

FoldFusion-PoC: Results from a Ligand Transplantation & Optimization Pipeline

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The FoldFusion Pipeline

A modular, pocket-centric workflow:

1. **Pocket Prediction (DogSite3):** Identify potential binding sites on the target AlphaFold model.
2. **Homolog Ensemble (SIENA):** Find experimentally solved structures with similar binding pockets.
3. **Ligand Extraction:** Extract the bound ligands from these homologous structures.
4. **Transplant & Optimization (JAMDA):** Place the ligand into the AlphaFold model and use the JAMDA scorer to optimize its position and score the fit.

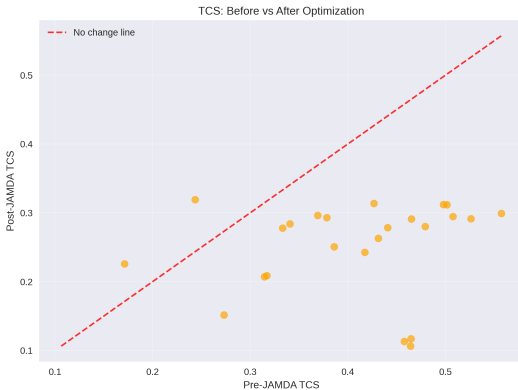
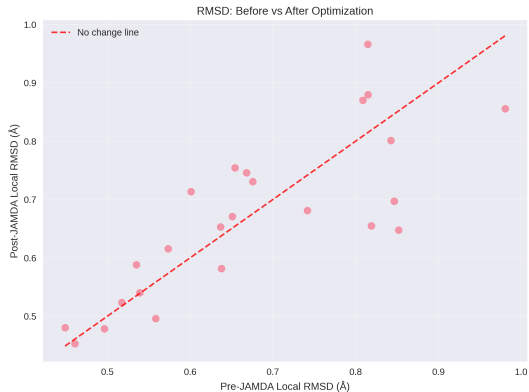
Key Quality Metrics

How do we measure the quality of a transplanted ligand?

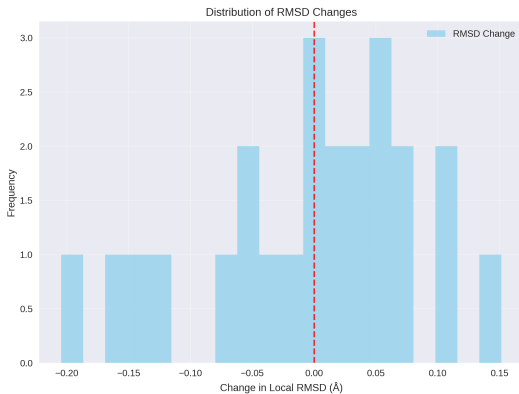
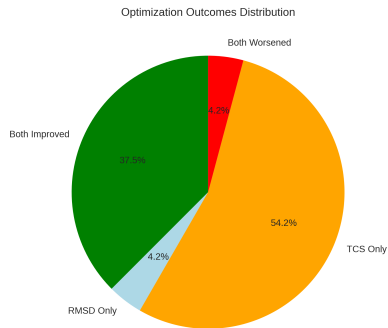
- ▶ **Local RMSD (Å):** The Root-Mean-Square Deviation of the ligand and surrounding protein atoms compared to the original experimental structure. A **lower** value means the local binding site geometry is more accurate.
- ▶ **Transplant Clash Score (TCS):** A measure of steric clashes (atomic overlaps) between the ligand and the protein. It is calculated as $\sqrt{\sum(\text{overlap})^2/N}$. A **lower** value means fewer clashes and a better physical fit.

The goal of optimization is to decrease both Local RMSD and TCS.

Optimization Regarding Fit and Clashes



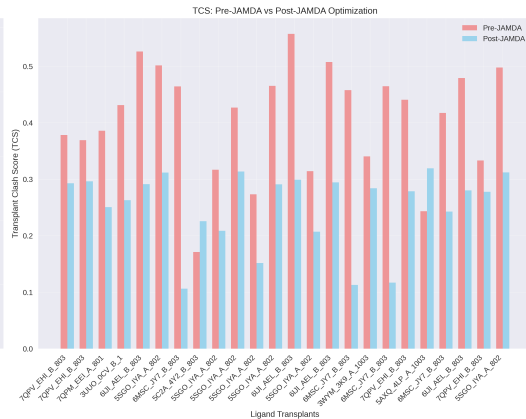
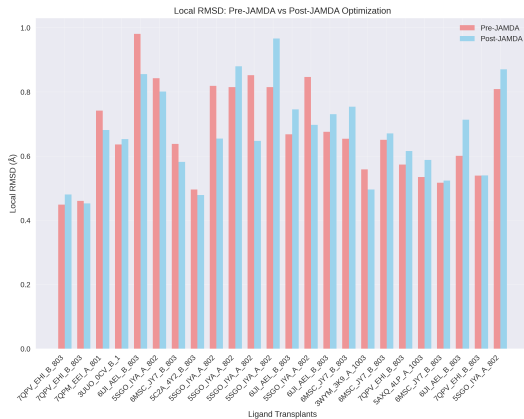
Optimization Regarding Fit and Clashes



Optimization Regarding Fit and Clashes

- ▶ The JAMDA optimization step is highly effective.
- ▶ **95.8%** of transplants improved in at least one metric (Pie Chart).
- ▶ Both Local RMSD (geometry) and TCS (clashes) show clear improvement on average.

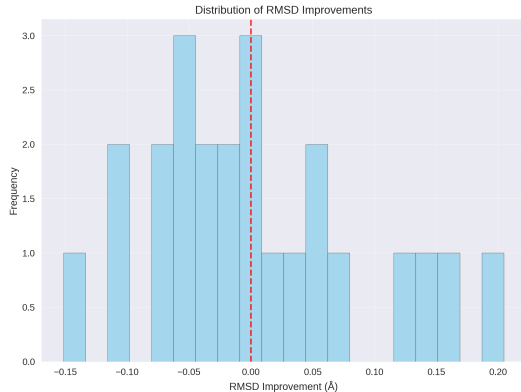
Consistent Improvements Across Diverse Transplants



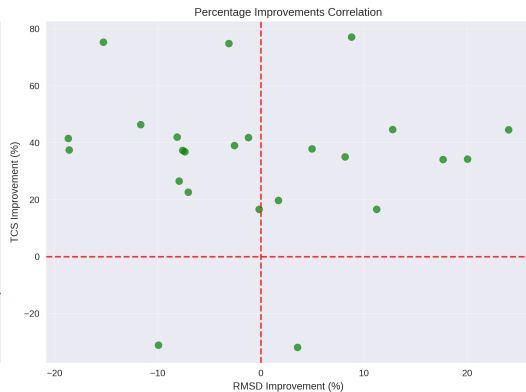
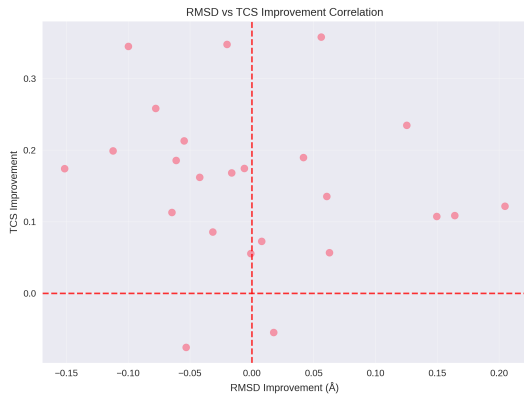
Consistent Improvements Across Diverse Transplants

- ▶ For nearly every case, the Post-JAMDA scores are lower than the Pre-JAMDA scores.
- ▶ This demonstrates that the optimization procedure is robust and performs well across a wide range of different protein-ligand systems.

Analyzing the Magnitude of Improvements



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Homolog Alignment Quality Moderately Correlates with Fit

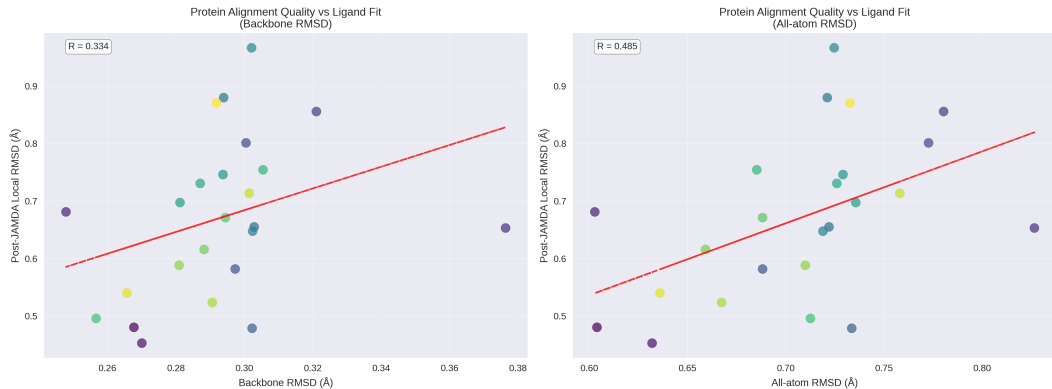


Figure: Final ligand fit (Post-JAMDA Local RMSD) vs. the structural alignment quality of the protein.

Homolog Alignment Quality Moderately Correlates with Fit

- ▶ We see a weak-to-moderate positive correlation ($R \approx 0.33 - 0.49$) between the initial protein alignment quality and the final ligand fit.
- ▶ However, the correlation is not perfect, indicating that other factors beyond simple backbone alignment are important for a successful transplant.

Next Steps & Roadmap

- ▶ Benchmark Against AlphaFill
- ▶ Investigate Outliers
- ▶ Increase Dataset/ Improve Performance
- ▶ Develop Confidence Scores

Thank you!

Questions?