SharpED improves the interpretability of low-resolution crystallographic electron-density maps

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SharpED

Machine-learning map restoration

From difficult diffraction data to an interpretable, crystallographic map.

PHASE STUDIO TUTORIAL - IUCr SOFTWARE FAYRE

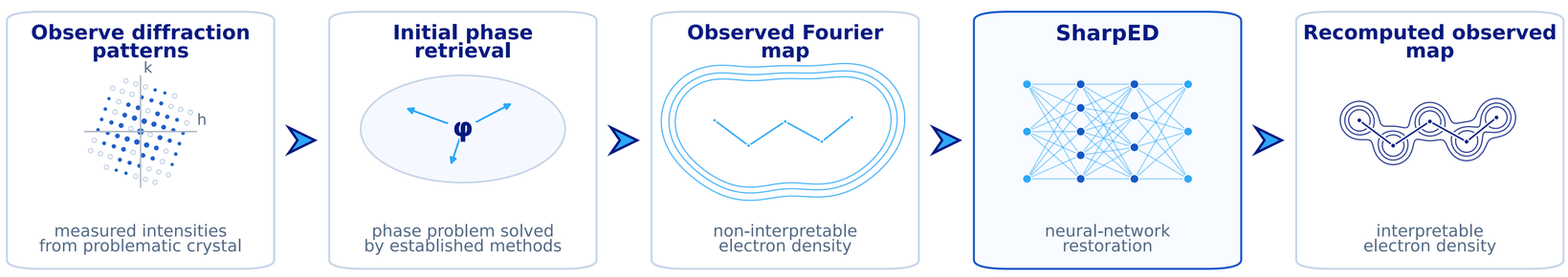
Friday, August 14 | 4:00–4:45 PM | Room 220

1 INTRODUCTION

Why map restoration?

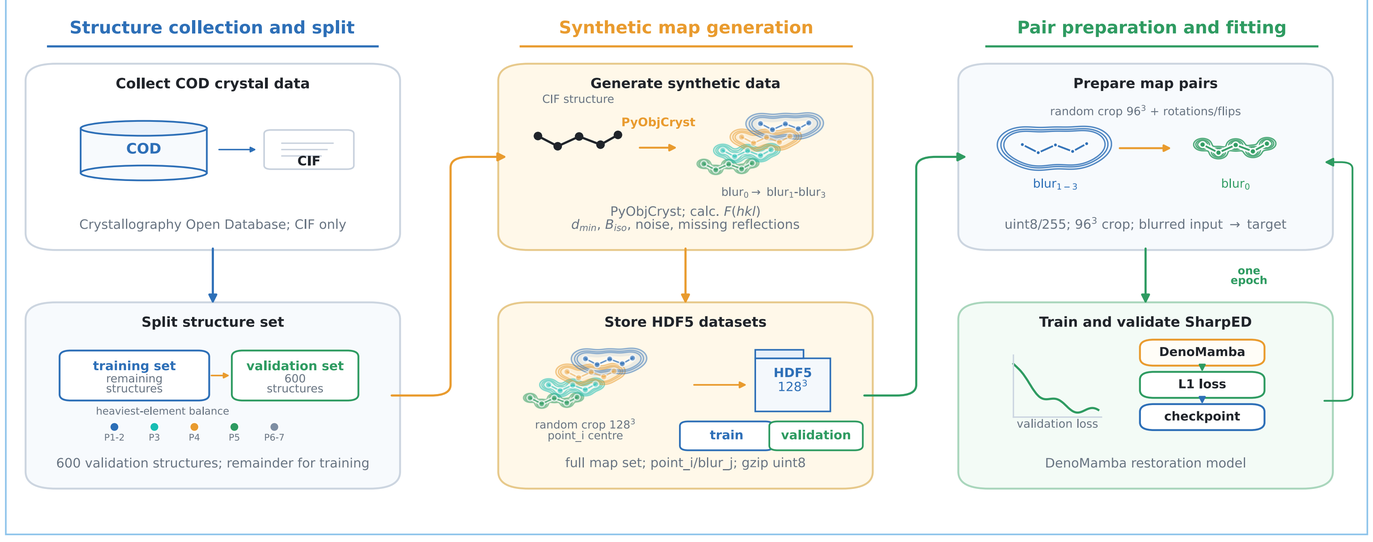
Limited crystal quality, suboptimal data collection, and instrumental constraints reduce the resolution, completeness, and accuracy of diffraction data. As a result, density maxima may broaden, merge, shift, split, or disappear, making the map difficult to interpret.

SharpED operates after conventional phasing, transforming the initial electron-density map into a more interpretable real-space representation that can be analysed using esteblished crystallographic tools for model building.

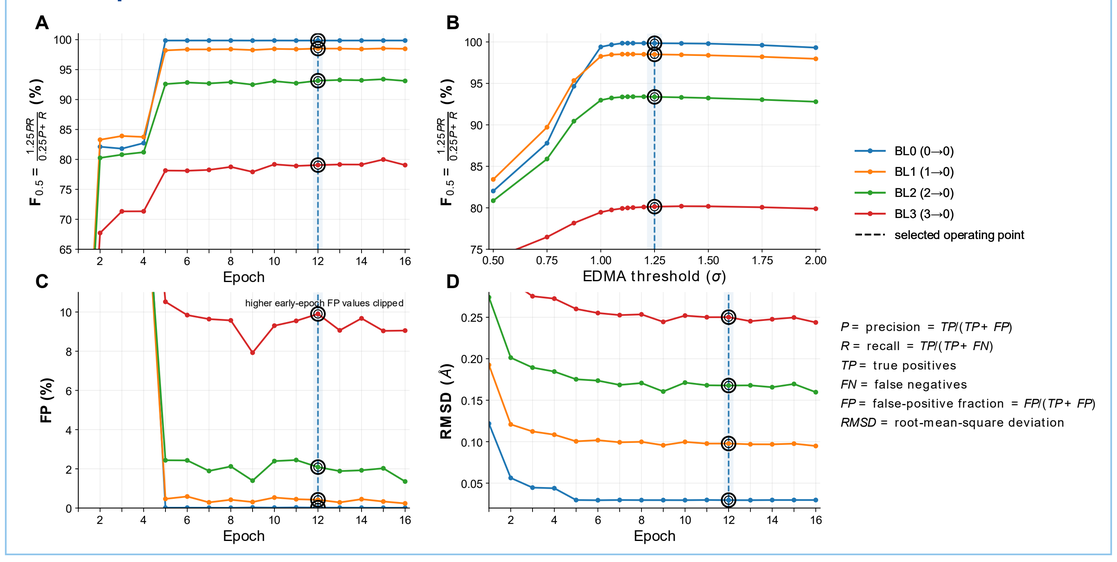


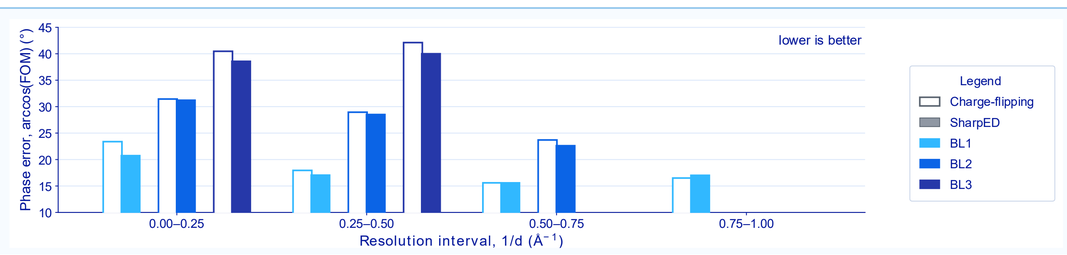
2 SHARPED

Training-data generation and model development



Real-space validation on held-out simulated data





Reciprocal-space validation on held-out simulated data

Mean phase error, arccos(FOM), evaluated as a function of reciprocal resolution, 1/*d*, across degradation levels in the held-out validation dataset.

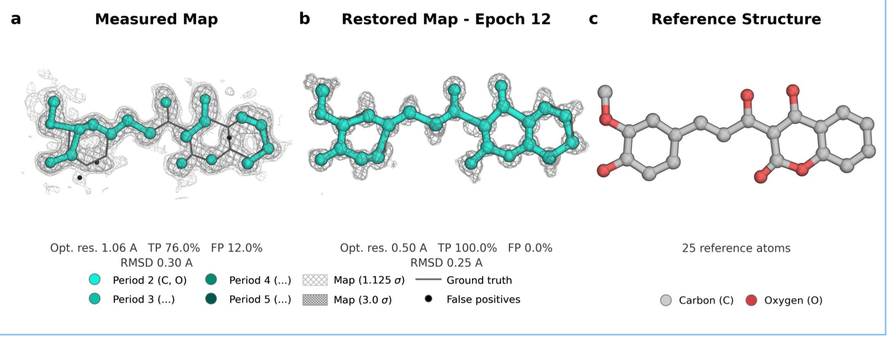
SharpED reduced the mean phase error in nearly all populated reciprocal-resolution intervals. The largest absolute improvements were observed for the most strongly degraded BL3 maps, whereas the gains for the less degraded BL1 maps were smaller and approached parity in the highest-1/d interval. Because SharpED operates exclusively on the real-space map, the improved phase agreement after Fourier transformation demonstrates that the restoration retains and enhances crystallographically relevant reciprocal-space information.

Real-space validation on unseen experimental maps

These experimental cases were absent from the COD-derived training set and therefore assess the transfer of SharpED from simulated training maps to real crystallographic measurements.

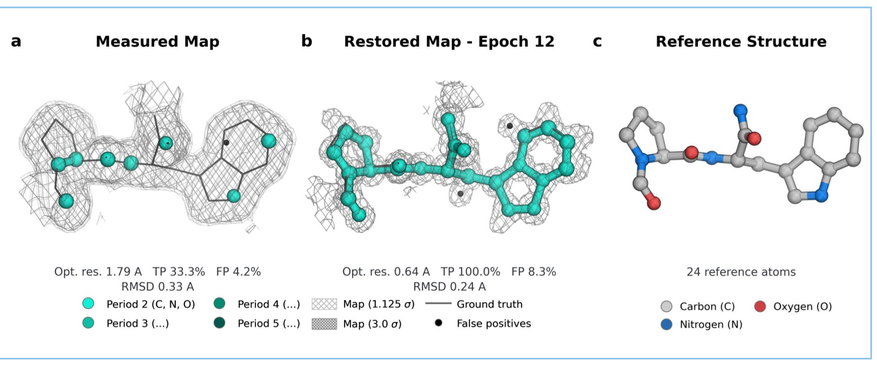
Vanillin chalcone

Organic powder-diffraction map obtained by charge flipping. Reflection overlap produces diffuse density and merged atomic maxima. SharpED improves peak separation, enabling EDMA to recover the complete reference structure and eliminating unmatched maxima.



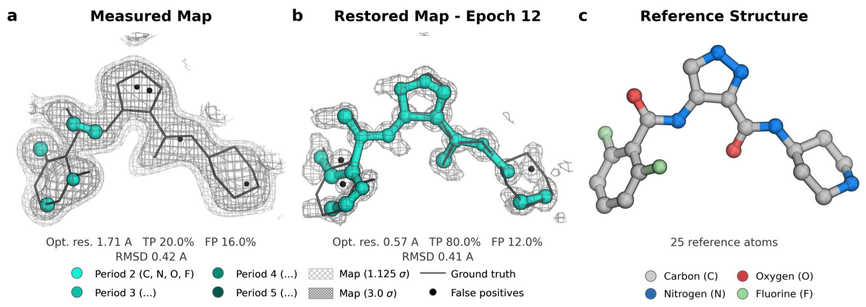
5MGS Pro-Trp segment

Local Pro–Trp segment from a macromolecular $2F_o-F_c$ map obtained by molecular replacement. SharpED improves the continuity and separation of peptide density, enabling EDMA to recover the complete reference segment with greater positional accuracy.



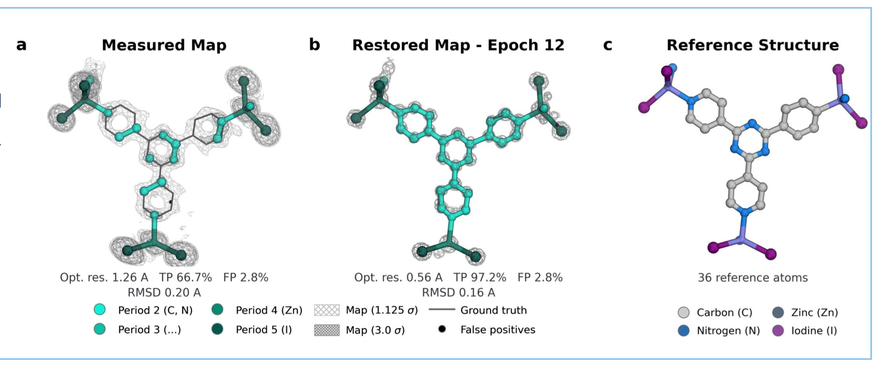
2VTQ LZA ligand

LZA ligand in the CDK2 binding site. Diffuse and incomplete $2F_o-F_c$ density complicates ligand placement. SharpED makes the density more continuous, increasing EDMA recovery and improving the positional accuracy of matched atoms.



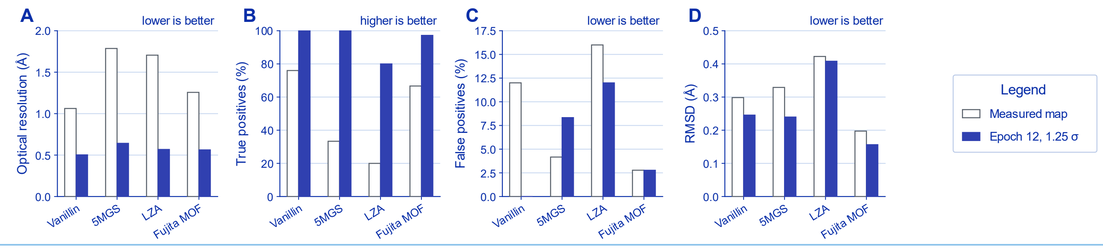
Fujita-type MOF linker

Fujita-type MOF linker from low-resolution SCXRD data. Strong Zn and I scattering suppresses weaker C and N density. SharpED recovers the linker topology and enables near-complete EDMA reconstruction with improved positional accuracy.



Experimental validation summary

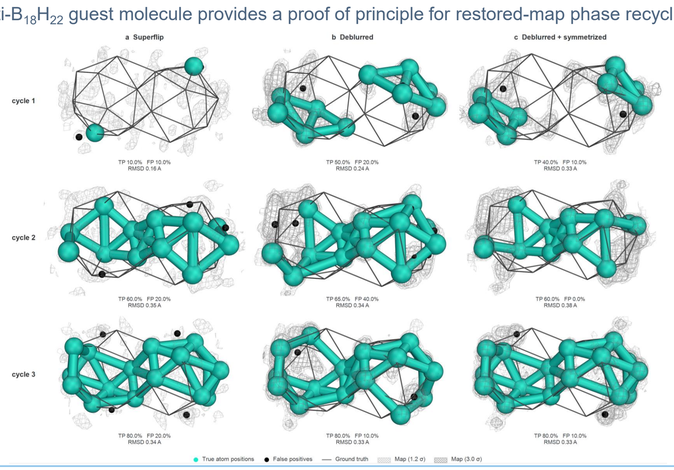
Across all four unseen experimental cases, SharpED improved the map-based optical-resolution estimate to 0.50–0.65 Å, consistent with the high-resolution reconstruction target used during training. EDMA recovery increased markedly in every case and yielded complete or near-complete recovery of the investigated structure. False-positive maxima remained controlled and disappeared entirely in two examples, while the positional RMSD decreased consistently by approximately 0.05 Å.



3 PHASE STUDIO powered by SharpED

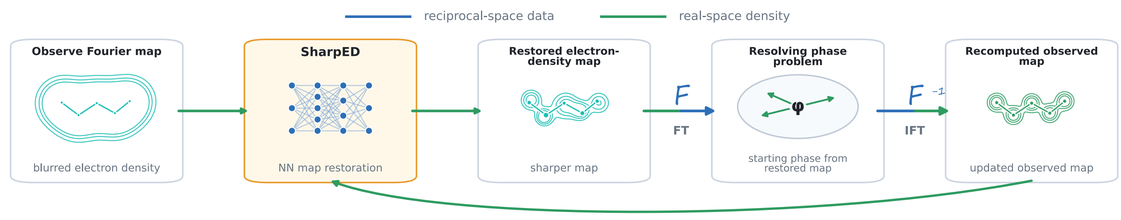
Demonstration: anti-$B_{18}H_{22}$ guest in a Fujita-type MOF

The anti-$B_{18}H_{22}$ guest molecule provides a proof of principle for restored-map phase recycling.

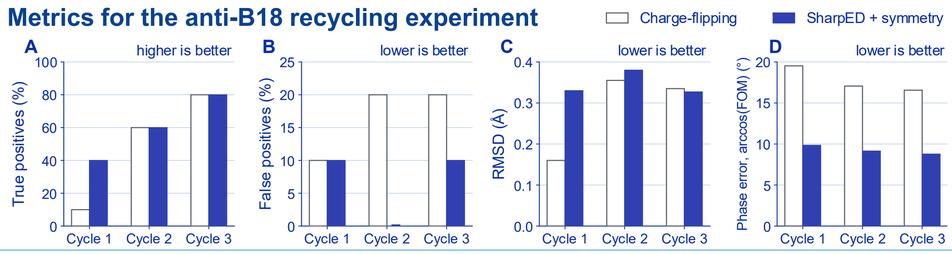


Phase recycling workflow

Phase Studio is an interactive tool that calculates starting phases from the SharpED-restored map and passes them to charge-flipping software as starting phases. Charge flipping combines these phases with the observed diffraction intensities to calculate a new electron-density map.



Metrics for the anti-B18 recycling experiment



In the first cycle, charge flipping was initiated from random phases and recovered only 10% of the anti-$B_{18}H_{22}$ guest structure. In the second and third cycles, Phase Studio supplied starting phases calculated from the SharpED-restored map obtained in the preceding cycle. This phase-recycling strategy increased structural recovery to 70% and 80%, respectively.

4 CONCLUSION

SharpED restores interpretable density in maps degraded by limited resolution, incomplete data, and measurement errors. Applied after conventional phasing, it improves peak separation and reciprocal-space phase agreement across simulated, powder, macromolecular, and MOF cases. Combined with Phase Studio, phase recycling increased anti-$B_{18}H_{22}$ guest recovery from 10% to 80%. Measured diffraction data remain the final validation standard.

ACKNOWLEDGEMENTS AND ACCESS

This work was supported by the Czech Grant Agency (GAČR) under grant no. 25-16442S.

FUNDED BY GAČR CZECH SCIENCE FOUNDATION

FZU Institute of Physics of the Czech Academy of Sciences

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