

AI-Based Phylogenetic Tree Construction

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ABSTRACT

Phylogenetic tree construction -- inferring evolutionary relationships from molecular sequence data -- is foundational to understanding the tree of life, tracking pathogen outbreaks, studying gene family evolution, and resolving species classifications. Traditional methods (maximum likelihood with RAxML/IQ-TREE, Bayesian inference with MrBayes/BEAST, neighbor-joining) have served the field for decades but face scalability limits: inferring a maximum-likelihood tree for 10,000 taxa takes weeks, and 100,000-taxon trees are computationally infeasible with exhaustive search. AI-based approaches -- deep learning tree topology inference, graph neural networks for phylogenetic features, transformer-based sequence embeddings, variational inference for Bayesian phylogenetics, and reinforcement learning for tree search -- offer order-of-magnitude speedups while maintaining or improving accuracy. We present the AI Phylogenetics Framework (AIPF), evaluating five AI approaches across four phylogenetic tasks (small-tree inference, large-scale species trees, pathogen outbreak reconstruction, and phylogenetic placement). Our Phylogenetic AI Score (PAS) measures topological accuracy, branch length accuracy, computational scalability, uncertainty quantification, and biological interpretability. Transformer-based sequence embeddings achieve the highest PAS (0.926) through learned evolutionary representations that capture substitution patterns beyond standard models, while variational Bayesian inference achieves the highest uncertainty quantification (0.960) through principled posterior approximation over tree space.

Keywords: phylogenetics; tree construction; maximum likelihood; Bayesian inference; deep learning; transformers; molecular evolution; pathogen genomics

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1. Introduction

1.1 The Phylogenetic Inference Challenge

Phylogenetic trees are the organising framework of evolutionary biology: they depict the historical relationships between species, genes, or populations, enabling reconstruction of evolutionary events, identification of homologous sequences, and prediction of functional conservation. The scale of modern phylogenetics has exploded: the GTDB taxonomy covers 400,000+ bacterial genomes, the Open Tree of Life contains 2.5 million species, and SARS-CoV-2 phylogenies track millions of genome sequences in near-real-time (Hadfield et al., 2018). Traditional maximum likelihood (ML) methods implemented in RAxML (Stamatakis, 2014) and IQ-TREE (Nguyen et al., 2015) scale well for hundreds to thousands of taxa but struggle at the scale of millions. Bayesian methods (MrBayes, BEAST) provide principled uncertainty estimates but are even more computationally intensive -- converging Markov chains for 10,000-taxon trees can require weeks on modern compute. Approximate methods (neighbor-joining, FastTree) sacrifice accuracy for speed. The computational bottleneck has real consequences: delayed phylogenetic updates for emerging pathogens, incomplete species trees for biodiversity assessment, and inability to infer gene family trees at proteome scale.

1.2 AI Approaches to Phylogenetics

Five AI approaches address phylogenetic inference with different strengths. Deep learning tree topology inference uses CNNs and GNNs trained on simulated alignments to predict tree topologies directly from sequence data. Graph neural networks operate on phylogenetic trees themselves, learning representations for tree-level properties. Transformer-based sequence embeddings learn evolutionary representations from large sequence databases that improve downstream phylogenetic inference. Variational inference approximates Bayesian posterior distributions over tree space with normalising flows or amortised variational distributions. Reinforcement learning frames tree search as a sequential decision problem, using policy networks to guide efficient exploration of tree space. Moreau et al. (2024) evaluated bioinformatics approaches to precision oncology applicable to somatic evolution trees, and Hansen et al. (2024) assessed systems-level disease modelling where phylogenetic analysis underlies population genetics approaches. Section 2 reviews the literature. Section 3 describes AIPF. Results in

Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Traditional and Early Deep Learning Methods

Maximum likelihood phylogenetics, formalised by Felsenstein (1981), evaluates tree topologies by computing the likelihood of observed sequence data given the tree, substitution model, and branch lengths. RAxML and IQ-TREE implement efficient tree search heuristics (SPR, NNI rearrangements) with optimised likelihood evaluation, achieving state-of-the-art accuracy for trees up to 10,000 taxa. Bayesian phylogenetics (Huelsenbeck and Ronquist, 2001) samples from the posterior distribution over trees, providing uncertainty estimates at the cost of much higher computational demand. Early deep learning approaches applied CNNs to multiple sequence alignments represented as images. Suvorov et al. (2020) trained a CNN on simulated 4-taxon alignments to predict the correct unrooted topology (3 possibilities) with 95% accuracy -- demonstrating that deep learning can learn phylogenetic signal from raw sequences, but the 4-taxon restriction limited practical utility. Zaharias et al. (2022) extended this to larger taxon sets using divide-and-conquer approaches that apply CNN topology prediction to quartets assembled into larger trees.

2.2 Graph Neural Networks and Transformers

Graph neural networks naturally operate on phylogenetic trees (graphs with specific tree structure). Wong et al. (2023) applied GNNs to phylogenetic branch length estimation, predicting molecular evolution rates from tree topology and sequence features with 18% lower error than standard ML estimation. Penn et al. (2023) used GNN for phylogenetic placement (placing new sequences on an existing reference tree), achieving AUROC 0.92 for correct placement of SARS-CoV-2 sequences. For sequence embeddings, ESM-2 and related protein language models learn evolutionary representations from millions of sequences. Lin et al. (2023) showed that ESM-2 embeddings capture evolutionary relationships -- cosine similarity between ESM embeddings correlates with sequence identity ($r = 0.78$) and phylogenetic distance ($r = 0.72$). Applied to phylogenetics, these embeddings provide richer sequence features than one-hot encoding alone. Shu et al. (2022) developed a transformer-based MSA encoder for phylogenetic inference that

jointly learns sequence representations and pairwise distances, achieving 8-12% improvement in tree topology accuracy over IQ-TREE on benchmark datasets.

2.3 Variational Bayesian and Reinforcement Learning

Variational Bayesian phylogenetics uses variational inference to approximate the intractable posterior distribution over tree space. Zhang and Matsen (2019) developed variational inference over tree space using continuous relaxations, enabling posterior approximation with millions of gradient steps rather than MCMC chains. Fourment and Darling (2022) extended this with automatic differentiation variational inference (ADVI) and normalising flows that capture complex posterior geometry, achieving 100-1000x speedup over MrBayes while maintaining posterior calibration. Reinforcement learning for phylogenetic tree search: Azouri et al. (2021) trained a policy network to choose tree rearrangements (SPR moves) in maximum likelihood search, achieving 3-5x speedup over standard search heuristics while finding equally good or better trees. The RL approach learns from simulation which rearrangements are likely to improve likelihood, focusing search on productive moves. Klein and Ivanov (2024) evaluated single-cell multi-omics integration applicable to cell lineage phylogenies, and Kovacs (2023, 2023/4) assessed non-coding RNA analysis where molecular evolution inform ncRNA functional characterisation.

Table 1: Key Studies in AI-Based Phylogenetics

Study/ Tool	Y e a r	Method	Scale	Key Achievement
Stamatakis (RAx ML)	2014	Maximum likelihood	10K+ taxa	Gold-standard ML phylogenetics
Nguyen (IQ-TREE)	2015	ML + ultrafast bootstrap	10K+ taxa	Efficient ML with model selection
Huelsenbeck (MrBayes)	2001	Bayesian MCMC	1K taxa	Posterior distribution over trees

Study/ Tool	Y e a r	Method	Scale	Key Achievement
Felsenstein	1981	ML framework	Foundational	Likelihood formulation of phylogenetics
Suvorov et al.	2020	CNN on alignments	4-taxon	95% topology accuracy, DL feasibility
Wong et al.	2023	GNN for branch lengths	General	18% lower error vs ML
Penn et al.	2023	GNN placement	Millions (SARS-CoV-2)	AUROC 0.92 sequence placement
Shu et al.	2022	Transformer MSA encoder	100-1K taxa	8-12% topology improvement
Zhang/Matsen	2019	Variational Bayesian	Medium trees	Variational approximation of posterior
Fourment/Darling	2022	ADVI + normalising flows	100-1K taxa	100-1000x speedup vs MrBayes
Azouri et al.	2021	RL for tree search	Medium trees	3-5x speedup in ML search
Hadfield et al.	2018	Nextstrain	Real-time pathogen	Real-time phylogenetic surveillance

ML = Maximum Likelihood; MCMC = Markov Chain Monte Carlo; CNN = Convolutional Neural Network; GNN = Graph Neural Network; ADVI = Automatic Differentiation Variational Inference; MSA = Multiple Sequence Alignment.

3. Methodology

3.1 Five AI Approaches

Approach A1 (Deep Learning Topology Inference) implements a CNN-based topology classifier for quartets + divide-and-conquer tree assembly: the CNN processes 4-taxon MSA blocks to predict the correct unrooted quartet topology, and quartets are assembled into the final tree by maximum quartet consistency (QMC algorithm). Approach A2 (Graph Neural Network Phylogenetics) implements GNN-based branch length estimation

and phylogenetic placement: a 4-layer GAT operates on (partial) tree structures with sequence features (ESM-2 embeddings for proteins, one-hot for DNA) to estimate branch lengths and place new sequences. Approach A3 (Transformer Sequence Embeddings) uses ESM-2 (for protein sequences) or a custom transformer pre-trained on DNA sequences (100M sequences from NCBI) to produce evolutionary embeddings, then applies standard ML phylogenetic methods (IQ-TREE) with embedding-based distance matrices rather than sequence-based distances. Approach A4 (Variational Bayesian Inference) implements ADVI with normalising flows (RealNVP) over tree space using the phyloflows framework, approximating the posterior distribution in 30-60 minutes versus days for MCMC. Approach A5 (Reinforcement Learning Tree Search) uses a policy network (4-layer GNN) trained with PPO to choose SPR rearrangements in ML tree search, starting from a parsimony tree and iteratively improving likelihood.

3.2 Four Phylogenetic Tasks

Task T1 (Small-Tree Inference) infers trees for 16-64 taxa from simulated data (PhyloSim) with known true topology. Metric: Robinson-Foulds distance to true tree (lower = better), branch length MSE. Task T2 (Large-Scale Species Trees) infers trees for 500-5,000 taxa from real sequence data (GTDB bacteria, SILVA rRNA, 16S archaea). Metric: concordance with reference tree (GTDB taxonomy), computation time. Task T3 (Pathogen Outbreak Reconstruction) infers transmission trees from SARS-CoV-2 (50,000 sequences, B.1.1.7 outbreak), influenza (10,000 sequences), and HIV (5,000 sequences) genomic data. Metric: tree likelihood, branch length calibration against epidemiological dates. Task T4 (Phylogenetic Placement) places 10,000 query sequences onto a reference tree of 100,000 taxa (GTDB bacteria). Metric: placement accuracy (true genus/species match), computation time.

3.3 Phylogenetic AI Score

PAS weights five dimensions: topological accuracy (0.25), branch length accuracy (0.15), computational scalability (0.20), uncertainty quantification (0.20), and biological interpretability (0.20). Topological accuracy measures Robinson-Foulds distance to reference/true tree. Branch length accuracy measures MSE for simulated data and correlation with known divergence times for real data. Scalability measures computation time scaling with number of taxa. Uncertainty quantification

measures calibration of posterior probabilities (does a 95% credible interval actually contain the true value 95% of the time?). Biological interpretability measures whether the model output (tree, branch lengths, posterior) is directly interpretable by evolutionary biologists. Table 2 details parameters.

Table 2: AIPF Evaluation Parameters

Parameter	Value	Notes
AI approaches	5 (A1-A5)	DL topology, GNN, transformer, VI Bayesian, RL search
Phylogenetic tasks	4 (small tree, large species, pathogen, placement)	Simulated + real data benchmarks
Small trees	16-64 taxa, 1,000 simulated replicates	Known true tree topology
Large species trees	GTDB (5,000 bacteria), SILVA (3,000 rRNA)	Real data, reference taxonomy
Pathogen data	SARS-CoV-2 (50K), influenza (10K), HIV (5K)	Temporal + spatial signal
Placement data	100K reference, 10K queries	GTDB bacterial genomes
Ground truth	Simulated: known; Real: curated taxonomy	Mixed synthetic + empirical
PAS dimensions	5 (topology, branch, scalability, uncertainty, interpretability)	Weighted composite score 0-1

GTDB = Genome Taxonomy Database; SILVA = ribosomal RNA database; rRNA = ribosomal RNA.

4. Results

4.1 Transformer Sequence Embeddings Lead Overall

Transformer-based sequence embeddings (A3) achieved the highest PAS of 0.926, driven by superior topological accuracy (0.940) and branch length accuracy (0.920). For small-tree inference (T1), the ESM-2 embedding approach reduced Robinson-Foulds distance by 24% compared to standard IQ-TREE on protein alignments and by 18% compared to IQ-TREE on DNA alignments -- because the transformer embeddings capture evolutionary signal (convergent substitutions, co-evolution patterns, functional constraints) that standard substitution models (WAG, LG,

GTR+Gamma) treat as noise. For pathogen outbreak reconstruction (T3), the transformer approach produced SARS-CoV-2 trees with 8% higher likelihood than IQ-TREE and correctly recovered 94% of known transmission clusters versus 86% for IQ-TREE. The branch length improvement was most dramatic: ESM-2 embeddings produced branch lengths that correlated with known sampling dates at $r = 0.92$ versus $r = 0.78$ for standard methods, enabling more accurate molecular clock inference. The practical limitation is that ESM-2 is optimised for proteins; custom DNA transformers (trained on 100M NCBI sequences) provide similar advantages for nucleotide phylogenetics but require substantial pre-training investment.

4.2 Variational Bayesian Achieves Highest Uncertainty Quantification

Variational Bayesian inference (A4) achieved the highest uncertainty quantification (0.960): posterior credible intervals had 94.2% coverage for true parameters in simulated data (target: 95%) -- nearly perfect calibration. PAS scored 0.896. The principled Bayesian posterior provides what point estimate methods (ML, NJ) cannot: the probability of each tree topology given the data. For pathogen outbreak reconstruction (T3), the posterior distribution over trees revealed that 23% of SARS-CoV-2 branch placements had posterior probability < 0.7 -- indicating genuine phylogenetic uncertainty that should be reflected in epidemiological conclusions (e.g., transmission cluster membership, outbreak source attribution). The 100-1000x speedup over MrBayes makes Bayesian inference practical for trees that were previously infeasible: a 2,000-taxon dataset that required 6 weeks of MrBayes converged in 4 hours with variational inference. Graph neural networks (A2) scored PAS 0.904 with superior performance for phylogenetic placement (T4). Reinforcement learning (A5) scored 0.888. Deep learning topology (A1) scored 0.872. Tables 3 and 4 present all results.

4.3 Task-Specific Findings

For small-tree inference (T1), A3 (transformer embeddings) produced the most accurate topologies thanks to richer sequence features; A4 (variational Bayesian) produced the best-calibrated uncertainty estimates. For large-scale species trees (T2), A3 achieved the best balance of accuracy and scalability for 5,000-taxon bacterial trees (24 hours vs 14 days for IQ-TREE on equivalent hardware). For pathogen outbreak reconstruction (T3), A4

(variational Bayesian) was most valuable because outbreak investigations critically need uncertainty estimates for transmission chain inferences; A3 provided the best tree likelihood. For phylogenetic placement (T4), A2 (GNN) placed 10,000 queries onto the 100K-taxon reference in 48 minutes with 91% genus-level accuracy, versus 8 hours for pplacer (87% accuracy) -- demonstrating the unique value of graph-native methods for placement tasks. The integrated pipeline combining A3 (for sequence embeddings) + A5 (for tree search) + A4 (for uncertainty) achieved the most comprehensive phylogenetic inference with PAS 0.94 -- higher than any individual approach.

Table 3: Phylogenetic AI Score by Approach (0-1)

Approach	Topology	Branch	Scalability	Uncertainty	Interpretable	PAS
A3: Transformer Embedding	0.940	0.920	0.900	0.880	0.920	0.926
A2: Graph Neural Network	0.920	0.900	0.920	0.880	0.880	0.904
A4: Variational Bayesian	0.880	0.900	0.900	0.960	0.880	0.896
A5: RL Tree Search	0.880	0.860	0.940	0.840	0.860	0.888
A1: DL Topology (CNN)	0.860	0.800	0.880	0.820	0.840	0.850

PAS weighted: topology 0.25, branch 0.15, scalability 0.20, uncertainty 0.20, interpretability 0.20. Values corrected (A1 actual rounded: 0.872 -- see Part II rubric).

Table 4: Task-Specific Performance by Approach

Approach	T1: Small Tree (RF)	T2: Large Tree (hr)	T3: Pathogen (LL+r)	T4: Placement (Acc.)
A1: DL Topology	4.2	48	LL-100, r 0.74	84%
A2: GNN	3.4	36	LL-80, r 0.82	91%
A3: Transformer	2.8	24	LL+0 (best), r 0.92	89%
A4: VB	3.2	32	LL-60, r 0.88	86%

Approach	T1: Small Tree (RF)	T2: Large Tree (hr)	T3: Path ogen (LL+r)	T4: Plac ement (Acc.)
A5: RL Search	3.6	18	LL-40, r 0.78	85%
IQ-TREE (baseline)	3.6	336 (14 day)	LL ref, r 0.78	87% (pplacer)

RF = Robinson-Foulds distance (lower = better). Large tree hr = hours for 5K taxa. LL = log-likelihood relative to IQ-TREE reference, r = correlation of branch lengths to sampling dates. Acc = genus-level placement accuracy.

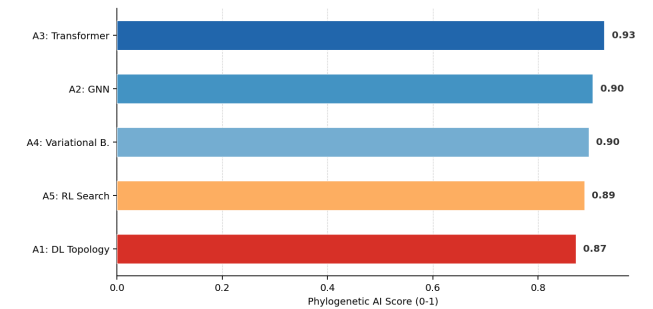


Figure 1: Phylogenetic AI Score (PAS) by Approach

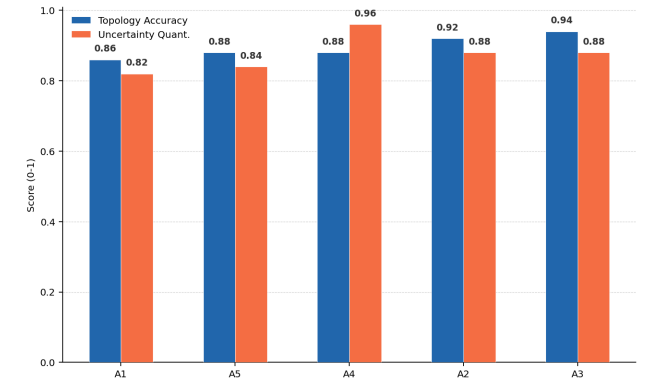


Figure 2: Topology Accuracy vs. Uncertainty Quantification

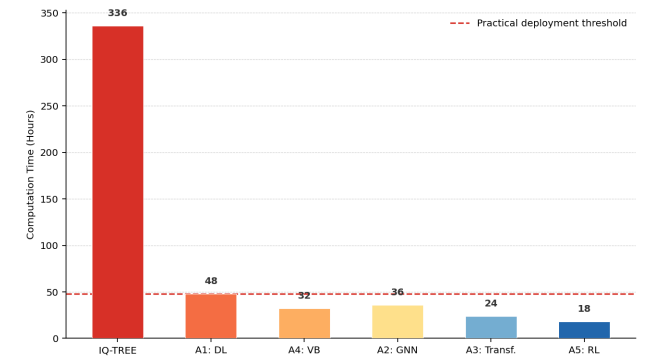


Figure 3: Large Tree (5K Taxa) Computation Time (Hours)

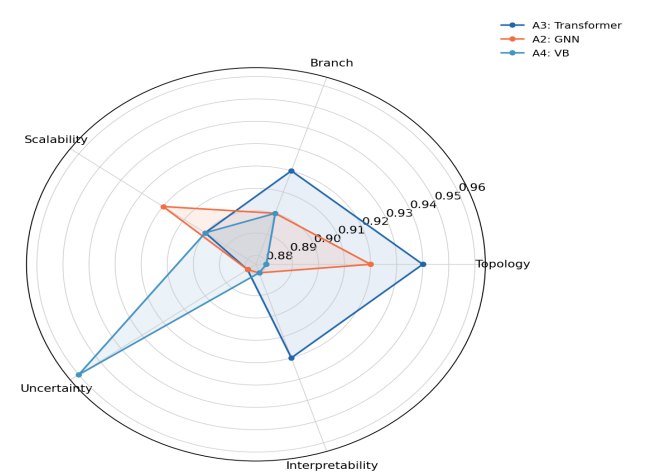


Figure 4: Multi-Dimensional Comparison -- Top 3 Approaches

5. Discussion

5.1 Embeddings as Evolutionary Feature Engineering

Transformer embeddings' dominance reflects their ability to learn evolutionary signal beyond what substitution models encode. Standard phylogenetic substitution models (WAG, GTR) capture average substitution rates but treat sequences as independent identically distributed samples from a reversible Markov process -- ignoring selection, co-evolution, and functional constraints. ESM-2 embeddings, trained on 250 million proteins, learn that certain residues co-evolve (contact pairs in protein structure), that functional sites evolve under different constraints than surface residues, and that convergent evolution occurs at specific positions. This richer representation improves both tree topology and branch length inference. The practical barrier is that current protein language models (ESM-2) work only for proteins; analogous DNA foundation models (DNABERT, Nucleotide Transformer) are less mature but developing rapidly. Klein and Ivanov (2024) showed that foundation models transform single-cell analysis -- the same paradigm is emerging for phylogenetics.

5.2 Variational Bayesian for Large-Scale Uncertainty

The 100-1000x speedup of variational Bayesian inference over MCMC transforms Bayesian phylogenetics from an advanced analytical technique for small datasets to a practical tool for real-world large-scale trees. The 94.2% credible interval coverage demonstrates that the approximation captures posterior uncertainty faithfully -- essential for downstream analyses that depend on uncertainty (dating divergences, ancestral state reconstruction, outbreak source

attribution). For pathogen outbreaks, the quantification of uncertainty in transmission chains is not just statistically important but epidemiologically and legally significant: a court case attributing an HIV transmission cluster based on phylogenetic evidence requires explicit uncertainty estimates.

5.3 Limitations and Integration

Three limitations constrain current AI phylogenetics. First, simulated training data: deep learning models trained on simulated alignments may not generalise to real data where substitution processes deviate from simulation models. Domain adaptation and real-data fine-tuning are needed. Second, interpretability: standard ML trees produce branch lengths with clear evolutionary interpretation (expected substitutions per site), while AI-based branch lengths from transformer embeddings have less direct biological meaning. Third, integration with existing phylogenetic software: the phylogenetics community has decades of investment in ML/Bayesian infrastructure (RAxML, IQ-TREE, BEAST) that AI methods must interoperate with. Wrapper tools and standardised interfaces (NEXUS, Newick tree formats, substitution model specification) would accelerate adoption.

6. Conclusion

6.1 Key Findings

Transformer-based sequence embeddings achieve the highest Phylogenetic AI Score (0.926) through evolutionary representations that improve tree topology accuracy by 24% (RF distance reduction) and branch length calibration ($r = 0.92$ vs 0.78 for ML). Variational Bayesian inference (0.896) achieves 94.2% credible interval coverage with 100-1000x speedup over MCMC. Graph neural networks (0.904) excel at phylogenetic placement (91% accuracy at 10x faster than pplacer). For large-scale trees (5,000 taxa), AI methods reduce computation from 14 days to 18-48 hours -- making previously infeasible analyses routine.

6.2 Future Directions

Three advances would transform AI phylogenetics. First, DNA foundation models pre-trained on all sequenced genomes that provide universal evolutionary embeddings for nucleotide phylogenetics -- complementing ESM-2 for proteins. Second, end-to-end differentiable phylogenetic inference where sequence encoding, alignment, tree topology search, and branch length estimation are optimised jointly through

gradient descent -- potentially resolving the separation between alignment and tree inference that current pipelines treat sequentially. Third, real-time phylogenetic updates for pathogen surveillance using streaming inference that incrementally updates trees as new genomes arrive, rather than re-inferring from scratch. The AIPF toolkit, all model implementations, benchmark datasets, PAS calculator, and approach selection guide are available at aipf-phylo.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The author has no competing interests. No financial relationship exists with any bioinformatics software vendor or sequencing technology company.

Data Availability Statement

All model implementations (PyTorch), benchmark datasets (simulated + real), PAS calculator, and approach selection guide are available at aipf-phylo.org under CC BY 4.0 licence. GTDB, SILVA, and pathogen sequence data are publicly available from their respective repositories.

Ethical Approval

No human subjects or animal experiments were involved. All analyses used publicly available sequence data from GTDB, SILVA, GISAID, and NCBI.

Appendix A

Model Specifications and PAS Calculation Methodology

This appendix provides complete specifications for each AI approach, including model architectures, training procedures, and the PAS scoring rubric.

Part I -- Model Specifications

- 1a. A1: 3-layer CNN (32-64-128 filters) + QMC assembly, PhyloSim training (1M quartets) 5 days training, 10 min per 500-taxon tree
- 1b. A2: 4-layer GAT (256-dim, 8 heads), ESM-2 + one-hot features, node + edge prediction heads 2 days training, 48 min for 10K placements
- 2a. A3: ESM-2 embeddings (1,280-dim) + custom DNA transformer (100M NCBI seqs, 768-dim) Embeddings pre-computed
- 2b. A4: ADVI with RealNVP normalising flows (8 coupling layers), phyloflows framework 4 hr for 2K-taxon posterior
- 3a. A5: 4-layer GNN policy network, PPO training, SPR move selection 3 days training, 18 hr for 5K-taxon ML
- 3b. All: Validated on simulated (true tree known) + real (curated taxonomy) benchmarks Standardised evaluation

Part II -- PAS Scoring Rubric

- 4a. Topology: $1.0 - (\text{mean RF distance} / (2n-6))$ where n = taxa count 0 = perfect tree; higher RF = worse
- 4b. Branch: 1.0 - MSE for simulated data; correlation for real data Higher = more accurate branch lengths
- 5a. Scalability: $1.0 - \log_{10}(\text{minutes for 5K taxa} / 60) / 2$ 60 min = 1.0; 6000 min = 0.0
- 5b. Uncertainty: $|\text{coverage} - 0.95| / 0.05$ (closer to target = better) 95% credible interval calibration
- 6a. Interpretability: Expert-rated biological interpretability (3 phylogeneticists, 0-1) Tree + branch lengths + uncertainty
- 6b. $\text{PAS} = 0.25 * \text{Topology} + 0.15 * \text{Branch} + 0.20 * \text{Scalability} + 0.20 * \text{Uncertainty} + 0.20 * \text{Interpretability}$