Faculty of Mathematics and Computer Science

Machine learning course (ML)

AlphaFold and Beyond: Recent Breakthroughs in Deep Learning for Protein Structure Prediction

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Abstract

Proteins are the fundamental molecular machines of life, yet their biological function is intricately linked to their complex three-dimensional shapes. For over fifty years, the protein folding problem, the challenge of predicting a protein's 3D structure from its linear amino acid sequence, remained a grand challenge in biology due to the vast number of potential configurations, a concept famously described as Levinthal's Paradox. This research report analyzes the transformative shift from traditional experimental methods, such as X-ray crystallography, to the deep-learning revolution led by Google DeepMind's AlphaFold. We detail the architectural progression of these models, beginning with AlphaFold 1's use of convolutional neural networks to predict inter-residue distances, followed by the landmark AlphaFold 2, which utilized an attention-based Evoformer to achieve near-experimental accuracy at CASP14. The scope further extends to the recently released AlphaFold 3, which introduces a multi-modal diffusion-based architecture capable of predicting interactions across the entire biomolecular spectrum, including nucleic acids and ligands. Beyond structural prediction, we examine the massive societal impact of the AlphaFold Database, which has democratized access to over 200 million predicted structures, accelerating research in drug discovery, vaccine development, and environmental engineering. Despite these breakthroughs, the paper critically discusses ongoing limitations regarding molecular dynamics, chirality, and point mutations. Finally, we conclude that the future of the field lies in the development of general biomolecular foundation models that move beyond static 3D coordinates to predict diverse functional properties, effectively serving as biological operating systems for the precision engineering of life.

1. Introduction

Proteins are fundamental to every biological process, acting as the machinery of life. To understand how they function, we must first understand their structure. This paper explores the transition from traditional experimental methods to the revolutionary computational approach provided by AlphaFold.

1.1. The structure of a protein

A protein begins its existence as a simple string of amino acids. Each amino acid is built around a central alpha carbon atom, connected to an amino group, a carboxyl group, and a hydrogen atom. The specific identity of the amino acid is determined by one of 20 different side chains, also known as residual groups.

As these amino acids bond together to form a chain, various physical forces, such as electrostatic interactions, hydrogen bonds, and solvent effects, cause the string to pull, push, and eventually coil into a specific shape. From an almost limitless number of possibilities, the protein finds a stable 3D configuration. This final structure is not random. It is precisely built for a specific purpose, as the components must be in the correct orientation to perform their biological tasks.

1.2. The first discovered protein

The history of identifying these shapes began with the work of John Kendrew [5], who spent 12 years using experimental techniques to solve the structure of a single protein. By turning the protein into a crystal and exposing it to X-rays, he created a diffraction pattern. This allowed scientists to work backward to determine the molecular arrangement. The result was a model of myoglobin, an oxygen-storing protein found in heart and muscle tissue. While successful, this process proved that manual discovery was incredibly slow and difficult.

1.3. The complexity of protein folding

The protein folding problem is defined by two major concepts. First, the research by Levinthal (1968) [6] showed that a protein's 3D shape is encoded entirely within its amino acid sequence. It does not need external help to find its shape, it happens naturally. Second, however, is the sampling problem. Even a small protein of 50 amino acids has so many possible shapes, roughly 10^{72}. That it would take longer than the age of the universe to test them all. This massive complexity, often called Levinthal's Paradox, is why predicting the final structure from a sequence remained a grand challenge in biology for decades.

1.4. The CASP and Protein Data Bank (PDB)

While scientists identified certain patterns like helices and sheets, known as secondary structures, they could not find a reliable way to predict the final 3D form of a protein. To address this, the Protein Data Bank (PDB) was established as a global library of structures determined through experimental work. In 1994, Professor John Moult initiated the Critical Assessment of Structure Prediction (CASP) competition [9]. The objective was to create a computer model that could accurately transform a sequence into a 3D structure.

For over twenty years, progress remained slow. Many algorithms reached a performance plateau, and accuracy even began to decline after 2008. This environment changed in 2018 with the introduction of AlphaFold. It is important to note that the current breakthroughs in this field were only possible because of these two institutions: while the PDB provides the vast amount of data necessary to train complex statistical models, CASP offers an unbiased and standardized way to measure success. Together, they created the foundation for the recent revolution in structural biology.

1.5. Purpose and structure of the paper

This paper aims to analyze the breakthrough of the AlphaFold models and their impact on structural biology. The report is organized as follows: Section 2 discusses the theoretical and practical importance of protein folding in domains like medicine and climate change. Section 3 details the architecture and experimental results of AlphaFold. Section 4 provides a critical discussion of the methodology and data, and Section 5 offers concluding remarks on the future of the field.

2. Importance and Relevance

The solution to the protein folding problem represents one of the most significant scientific milestones of the 21st century. By determining a protein's 3D structure solely from its amino acid sequence, researchers have unlocked a molecular map that was previously invisible to the human eye.

From a theoretical standpoint, the importance of protein folding lies in the biological axiom that structure dictates function. Proteins are molecular machines, just as the shape of a key determines which lock it can open, the physical arrangement of a protein determines its ability to bind to other molecules. Even a minor error in folding can have catastrophic results. For instance, misfolded proteins are at the heart of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. Understanding the correct fold allows scientists to see exactly where a biological process is failing, providing a theoretical foundation for nearly all modern life sciences research.

In practice, AlphaFold has accelerated research in fields that directly affect human welfare and the environment[2]. One of the most notable successes is in the development of a highly effective malaria vaccine. By predicting the structure of the $Pfs48/45$ protein, researchers were able to identify the exact sites where antibodies bind, a task that would have taken years using traditional methods.

Beyond medicine, this technology is being used to address climate change. Scientists have leveraged these structural predictions to engineer plastic-eating enzymes. These modified proteins are designed to break down polyethylene terephthalate (PET) waste more efficiently, offering a biological solution to the global pollution crisis. Furthermore, in agriculture, AlphaFold assists in designing heat-tolerant crops, ensuring food security in a warming world.

The scale of this breakthrough is best illustrated by the sheer volume of data produced. Over the last 60 years, the global scientific community managed to experimentally determine the structures of approximately 150,000 proteins. In contrast, the collaboration between DeepMind and the EMBL-EBI has resulted in the AlphaFold Database, which now contains over 200 million predicted structures. This effectively covers nearly every protein known to exist in nature. This massive release has democratized science, allowing researchers in low-resource settings to access structural data that previously required millions of dollars in equipment.

Machine learning has a long history in protein analysis, but it was historically limited to predicting small, one-dimensional features such as secondary structures or torsion angles. As noted by AlQuraishi [1], the shift toward End-to-End Differentiable Learning marked a turning point. Instead of building a protein piece-by-piece, these modern architectures process the entire sequence at once.

By incorporating successful strategies from other AI fields, such as convolutional neural networks from image processing and the attention mechanism from natural language processing, AlphaFold can attend to distant amino acids that might interact once the protein is folded. This ability to capture complex, long-range dependencies is what gives these architectures their unprecedented predictive power.

3. Main Sections: The Evolution of AlphaFold

The emergence of AlphaFold represents a significant shift in structural biology. For many decades, the scientific community struggled to predict the 3D shapes of proteins from amino acid sequences. This challenge is vital for understanding how life works, discovering new medicines, and identifying the mechanisms behind various diseases. The development of AlphaFold, from its initial version to the most recent iterations, has provided transformative insights that have fundamentally changed the field.

3.1. AlphaFold 1: A Co-evolutionary Approach

The first version of AlphaFold [10] was based on a workflow that relied heavily on co-evolutionary data. The system used a deep convolutional neural network (CNN) as its primary component. The input for this model consisted of the target protein sequence and statistics from Multiple Sequence Alignments (MSA). The model was built on the biological observation that amino acids in physical contact tend to show patterns of correlated mutations over time.

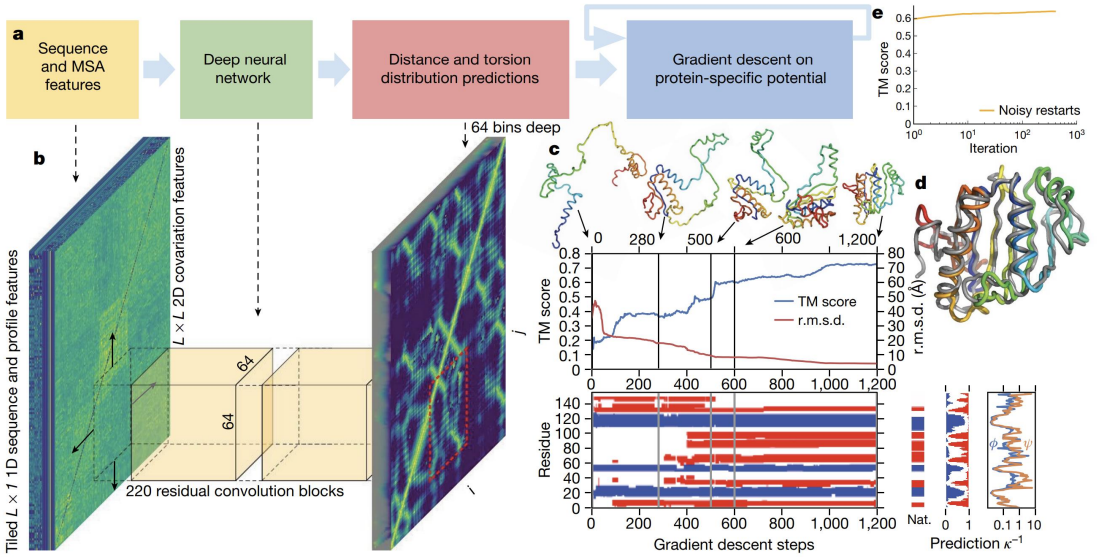

Fig. 1. AlphaFold 1 Structure

3.1.1. Deep Convolutional Neural Network (CNN) Stage

Taking inspiration from the RaptorX-Contact server [11], AlphaFold 1 treated the 3D structure prediction problem as a computer vision task. The central goal was to generate distograms (histograms that show the distances between pairs of amino acids).

The architecture used a deep residual network consisting of 220 blocks. Each block processed 64 × 64 residue regions and comprised of layers that interlace 3 batch normalization layers,2 1 × 1 projection layers, a 3 × 3 dilated convolution layer and exponential linear unit nonlinearties. The network did not just predict a single distance, instead, it produced a probability distribution over 64 different distance bins (ranging from 2 to 22 Å- Angstrom). This allowed the system to express a level of confidence in its predictions. Additionally, the network predicted the angles of the protein backbone (torsion angles) to help define the overall geometry.

3.1.2. Gradient Descent and Potential Minimization

The second stage of the AlphaFold 1 process involved building a protein specific potential field. To create this field, the system used the negative log probabilities from the distogram bins. A mathematical function called a spline was then fitted to these values to create a smooth surface.

To find the most stable structure, the system performed Gradient Descent. This is an optimization process that searches for the lowest energy state of the protein. Several steps were taken to make this accurate. A reference distribution was subtracted to correct for data bias. A smoothing score was added to prevent steric clashes, where non-bonded atoms come too close together, viloating their van der Waals radii. The process was repeated using a genetic algorithm, which added noise to the torsion angles to explore different possibilities and find the absolute best structure.

3.1.3. Limitations of the Convolutional Approach

While AlphaFold 1 was revolutionary, the use of convolutional neural networks had specific drawbacks. First, these networks are translation invariant, meaning they are excellent at recognizing an object regardless of its position, but they may struggle when the exact position in a sequence carries specific meaning. Second, they focus primarily on local information. In an image, a pixel in one corner usually does not affect a pixel in the opposite corner. However, in protein folding, an amino acid at the very beginning of a chain might interact strongly with one at the very end. This limitation suggested that a more global approach to processing information was needed.

3.2. AlphaFold 2: The End-to-End Revolution

AlphaFold 2 introduced a paradigm shift by moving away from traditional homology modeling. While previous tools required similar known structures to make a prediction, AlphaFold 2 can predict entirely novel folds using only the amino acid sequence. This capability is supported by two main data sources from the Protein Data Bank: high-quality experimental structures determined by scientists and a large set of unsolved sequences that the model used for self-distillation.

3.2.1. The Evoformer: Integrating Evolution and Geometry

The core innovation of AlphaFold 2 is the Evoformer, a specialized transformer architecture. Unlike standard transformers used in natural language processing, which handle a single sequence of words, the Evoformer processes two types of information in parallel through two connected towers.

The first tower processes the Multiple Sequence Alignment (MSA). Here, the model applies attention mechanisms to rows and columns of evolutionary data. By looking across rows, it identifies mutations in a sequence; by looking down columns, it finds amino acids that have been conserved across different species. This helps the model understand which parts of the protein are vital for its survival and structure.

The second tower handles the Pair Representation, which represents the geometric relationships between every pair of amino acids. A bridge connects these two towers, allowing them to exchange information. For example, if the evolutionary tower identifies two amino acids that always mutate together, it signals the geometry tower that these residues are likely physically close in 3D space.

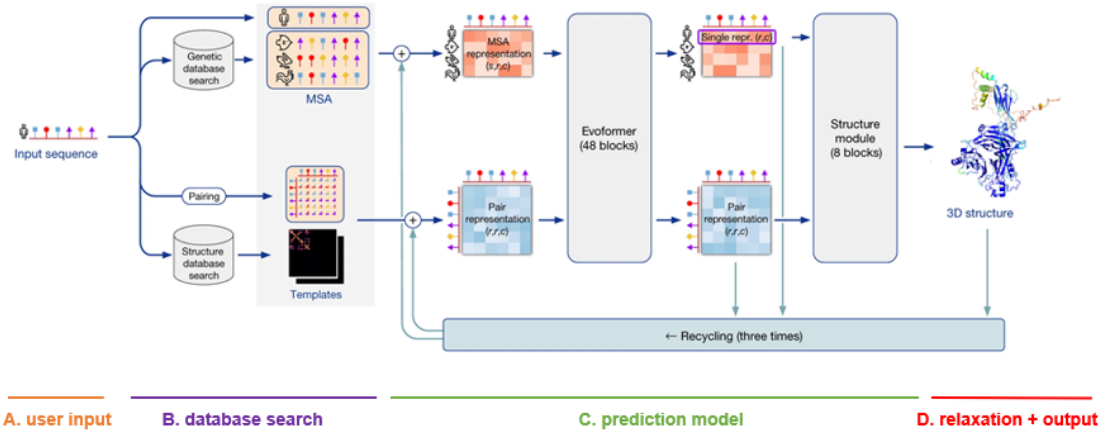

Fig. 2. AlphaFold 2 Structure

3.2.2. Triangular Attention and Consistency

To ensure the geometric predictions are physically possible, AlphaFold 2 uses a concept called triangular attention. This mechanism enforces the triangle inequality, which states that for any three amino acids, the distance between two must be less than or equal to the sum of the distances to the third. By having triplets of amino acids attend to each other, the model can filter out impossible shapes. If the geometry tower decides two residues cannot be close, it informs the evolutionary tower to ignore their relationship. This exchange happens 48 times per cycle, refining the model's internal hypothesis with each pass.

3.2.3. The Structure Module and Frame Representation

After the Evoformer reaches a consensus, the features are passed to the Structure Module. In this stage, the model treats the protein not as a string, but as a collection of independent amino acids in space. Each amino acid is represented by a frame, which is a local coordinate system based on three specific atoms.

The network predicts the exact rotation and translation needed to move each frame from a random starting point to its correct 3D position. Interestingly, the model begins with a bag of amino acids and does not initially know they must be connected. It learns the connectivity and the final shape simultaneously through a process of iterative refinement.

3.2.4. Recycling and Iterative Refinement

To achieve high accuracy, AlphaFold 2 employs a recycling mechanism. The entire prediction process, including the Evoformer and the Structure Module, is repeated at least three times. The output of one iteration is fed back into the beginning of the next as an additional input. This allows the model to continuously correct its own mistakes and gradually settle into the most stable configuration.

3.2.5. Improvements over AlphaFold 1

The rigid information flow of the convolutional neural network used in AlphaFold 1 was replaced by a dynamic, attention-based architecture. While CNNs are limited to looking at local neighbors in a sequence, the attention mechanism in AlphaFold 2 allows the network to control the flow of information globally. This means the model can focus on specific interactions between distant amino acids that are crucial for the final fold, regardless of their position in the string.

Second, AlphaFold 2 embeds physical and geometric principles directly into its neural architecture. In the first version, geometry was handled in a separate step through an optimization search. By integrating these notions into the model itself, AlphaFold 2 significantly restricts the search space. It does not waste computational resources exploring or even considering physically impossible configurations, leading to much faster and more accurate results.

Finally, the way the model handles evolutionary data has been upgraded. AlphaFold 1 relied on pre-computed MSA statistics, which simplified the data before the model could see it. In contrast, AlphaFold 2 uses an embedding that contains the full sequences found in the MSA along with potential structural templates.

3.2.6. Limitations and the Native State Problem

Despite its success, AlphaFold 2 has specific limitations. Because it was trained primarily on the Protein Data Bank, the model is biased toward predicting proteins as they appear in experimental conditions. In nature, many proteins are dynamic or require special environments, such as the presence of specific ions or other proteins, to fold correctly. AlphaFold 2 often predicts a single static snapshot of a protein and may fail to show the multiple shapes a protein might take in different biological contexts. This is particularly noticeable for proteins that only fold when they interact with other molecules.

3.3. AlphaFold 3: A Multi-Modal Atomic Revolution

AlphaFold 3 represents a significant leap from its predecessors by moving beyond the prediction of single protein chains. While AlphaFold 2 was primarily a protein-folding tool, the third iteration is a multi-modal system capable of predicting the structures of complexes involving proteins, nucleic acids, and small molecules. This shift required the architecture to move from a residue-level focus to a high-resolution, all-atom representation, enabling it to model intricate molecular interactions that were previously challenging to depict.

3.3.1. The Wedding Seating Plan: A Conceptual Shift

To understand the difference between the versions, one can use an analogy from the Google DeepMind podcast involving Hannah Fry. Organizing a protein structure is like designing a seating plan for a wedding reception, where the guests are amino acids and the goal is to find where everyone fits best. AlphaFold 2 was an organizer obsessed with history, constantly checking evolutionary records to see who had sat together in the past. This worked for proteins, but once other ”guests” like DNA or new drug molecules are invited, historical data is less relevant because these molecules do not share the same evolutionary history. Consequently, AlphaFold 3 was designed to rely less on this history, emphasizing the universal geometric information that is always present.

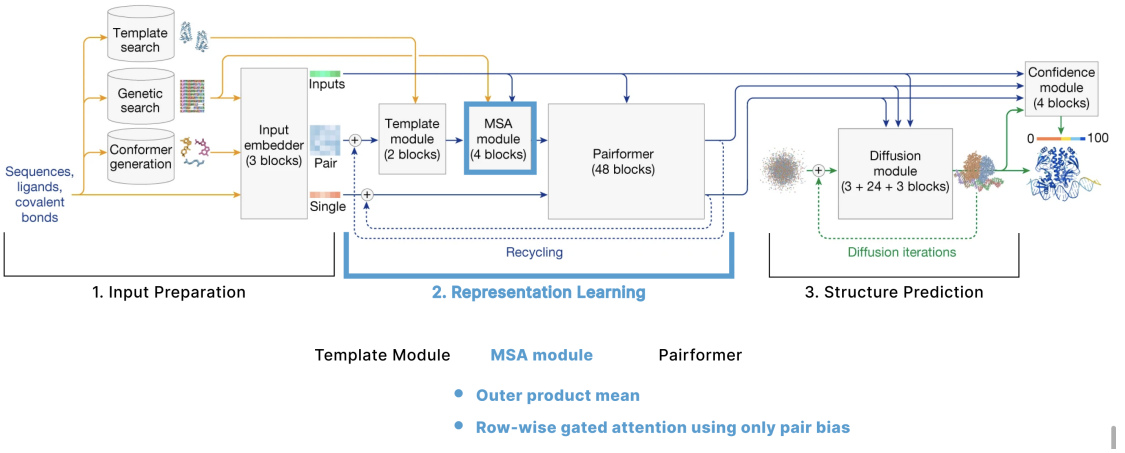

Fig. 3. AlphaFold 2 Structure

3.3.2. Architecture Stage 1: Input Preparation

The process begins with Input Preparation, which involves gathering diverse chemical data including sequences, ligands, and covalent bonds. This stage combines three specialized search types: a Template search to find similar known structures in the PDB, a Genetic search for evolutionary patterns, and a Conformer generation for initial 3D molecular shapes. These results are processed by an Input Embedder consisting of three blocks, which produces the initial single and pairwise representations that the rest of the network will refine.

3.3.3. Architecture Stage 2: Representation Learning

The second major phase is Representation Learning, where the model builds a deep understanding of how these molecules relate to one another. This section is modular, beginning with a Template module of two blocks and an MSA module of four blocks. Notably, AlphaFold 3 replaces the older Evoformer with a simpler Pairformer module containing 48 blocks. This module is more efficient because it reduces the amount of multi-sequence alignment data processed, focusing instead on a richer pairwise representation. To maintain geometric consistency, it utilizes triangular attention, ensuring that atom relationships satisfy the triangle inequality.

3.3.4. Architecture Stage 3: Structure Prediction via Diffusion

The final and most innovative component is the Diffusion module, which replaces the Structure module of AlphaFold 2. Instead of predicting the specific rotation of amino acid frames, this module operates on raw atomic point clouds. During the prediction phase, the system starts with random noise and gradually ”denoises” the structure through multiple iterations until the precise atomic coordinates are revealed. This generative approach allows AlphaFold 3 to achieve unprecedented accuracy at small scales. Finally, a Confidence module assesses the reliability of the output, providing scores that reflect the model’s certainty in each atom’s position.

4. Evaluation of Experimental Results

The evaluation of computational folding models is centered on the Critical Assessment of Structure Prediction (CASP) competition, which operates as a double-blind experiment where participants predict structures for sequences that have been experimentally solved but not yet released to the public. This ensures that assessors do not know the identities of the submitters, and participants cannot access the ground-truth data, providing a strictly unbiased metric of success.

4.1. Performance Metrics and Scoring Systems

To determine the quality of a predicted model, structural biologists utilize three primary metrics. The Global Distance Test (GDT) measures the maximum number of atoms in the prediction that fall within a certain distance threshold of the reference structure. Specifically, the CASP Total Score (GDT_TS) averages these counts at 1, 2, 4, and 8 Å. While GDT evaluates global alignment, the Local Distance Difference Test (lDDT) determines the fraction of preserved local atom-to-atom distances, focusing on the quality of local neighborhoods without requiring global superposition. Lastly, the Template Modeling (TM) score assesses the global fold similarity on a scale from 0 to 1, where a score above 0.5 typically indicates that the predicted structure possesses the correct biological fold.

4.2. From CASP13 to CASP16

AlphaFold 1 debuted at CASP13 in 2018, significantly outperforming all other groups by achieving a median GDT of 68.5 across all targets. It was particularly successful in the ”Free Modeling” (FM) category, where no existing templates were available, scoring 58.9 GDT compared to 52.5 for the runner-up. This was followed by the landmark performance of AlphaFold 2 at CASP14, where it reached a median GDT of 92.4, effectively solving the single-chain protein folding problem with accuracy comparable to experimental methods.

At CASP15, DeepMind did not officially participate. However, the influence of AlphaFold was overwhelming; approximately 90% of the assembly targets were successfully predicted, largely because the majority of groups used ”AlphaFold-Multimer” as the core engine of their custom pipelines. Many teams improved upon the base model by engineering multiple sequence alignments (MSAs) or utilizing massive sampling techniques to refine results.

The recent CASP16 competition provided the first blind benchmark for AlphaFold 3. While AF3 performed exceptionally well for easier protein targets and offered close to state-of-the-art results for complexes, it did not secure the top position in every category. Other groups, such as the MULTICOM4 system [8], achieved higher TM-scores by using ensemble strategies and extensive model ranking. For harder targets and manual submissions, the AF3 server was sometimes outperformed by methods that applied massive sampling to older AlphaFold 2 frameworks, suggesting that AF3 has a slight disadvantage on the most difficult protein folds.

4.3. Current Limitations and Findings

Despite the move to a diffusion-based model that predicts all-atom interactions, AlphaFold 3 faces several persistent challenges. Recent benchmarks using PoseBusters [4] have revealed that AF3 struggles with chirality; it showed a 51% chirality violation rate when predicting D-peptide complexes, making it effectively no better than random chance for those specific interactions. Furthermore, the model remains insensitive to single-point mutations; because it relies so heavily on evolutionary history, it often predicts the ”healthy” wild-type structure even when a mutation should physically disrupt the fold.

Additionally, AF3 is known to ”hallucinate” structures in disordered regions, sometimes creating alpha-helices where a protein should naturally be unstructured. These limitations indicate that while the model has mastered the ”average” patterns found in the PDB, it has not yet fully integrated the fundamental laws of physics, such as electrostatics or van der Waals forces, that govern how molecules behave in real-time, dynamic environments.

4.4. Beyond AlphaFold: The Expanding AI Landscape

Since the breakthrough of AlphaFold, a diverse ecosystem of AI models has been developed by academic laboratories and biotechnology companies. This landscape includes tools such as EvoBind [3], ESMFold [7], and RoseTTAFold [12], which not only predict traditional protein structures but also explore the folding of nucleic acids like DNA and RNA. These systems have significantly broadened the scope of computational biology by modeling complex molecular interactions between various biological ligands and their receptors.

A particularly influential model in this field is RFdiffusion, which is built upon the open-source RoseTTAFold algorithm developed by David Baker’s laboratory. RFdiffusion operates as a generative model, creating entirely new protein structures in a manner analogous to how DALL-E or Midjourney generate visual art. This tool has proven ca-

pable of addressing advanced design challenges, such as the creation of specific molecular binders and the engineering of complex oligomers.

Both RoseTTAFold and RFdiffusion have recently been upgraded to All-Atom (AA) versions. This technical advancement enables the modeling of integrated biological complexes that contain more than just protein chains; they can now represent DNA, RNA, small molecules, metals, and various bonded atoms within a single structural framework. By treating every atom in a complex with high precision, these models allow researchers to design proteins that interact specifically with non-protein targets, such as heme groups or enzymatic cofactors.

5. Conclusions and future work

The development of AlphaFold has introduced a transformative era in the life sciences. Before its emergence, the scientific community had determined the 3D structures of only about 17% of the 20,000 proteins in the human body through decades of costly experimental work. Today, structural data exists for virtually the entire human proteome (98.5%), with 36% of these structures predicted with very high accuracy. This technology has successfully bridged the gap between genomic sequences and biological functions, evolving from a competition entry into a foundational tool for millions of researchers.

5.1. Generative Design and the All-Atom Universe

The focus is also rapidly shifting from prediction to design. Researchers are now leveraging the principles of AlphaFold for de novo protein design, by creating synthetic proteins that do not exist in nature. These custom molecules could serve as highly specific drugs, sensors, or even catalysts for industrial carbon capture. As generative AI continues to integrate with experimental science, the ability to engineer biology at the molecular level will provide new solutions for global health and environmental sustainability.

5.1.1. Toward General Biomolecular Foundation Models

The next generation of models is expected to become significantly more generalized, moving beyond the constrained problem of simple 3D coordinates. Much like Large Language Models in natural language processing, future biomolecular models will likely handle multiple types of inputs and produce a variety of functional outputs. Instead of outputting a single static structure, these systems could predict a wide range of molecular properties simultaneously. For instance, they might quantify binding affinities to show exactly how strongly a drug candidate attaches to a target protein, or predict enzymatic rates to determine the speed at which a synthetic enzyme processes a substrate. Furthermore, these models could assess solubility and stability to ensure a designed protein performs well in industrial conditions, while also simulating toxicity and metabolic paths to understand how a new molecule is processed by the human body. By integrating these diverse outputs, future versions of AlphaFold will likely function as comprehensive biological operating systems, allowing scientists to not only see the machinery of life but to program it with unprecedented precision.

By integrating these diverse outputs, the future models will function as a comprehensive biological operating system, allowing scientists to not only see the machinery of life but to program it with unprecedented precision.

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