Which pLM to choose? A comparative evalutaion

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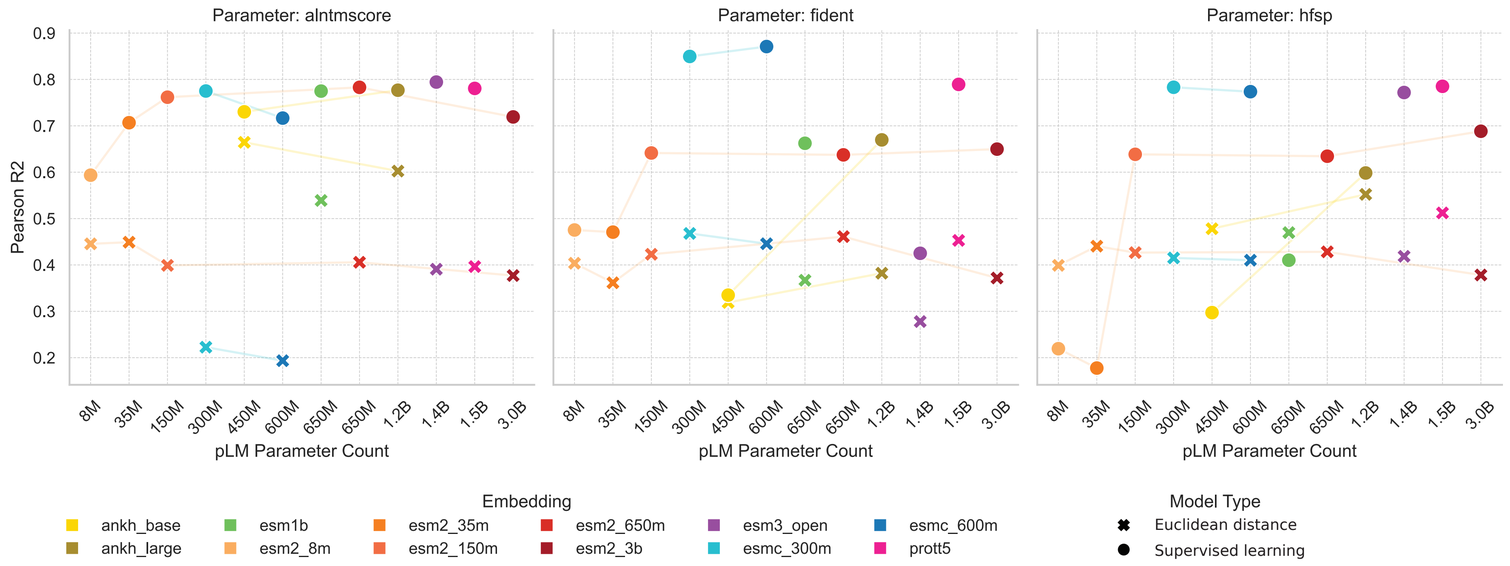
Background

Protein language models (pLMs) create conflicting maps of sequence space—like early cartographers charting unknown territories. Current models range from 8M to 15B parameters (ProtT5 [1], ESM2 [2], Ankh [3], ESM-C [4]), yet the relationship between size and biological representation quality contradicts NLP scaling laws [5]. We distinguish between raw embedding information (accessible through Euclidean distance) and extractable information (supervised learning).

Model size does not correlate with performance

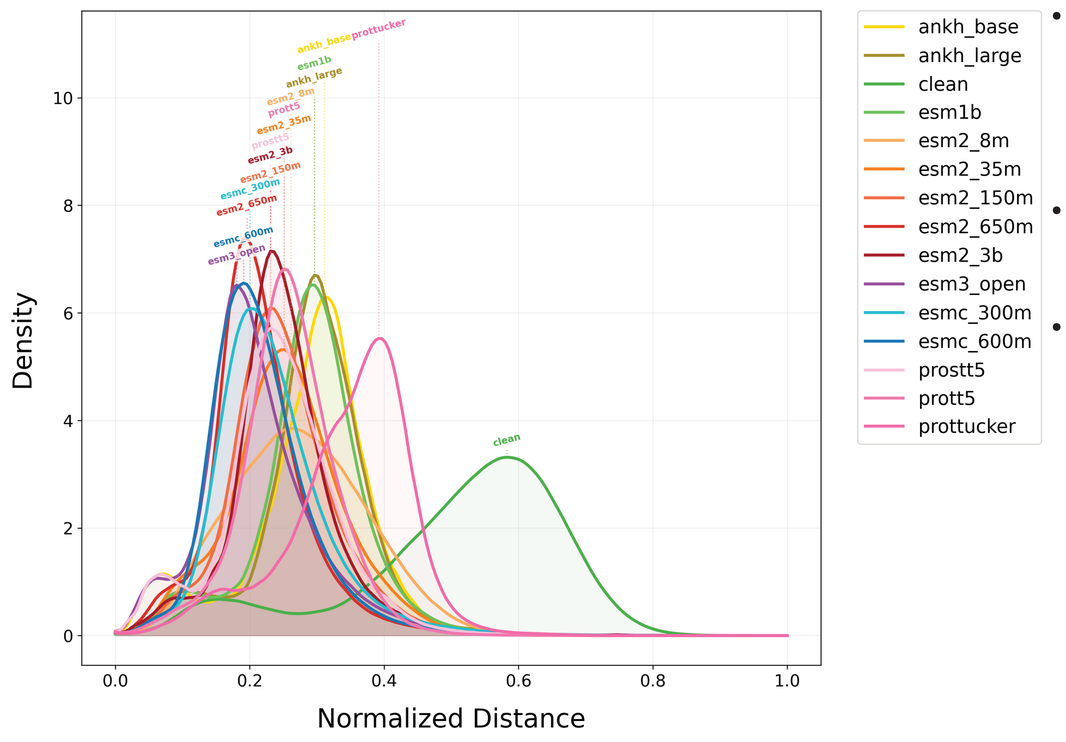


- Smaller models (≤150M) match or outperform billion-parameter variants for raw embeddings
- Supervised learning reverses this trend: larger models tend to unlock richer latent information
- ESM-C [4] models, while small, show remarkable improvements over similar sized older models

Methodology

1. Benchmarked 15 pLMs (8M-3B parameters) on < 2.5M protein pairs from SwissProt-pre2024 (542K proteins) [6]
2. Evaluated three biological similarity metrics: sequence identity (MMseqs2 [7]), structural similarity (Foldseek [8], TM-scores), and functional similarity (HFSP scores [9])
3. Compared Euclidean distances versus supervised learning
4. Analyzed embedding space topology and cross-model correlations

Bimodal distribution reflects learned similarities



- Bimodal distributions expose natural protein organization: functionally similar clusters (left peak) vs divergent sequences (right peak)
- Contrastive learning amplify separation: CLEAN [10] doubles normalized distances
- Near unimodal patterns in ESM-C [4] and ProtT5 [1] suggest fundamentally different organizational principles

Conclusion

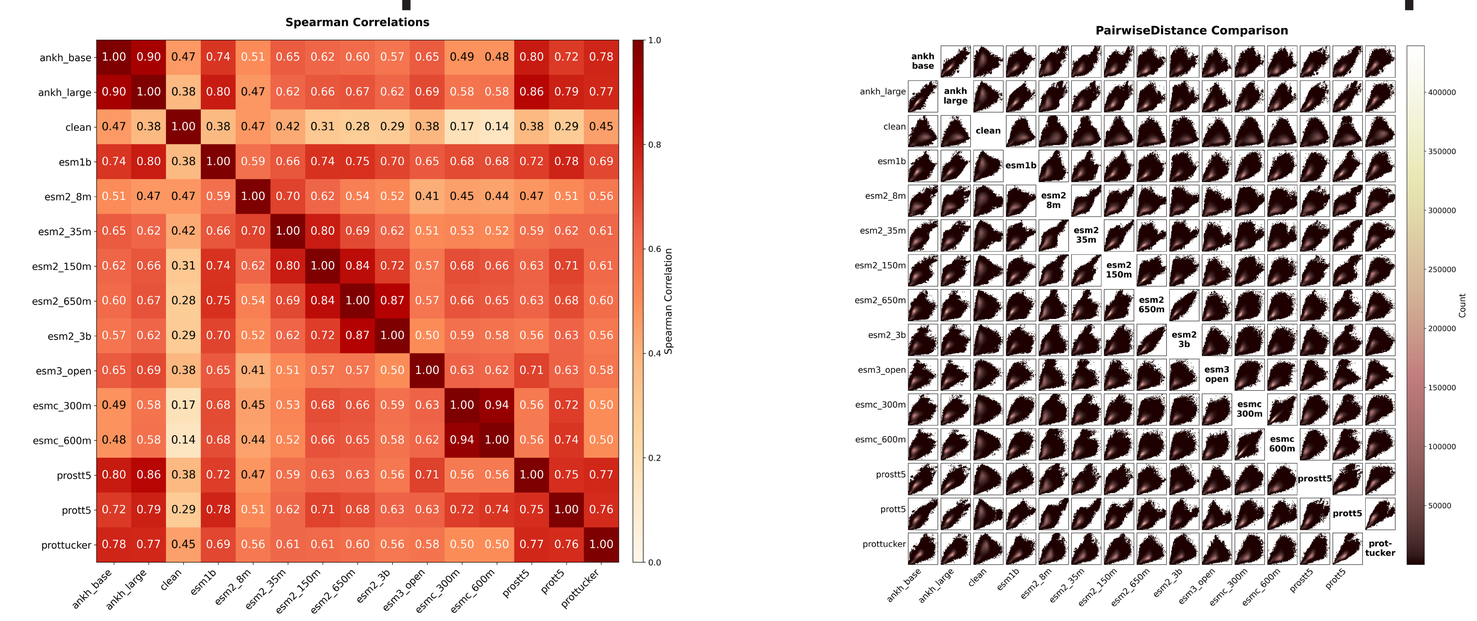
Need immediate insights? Choose foundation models ≤150M parameters (optimal cost-benefit ratio)

Have GPUs and labeled data? Use 1-3B models for supervised learning

Specific task only? Contrastive learn specialist, but accept limited versatility

Future Directions: Progress requires smarter training objectives and better data curation, not merely more parameters.

Pairwise comparison shows different learned space



- Model families mostly maintain signature correlations (ρ>0.75) regardless of size: architecture defines embedding topology
- Surprising: Ankh-large [3] and ProstT5 [1] achieve ρ>0.80 despite different frameworks
- Contrastive training breaks family bonds: CLEAN [10] - ESM1b [11] correlation drops to ρ=0.38

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