SIGMA Co-Fold Verification Report

Target: MCL-1 / OpenFold3 / 5FDR | Invariant Research | invariant.pro/cofold

Learned parameters	GPU required	Reference at verification	Signing
0	**No**	**No**	**Ed25519**

Ranking Comparison

All five OpenFold3 MCL-1 seed_42 samples verified by SIGMA and compared post hoc against the experimental 5FDR crystal structure.

1	4	2	0.9643	0.9516	1.0000	1.051	0.506
2	2	3	0.9489	0.9423	0.9556	1.140	0.330
3	5	4	0.9439	0.9245	0.9567	1.052	0.387
4	3	**1**	**0.9786**	0.9615	0.9743	1.074	0.257
5	1	**5**	0.9195	0.7374	1.0000	1.133	0.389

*ChainRMSD and Contact.J are post hoc experimental comparison metrics. They are not used by SIGMA during verification.

Key Finding

OpenFold3's top-ranked sample (Sample 5, score=0.5296) is SIGMA's lowest-ranked co-fold candidate (CoFold=0.9195), driven by the worst interface geometry in the set (0.7374).

SIGMA's top-ranked sample (Sample 4, CoFold=0.9786) has the strongest interface geometry and the highest co-fold quality of the five. By direct structural comparison to the experimental 5FDR coordinates, Sample 1 is the closest contact match (Contact.J=0.506).

Consensus Obstructions (Model-Systematic)

Residues flagged across multiple stochastic OpenFold3 samples, indicating model-systematic structural uncertainty rather than sample noise. The C-terminal region (residues 152-156) shows 3-12 Angstrom displacement from experimental 5FDR across all 5 samples.

AGLY23	4/5 (80%)	backbone bond/angle
AGLY34	3/5 (60%)	backbone angle
AVAL152-AASP154	2/5 (40%)	backbone angle
AASP2-AASP3	2/5 (40%)	backbone bond
AASN113	2/5 (40%)	backbone angle
AGLY157	2/5 (40%)	backbone angle

SIGMA Decomposition

SIGMA does not produce a single confidence score. It decomposes each candidate into four structural axes:

- **Backbone quality:** Bond lengths, bond angles, planarity, Ramachandran compliance. Per-chain geometry verified independently.
- **Interface sufficiency:** Does the ligand make enough contacts with the protein pocket? Contact density per ligand heavy atom. Distinct residue coverage.
- **Interface geometry:** Are those contacts clash-free and chemically plausible? Steric violations, hydrogen-bond geometry, contact distance distribution.
- **Consensus stability:** Recurring obstructions across multiple stochastic samples. Separates model-systematic uncertainty from random sample noise.

Scope and Non-Claims

- SIGMA does not generate structures. It verifies them.
- SIGMA does not replace OpenFold3 or any co-folding model.
- SIGMA does not claim to predict binding affinity or activity.
- The co-fold quality ranking is a structural geometry measure, not a biological activity prediction.

SIGMA adds deterministic post-prediction verification and failure-mode decomposition to co-folding workflows. It tells you why a candidate is structurally risky, not whether it will work as a drug.
