beneficial in Stage 1a (without waters)

Pose ranking: very hard (with both scoring function and MM/GBSA)

Acknowledgements

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Diogo Santos-Martins
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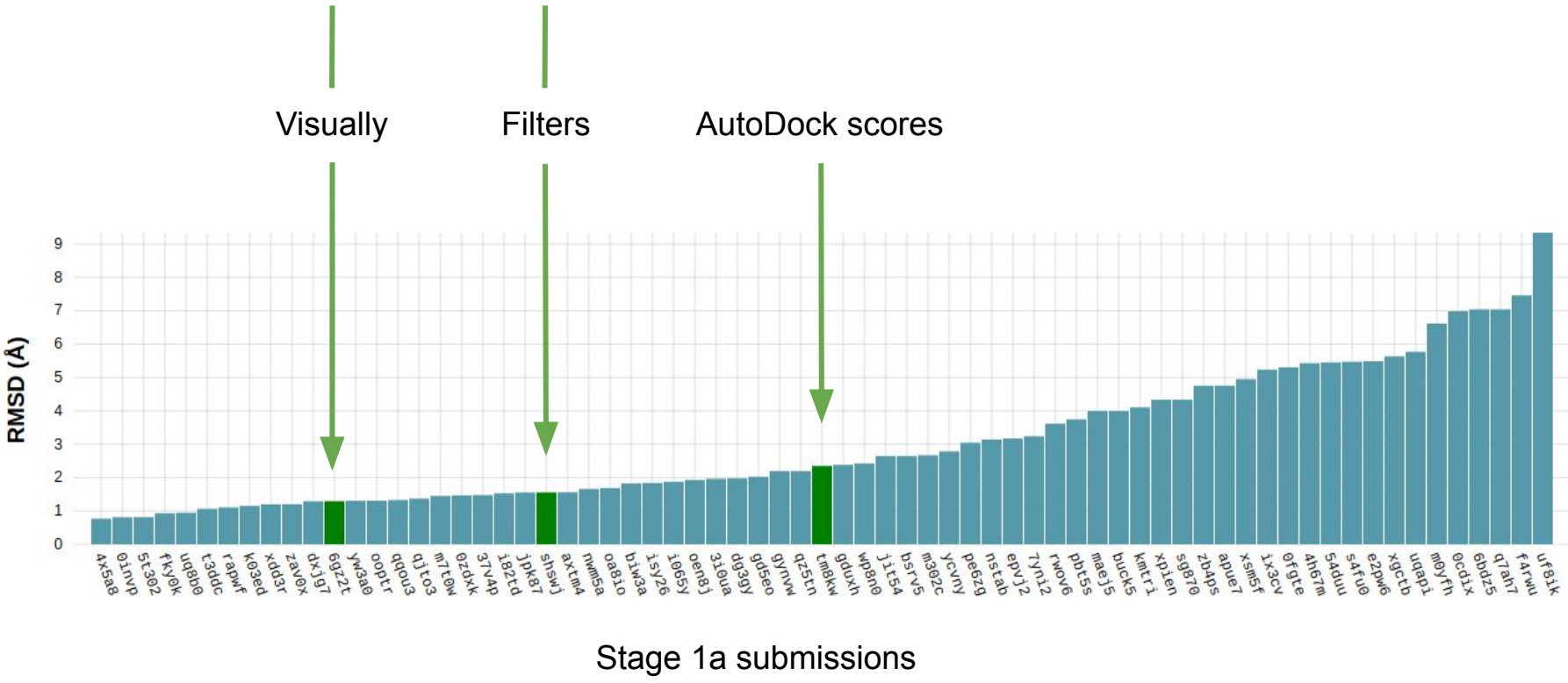
Ranking in Stage 1a

Exclusion of poses that do **not** match
the native pose of known ligands



Stage 1a submissions