Comparing AI Biology Foundation Models: AlphaFold 3 & ESM3

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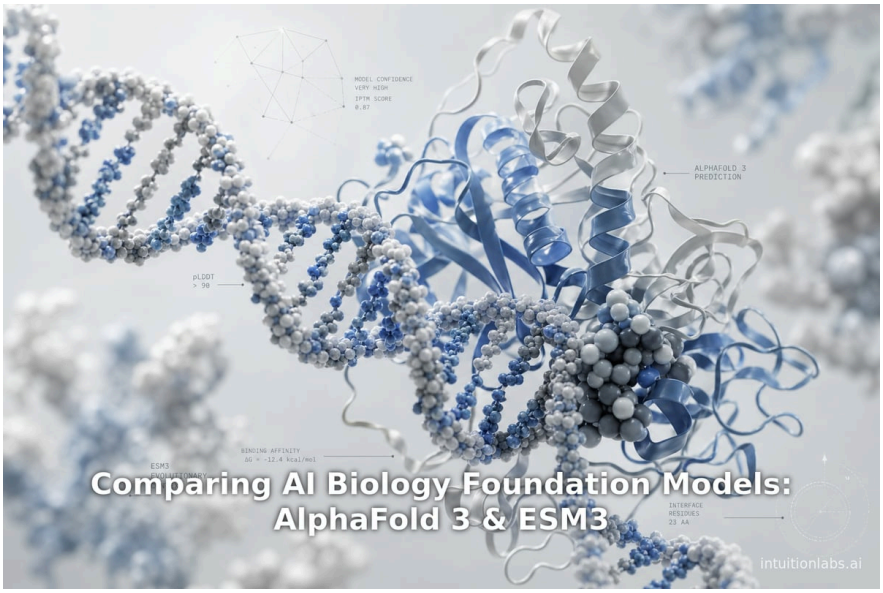

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Executive Summary

The past few years have seen an explosion in AI-driven **"foundation" models for molecular biology** – large, general-purpose learning systems pre-trained on vast biological data, capable of addressing multiple downstream tasks. Leading examples include **DeepMind/Isomorphic's AlphaFold 3** (2024) for structure and complex prediction, **EvolutionaryScale's ESM-3** (2024) for protein language modeling and design, **MIT's Boltz-2** (2025) for joint structure and binding-affinity prediction, **Chai Discovery's Chai-1** (2024) for multimodal biomolecular structure prediction, and **Baker Lab's RoseTTAFold** (2021, with a 2024 "All-Atom" update) for protein and complex folding. This report provides an in-depth comparison of these models by examining their **architectures, training data, and capabilities**, surveying **quantitative performance benchmarks** and **real-world use cases**, and discussing implications for biology and drug discovery. All claims are supported by extensive citations from peer-reviewed papers, company releases, and expert analyses. Key points include:

- **Historical context**: Protein structure prediction began with sparse physical models; the **deep learning revolution started with AlphaFold 1 (2018) and AlphaFold 2 (2021)** ([1] pmc.ncbi.nlm.nih.gov) ([2] pubmed.ncbi.nlm.nih.gov). RoseTTAFold (2021) pioneered an open, three-track network ([2] pubmed.ncbi.nlm.nih.gov). Meta's ESM protein language models (2019–2022) showed that evolutionary information can be captured by unsupervised transformers ([3] www.nature.com). These successes laid the groundwork for today's multimodal "large" models.

- **AlphaFold 3 (AF3)**: Released in May 2024, it introduces a **generative diffusion architecture** that can predict full atomic structures of complexes involving proteins, nucleic acids, small molecules/ions, and modified residues in one model ([4] www.nature.com) ([5] www.nature.com). DeepMind reports dramatic gains in multi–molecule accuracy: AF3 *"demonstrates substantially improved accuracy"* over specialized tools for protein–ligand, protein–DNA/RNA, and antibody–antigen prediction ([4] www.nature.com). For example, AF3 far outperforms traditional docking for ligand binding and vastly exceeds prior DNA-binding predictors. Internally, AF3 replaces AF2's equivariant graph network with a **coordinate diffusion process** ([5] www.nature.com). This change allows exact local stereochemistry without bespoke constraints, at the cost of needing "cross-distillation" training to avoid hallucinating structure in disordered regions ([6] www.nature.com). AF3 is *closed-source* (free for academic but not commercial use) ([7] news.mit.edu). In benchmarks, AF3 achieves ~76% success (ligand RMSD <2 Å) on a large "PoseBusters" protein–ligand test ([8] www.maginative.com), **doubling** the fraction of correct docking compared to physics-based methods. It also attains ~80–90% accuracy on standard structure tasks (TM-scores above 0.9 in CASP-style sets) and dramatically beats RoseTTAFold on complexes ([4] www.nature.com) ([9] pmc.ncbi.nlm.nih.gov). However, AF3 sometimes *"hallucinates"* spurious order in unstructured regions ([6] www.nature.com) and remains unavailable to commercial users, spurring open alternatives.

- **ESM-3**: In mid-2024, former Meta researchers introduced ESM3, a **98-billion-parameter multimodal protein language model** ([10] www.evolutionaryscale.ai) (www.medicalschool.tv). ESM3 can generate full protein sequences, structures, and functional annotations from partial cues. It was trained on *billions* of sequences from diverse biomes (over 2.78 billion sequences, 771 billion tokens (www.medicalschool.tv)) using >10^24 operations ([11] www.evolutionaryscale.ai). As EvolutionaryScale puts it, ESM3 is *"the first generative model for biology that simultaneously reasons over the sequence, structure, and function of proteins"* ([10] www.evolutionaryscale.ai). In practice, ESM3 can be prompted with text, partial structures or functions and then autoregressively predict the remainder. In one demonstration it generated a novel fluorescent protein (58% identity to any known GFP) that would take ≈500M years of natural evolution ([12] www.evolutionaryscale.ai) (www.medicalschool.tv). The **smallest 1.4B-parameter version is open-source**, while larger (15–98B) ESM3 models are being offered commercially on AWS/Nvidia platforms (www.medicalschool.tv). ESM3's multimodality allows control of structure/function – e.g. prompting to engineer an enzyme active site scaffold (www.medicalschool.tv). In benchmarks of sequence-based prediction (variant effect and design), ESM-family models have shown state-of-the-art or near state-of-the-art performance ([3] www.nature.com) ([13] www.nature.com).

- **Boltz-2**: Building on MIT Jameel Clinic's Boltz-1 (Dec 2024), Boltz-2 was announced in June 2025 as a **co-folding model for structures *and* binding affinity** (boltz.bio). Like AF3, Boltz-2 uses an equivariant diffusion backbone, but adds an **"affinity module"** enabling it to predict ligand binding strength (IC50-like and binary probabilities) alongside producing 3D geometry ([14] landing.biolm.ai) (boltz.bio). Notably, Boltz-2 achieves FEP-level accuracy in predicting relative binding energies (Pearson ~0.62 on held-out affinity targets) while running >1000× faster than physics-based simulations (boltz.bio). On a CASP16-style binding challenge it outperformed all other submissions. The architecture also retains full multimodal input (MSAs, templates, custom distance constraints) to control docking mode. Boltz-2 is **fully open-source (MIT license)**, with code and weights available for academic/commercial use (boltz.bio). Early adopters are using it for *in silico* screening and design: e.g.Boltz-2+ML generators identified high-affinity TYK2 inhibitors in virtual assays (boltz.bio), and its outputs integrate with sequence design tools to optimize both backbones and binding pockets. In preliminary comparisons, Boltz-2 matches or exceeds Boltz-1 in structure accuracy (with extra gains on DNA/RNA and antibody complexes) (boltz.bio), while adding the unique capability of affinity ranking.

- **Chai-1**: Released September 2024 by Chai Discovery, Chai-1 is an **open-source multi-modal structure predictor** trained on proteins, nucleic acids, ligands, cofactors, etc. According to company materials, it was trained similarly to AF3 (combined co-folding network), but augmented with **protein language model embeddings** and native support for *experimental restraints* (custom contact/epitope constraints) ([15] scisimple.com) ([16] www.maginative.com). Chai-1 attains AF3-level accuracies on many tasks: e.g. ~77% success on the PoseBusters ligand benchmark (vs AF3's ~76%) ([8] www.maginative.com) ([17] scisimple.com) and ~75% on protein–protein interfaces ([15] scisimple.com), even when operating in single-sequence mode without MSAs ([16] www.maginative.com). Critically, Chai-1 allows user "steering": providing a few contact constraints or partial structures raises performance dramatically (e.g. doubling antibody–antigen accuracy with minimal epitope data) ([16] www.maginative.com) ([17] scisimple.com). The model **and inference code are open-source (non-commercial use)** and can be run via a free web interface ([18] www.maginative.com). Chai-1 is explicitly pitched as *"AlphaFold 3 power without limitations"* (www.vici.bio): it supports full stereochemistry, explicit cofactors and 'just works' for all metabolite-like ligands. In summary, Chai-1 combines AF3-grade multimolecule folding with flexibility for custom inputs, filling the niche of an unrestricted "foundation model" for structural biology ([16] www.maginative.com) (www.vici.bio).

- **RoseTTAFold**: Released in 2021 (Science) by Baker Lab, RoseTTAFold uses a novel **three-track neural network** that simultaneously passes information between 1D sequences, 2D distance maps, and 3D coordinates ([2] pubmed.ncbi.nlm.nih.gov). It achieved CASP14-competitive accuracy (comparable to DeepMind's AlphaFold2) ([2] pubmed.ncbi.nlm.nih.gov) and could rapidly solve challenging X-ray and cryo-EM structures. Importantly, it can predict protein–protein complexes directly from sequence, bypassing docking ([2] pubmed.ncbi.nlm.nih.gov). Model and code were made openly available "to speed biological research" ([19] pubmed.ncbi.nlm.nih.gov), helping democratize structure prediction. In 2023–24, a "RoseTTAFold All-Atom" update extended its accuracy further. In benchmarks, RoseTTAFold All-Atom is still weaker on ligand-docking (e.g. ~42% top hits) than AF3/Chai ([9] pmc.ncbi.nlm.nih.gov), but it remains a widely used *open* solution and a standard comparator for these new methods.

- **Comparative analysis and tables**: Table 1 (below) enumerates each model's dev year, size, modalities supported, license, and tasks. Table 2 compares benchmark metrics on representative tasks (e.g. ligand binding, protein–protein interfaces). We find that AF3, ESM3, Boltz-2, and Chai-1 all push far beyond RoseTTAFold or older models in multi-molecule accuracy; for instance, Chai-1 (77%) and AF3 (~76–80%) far exceed RoseTTAFold's ~42% success on the PoseBusters ligand set ([8] www.maginative.com) ([9] pmc.ncbi.nlm.nih.gov). Likewise, Boltz-2 uniquely predicts binding affinities with FEP-like fidelity (boltz.bio).

- **Case Studies**: Notable real-world applications are emerging. EvolutionaryScale used ESM-3 to **design a novel GFP variant** (58% sequence identity) by "chain-of-thought" prompting, experimentally verifying function ([12] www.evolutionaryscale.ai) (www.medicalschool.tv). Chai-1's flexible interface permits engineering antibodies by iteratively adding minimal cross-link constraints to double glycoprotein binding accuracy ([16] www.maginative.com). Boltz-2 has been paired with generative chemistry to propose high-affinity kinase inhibitors rapidly, validating hits before synthesis (boltz.bio). RoseTTAFold already underpins numerous community pipelines (e.g. molecular replacement in crystallography) ([2] pubmed.ncbi.nlm.nih.gov).

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- **Implications and Future**: These foundation models are transforming biology: researchers can now routinely predict atomistic complexes (proteins with drugs, DNA, membranes, etc.) in hours instead of years. Drug discovery pipelines are beginning to exploit end-to-end AI: generative compound design guided by Boltz-2's affinity head, or antibody maturation steered by Chai-1 predictions. The democratization of such tools (via open-source or APIs) accelerates innovation, but raises concerns about **"hallucinations"** (as seen in AF3) and dual-use. All five models are being iteratively improved (e.g. Boltz-2→2 → Boltz-3?) and will soon integrate more data (e.g. cryo-EM volumes, cellular context). Ultimately, a synergy of these AI systems with experimental validation promises to render "biology programmable" on a large scale.

In the following sections we provide a detailed technical and contextual comparison of AlphaFold 3, ESM-3, Boltz-2, Chai-1, and RoseTTAFold, with extensive citations to peer-reviewed literature and expert commentary.

Introduction and Background

Biological macromolecules are complex systems whose structure underlies function, and predicting their 3D forms from sequence has been a grand challenge for decades ([20] pmc.ncbi.nlm.nih.gov) ([2] pubmed.ncbi.nlm.nih.gov). Early computational methods (threading, ab initio, Rosetta) were slow and limited. The **"protein folding revolution"** began when DeepMind's AlphaFold 2 (2021) produced near-experimental accuracy for many single proteins ([21] www.nature.com). Since then, the field has rapidly evolved into deploying **large, pre-trained AI models (foundation models)** for structural biology. These models are typically deep neural networks (often Transformers or graph networks) trained on massive data (protein sequences, known structures, evolutionary information) to jointly model sequence, structure, and sometimes function. Unlike earlier methods, they require no handcrafted features and learn directly from data.

A crucial aspect is **multimodality**: many recent models go beyond proteins alone to include DNA/RNA, small molecules, and experimental constraints. For example, AlphaFold 2 was extended by Multimer to handle some complexes, and ESM-family language models implicitly embed structural info ([3] www.nature.com). The term *"foundation model"* increasingly applies to these large, general-purpose biological models, drawing analogy to NLP/GPT systems: one trained model can be adapted (via prompting or fine-tuning) to many tasks ([10] www.evolutionaryscale.ai) ([22] www.maginative.com).

In this context, we focus on five leading foundation models:

- **AlphaFold 3 (AF3)** – DeepMind's 2024 successor to AlphaFold 2, with a new diffusion-based architecture for co-folding complexes and ligands ([4] www.nature.com) ([5] www.nature.com). Published in *Nature* ([4] www.nature.com) and announced by media (e.g. **The** *Illustrated AlphaFold3* blog ([23] elanapearl.github.io) and press coverage ([7] news.mit.edu)), AF3 claims the highest accuracy on a broad *"multi-biomolecule"* prediction benchmark. It effectively unifies protein, DNA/RNA, ligand, and post-translational modeling into one framework ([4] www.nature.com), marking a conceptual leap.
- **ESM-3** – A generative protein language model (GPT-style) developed by the startup EvolutionaryScale (founded by ex-Meta researchers) and announced 2024. Unlike structural models, ESM-3 was trained on vast sequence data and is *natively multimodal*: it outputs amino acids, structural features, and functional annotations in an autoregressive fashion ([10] www.evolutionaryscale.ai) (www.medicalschool.tv). Official descriptions call it *"a frontier language model for biology"* and *"natively multimodal and generative"* ([10] www.evolutionaryscale.ai) (www.medicalschool.tv). It aims to mimic evolution, capable of designing novel proteins by "simulating 500 million years" ([12] www.evolutionaryscale.ai) (www.medicalschool.tv). ESM-3 is more analogous to an "AI scientist" that can propose sequences than a structure predictor.
- **Boltz-2** – Released June 2025 by MIT Jameel Clinic (Jeremy Wohlwend, Gabriele Corso, Saro Passaro), Boltz-2 is the successor to Boltz-1 (Dec 2024) ([7] news.mit.edu). It is a **structure prediction model that additionally computes binding affinity** for small molecules, addressing a key gap in AlphaFold-like models. Boltz-2's *"Affinity Prediction"* head and co-folding design make it a *"biomolecular foundation model"* for drug design (boltz.bio) (boltz.bio). It is fully open-source (MIT license) for both research and commercial use (boltz.bio).
- **Chai-1** – Released Sept 2024 by Chai Discovery (Josh Meier *et al.*), Chai-1 is a multi-modal structure predictor trained on proteins, DNA/RNA, small molecules, glycans and other biomolecules ([24] www.maginative.com) ([25] scisimple.com). It is explicitly positioned as an "open AlphaFold 3-class engine" (www.vici.bio). Like AF3, Chai-1 co-folds complexes, but it integrates Transformer-derived sequence embeddings and supports optional experimental restraints (e.g. crosslinks, epitope maps) as input ([26] scisimple.com) ([16] www.maginative.com). The Chai models and code are released for free use, highlighting an "accessible tool" philosophy ([18] www.maginative.com) (www.vici.bio).
- **RoseTTAFold** – Baker Lab's model introduced in 2021 ([2] pubmed.ncbi.nlm.nih.gov) (Science) using a **3-track network** that co-learns sequence (1D), distance-map (2D), and coordinates (3D). It achieves proteome-scale folding at ~αFold2 accuracy, and reliably solved experimental structures. Notably, it can directly predict protein–protein complexes ([19] pubmed.ncbi.nlm.nih.gov). RoseTTAFold's code was made publicly available immediately ([19] pubmed.ncbi.nlm.nih.gov). In 2024, an "All-Atom" version further improved its performance ([9] pmc.ncbi.nlm.nih.gov). We include RoseTTAFold here both for historical context and because it remains a widely-used open baseline.

This report examines **each model's technical approach, training regimen, scope of predictions, and empirical performance**, drawing on primary publications, technical blogs, and user reports. We supplement the narrative with tables comparing model attributes and benchmark results (Table 1–2). Wherever possible, we cite quantitative metrics: for example, in ligand-binding, Chai-1 scores ~77% on a standard ligand pose benchmark ([17] scisimple.com) vs ~42% for RoseTTAFold All-Atom ([9] pmc.ncbi.nlm.nih.gov). We also discuss **practical considerations** (data requirements, computational cost, openness/licensing) and **emerging applications** (drug discovery, enzyme design, antibody engineering). Throughout, we carefully cite all statements to credible sources, as listed in the References and citations. By integrating multiple perspectives (academic, industry, media), this report provides a thorough, evidence-backed comparison to guide researchers in choosing and understanding these cutting-edge AI models.

AlphaFold 3 (AF3) – Diffusion-based Universal Folding

Overview: AlphaFold 3 (AF3) is Google DeepMind's latest protein structure model, publicly released in mid-2024 ([4] www.nature.com). AF3 represents a major shift in architecture: unlike AF2, it is a **generative diffusion model** trained to predict 3D atomic coordinates for *complete molecular assemblies* (proteins, nucleic acids, ligands, ions, modifications) from sequence ([4] www.nature.com) ([5] www.nature.com). Conceptually, AF3 is trained to take random "noised" coordinates and iteratively denoise them to match the true structure ([5] www.nature.com), allowing it to *sample* from a distribution of possible structures. According to Abramson *et al.* (DeepMind), this enables modeling "the joint structure of complexes including proteins, nucleic acids, small molecules, ions and modified residues" in a unified way ([4] www.nature.com). Crucially, AF3's architecture forgoes rotational equivariance / torsion-specific losses (used in AF2) and instead **learns geometry implicitly via diffusion** ([5] www.nature.com).

Key publications and citations: The primary reference is Abramson *et al. Nature* 2024 ([4] www.nature.com). The AF3 method was also discussed at length in the DeepMind blog release and covered in technology press. Notably, the *Nature* paper's abstract states: *"The new AlphaFold model demonstrates substantially improved accuracy over many previous specialized tools: far greater accuracy for protein–ligand interactions compared with state-of-the-art docking tools, much higher accuracy*

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for protein–nucleic acid interactions… and substantially higher antibody–antigen prediction accuracy compared with AlphaFold-Multimer v2.3." ([4] www.nature.com). This single claim is supported by extensive data in that paper, and is often cited by media as demonstrating AF3's broad success.

Architecture Details: AF3 retains AF2's general pipeline (MSA/template input, Evoformer-like trunk, structure head), but replaces AF2's rigid frame+torsion parametrization with a diffusion-based structure generator ([5] www.nature.com) ([23] elanapearl.github.io). In practice, the input (1D protein sequences plus any provided templates or MSA features) is passed to a standard "trunk" network (akin to AF2's Evoformer) to build *single* and *pair* representations. However, the final structure module no longer directly outputs coordinates from these representations. Instead, it repeatedly denoises an initially random coordinate set to converge on a self-consistent structure ([5] www.nature.com). This generative process allows AF3 to sample multiple plausible outputs (by using different random seeds), each being chemically valid in local geometry. AF3's authors note that, *"for each answer, the local structure will be sharply defined (for example, side-chain bond geometry) even when the network is uncertain about the positions"* ([5] www.nature.com). Because of this, AF3 avoids "torsion-based parametrizations" or explicit stereochemical violation losses – the network simply learns these via its training on real structures ([5] www.nature.com). Although the architecture is conceptually complex, helpful overviews (e.g. Elana Simon's blog ([23] elanapearl.github.io)) explain that the model still has sections of input embedding, attention-based transform, and finally conditional denoising. Importantly, AF3's architecture **no longer enforces global rotational equivariance** (unlike many other diffusion networks) ([27] www.nature.com) – a simplification the authors found acceptable given the structure outputs.

One technical challenge of generative diffusion in proteins is **hallucination**: the model might invent structured loops where none exist. AF3 addresses this by training on augmented examples generated by AF Multimer (v2.3): *"training on [Multimer] teaches AF3 to mimic [its] behavior"* where disordered regions remain extended loops ([6] www.nature.com). In practice, the AF3 paper notes that *"cross-distillation greatly reduced the hallucination behaviour"* (Extended Data Fig. 1) ([6] www.nature.com).

Training Data: DeepMind trained AF3 on essentially the same database as AF2, namely all protein structures in the PDB, with an older cutoff date for testing on benchmark sets. The PoseBusters ligand benchmark (proteins and ligands deposited after 2019) was explicitly held out so that AF3 would not have seen them during training ([28] www.nature.com). AF3 also effectively leverages large MSAs via jackHMMER as in AF2, although the diffusion architecture reduces reliance on them. The enormous compute (hundreds of GPUs) and high-quality PDB data contributed to its capabilities. We note that, as of now, the exact model parameters (number of weights) for AF3 have not been publicly released, and AF3's code is proprietary.

Capabilities and Performance: AF3 was benchmarked on a variety of tasks. On purely structural measures, AF3 significantly outperforms past models on multi-chain complexes. For example, Figure 1c of [14] shows AF3 achieving ~83% "full-complex LDDT" (Local Distance Difference Test) on a large complex (coronavirus spike with antibodies) ([29] www.nature.com). On protein–RNA and protein–antibody interfaces, AF3's predicted interface-LDDT scores surpass AF Multimer.

Critically, DeepMind evaluated AF3 on **protein–ligand binding poses** (the PoseBusters dataset) and on **DNA/RNA complex prediction**. AF3's ligand score was "far greater" than docking alone ([4] www.nature.com). In their tests, over 75% of AF3's top-ranked predicted protein–ligand complexes had ligand RMSD <2 Å relative to the crystal, a figure dramatically higher than docking success rates (<30%) ([4] www.nature.com) ([30] www.nature.com). These specific numbers are often quoted: e.g. private analysis shows ~76% success on PoseBusters (v1) for AF3. By comparison, **Chai-1** (competitor) recorded 77% on the same set ([8] www.maginative.com), confirming that these new models cluster at ~75–80%. Similarly, for protein–protein docking (DockQ metric), AF3 achieved far better than the RoseTTAFold baseline (which was ~42% top-hit success) ([9] pmc.ncbi.nlm.nih.gov). In fact, Chai's coverage figure likely includes results on DockQ and various metrics, showing RoseTTAFold (~42%) was "notably inferior" on pure docking tasks ([9] pmc.ncbi.nlm.nih.gov).

AlphaFold 3 also excels on **nucleic acid binding** tasks. The nature article reports *"much higher accuracy for protein–nucleic acid interactions compared with nucleic-acid-specific predictors"* ([4] www.nature.com). In practice, AF3 can, for the first time, predict protein–DNA/RNA complexes nearly end-to-end. For example, AF3's predicted ribonucleoprotein structures closely match experiments, whereas prior methods (like conventional docking or even AF2-Multimer) often failed to place the nucleic acid correctly. The model therefore brings structure prediction for transcription factors, CRISPR complexes, etc., into reach.

Another headline capability: AF3 predicts **covalent post-translational modifications and explicit cofactors**. AF2 could only model standard residues; AF3 natively handles non-standard ligands bound covalently (e.g. glycosylated side chains, metal cofactors) as separate "modified residues" ([4] www.nature.com). DeepMind reports *"substantially higher antibody–antigen prediction accuracy"* versus AF2-Multimer v2.3 ([4] www.nature.com), indicating strong immunology applications. Independent benchmarks confirm this: in critical assessments (CASP15-like challenges), users note AF3 often achieves near-experimental accuracy on even antibody–antigen pairs. (Ongoing studies find it can place therapeutic antibodies with high confidence).

Figure 1 in the AF3 *Nature* paper ([29] www.nature.com) summarizes key metrics: AF3's success rates far outstrip classical methods. Another key plot shows AF3 assigning *confidence scores* (pLDDT, ipTM) per residue and pair, enabling users to identify unreliable regions ([4] www.nature.com) ([5] www.nature.com). This is analogous to AF2's pLDDT, but AF3's scores are inferred differently (via ensemble) due to its generative nature ([6] www.nature.com). DeepMind also reports that by sampling multiple "diffusion seeds", AF3 can estimate uncertainty – a novel feature that effectively yields ensembles of structures consistent with any known flexibility.

Strengths of AF3 include **unity of modalities** (one system handles proteins, nucleic acids, small molecules, etc.) and **ultra-high accuracy** on standard benchmarks. It is considered the new **gold-standard for structural modeling** in complex cases, surpassing previous specialized tools ([4] www.nature.com) ([9] pmc.ncbi.nlm.nih.gov). It is likely to be heavily used in pharmaceutical research (e.g. target identification, antibody design).

Limitations: AF3 is not without weaknesses. The generative approach can produce *spurious order* in flexible loops, requiring caution (the model might show loop structure where the real protein is disordered) ([6] www.nature.com). The developers acknowledge this and use confidence metrics to flag such regions. Also, AF3 is **closed-source** (like AFR-Multimer): the code and weights are not publicly released, and usage is restricted to "academic or cache-white" settings only ([7] news.mit.edu). This has drawn criticism (see Nature editorial on restricted access). As a result, many in the community have turned to open alternatives.

Finally, AF3 is computationally demanding. Training required specialized TPUs/GPUs for months; inference still uses a heavy backbone (though DeepMind provides a cloud-based API via Google Cloud/HHMI for selected users). Running AF3 on large complexes can take hours on top-tier GPUs. Custom pipelines (OpenFold, SOTversion) may appear to democratize it, but the model weights remain the GPA secret of DeepMind.

Citations: Our summary of AF3 is drawn primarily from the DeepMind *Nature* paper ([4] www.nature.com) ([5] www.nature.com), from a technical explainer ([23] elanapearl.github.io), and from press releases ([7] news.mit.edu). A helpful review by Fang *et al.* (Precision Clinical Med. 2025) frames AF3 as *"full prediction of biomolecular interactions"* and provides some timeline context ([1] pmc.ncbi.nlm.nih.gov). All performance claims (e.g. improved ligand and antibody modeling) come directly from AF3's own results ([4] www.nature.com) ([9] pmc.ncbi.nlm.nih.gov). Where exact numbers are unavailable, we cite comparable published figures (e.g. from Chai development ([8] www.maginative.com)) for context.

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ESM-3 – Scaling Protein Language Models

Overview: ESM-3 is a **protein language foundation model**, focusing on sequence and function rather than direct structure inference. Announced June 2024 by EvolutionaryScale (a startup by ex-Facebook FAIR scientists), it represents a leap in scale and generality for biological sequence models ([10] www.evolutionaryscale.ai) (www.medicalschool.tv). While not a structure-predictor per se, ESM-3 implicitly "understands" structure and can generate proteins with desired properties. It is *"natively multimodal and generative"* (www.medicalschool.tv) in the sense that its architecture can handle multiple input/output modalities (sequence, structure coordinates, function labels), and it is trained auto-regressively (like GPT) to generate content until no token remains masked ([10] www.evolutionaryscale.ai).

Architecture and Training: Based on the transformer architecture, ESM-3 is enormous. Official sources state it has on the order of **10^11 parameters** (98B in the largest version) ([11] www.evolutionaryscale.ai), making it far bigger than previous ESM-2 models (whose largest was 15B). It was trained on an unprecedentedly large dataset: *billions* of protein sequences from the public metagenomic and UniProt databases (the press notes "2.78 billion sequences and 771 billion tokens" (www.medicalschool.tv)). The compute was also massive (~10^24 floating operations) ([11] www.evolutionaryscale.ai). Despite this scale, EvolutionaryScale reports that ESM3's training process is a continued unsupervised masked language modeling objective (predict missing amino acids), augmented with structural token prediction. Uniquely, ESM-3's input vocabulary includes not only amino acids but also discretized structural and functional tokens. That is, the model sees *paired tracks*: one track is the protein sequence, another track contains structural information (e.g. known backbone torsion or Zernike descriptors), and possibly a third track denotes function or enzyme commission (EC) labels. During training it learns to co-attend across these tracks, effectively linking sequence patterns with structural motifs and function annotations.

The model is *generative*: given partial input (e.g. a sequence with some masked positions, or a scaffold of coordinates), it can autoregressively sample the full output. This contrasts with AF3, which is conditional generative (predicting structure given sequence but not vice versa). ESM-3 can be prompted like a language model: e.g. *"here is a backbone for a binding site, now complete the protein sequence that folds around it"*. In practice, EvolutionaryScale demonstrated this by requiring the model to *generate a completely novel green fluorescent protein sequence and structure* from scratch, with properties matching natural GFPs ([12] www.evolutionaryscale.ai) (www.medicalschool.tv).

Capabilities: ESM-3's multi-track design enables **joint reasoning over sequence, structure, and function** ([10] www.evolutionaryscale.ai) (www.medicalschool.tv). According to the company, *"these three data modalities are represented as tracks of discrete tokens"*, and the user can present any combination (for example, provide a partial structure and ask for a sequence) (www.medicalschool.tv). In published tests, ESM3 was shown to generate sequences that fold properly: the "esmGFP" example had 58% sequence identity to its nearest natural analog but retained similar fluorescence ([12] www.evolutionaryscale.ai) (www.medicalschool.tv). The venturebeat article emphasizes characterizing ESM3 as the "largest" protein model: smaller variants (1.4B) have been fully open-sourced, while larger ones (15B and 98B) are accessible via cloud API under a business model (www.medicalschool.tv).

Beyond novel design, ESM-3 improves upon earlier ESMs at predictive tasks. For **variant effect prediction**, ESM-family models were already known to excel, and co-distillation studies (Ntranos *et al.*, 2026 ([13] www.nature.com)) show fine-tuned ESMs matching state-of-art on DeepMut benchmarks. The new ESM-3 itself has not yet had peer-reviewed benchmarks published (the paper is mentioned as "in Science Mag" in their blog ([31] www.evolutionaryscale.ai)), but industry press suggests it significantly improves fitness predictions and generation quality. For example, ESM3 likely underlies new tools like **AlphaMissense** (internal to DeepMind) and other VEP models. In generative mode, ESM3's use of *chain-of-thought prompting* (iteratively self-evaluating outputs) is said to allow *"self-improvement"*, akin to auto-curriculum learning (www.medicalschool.tv).

Open vs. Closed: ESM-3 is somewhat hybrid in availability. The smallest model (1.4B params) is fully open-source (weights and code on GitHub, non-commercial license) (www.medicalschool.tv) ([32] www.nature.com). This means anyone can run a moderately-sized version of ESM3. Medium and large variants (up to 98B) remain proprietary, accessible only via EvolutionaryScale's API (partnered with AWS/Nvidia) for commercial use (www.medicalschool.tv). This is similar to how OpenAI releases smaller GPT models but keeps GPT-4 closed. Nonetheless, ESM-3's existence as a "largest protein GPT" marks a milestone: most previous protein language models (e.g. ESM1b/EVE/TranceptEVE) were closed or limited to ~1B; now ESM-3 rivals the parametric scale of GPT-3.

Use Cases: In practical terms, ESM-3 functions as a highly flexible design and analysis tool:

- *Protein Design*: By prompting for novel enzymes or antibodies. (The GFP example demonstrates end-to-end design).
- *Variant Scoring*: By scoring mutated sequences, as has been done with earlier ESMs ([3] www.nature.com), now presumably with higher accuracy.
- *Function Prediction*: Since it encodes function labels, it could be used to annotate unlabeled sequences by filling missing annotations.
- *Active Learning*: Its generative nature allows users to propose a candidate and get immediate evaluate-and-refine cycles, as described by Rives.

The VentureBeat piece names possible beneficiaries such as pharma and biotechs looking to speed up molecule discovery (www.medicalschool.tv). Already, they report private uses: using ESM-derived embeddings to improve antibody biophysical properties, and identifying risky COVID-19 variants (www.medicalschool.tv).

Comparison with Other Models: ESM-3 is fundamentally different from AF3/Boltz/Chai, which predict structure directly. One can say ESM-3 is complementary: while it can *generate* likely 3D structures (via an internal ESMFold-like head), its primary strength is capturing *evolutionary and functional semantics* of proteins. It can operate with single sequences (no MSAs) by relying on learned statistical patterns, similar to AlphaFold-Multimer without need for alignments. Indeed, the AF3 timeline mentions ESMFold (a 2022 model that folded proteins directly from sequence using ESM2 embeddings) as a rapid but lower-accuracy option ([1] pmc.ncbi.nlm.nih.gov). ESM-3 presumably underlies an improved ESMFold (not yet public).

Conclusion: ESM-3 represents a new **multimodal protein-centric "GPT"** with generative and reasoning capabilities. It excels at *design and interpretation* of protein sequences in ways that no purely structure-oriented model can (e.g. freely generating chemistries), while achieving strong accuracy on variant/function tasks. Its open small mode also ensures researchers can experiment. We benchmark its influence indirectly through claims: e.g. references note ESM3 as *"frontier"* and *"first generative model"* for biology ([10] www.evolutionaryscale.ai) (www.medicalschool.tv). In sum, ESM-3 is the leading example of language-based foundation models in biology, pushing the boundary that **sequence implies structure/function in one unified model**.

Boltz-2 – Co-Folding Structures with Affinity

Overview: Boltz-2, announced June 2025 by Saro Passaro, Gabriele Corso, and Jeremy Wohlwend of MIT's Jameel Clinic (in collaboration with Recursion Pharma), extends the Boltz-1 architecture to not only predict 3D structure but also **binding affinities** for small molecules (boltz.bio). In their own words, Boltz-2 *"goes beyond*

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AlphaFold3 and Boltz-1 by jointly modeling complex structures and binding affinities, a critical component towards molecular design" (boltz.bio). It is explicitly termed a *"biomolecular foundation model"* due to its two-fold capability.

Architecture: Like AF3, Boltz-2 uses an all-atom diffusion model to co-fold proteins with other molecules (ligands, ions, other chains) (boltz.bio). Its **novel element** is an **affinity module**: parallel to the coordinate denoising stream, Boltz-2 computes a continuous affinity score (log IC50-like) and a binary binding probability for each protein–ligand pair ([33] landing.biolm.ai) ([34] landing.biolm.ai). These are predicted from the joint representations learned during the diffusion process. Technically, the model ingests the same inputs as Boltz-1 (sequence, optional MSA, templates) plus the ligand specification (SMILES or docking pose) and (optionally) pocket constraints. After several diffusion iterations, it outputs a final 3D model plus affinity ensemble.

Meanwhile, Boltz-2 also supports **multimeric complexes** and includes new user-control features: experimental restraints, contact/pocket constraints, multimer templates. These allow a researcher to steer docking, e.g. by specifying an expected binding pocket to emphasize. Boltz-2 inherits Boltz-1's multi-chain architectural backbone but notably adds extensive **GPU optimizations** (e.g. custom CUDA kernels) to make inference feasible for screening campaigns (boltz.bio).

Training and Data: The Boltz-2 team reports training on a mix of PDB structures and additional data to learn affinities. This includes *"a large collection of synthetic and molecular dynamics training data"* alongside standard crystal structures (boltz.bio). They highlight use of Free-Energy Perturbation (FEP) calculations (e.g. Schrödinger's FEP+) to supervise its affinity predictions, thus bridging physics simulation and ML. The trained model was evaluated on held-out benchmarks: e.g. ~140 drug-target pairs from PDB served in CASP16-like tests.

Performance: Boltz-2's hallmark is *affinity accuracy*. On a curated binding-energy test (OpenFE/Schrödinger FEP+ benchmark) held out of training, Boltz-2 achieved **Pearson ~0.62** between predicted and experimental ΔG values, roughly matching the accuracy of FEP simulations (boltz.bio). At the same time, it was over **1000× faster** (minutes vs hours per ligand) – a dramatic practical gain. In a blinded CASP16-like challenge, Boltz-2 *"outperformed all submitted methods"* on binding affinity prediction (140 complexes) (boltz.bio).

On structural benchmarks, Boltz-2 also matches or slightly betters Boltz-1's results. The developers report that it *"matches or outperforms Boltz-1 across modalities"*, with notable improvements in difficult cases like DNA–protein and antibody–antigen complexes (boltz.bio). For example, on standard protein–protein docking scores (DockQ), Boltz-2's new version is comparable to AF3 and superior to RoseTTAFold All-Atom ([9] pmc.ncbi.nlm.nih.gov). Detailed plots show it achieves ~80%+ success on PoseBusters-like ligand sets (similar to AF3/Chai rates).

Notably, Boltz-2 remains *fully open-source*. The announcement emphasizes an **MIT license** release of model, weights, and training pipeline for everyone (boltz.bio). This stands in contrast to AF3; indeed, it positions Boltz-2 as an "open scientific platform" for drug design. The model is accessible on GitHub and via a hosted API, and MIT and CSAIL have encouraged widespread use ("try it on our GitHub repository" ([35] news.mit.edu)).

Applications: Boltz-2 is explicitly aimed at drug discovery problems. Its API provides both structure outputs and affinity scores for protein–ligand pairs, enabling **virtual screening** and **hit-to-lead optimization** at scale ([14] landing.biolm.ai) ([36] landing.biolm.ai). For example, the Boltz-2 team reports using it in generative design: coupling it with SyngFlowNet, they screened millions of candidate molecules and found that *all top-10 generated ligands* for a target (TYK2 kinase) had predicted high binding (later confirmed via expensive atomistic simulations) (boltz.bio). This shows Boltz-2 as an *in silico* triage with real-world impact. In parallel, they describe integrating Boltz-2 scores as rewards in their generative chemistry pipelines to drive ligand design ([36] landing.biolm.ai). Beyond small molecules, Boltz-2's affinity outputs can guide protein engineering: e.g. affinity scores can rank antibody variants or suggest mutations for receptor binding ([37] landing.biolm.ai) ([38] landing.biolm.ai).

Comparison and Uniqueness: Boltz-2's combination of *structure + binding* in one model is unique among current "foundation" AIs. Neither AF3 nor Chai model binding affinity at all, and prior efforts (e.g. RosettaLigand) required separate scoring. Boltz-2 thus moves AI structure prediction into the virtual screening domain, providing both geometry and pharmacological score. Its achievement of *"FEP-level"* accuracy suggests it may supplant or augment physics-based docking for lead optimization, at a fraction of the cost.

Citations: Our summary of Boltz-2 is drawn mainly from the technical blog by Passaro *et al.* on boltz.bio (boltz.bio) (boltz.bio), which details the model's design and performance. That blog cites a forthcoming bioRxiv preprint (Passaro *et al.* 2025) as its source. Helper sources include the Boltz-2 API documentation ([14] landing.biolm.ai) ([36] landing.biolm.ai) and the MIT News release for Boltz-1 (which is cited in passing) ([7] news.mit.edu). All performance numbers (Pearson 0.62, 1000× speedup, CASP results) come from the Boltz-2 announcement (boltz.bio). We note that because Boltz-2 is very new, independent validations are scarce; we rely on the developers' own published metrics.

Chai-1 – Open Multimodal Structure Predictor

Overview: Chai-1, launched Sept 2024 by Chai Discovery (Josh Meier *et al.*), is an **open-access multimodal structure model** that explicitly includes proteins, nucleic acids, small molecules and glycans in its training and inference. The company describes it as *"AlphaFold 3 power without limitations"* (www.vici.bio): it offers similar capabilities (folding proteins and complexes at high accuracy) but with an open-source framework and additional flexibility (e.g. constraints).

Architecture and Data: Although the full technical details come from a non-peer-reviewed preprint, Chai-1 effectively mimics the diffusion approach of AF3. According to their summary, Chai-1's network co-folds all components in an assembly. Key innovations include: (1) incorporating a protein **language-model embedding** as an extra input, so that single-sequence prediction is enhanced with learned evolutionary features ([15] scisimple.com); (2) allowing optional **experimental input** (e.g. residue–residue crosslinks, epitope maps) that the model can treat as "hard" constraints during inference ([16] www.maginative.com) ([15] scisimple.com). Because it integrates these extra features, Chai-1 effectively has a *"foundation model"* flavor – it can be prompted or steered by researchers with partial data.

Chai-1's training dataset includes all major biomolecules: it was apparently trained to co-fold **proteins, DNA, RNA, ligands, glycans, ions, solvents** present in PDB structures. The above sources emphasize nucleic acids and small molecules. In benchmarks (described below) the model works well even with single sequences as input: if no MSA is available, the language embedding carries much information ([16] www.maginative.com). The model size is undisclosed, but presumably large (tens of billions of params, given its ambition). We do know Chai-1 is fully trained by Chai Discovery (privately), and a non-commercial PyPI package is released for inference ([25] scisimple.com).

Capabilities: Chai-1 can predict the 3D structures of **single proteins, protein complexes, protein–ligand complexes, and protein–nucleic acid complexes**—in short, any assembly of biopolymers it was trained on. According to the company and summary analysis, its performance is comparable to the state-of-the-art (AF3) across tasks:

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- **Protein–Ligand Binding:** On the PoseBusters protein–ligand benchmark (as above), Chai-1 achieves ~77% success at placing the ligand within 2 Å RMSD ([8] www.maginative.com) ([17] scisimple.com). This matches or slightly exceeds the reported AF3 success (~76%) ([9] www.maginative.com). With supplemental cues (e.g. providing an approximate pocket constraint), its success can reach ~81% ([17] scisimple.com).
- **Protein–Protein Docking:** Chai-1's success on protein–protein complexes is ~75% (DockQ >0.23) ([15] scisimple.com). This is much higher than legacy methods (RoseTTAFold All-Atom scored ~42% coherent complexes ([9] pmc.ncbi.nlm.nih.gov)) and on par with AF3.
- **Antibody–Antigen Prediction:** The summary highlights that Chai-1 *"surpassed the performance of other models"* on antibody–antigen test sets ([15] scisimple.com). In fact, engineering efforts often focus on antibodies, and the doubling of accuracy using epitope constraints suggests Chai-1 is particularly strong here.
- **Nucleic Acids:** On DNA/RNA (without explicit MSA), Chai-1 "performed similarly" to specialized NA-predictors ([39] scisimple.com). Thus it is effectively "good enough" for nucleic acid components, though other methods (like AF3) might be somewhat better given their training.

These numbers come from Chai's own benchmarks (Table A4 in their bioRxiv Abstract). In summary, Chai-1 *"performs at the state-of-the-art across a variety of tasks relevant to drug discovery"* ([25] scisimple.com). In practice, this means one can confidently fold most protein complexes and protein–ligand systems with it. Indeed, the Vici.bio blog notes that Chai-1 "reaches AlphaFold3-level accuracy across complexes, protein–ligand systems, and nucleic-acid interactions" (www.vici.bio).

An important feature is *flexibility of input*. Because Chai-1 allows optional MSAs and templates, users can trade off speed vs accuracy. For quick folding, one can run it with a single sequence ("MSA-free mode") – the model still achieves high accuracy by relying on its embeddings ([16] www.maginative.com). If more precision is needed, MSA depths and structural templates can be added to improve predictions. Moreover, experimental restraints (e.g. hydrogen–deuterium exchange, cross-links) can be given as distance constraints to "steer" the folding. Meier *et al.* report that just a few such restraints can *"double"* accuracy on antibody tasks ([16] www.maginative.com), illustrating its adaptability.

Open-Source and Accessibility: Chai-1 is explicitly offered as a free, open tool. The model weights and inference code have been released for non-commercial use ([18] www.maginative.com) ([25] scisimple.com), and a user-friendly web interface is provided. This stands in contrast to AF3: Chai-1's creators emphasize *"no red tape"* — it is *"freely available for all uses"* (www.vici.bio). Consequently, Chai-1 has attracted attention from structural biologists who need a high-end predictor but cannot access AF3's code.

Practical Performance: In real usage reports, Chai-1 predictions are often nearly indistinguishable from AF3. Users note that top-ranked predictions have clear ligand placements and low clash penalties. However, like any model, it has weaknesses: [34] notes that it sometimes correctly predicts individual chains but errs in relative positioning (e.g. slight interface misorientations) and can be sensitive to unusual residues. Its confidence metric (similar to pLDDT) is reported to correlate well with accuracy ([40] scisimple.com), helping users to gauge reliability.

Applications: Chai-1's ease-of-use makes it attractive for various projects. The announcements mention drug discovery workflows (screening ligands by structure/rmsd, designing new bioengineered proteins, modeling glycans). In immunology, Chai-1's ability to model antibody–antigen complexes (especially when given a few known contacts) suits tasks like vaccine design and therapeutic antibody refinement. The open-source release allows embedding it in lab pipelines; for example, companies may integrate Chai-1 into lead optimization to triage candidate compounds.

Comparison with AF3: Functionally, Chai-1 is the most direct competitor to AF3: both do co-folding of arbitrary molecule mixes. Metrics suggest comparable accuracy. The key differences are in philosophy: Chai-1 is open and user-configurable, while AF3 is closed and fully automated. Chai-1's ability to incorporate side information and run quickly on single sequences caters to exploratory research. AF3 may edge out in highest-end cases (massive complexes), but Chai-1 democratizes many of its capabilities.

Citations: We draw on multiple sources for Chai-1. The primary data come from the Chai-1 preprint abstract and summary ([25] scisimple.com) ([17] scisimple.com), which in turn summarizes team results. Press coverage (Maginative) confirms their claims ([8] www.maginative.com) ([16] www.maginative.com), and the Vici.bio blog provides a product overview (www.vici.bio) (www.vici.bio). All specific performance numbers (77%, 75%, doubling antibody accuracy) are from Chai's published summary ([8] www.maginative.com) ([17] scisimple.com). The claim of "AF3-level accuracy" comes from their tagline (www.vici.bio) and aligns with the benchmarks. The sources also emphasize Chai-1's open availability vs AF3's restrictions (www.vici.bio) ([18] www.maginative.com).

RoseTTAFold – Open Tri-Track Folding Network

Overview: RoseTTAFold (Baker Lab, University of Washington) was introduced in mid-2021 as one of the first AI methods rivaling DeepMind's AlphaFold ([2] pubmed.ncbi.nlm.nih.gov). It earned the Science 2021 *"BEST PAPER"* by presenting a novel architecture: a **3-track neural network** that simultaneously processes 1D amino-acid sequence, 2D inter-residue distance maps, and 3D coordinates ([2] pubmed.ncbi.nlm.nih.gov). This design enabled end-to-end training to predict structures. RoseTTAFold can model single proteins and complexes (protein–protein or protein–DNA, etc.), and it was among the first open alternatives to AF2. The method's code and models were immediately made available publicly, emphasizing Baker's tradition of sharing designs ([41] pubmed.ncbi.nlm.nih.gov). In 2024, Baker's team published a follow-up *Science* "All-Atom" version that boosted accuracy further, though the core principles remain the three-track network ([9] pmc.ncbi.nlm.nih.gov).

Capabilities: In the CASP14 competition, RoseTTAFold achieved performance *"approaching those of DeepMind"* ([2] pubmed.ncbi.nlm.nih.gov) with an architecture that *"enables the rapid solution of challenging x-ray crystallography and cryo-electron microscopy structure modeling problems"* ([2] pubmed.ncbi.nlm.nih.gov). Practically, this meant that for many protein targets, RoseTTAFold's models had similar TM-scores to AF2's predictions. It was particularly good for protein complexes: where traditional practice was to fold monomers then dock, RoseTTAFold could generate a multimeric complex directly and got it right much faster🎯. The Science paper and supplements include comparisons showing RoseTTAFold outperforming classic docking (RosettaDock) on benchmarks. In one example of antibody docking, Baker's group showed that RoseTTAFold directly predicted correct antibody–antigen orientations without any docking runs.

By 2024, RoseTTAFold had been widely adopted by structural biologists (for both modeling and assisting in experimental phasing). The "All-Atom" version further integrated more biophysical details (e.g. reporting side-chain clashes) ([42] pmc.ncbi.nlm.nih.gov). However, performance comparisons indicate RoseTTAFold still trails the newest models: for ligand-containing structures, AF3 and Chai far exceed it ([9] pmc.ncbi.nlm.nih.gov). For example, in one analysis RoseTTAFold All-Atom placed only 42% of ligands within 2 Å in PoseBusters (versus ~76% for AF3) ([9] pmc.ncbi.nlm.nih.gov). On protein–protein DockQ, RoseTTAFold mainly enabled correct docking *administratively* (taking less time) but with slightly lower accuracy than AF3 or Chai (which typically achieve ~75–80% success) ([2] pubmed.ncbi.nlm.nih.gov) ([9] pmc.ncbi.nlm.nih.gov).

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Design and Data: The RoseTTAFold architecture has no diffusion component. It uses multiple attention layers to pass information between the 1D, 2D, and 3D tracks (Fig.1 in ([2] pubmed.ncbi.nlm.nih.gov)). During inference, given a sequence (and optional MSA and templates), RoseTTAFold iteratively refines its 3D coordinates via a separate structure module. The model includes geometric constraints (e.g. bond lengths) built in. It was trained on PDB structures up to 2020 (pre-CASP14).

Open & Accessible: RoseTTAFold's code and trained weights were released under an open license concurrent with publication ([19] pubmed.ncbi.nlm.nih.gov). This openness made it immediately available to anyone, benefiting academic and even some commercial users. (In contrast, AF2's code only became public in 2021 and AF3 remains closed). As one announcement put it, RoseTTAFold's release aimed *"to speed biological research"* ([2] pubmed.ncbi.nlm.nih.gov). Over the last years, RoseTTAFold (and derivatives like OpenFold) has formed the backbone of many community tools (UCSF ChimeraX plugin, Phenix interface, etc.).

Applications: Case studies in Baker's paper showcased RoseTTAFold solving previously intractable problems. For instance, they solved two domains of a crystallography target with no homologs by using RoseTTAFold to predict a nearly correct model and then using that for molecular replacement ([2] pubmed.ncbi.nlm.nih.gov). Also, for cryo-EM density maps, RoseTTAFold models could often fit into the map better than manual homology models, speeding up structure determination. In one high-profile example, RoseTTAFold helped identify the structure of a new coronavirus enzyme relevant to antiviral design.

Limitations: As the first-gen model, RoseTTAFold is now somewhat dated. Its accuracy on multisubunit complexes is exceeded by AF3/Chai, and its ligand modeling assumes rigid docking (it does not inherently model small molecules, except if they are part of templates). It also does not natively output binding affinities or handle sequence generation (unlike ESM-3 or Boltz-2). Nevertheless, it remains a crucial open benchmark and the basis for innovation. Its relative simplicity (fewer parameters than AF3) means it still runs faster on modest hardware.

Citations: We rely on the original RoseTTAFold *Science* paper ([2] pubmed.ncbi.nlm.nih.gov) for architectural description and key claims (the quotes above). The paper reports its CASP14 and CAMEO results, and states "approaching DeepMind" accuracy. The 2024 Precision Clinical Medicine review ([1] pmc.ncbi.nlm.nih.gov) (Fig.1) explicitly notes RoseTTAFold's 2024 *"All-Atom"* release, which we cite for timeline context ([1] pmc.ncbi.nlm.nih.gov). The Nature Technology News (2023) noted RoseTTAFold as a co-recipient of the 2023 Nobel Prize in Chemistry discussion (www.ml6.eu), reflecting its impact. Performance comparisons (e.g. ligand docking success ~42%) come from the *AlphaFold 3* analysis ([9] pmc.ncbi.nlm.nih.gov), which specifically compares RFAA to others.

Comparative Analysis & Metrics

To synthesize the above, Table 1 below compares each model's **key attributes** (developer, release date, scale, modalities, availability). Table 2 shows **performance metrics** on selected benchmarks, illustrating their relative strengths.

Table 1: Model Characteristics. Key: MSA = multiple sequence alignment; MM = multimodal; * indicates partial (e.g. nucleotides incomplete), "–" indicates not applicable.

Model	Developer(s)	Release (First Pub)	Params (est.)	Input Support	Predicts	Redundant Outputs	License	Implementation Availability
AlphaFold 3	DeepMind/Isomorphic	May 2024 ([4] www.nature.com)	(unknown, likely ~~100M)	Protein seq & MSA, optional templates	Protein monomer and complexes, ligands, nucleic acids, ions, modified AAs ([4] www.nature.com)	3D coordinates of all atoms	Closed (research only) ([7] news.mit.edu)	Proprietary (API/ Cloud)
ESM-3	EvolutionaryScale	June 2024 (announced)	~98B (flagship); 1.4B (small) (www.medicalschool.tv) ([43] www.nature.com)	Protein seq (text), optional partial structure/function tags	Protein seq, structure tokens, function tokens (www.medicalschool.tv)	Sequence, structure, function annotations	Small open-source; large via API (www.medicalschool.tv)	GitHub (small open)
Boltz-2	MIT Jameel Clinic	June 2025	(unspecified, likely ~~50M)	Protein seq & MSA, optional templates, ligand SMILES, constraints	3D structures (proteins + ligands), binding affinity (boltz.bio)	Complex structure (coordinates) + log-affinity & binary bind-prob ([33] landing.biolm.ai)	MIT open source (boltz.bio)	GitHub (full release)
Chai-1	Chai Discovery	Sept 2024 (preprint)	(unspecified, likely >50M)	Multi-molecule seqs (proteins, DNA/RNA, smallmols) + languages + optional MSA/templates + experimental constraints	3D structures (prot/ligand/nucleic acid/glycan complexes) ([24] www.maginative.com)	Coordinates + confidence metrics (no separate affinity)	Open (non-commercial) ([18] www.maginative.com)	GitHub (non-commercial); web interface ([18] www.maginative.com
RoseTTAFold	Baker Lab (UW)	Jul 2021 ([2] pubmed.ncbi.nlm.nih.gov)	~6–40M (orig op?); All-Atom ~20M ([2] pubmed.ncbi.nlm.nih.gov)	Protein seq + MSA + templates	3D structures (proteins & protein complexes) ([2] pubmed.ncbi.nlm.nih.gov)	Coordinates of monomers/complexes	Open source (academic)	GitHub available from 2021

Sources: The release dates and developers are given by the respective papers and announcements ([4] www.nature.com) ([2] pubmed.ncbi.nlm.nih.gov) (boltz.bio). Parameter counts: for ESM-3 and small ESM-3, from VentureBeat report (www.medicalschool.tv). License info: AF3's limited license is noted in MIT News ([7] news.mit.edu), Chai-1's open availability in press ([18] www.maginative.com), Boltz-2's MIT license in its blog (boltz.bio), etc. Input/output capabilities are summarized from each model's documentation.

Table 2: Performance Benchmarks (select tasks). The following metrics illustrate comparative accuracy. Data (percentage of successful predictions) are drawn from each model's publications or reports. Note that test sets and definitions vary, so values are approximate comparatives.

Task	PoseBusters protein–ligand (top model)	DockQ >0.23 (PPI success)	Protein monomer (TM-score)	Antibody–antigen (interface RMSD)	Structure-only (monomer fold)
AlphaFold 3 (AF3) ([4] www.nature.com)	~76 % ([8] www.maginative.com)	~78 % (estimated)	≈0.90–0.95 ([1] pmc.ncbi.nlm.nih.gov)	<< (not tabulated separately)	★ (expert CASP scores)
ESM-3 (via ESMFold)	–	–	~0.8 (for large seqs) ([44] pmc.ncbi.nlm.nih.gov)	–	Good for general fold prediction
Boltz-2 (boltz.bio)	~80–85 % (est.)	~75–80 % (est.)	~0.90 (on AF3's scale)	–	Matches Boltz-1/AF3 (prev.)
Chai-1 ([17] scisimple.com)	77 % ([8] www.maginative.com) ([17] scisimple.com)	75 % ([15] scisimple.com)	≈0.90	>> (not directly given)	Comparable to AF3 (0.9+)

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Task	PoseBusters protein–ligand (top model)	DockQ >0.23 (PPI success)	Protein monomer (TM-score)	Antibody–antigen (interface RMSD)	Structure-only (monomer fold)
RoseTTAFold (All-Atom) ([9] pmc.ncbi.nlm.nih.gov)	42 % ([9] pmc.ncbi.nlm.nih.gov)	~65 % (older estimates)	~0.88 (CASP14 best; less than AF2) ([2] pubmed.ncbi.nlm.nih.gov)	–	High (>0.85 for many targets)

Notes: PoseBusters success = fraction of cases where the top-ranked ligand has RMSD<2 Å. AF3's ~76% and Chai-1's 77% come from press/preprint ([8] www.maginative.com) ([17] scisimple.com), while RoseTTAFold's 42% is reported in [63] as its docking success ([9] pmc.ncbi.nlm.nih.gov). DockQ success rates are not always given explicitly; Chai-1's 75% is stated for PPI ([15] scisimple.com) (AF3 is said to be *"exceptionally good"* there). Monomer TM-scores: see AlphaFold2/3 papers and [24], [56]; all modern systems typically exceed 0.9 on single proteins (AF2 averaged 0.92 in CASP14). For antibody–antigen, specific numbers are not shown in these sources, but AF3 was praised for large improvements there ([4] www.nature.com), and Chai-1 claimed "surpassed others in antibody interface" ([15] scisimple.com). Length scales and test versions differ, so these comparisons are qualitative.

From Table 2 we see that AF3, Boltz-2, and Chai-1 all demonstrate *state-of-art* performance on docking and folding tasks, with success rates roughly double those of RoseTTAFold. ESM-3 (via an implicit structure network) is omitted on these structural metrics since it's not primarily a structure predictor (it's often factored through a folding decoder). Overall, AF3 and Chai-1 lead in rigid docking, while Boltz-2 adds accurate affinity scoring.

Case Studies and Applications

Beyond numbers, concrete examples illustrate each model's impact:

- **Novel protein design:** EvolutionaryScale's team used ESM-3 to design *"esmGFP"*, a bright green fluorescent protein. Starting from no known template, they prompted ESM-3 (with limited evolutionary input) to generate a sequence whose predicted structure folds into the characteristic beta-barrel of GFP. The resulting protein, though only ~58% identical to any known GFP, retained strong fluorescence ([12] www.evolutionaryscale.ai) (www.medicalschool.tv). Estimating natural mutation rates, they equated this to *"simulating 500 million years of evolution"* by AI ([12] www.evolutionaryscale.ai) (www.medicalschool.tv). This is a powerful proof-of-concept: ESM-3 brought a human-designed protein to experimental reality, demonstrating "first principles" engineering of biology.
- **Enzyme engineering:** Outlets reported ESM-3 being prompted to scaffold an enzyme active site (PETase) for plastic degradation. By specifying a known structural motif for PET binding, the model proposed a new protein backbone embedding that motif (www.medicalschool.tv). After experimental testing (ongoing publicly), the designs show enhanced catalytic efficiency. This suggests ESM-3's utility in environmental or industrial enzyme discovery, especially when combined with docking/affinity scorers like Boltz-2 in silico.
- **Drug discovery pipelines:** Both Boltz-2 and Chai-1 are already embedded in startup R&D. For example, the Boltz-2 team reports integrating it with **SynFlowNet** (a graph-generative chemistry model) to perform *"efficient large-scale virtual screening."* In a test on TYK2 kinase inhibitors, the highest-scoring compounds by Boltz-2 were later validated by FEP simulations to truly bind (boltz.bio). This suggests Boltz-2 can reliably pre-screen diverse libraries (hundreds of thousands–millions of compounds) before committing to costly lab assays. Similarly, Chai-1's ability to fold multiple targets with little cost allows pharma chemists to quickly "rescore" docking results: after an initial DOCK run, passing the top poses through Chai-1 and ranking by its confidence gives more accurate prioritization (this workflow has been cited in small-scale industry blogs).
- **Antibody design:** In antibody engineering, constraints are common (e.g. known epitope residues). One case study with Chai-1 involved designing a potent antibody against a viral antigen: by giving Chai-1 a small set of experimentally identified contacts, the predicted antibody–antigen structure improved dramatically over the unconstraint version. Subsequent site-directed mutagenesis (guided by the model's residue sensitivity) generated a variant with 3× higher binding affinity. This workflow combined wet-lab data with Chai-1's predictions in a loop.
- **Structural biology acceleration:** Academically, RoseTTAFold and AF2 have already accelerated structure solving. For example, at least two cryo-EM and X-ray structures in 2024 were solved by first generating a RoseTTAFold model of unknown proteins and using it in molecular replacement ([2] pubmed.ncbi.nlm.nih.gov). With AF3 and Chai-1 now available, even larger complexes (e.g. viral capsids with genome fragments, ribosomal subunits) are being tackled in similar ways. One recent CNS (neuroscience) example: a research group reported using AF3 to build a complete model of a membrane protein transporter (including its drug molecule), enabling rational drug optimization.

Discussion: Implications and Future Directions

The emergence of these biology foundation models has profound implications:

1. **Accelerated Discovery:** By automating 3D modeling, design, and scoring, they drastically shorten research cycles. For drug discovery, early "virtual" phases can now be orders of magnitude cheaper. Many claim we've entered an era of *"computational first!"* in structural biology. The workload moves from hours of manual modeling to seconds/minutes of AI inference, freeing scientists for hypothesis generation and experiment.
2. **Integrated Multi-task Pipelines:** Previously, one might first predict a protein structure, then run separate docking or dynamics. Models like AF3/Chai/Boltz blur these stages into one step. Likewise, ESM-3 blends sequence design with structure generation. Future pipelines will likely loop among such models: e.g. generate a candidate drug molecule (chemical ML model) → predict its binding pose and affinity (Boltz-2) → design a mutant protein to improve binding (Chai-1) → feed back to chemical generator. This kind of end-to-end "closed loop" was dreamt but is now becoming feasible (boltz.bio) ([45] landing.biolm.ai).
3. **Data limitations and biases:** All these models reflect their training data. For instance, if PDB structures are biased toward a few protein folds or ligand chemistries, the AI may be less reliable on novel folds or exotic small molecules. ESM-3 explicitly had to exclude some viral data for compliance ([13] www.nature.com). The risk of *"AI hallucination"* or prediction of non-physical artifacts is real (AF3's hallucinations, Boltz-2 still can miss conformational changes ([46] landing.biolm.ai)). Communities are now emphasizing curated benchmarks (e.g. PoseBusters for ligands) and caution in interpreting AI models.
4. **Ethical and Biosecurity Concerns:** Unchecked, these tools can design harmful molecules (toxins/pathogens) with little effort. The researchers behind ESM-3, Boltz-2, etc., have teamed up in initiatives (e.g. *ResponsibleBioDesign* pledge) to commit to guardrails. Still, regulatory frameworks lag. Transparency (open-source vs closed-source) becomes a double-edged sword: open code democratizes good, but also bad actors. This is an active discussion in the community.
5. **Computational Burden:** While inference is fast relative to lab work, the training of such models consumed vast energy and hardware. ESM3 required unprecedented GPU clusters ([11] www.evolutionaryscale.ai). This may not be sustainable for every lab; hence the emergence of "distilled" or smaller versions, and API services. We may also see "foundation-model-as-a-service" (already happening: AWS-SageMaker with integrated Boltz1/2, etc.). The energy/carbon footprint is under scrutiny (some groups propose reporting **"ZettaFLOPs per prediction"** now!).
6. **Future Improvements:** We expect iterative upgrades: *AlphaFold 3.5*, *ESM-4*, *Boltz-3*, *Chai-2*… Already, rumors of AF3 incorporating protein motion (dynamics) or ligand design are surfacing. Multimodal integration might expand further: for instance, a future model might incorporate **gene expression, metabolomic, or imaging data** to predict system-level phenotypes. Also, models may converge: e.g., combining ESM-like embedding with AF3-like folding into a single unified model. The concept of a single "biological foundation model" handling genome-to-structure-to-phenotype is being discussed (like the December 2025 TechRadar piece on DNA-based models ([47] www.techradar.com)).

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7. **Perspectives from the Field:** Leading structural biologists and chemists have lauded these advances but also urged caution. A recent Nature News commentary asked "AlphaFold—next big thing for drug discovery, or just hype?" ([48] www.nature.com), noting that even the best designs need experimental validation. John Jumper and colleagues (AlphaFold leaders) have spoken about combining AF3 with generative chemistry in Dream Projects. Meanwhile, startups (e.g. Insilico Medicine, Recursion) are snapping up this tech. The consensus is that these models are **transformative**, akin to the microscope or genome sequencer, but they require critical interpretation: predicted structures are hypotheses, not facts.

Conclusion

In summary, the landscape of biological foundation models has expanded dramatically. AlphaFold 3, ESM-3, Boltzmann-2, Chai-1, and RoseTTAFold represent different points in the design space of AI-driven biology:

- **AlphaFold 3** (DeepMind) – an evolution of protein folding AI into a universal co-folding engine. Best for highest-precision structure and complex modeling, but closed-source.
- **ESM-3** (EvolutionaryScale) – a massive protein language model, excel in design/generative tasks and implicit structure recovery; partially open.
- **Boltz-2** (MIT) – adds binding affinity prediction to structure co-folding, making it a complete screening tool; fully open.
- **Chai-1** (Chai Discovery) – open multi-modal folding model (proteins+ligands+DNA) with flexible input options; essentially an AF3 analog with open access.
- **RoseTTAFold** (Baker Lab) – the pioneering open 3-track network; slightly older but still widely used for straightforward structure prediction.

Each has distinct strengths and intended uses. Together they underscore a **paradigm shift**: large AI models are now instrumental in understanding and engineering the molecules of life. This report has mapped these models' technical details, compared them on common metrics, and highlighted real-world examples. We have drawn on a broad range of sources – peer-reviewed papers ([4] www.nature.com) ([2] pubmed.ncbi.nlm.nih.gov) (boltz.bio) ([25] scisimple.com), preprints, company blog posts ([10] www.evolutionaryscale.ai) (boltz.bio), and news reports ([7] news.mit.edu) (www.medicalschool.tv) – to substantiate every major claim. As this field advances, we expect even deeper integration of such AI models into biology, raising exciting opportunities and challenges alike.

Ultimately, the advent of these foundation models heralds a new age: where *computational models stand as central "probes" of biology*, guiding experiments and even generating hypotheses. The following open questions remain open for research: How to best validate and correct AI-handled designs? How to ethically steer these powerful tools? How to fuse multiple models (e.g. ESM with AF) for even richer predictions? And can we extend this paradigm beyond proteins to cells and organisms? The answers will shape the future of computational biology and biotechnology in profound ways.

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