CryoSAMU: Enhancing 3D Cryo-EM Density Maps of Protein Structures at Intermediate Resolution with Structure-Aware Multimodal U-Nets

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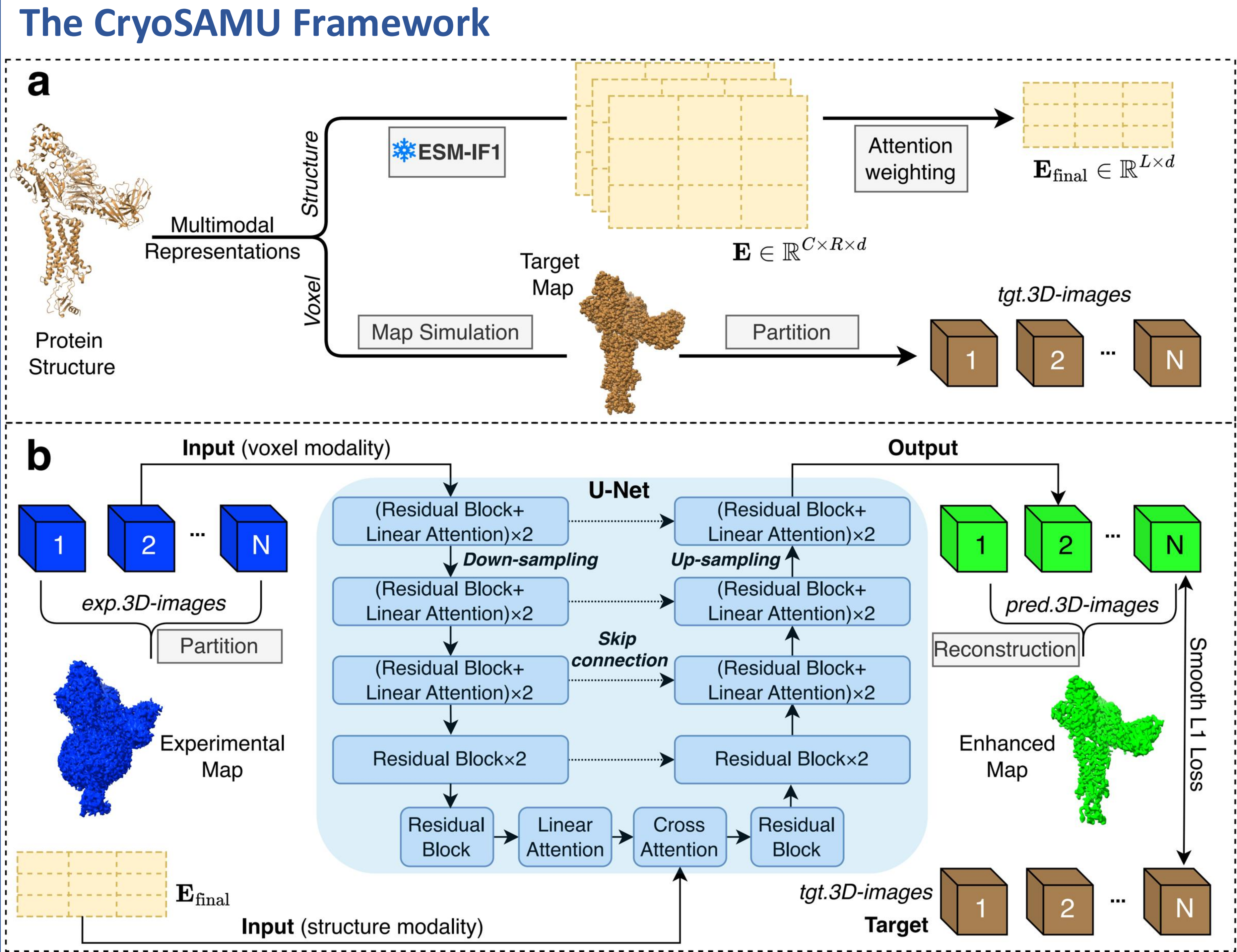
Motivations

- Intermediate-resolution cryo-EM maps (4–8 Å) are common but challenging for accurate protein structure modeling due to low contrast and structural ambiguity.
- Existing enhancement methods are not optimized for this resolution range and use only density information, ignoring valuable structural context.
- Protein Language Models (pLLMs) like ESM-IF1[1] offer rich structural embeddings but remain underutilized in map enhancement.
- There's a need for fast, accurate, and structure-aware approaches to facilitate map interpretability for downstream applications like protein structure modeling.
- ✅ To address these challenges, we developed **CryoSAMU** — the first multimodal network that integrates protein structural embeddings into a 3D voxel-based U-Net using cross-attention[2], enabling enhanced cryo-EM maps optimized for intermediate resolution.

Methods

The CryoSAMU Framework



Self-Attention Weighting for Structural Embeddings

- Handles proteins with variable chains and residues
- Use soft attention to preserve informative structures
- Produce fixed-size structural embeddings for multimodal learning

Procedure:

1. Output from ESM-IF1 for all chains and residues:

$$E \in \mathbb{R}^{C\times R\times d} \quad (C\text{: no. chains}, R\text{: no. residues}, d\text{: emb size})$$

2. Aggregate residue embeddings into chain-level embeddings:

$$E_i^{chain} = \frac{1}{R}\sum_{j=1}^{R} E_{i,j} \implies E^{chain} \in \mathbb{R}^{C\times d}$$

3. Compute pairwise chain similarity and Softmax attention weights:

$$S = E^{chain}\cdot (E^{chain})^{\mathrm{T}}, \quad W_{ij} = \frac{\exp(S_{ij})}{\sum_k \exp(S_{ik})}$$

4. Get chain importance and perform weighted aggregation:

$$w_i = \frac{1}{C}\sum_j W_{ij}, \quad E^{pooled} = \sum_{i=1}^{C} w_i \cdot E_i \implies E^{pooled} \in \mathbb{R}^{R\times d}$$

5. Repeat the above steps to E^{pooled} for residue-level attention to obtain a scalar weight α_j for each residue j = 1,2, ..., R.

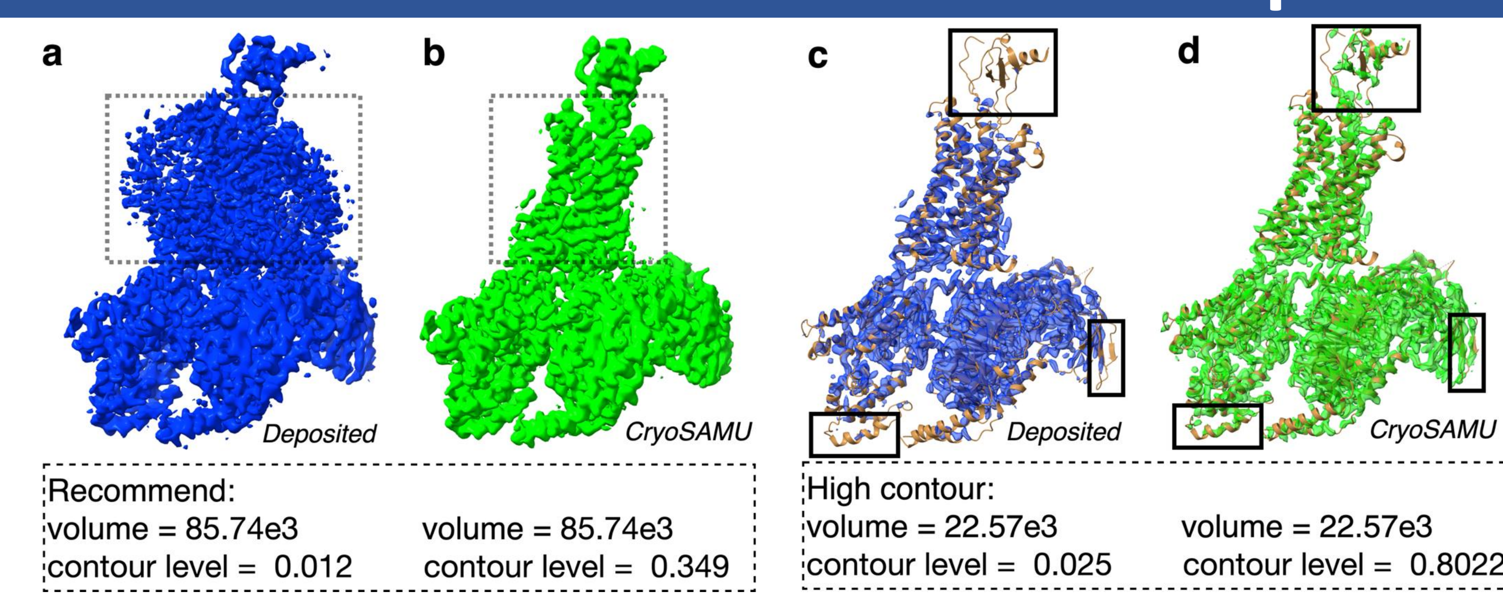
6. Normalize and resample E^{pooled} w.r.t α_j to select top-L informative residues:

$$E^{final} \in \mathbb{R}^{L\times d}$$

Dataset

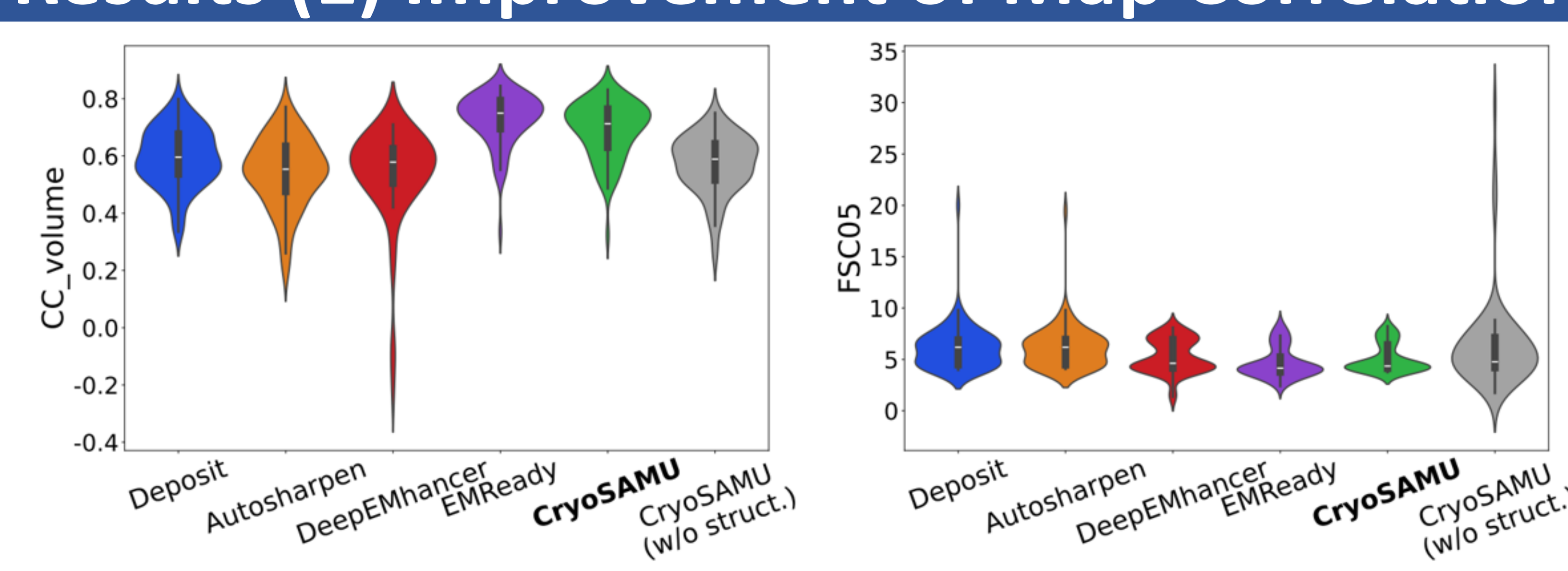
- Dataset includes 384 pairs of cryo-EM density maps and protein structures from EMDB[3] and PDB[4].
- Excluded maps with misaligned PDB structures or non-protein macromolecules.
- Filtered pairs with correlation score below 0.65 to ensure complete mappings.
- Retained unique PDB structures with sequence identity over 30%.

Visualization of Enhanced Maps



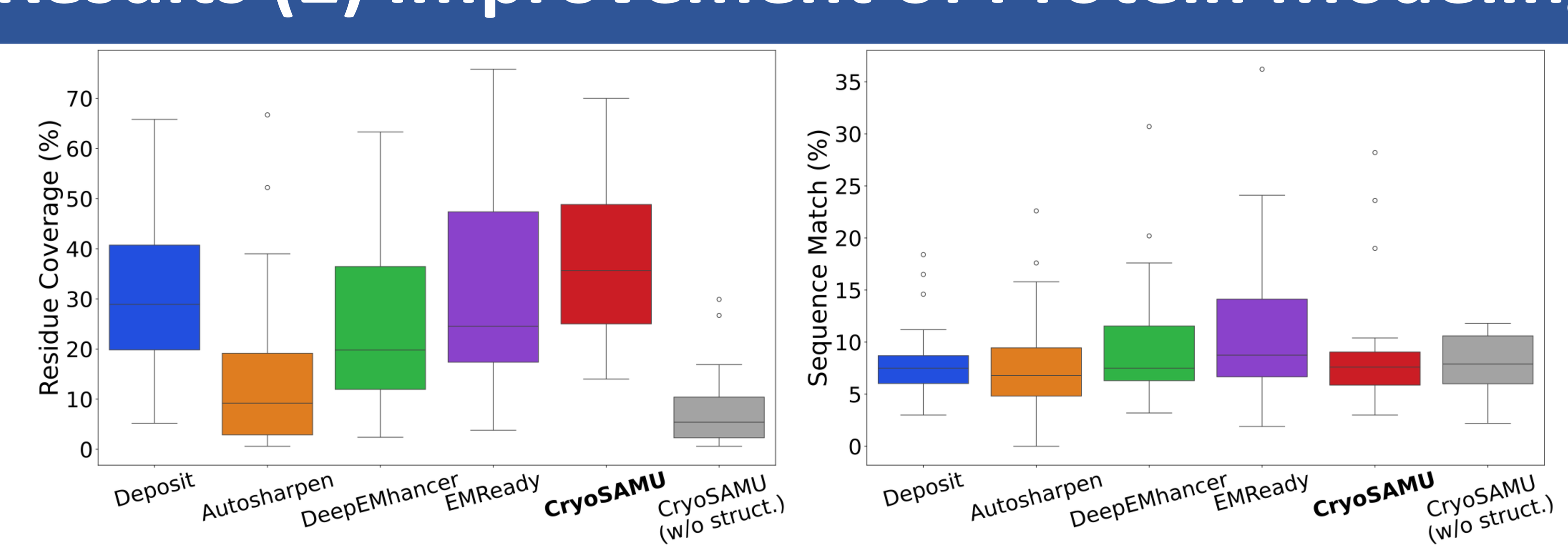
- CryoSAMU-enhanced maps exhibit better alignment with corresponding protein structures, revealing more structural details, outlined by black boxes in Figure (d).

Results (1) Improvement of Map Correlation



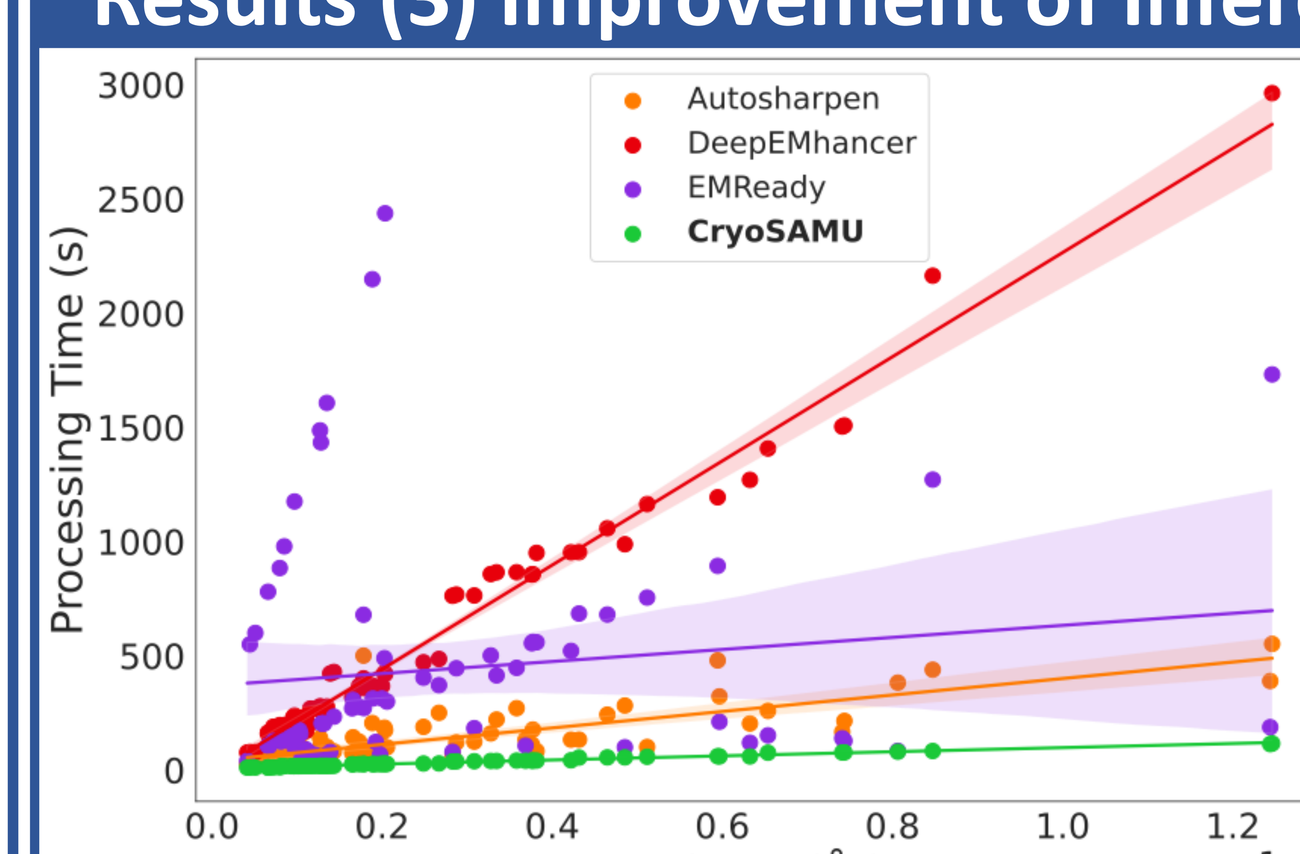
- CryoSAMU outperforms deposited maps in both real-space and Fourier-space correlation
- CryoSAMU shows competitive performance compared to SOTAs, such as EMReady[5].

Results (2) Improvement of Protein Modeling



- CryoSAMU achieves the best residue coverage score, while the sequence match score is slightly lower than EMReady[5] and DeepEMHancer[6].
- Integrating structural embeddings enhances the continuity and interpretability of generated maps, improving protein structure prediction.

Results (3) Improvement of Inference Speed



- CryoSAMU achieves an average processing time of 32.49 seconds, approximately 13.6 times faster than EMReady.
- Promising tool for large-scale and practical applications.

References

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4. Berman et al., Acta Crystallogr. D, 2002, pp. 899–907.
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