A Composable and Modular Framework for Protein Structure Prediction on HPC

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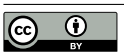
Abstract

Current AI protein structure prediction models involve multi-stage processing that combines deep neural networks with bioinformatics tools such as multiple sequence alignment (MSA). Researchers increasingly rely on intermediate or penultimate-layer activations from these models for downstream tasks including contact prediction, binding-site identification, and model interpretability. We describe the VizFold plugin, a modular framework that can be extended toward end-to-end composable pipelines. We demonstrate feasibility through standardized hook-based tracing for ESMFold and Boltz-2, archive validation, and reproducible deployment on an HPC cluster using managed caches, modules, quotas, and Slurm workflows. The framework extracts attention maps from user-selected layers and exports intermediate representations in a backend-specific run bundle (Boltz) or a canonical archive tree (ESMFold), with shared trace text conventions and explicit provenance metadata suitable for cross-model comparison. We provide step-by-step documentation for instrumentation and deployment so that other groups can reproduce or extend the pipeline on their own clusters. The framework and instrumentation code are open-source and available at https://github.com/AI2Science/vizfold-foundation.

CCS Concepts

• **Applied computing** → **Computational biology**; • **Computer systems organization** → **High-performance computing**; • **Mathematics of computing** → *Probabilistic algorithms.*



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Keywords

protein structure prediction, HPC deployment, intermediate representations, attention extraction, ESMFold, Boltz-2, composable pipelines

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1 Introduction and Background

AI-based methods have transformed protein structure prediction. AlphaFold2 [1, 2] demonstrated near-experimental accuracy and was recognized with the Nobel Prize; since then, newer architectures have expanded the design space, including AlphaFold3 [3], Boltz-2 [4], and ESMFold [5].

Despite their diversity, these models share many similarities and often include three components: (1) input encoding—MSA-based co-variation (AlphaFold2/3, Boltz-2) or protein language model embeddings (ESMFold via ESM-2 [6]); (2) a multi-layer attention network (Evoformer or Pairformer) that builds pair representations; and (3) a structure module that converts these into 3D coordinates via prediction or diffusion. AlphaFold and Boltz architectures execute these stages sequentially. Accessing intermediate outputs at each stage has also become critical for a wide range of downstream applications and interpretability research. Yet constructing flexible, reproducible, and modifiable workflows involving these components remains challenging because implementations differ in how inputs and outputs are represented and exposed through APIs. Thus, a modular and composable framework for computing these components on HPC systems can support a wide range of applications in protein science.

In this work, we present an initial step toward a fully modular multi-backend framework for protein structure prediction. We demonstrate these capabilities with ESMFold and Boltz-2 backends. In §2 we elaborate the broader context for the long-term vision; §3–8 present the interface, methods, engineering challenges, HPC deployment, and evaluation.

2 Vision and Scope

The long-term goal is a system in which users can compose predictors, MSA generation, and post-hoc analysis stages, with intermediates cached on cluster scratch and reused across Slurm job steps. This paper demonstrates a concrete subset: (i) hook-based tracing with distinct on-disk layouts—a canonical archive tree for ESMFold versus a flat Boltz-2 run bundle (`pred/`, `attn_txt/`, `act_npz/`, `arc_png/`, `manifest.json`)—using shared trace-text conventions and explicit provenance metadata; (ii) environment patterns on Georgia Tech PACE ICE; (iii) validation of extracted artifacts; and (iv) representative end-to-end runs including arc-diagram exports. Benchmarking, accuracy claims, and workflow-manager support are future work.

3 Framework Design

The VizFold plugin defines a backend-agnostic interface with FASTA input, optional layer/head/residue filters, and validated intermediate artifacts. ESMFold writes a canonical archive tree (`structure/`, `trace/attention/`, `trace/activations/`, `meta.json`). Boltz-2 currently writes a flat run directory (`pred/`, `attn_txt/`, `act_npz/`, `arc_png/`, `manifest.json`) with component-separated traces under `attn_txt/components/...`; strict validation enforces internal consistency of paths and metadata. Hooks do not alter weights. Batch wrappers isolate the environment (`HF_HOME`, `PYTHONNOUSERSITE`, etc.); a researcher requests a GPU via `sbatch`, sets trace variables, and invokes the backend driver. Figure 1 shows the architecture.

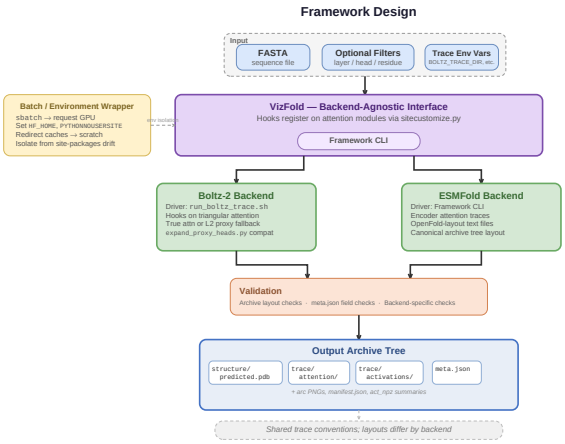


Figure 1: VizFold plugin framework architecture. Backends share hook-based extraction and validation discipline, but may differ in on-disk layout (canonical archive tree for ESMFold vs. flat run bundle for Boltz-2). Hooks extract intermediate representations without altering model weights. Batch wrappers handle HPC environment isolation (caches, modules, Slurm).

4 Modular Components of AI Protein Structure Prediction

4.1 Computing MSA

For MSA-based models (AlphaFold2/3, Boltz-2), the first stage aligns the input sequence against a protein database. The VizFold plugin does not re-implement MSA generation; instead, it consumes the MSA produced by the backend (or operates without one in single-sequence mode) and extracts attention and pair representations from subsequent stages.

4.2 Using Embeddings from a Protein Language Model

ESMFold replaces MSA with ESM-2 [6], a protein language model trained on ∼250M sequences. Our hooks capture attention maps and hidden states from all 36 encoder layers, plus IPA attention and backbone positions from the structure module at each recycling step.

4.3 Extracting Intermediate Representations

Hooks capture intermediate tensors dynamically without modifying the underlying model weights.

ESMFold. We hook `EsmForProteinFolding` [7] at each encoder self-attention layer, forcing `output_attentions=True`. Attention maps are $(N{+}2)^2$ before slicing to $N{\times}N$. `msa_row` files contain reformatted encoder self-attention for arc-diagram compatibility [8]. Structure-module extraction is detailed in §4.4.

Boltz. Setting `BOLTZ_TRACE_DIR` activates a `sitecustomize.py` import hook on triangular attention modules [4, 9]. When true attention tensors are exposed through the attention modules, we export head-structured matrices; otherwise we fall back to an L2 norm over pair channels of the triangular-attention output tensor, normalized to $[0, 1]$. This proxy is not an attention probability distribution. It is a visualization/diagnostics surrogate recorded as `proxy_pair_norm` (or related) in `component_status.json`. When `BOLTZ_TRACE_HEAD=all` but only a single proxy head is emitted, we optionally duplicate head blocks via `expand_proxy_heads.py` to preserve tooling expectations (duplicate heads are identical copies, not independent attentions). Outputs include VizFold-compatible `msa_row` and triangle trace text under `attn_txt/`, optional `act_npz/` summaries, `arc_png/` diagrams, and `manifest.json`. An experimental MSA hook (`BOLTZ_TRACE_EXPERIMENTAL_MSA=1`) may write additional traces when compatible modules are discoverable.

4.4 Extracting from the Structure Module

In ESMFold, the IPA-based structure module iteratively refines backbone frames over eight recycling steps; our `CapturingSoftmax` wrapper captures per-block attention ($[B, 12, N, N]$) and backbone positions ($[8, 1, N, 14, 3]$) at each step. Boltz-2 uses a diffusion-based structure module; Pairformer pair representations (from the triangular-attention hooks above) serve as the closest analogue. Per-diffusion-step coordinate extraction is deferred to future work.

Table 1: ESMFold environment (PACE ICE).

Component	Version
Python	3.10
PyTorch	2.10
transformers	4.38.2
CUDA	12.4
GPU	NVIDIA H200
Cluster	PACE ICE

Table 2: ESMFold outputs (N: sequence length).

Output	Shape	Source
Attention (36)	$[1, 40, N, N]$	Encoder
Activations (36)	$[1, N{+}2, 2560]$	Encoder
s_s	$[N, 1024]$	Structure
IPA (8 blocks)	$[1, 12, N, N]$	Structure
Backbone	$[8, 1, N, 14, 3]$	Structure
PDB	—	Full model

5 Issues Faced by Extraction and Solutions

ESMFold. `EsmAttention` discards raw weights; we hook `EsmSelfAttention` directly and inject `output_attentions=True`, inspecting the call signature at runtime to handle positional-vs-keyword mismatches across `transformers` builds. The IPA softmax requires wrapping in an `nn.Module` node, so we wrap it in a `CapturingSoftmax` subclass [10]. Full-layer trace archives can reach 6–15 GB; the `--layers` and `--heads` CLI flags select subsets, and `.detach()` prevents gradient-graph memory inflation.

Boltz. Triangular-attention internals vary across releases; we attempt true-attention capture first and fall back to a pair-norm proxy (L2 over pair channels, normalized to $[0, 1]$), recording provenance in `component_status.json`. `expand_proxy_heads.py` duplicates the single proxy head into multi-head slots for tooling compatibility. Tracing activates only when `BOLTZ_TRACE_DIR` is set; otherwise Boltz runs unmodified.

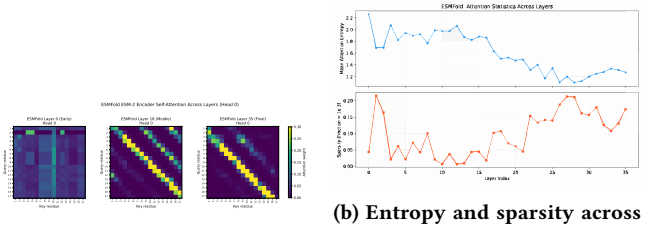
6 HPC Deployment Challenges and Solutions

6.1 ESMFold

The 8.4 GB checkpoint can exceed home-directory quota on PACE ICE; we redirect `HF_HOME` to scratch and pin `transformers==4.38.2` with `PYTHONNOUSERSITE=1`. Weights load via `use_safetensors=True` to avoid the pickle path affected by CVE-2025-32434 [11].

6.2 Boltz

Boltz requires compiled C++ extensions and RDKit [12]; under mixed conda/pip environments, RDKit can fail on compiled symbols at inference time. Installing Boltz extras with `pip install --no-deps` while keeping PyTorch and CUDA conda-pinned avoids conflicts. Our Slurm driver `run_boltz_trace.sh` redirects caches to scratch (`TMPDIR`, `PIP_CACHE_DIR`, `XDG_CACHE_HOME`, `HF_HOME`, `TORCH_HOME`, `WANDB_DIR`). One-time environment creation (`setup_boltz_env.sh`) exports `PYTHONNOUSERSITE=1` (and `PIP_USER=0`) during that script so pip installs avoid user site-packages; we recommend the same in interactive or Slurm shells



(a) Self-attention (layers 0, 17, 35) (b) Entropy and sparsity across layers

Figure 2: ESMFold encoder (head 0) for MKTFFVLLLCTFTVVSS. (a) Self-attention heatmaps at early, middle, and final layers. (b) Mean attention entropy and sparsity fraction across all 36 ESM-2 layers.

when diagnosing mixed-path import issues. The `--no_kernels` flag disables runtime CUDA compilation on ICE H100 nodes.

7 Benefits of HPC Execution Environments

ESMFold's checkpoint (~8.4 GB) plus dense traces (up to ~2 GB per run) exceed typical workstation resources. An H200 node reduced a 191-residue run to under 30 s. On one H100, our default Boltz-2 trace (layer 0, single residue, top-k=50, `BOLTZ_TRACE_HEAD=all` with proxy head expansion, including validation and arc rendering) completed in 204 s (Slurm `Elapsed`), while a deeper demonstration (Pairformer layers $\{0, 8, 16, 24, 32\}$ at residues $\{18, 50\}$, top-k=50) completed in ~272 s (~4.5 min) end-to-end. HPC also enables cross-model workflows—running the same target through multiple backends and caching intermediates on scratch for comparison—that are impractical locally.

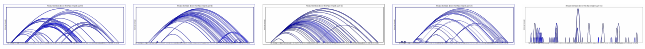
8 Results and Evaluation

8.1 ESMFold

A 17-residue CPU run yielded 36 attention tensors $[1, 40, 17, 17]$, 36 activations $[1, 19, 2560]$, `out.s_s` $[17, 1024]$, and reference-format text files [8]. Table 2 summarizes shapes. Figure 2 shows attention evolution and per-layer statistics. 6KWC (191 residues) on H200 ran in <30 s including load; synthetic checks validated IPA and backbone tensors. These layer-wise entropy and sparsity statistics themselves represent a downstream analysis enabled by the extracted archives, illustrating how stored intermediates support interpretability without re-running inference.

8.2 Boltz

Unless noted otherwise, our default ICE/Slurm run configuration traces layer 0 at residue 18, producing three trace text files and twelve arc diagrams after optional proxy head expansion. Separately, we also demonstrate deeper Pairformer tracing by selecting multiple layers. On PACE ICE (one H100), tracing layers $\{0, 8, 16, 24, 32\}$ with `top-`k `= 50` took ~4.5 min end-to-end. The run used an empty MSA (single-sequence mode) and, for layers $\{0, 8, 16, 24, 32\}$ at residues $\{18, 50\}$ with top-k=50, produced 25 top-level trace text files and 100 arc-diagram PNGs (4 heads after proxy expansion), plus `manifest.json`; `component_status.json` recorded `proxy_pair_norm`. Figure 3 shows edge patterns evolving across Pairformer depth: early layers are diffuse while deeper layers



(a) L 0 (b) L 8 (c) L 16 (d) L 24 (e) L 32

Figure 3: Boltz-2 Pairformer arcs (head 0, layers 0–32, proxy norm). Empty MSA; PACE ICE H100; top-k 50.

concentrate on fewer residue pairs, consistent with iterative geometric refinement. ESMFold inference is deterministic; repeated runs produce identical archives. Boltz traces with a fixed seed (`--seed 0`) produced consistent Pairformer proxy traces across runs; diffusion-stage coordinates may vary. These visualizations demonstrate a second downstream use case: cross-layer structural analysis from archived traces.

8.3 Performance Overhead and Downstream Impact

To quantify the extraction overhead on HPC workloads, we compared vanilla inference against hooked tracing. Boltz-2 exhibited ~5% wall-time overhead for hooked versus vanilla `boltz predict` under our default targeted-layer trace settings (predict step only; excludes arc rendering and post-run validation). ESMFold hook overhead was under 5% for targeted layer extraction (attention-only); the dominant cost is GPU-to-CPU transfer of captured tensors, not additional computation. Full 36-layer tracing adds further I/O overhead from writing the resulting ~2 GB trace archives. Despite this cost, the exported attention and pair summaries enable downstream analytical tasks without repeating full-model inference—for example, lightweight classifiers for binding-site prediction or layer-wise entropy metrics for flagging potentially misfolded regions.

9 Conclusion

We described the VizFold plugin framework and its hook-based extraction mechanisms for ESMFold and Boltz-2 on an HPC system (Georgia Tech PACE ICE). ESMFold conforms to a canonical archive tree (`structure/`, `trace/`, `meta.json`), while Boltz-2 currently emits a flat run bundle (`pred/`, `attn_txt/`, `act_npz/`, `arc_png/`, `manifest.json`) with explicit provenance in `component_status.json`. Unifying these into one on-disk standard is straightforward engineering (export/adapt) and is the next integration step for cross-backend dashboards. The intermediates from this plugin can be extended for downstream tasks—binding-site prediction from attention patterns, misfolded-region detection via layer-wise entropy, or lightweight classifiers on pair features. Our work can be extended to cross-model comparison on shared targets and broader backend support including OpenFold variants, together with adapters or export steps that map Boltz-2's flat run bundle onto the same dashboards as ESMFold's canonical tree.

Data and Code Availability

The VizFold plugin framework, extraction hooks, and deployment scripts are open-source. The code and documentation can be accessed at https://github.com/AI2Science/vizfold-foundation.

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