Improving protein structure prediction using petascale sequence search

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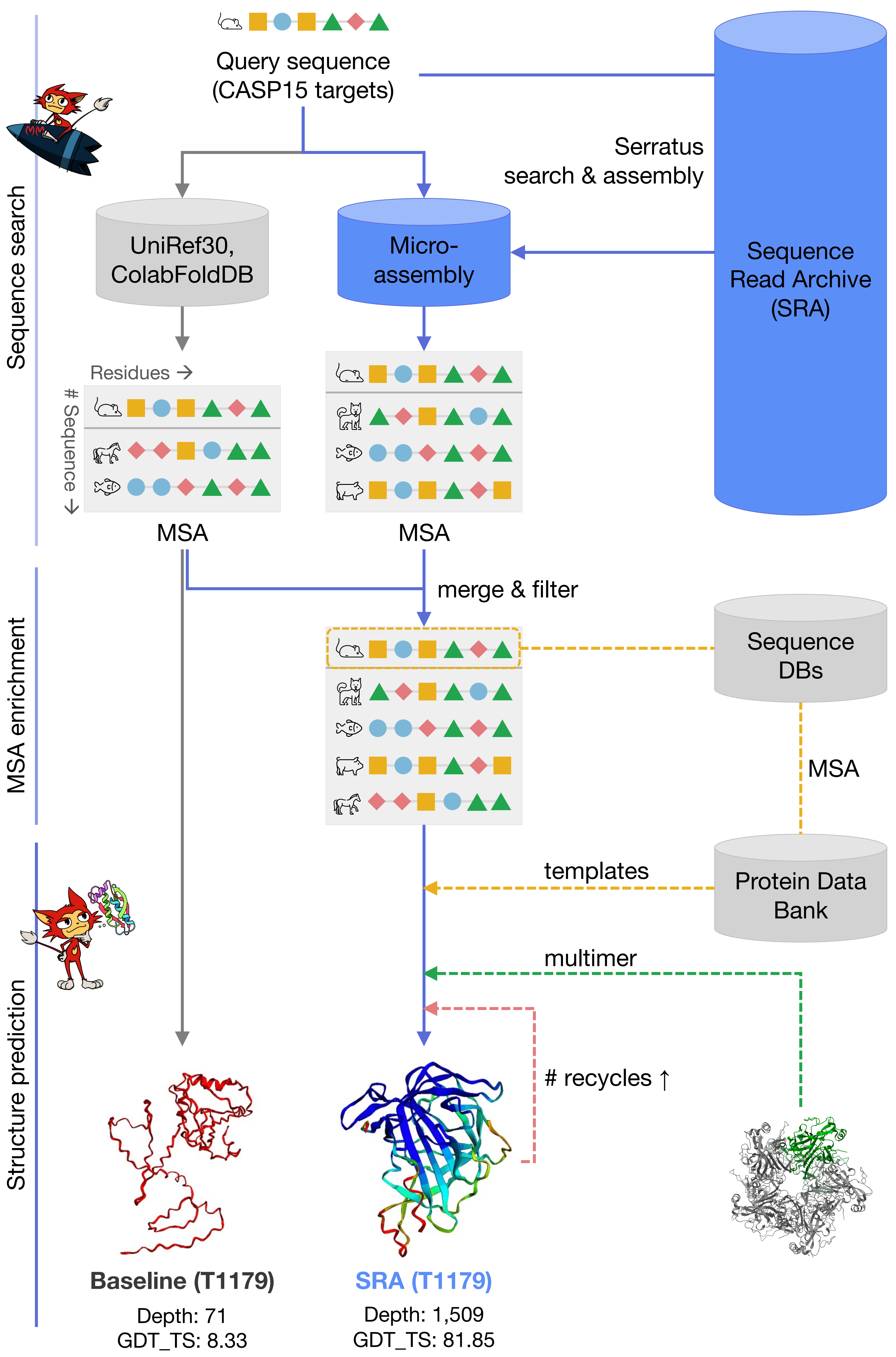
Abstract

In the recent CASP15 competition, the crucial role of multiple sequence alignments (MSAs) in protein structure prediction was underscored by the success of AlphaFold2-based models. To push the boundaries of MSA utilization and understand its limits, we conducted an exhaustive, petabase-scale search of the Sequence Read Archive (SRA), the world's largest public sequence database. Utilizing ColabFold—an accelerated version of AlphaFold2 offering numerous advanced features—we applied the MSAs to predict the structures of CASP15's designated "hard" protein targets. This approach significantly improved accuracy, achieving GDT_TS >70 for 66% of these targets, a substantial leap from the 52% achieved with baseline ColabFold MSAs. Enabling ColabFold's advanced features, including increased recycles, templates, and multimer models, contributed to a further performance boost. This methodology improves our ranking from 11th to 3rd place among 47 server groups in CASP15. By exploring MSAs derived from the large-scale exploration of the SRA and the advanced features of prediction models, this study aims to enhance our understanding of protein structure prediction.

Deep & wide sequence search for structure prediction



Sequence search

Query sequence
(CASP15 targets)

Serratus
search & assembly

UniRef30,
ColabFoldDB

Micro-
assembly

Sequence
Read Archive
(SRA)

Residues →

# Sequence →

MSA

MSA

MSA enrichment

merge & filter

Sequence
DBs

MSA

Protein Data
Bank

templates

multimer

# recycles ↑

Structure prediction

Baseline (T1179)
Depth: 71
GDT_TS: 8.33

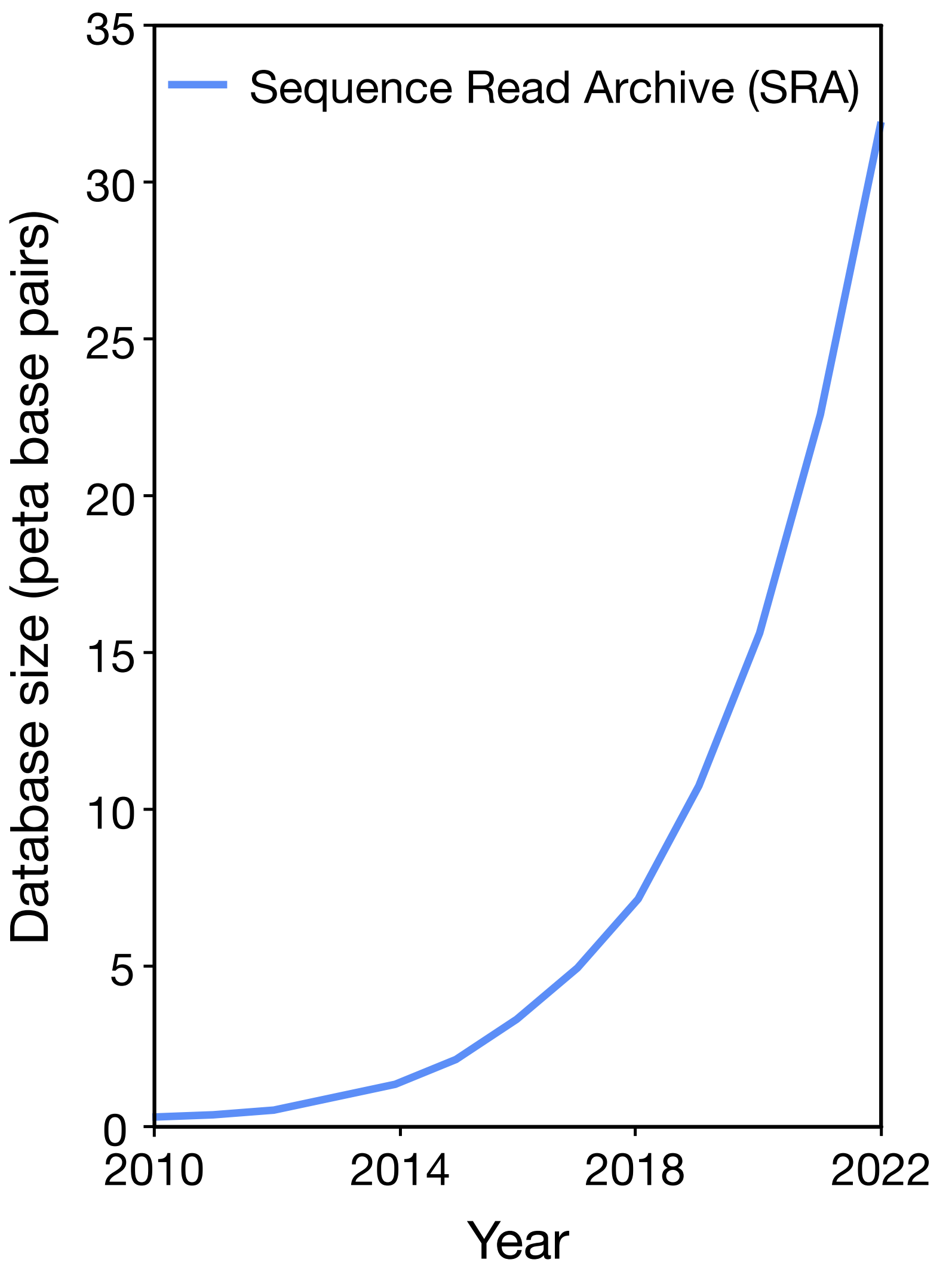
SRA (T1179)
Depth: 1,509
GDT_TS: 81.85

SRA: the largest public sequence database

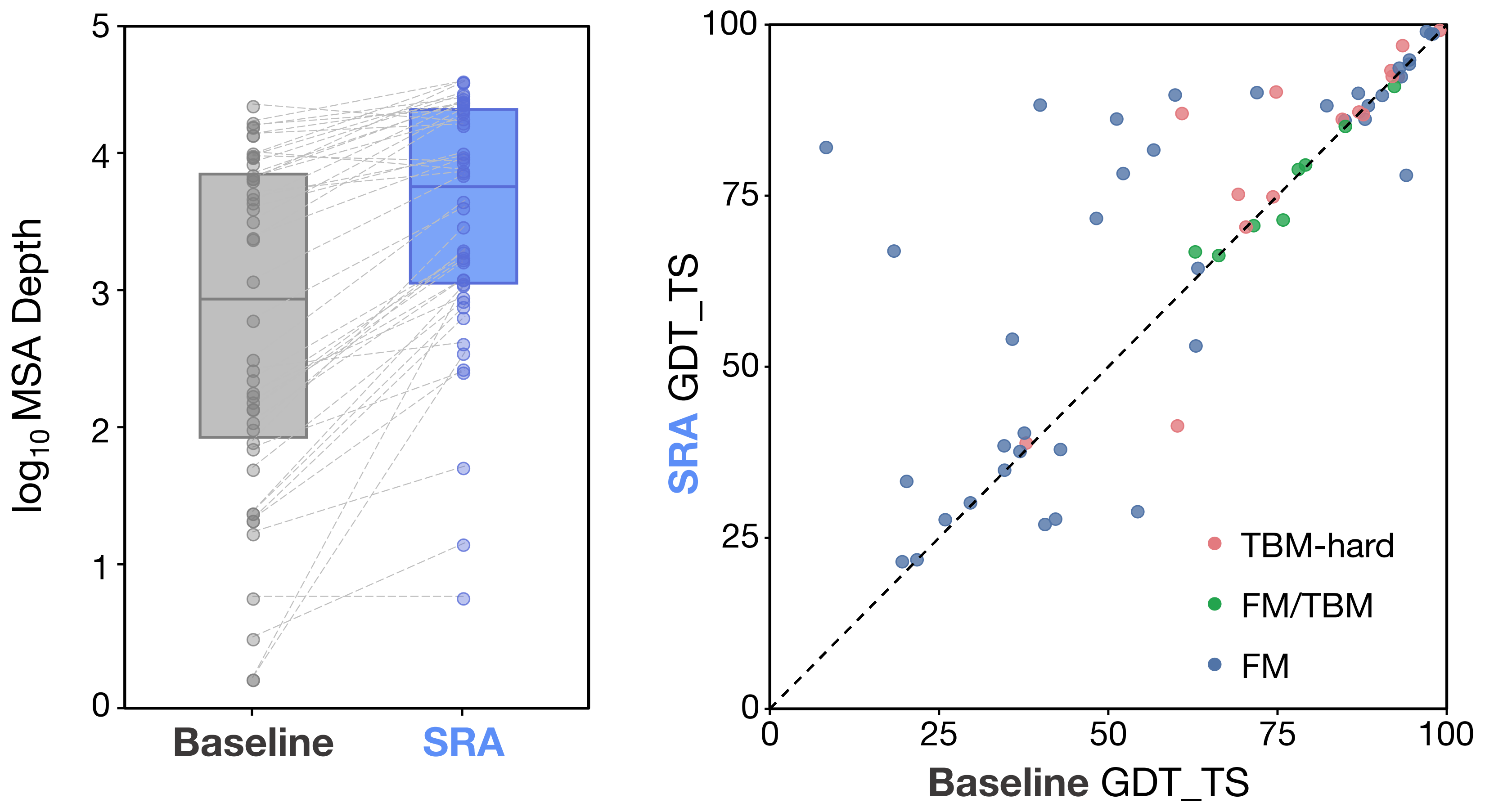
Database	Giga base pairs
SRA	**32,000,000**
IMG/M	27,000
BFD*	2,600
Metaclust*	1,700
Microassembly	**1,500**
ColabFoldDB*	800
MGnify*	300
UniRef30*	30

*Estimated based on number of sequences

Microassembly:
assembled *search results* from SRA

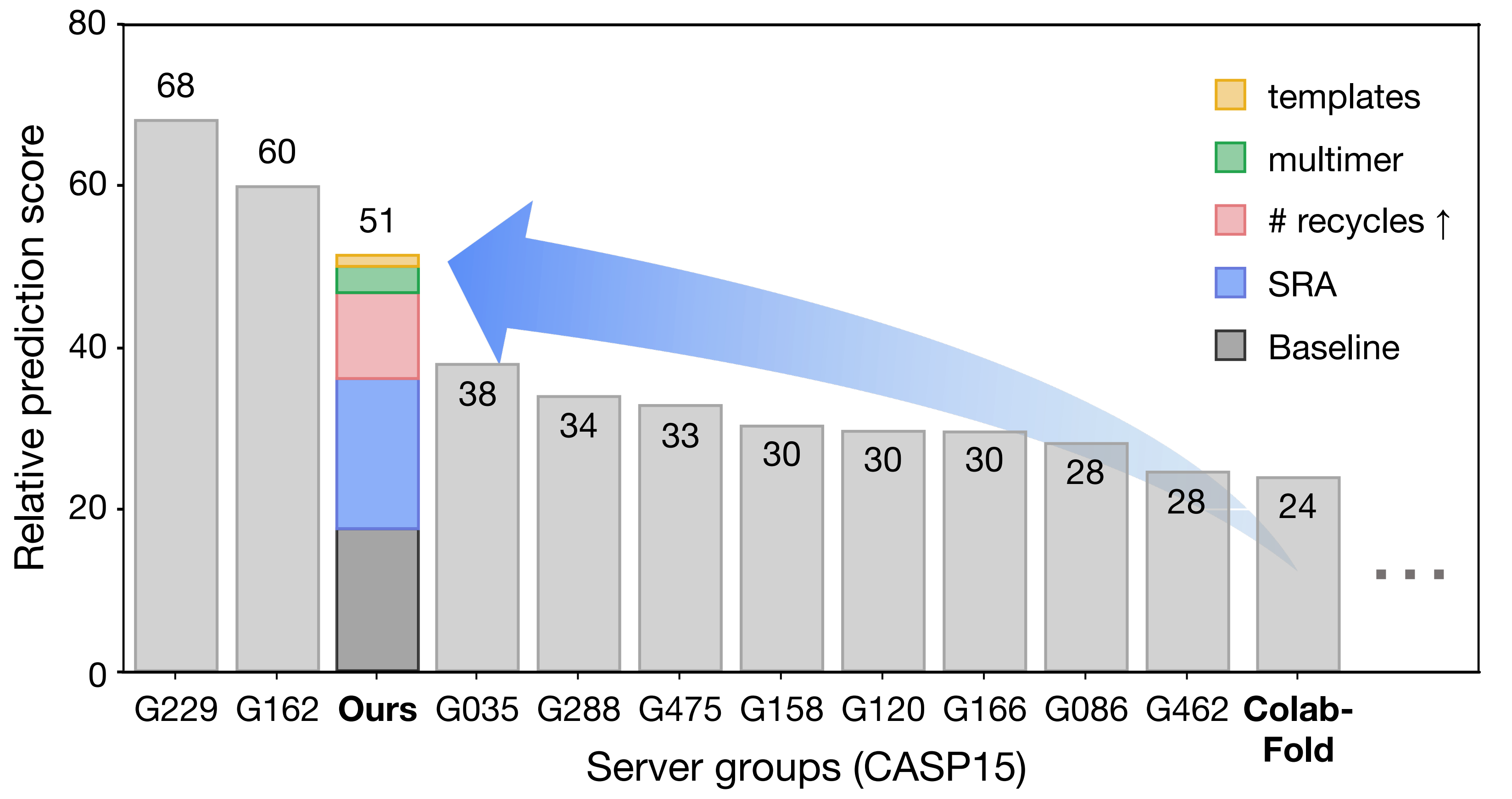


SRA-enriched MSAs lead to better predictions



TBM: templated-based modeling; **FM:** free-modeling
GDT_TS (global distance test): prediction accuracy

Factors contributing to improved prediction



Score: sum of GDT_TS (accuracy) Z-scores over 0
Contribution: SRA > # recycles ↑ (3 → 12) > multimer > templates
CASP15 rank: 11th → 3rd among 47 server groups

References

Kryshtafovych, A., et al. *Proteins*, *89,* 1607-1617 (2021).
Jumper, J., et al. *Nature*, *596*, 583-589 (2021).
Ovchinnikov, S., et al. *Science*, *355*, 294-298 (2017).
Mirdita, M., et al. *Nat. Methods*, *19*, 679-682 (2022).
Edgar, R. C., et al. *Nature*, *602*, 142-147 (2022).
Steinegger, M., & Sӧding, J. *Nat. Biotechnol.*, *35*, 1026-1028 (2017).

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