AI in the Lab:
AlphaFold2's Impacts on Human-Produced Knowledge*

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Abstract

This paper evaluates how Artificial Intelligence (AI) shapes scientific knowledge production by human researchers, taking Google's AlphaFold2 (AF2) as a case. AF2 predicts protein structures with near-experimental accuracy at a fraction of the cost. Exploiting variation in AF2's prediction confidence in a difference-in-differences design, I find that experimental output for well-predicted proteins falls by about 35%. This decline is more pronounced for proteins that are costly to experiment on or have limited downstream demand. The reallocation of effort is also heterogeneous across experimental methods, concentrated in widely accessible X-ray crystallography while leaving capital-intensive cryo–electron microscopy (Cryo-EM) method largely unaffected. Meanwhile, AF2 has little effect on the quality of execution but appears to alter incentives: the academic reward for working on experimentally unattempted but well-predicted structures largely disappears, as reflected in a sharp drop in the probability of publication in top-tier journals. Overall, AF2 shifts experimental effort toward not-well-predicted areas where human comparative advantage persists.

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1 Introduction

The development of artificial intelligence (AI) has not only transformed the production of goods and services but also begun to reshape the innovation process itself (Aghion et al., 2018; Cockburn et al., 2019; Trammell and Korinek, 2023). Over the past decade, AI tools have been increasingly integrated in almost all scientific fields (Gao and Wang, 2023; Chen et al., 2025). A defining characteristic that makes AI particularly salient for scientific discovery is its exceptional ability to generate data-driven predictions at low cost (Agrawal et al., 2019), thereby lowering barriers to domain knowledge and complementing the expertise of scientists. Yet as algorithms improve, AI-generated predictions may increasingly rival the outputs of lab experiments, raising the possibility that AI could substitute for scientists' work. Recent work also highlight broader concerns: AI may steer inquiry toward domains where it performs best (a "streetlight effect"), potentially overlooking superior alternatives and narrowing the diversity of inquiry (Hoelzemann et al., 2024). It may also incentivize knowledge workers to be more inclined to withhold newly generated knowledge when AI can expropriate and replicate their expertise with little compensation (Cullen et al., 2025). Understanding whether, and under what conditions, AI complements or substitutes for scientists' work and how it shapes the volume and direction of knowledge production is therefore central to the future development of science and innovation.

The introduction of AlphaFold2 (AF2) provides an ideal setting to empirically evaluate how AI affects scientific work. Developed by DeepMind, a subsidiary of Google, AF2 is the first AI system capable of predicting the three-dimensional (3D) structure of proteins with an accuracy comparable to the outcome of leading experimental methods. In addition to its precision, AF2 achieves extraordinary breadth: DeepMind provides predictions for over 214 million proteins, effectively mapping much of the known protein universe by 2021. The model, its code, and a database storing predictions were released openly, making a large volume of high-quality structural predictions freely accessible to researchers around the world. This groundbreaking achievement has been viewed as one of the most successful AI applica-

tions in the scientific discovery process. As recognition, the main developers were awarded the 2024 Nobel Prize in Chemistry.

In this paper, I study how the release of AF2's predictions has affected the quantity, composition, and quality of human-produced knowledge in structural biology. Structural biology focuses on determining the 3D structures of biological molecules, primarily proteins, through experiments, providing a foundation for understanding biological functions and downstream applications. For example, solving the structures of SARS-CoV-2 proteins has been essential for developing vaccines and therapeutics during the COVID-19 pandemic, by revealing key drug targets (Gordon et al., 2020; Wrapp et al., 2020). AF2's ability to "solve" protein structures via prediction, at an accuracy comparable to many experimentally determined structures, directly overlaps with a central task of structural biologists. This paper empirically examines whether this flood of predictions complements or substitutes for the work of structural biologists.

Solving protein structures through experiments has historically been a slow, resource-intensive, and uncertain process (Edwards et al., 2011). Current experimental methods each have limitations: mainstream X-ray crystallography requires growing high-quality crystals, a trial-and-error process that can take months or even years (Spence, 2017). Modern cryo–electron microscopy (Cryo-EM) bypasses the crystallization bottleneck (Shoemaker and Ando, 2018), but the installation can cost over $5 million with a continuing expensive maintenance fee (Fernandez-Leiro and Scheres, 2016), and the technique remains less suitable for smaller macromolecules (Wu and Rapoport, 2021). As a result, progress in mapping the "protein structure universe" has been incremental. By 2020, the Protein Data Bank (PDB) contained roughly 180,000 deposited 3D structures, corresponding to around 55,000 distinct proteins—less than 0.1% of all known protein sequences by that time (Varadi et al., 2022).

In conceptual terms, solving proteins' structure can be modeled as a production process in which scientists' expertise and experimental capital are combined to generate knowledge outputs. The introduction of AF2 serves as a large, target-specific productivity shock to

this field. For proteins with high-quality AF2 predictions, the marginal cost of obtaining the structural information may be substantially reduced to a large extent. This raises two opposing possibilities. On the one hand, lower costs may attract scientists toward these well-predicted targets, leading to an influx of effort and a surge in follow-up experimental work. On the other hand, if AF2 already supplies much of the relevant structural information, the expected returns to additional experimental work may fall as well, leading scientists exit from these areas, reallocating effort toward regions where human experimentation remains essential. The empirical analysis that follows tests these hypotheses by tracing how experimental effort, target selection, and downstream impact respond to this heterogeneous productivity shock across proteins and methods.

My empirical analysis builds on two unique data sources: the Protein Data Bank (PDB) and the AlphaFold Protein Structure Database (AFDB). The PDB is a comprehensive repository of experimentally determined protein structures submitted by scientists worldwide. Since the early 1990s, major journals and funding agencies have required structural biologists to deposit the 3D structures they solved into the PDB prior to publication or grant review (Berman et al., 2000, 2016). As a result, the PDB provides a near-universe of completed experimental projects in structural biology and has been widely used in prior work (Hill and Stein, 2025a,b; Kim, 2023). Through the specific protein target being studied, I match each human-solved structure in the PDB to the corresponding prediction in the AFDB, which stores over 200 million protein structures predicted by AF2's algorithm.

I leverage variation in AlphaFold's prediction confidence to define treatment and control groups. For each protein, AF2 reports a confidence score indicating how closely the predicted 3D structure is expected to match an experimental one. Higher scores indicate that the predicted 3D structure is more likely to be very close to what an experiment would find, while low scores indicate a limited performance. I partition the entire structure "search space" into regions by prediction confidence. Structures targeting proteins in the highest-confidence region form the treated group; those targeting all other regions serve as controls. I then use

a difference-in-differences design to compare how the quantity and quality of experimentally solved structures evolve for well-predicted versus less- or unpredicted regions before and after AF2's release. Event-study estimates show no systematic pre-treatment differences between these groups, supporting the assumption that, absent AF2, experimental effort would have followed similar trajectories across regions.

Starting with quantity, I show that overall structure depositions has been growing steadily both before and after AF2's release. On average, the total number of structures deposited per quarter rose by about 21.1% after AF2's introduction. But the experimental effort is sharply reallocated, reflected by a pronounced shift in the composition of deposited structures. Regions with very high confidence predictions experienced a 34.8% to 42.8% decline in total structure depositions relative to regions where predictions are weaker or absent. The contraction is especially pronounced for certain types of proteins such as first-attempt structures working on previously experimentally unattempted proteins, which are more exploratory and ex ante uncertain; and non-human proteins that are further from immediate clinical demand. These patterns suggest that scientists reallocate effort away from validating structures that AF2 can already predict accurately. Interestingly, I also find that this reallocation occurs without changing the typical experimental team size for structures continued to be pursued across prediction regions.

I also document that this reallocation of effort is highly uneven across experimental methods. The heterogeneous analysis by experimental method suggests most of the substitution away from experimental work on well-predicted proteins is concentrated in X-ray crystallography, the more traditional and widely available method. In contrast, Cryo-EM, a capital-intensive new method, appears largely insensitive to AF2's prediction confidence, with no significant evidence of reallocation across structure types. This divergence suggests that the impact of AI automation depends critically on the underlying constraints of the experimental technology.

Finally, I examine how AF2 affects the quality of structures that scientists continue to

pursue, along both the execution and innovation margins. To measure execution precision, I use experimental resolution and find limited evidence that AF2's predictions improve execution quality for either method. The more striking changes appear on the innovation margin: structures targeting well-predicted proteins face a "publication penalty", being 4.9 percentage points less likely to appear in top-decile journals than comparable structures on less well-predicted targets. This penalty is especially severe for first-attempt structures on well-predicted proteins, where the probability of publication in a top-decile journal falls by 11.2 percentage points, suggesting that AF2 erodes the "novelty premium" previously associated with being the first to solve an experimentally unsolved structure.

Taken together, my findings suggest the opposite of the streetlight worry that scientific efforts may disproportionately flock to problems where AI performs best. In this case, AF2 operates more like a "floodlight" that illuminates the entire search space, sharply reducing uncertainty about many protein structures and encouraging scientists to move toward the large set of underexplored areas where their comparative advantage over AI remains strongest. At the same time, the reallocation response is method-specific: the floodlight pattern appears primarily in the widely accessible X-ray crystallography, while the capital-intensive Cryo-EM adjusts less and continues to expand. This suggests that AF2 may also reshape the distribution of scientific opportunity, widening gaps across labs with unequal access to frontier equipment.

This paper contributes to several threads of literature. First, it joins the large body of literature on how automation technology may affect labor productivity and the organization of work (Schumpeter, 1942; Autor et al., 1998; Bresnahan et al., 2002; Autor et al., 2003; Autor, 2015; Graetz and Michaels, 2018; Acemoglu and Restrepo, 2019, 2020) and more recent work on the impact of AI (Brynjolfsson et al., 2018; Webb, 2019; Zolas et al., 2021; Acemoglu et al., 2022; Noy and Zhang, 2023; Dell'Acqua et al., 2023; Brynjolfsson et al., 2025a,b; Cui et al., 2025). Existing measures of "AI exposure" typically construct occupation-level indices by inferring affected tasks from occupation descriptions (Frey and

Osborne, 2017; Felten et al., 2018; Webb, 2019; Eloundou et al., 2024). While this approach fits the general-purpose nature of generative AI (Goldfarb et al., 2023), it is inherently indirect and masks how different types of work within the same occupation are differentially affected. In this paper, I build a unique new measure that directly reflects AI's exposure over the full search space of structural biology and provides clear evidence of a substantial reallocation of work caused by AI.

This paper also contributes to the emerging literature on how AI affects innovation and the knowledge production process. Relative to the rich set of theoretical frameworks (Cockburn et al., 2019; Agrawal et al., 2023, 2024; Ide and Talamas, 2024; Jones, 2025; Mullainathan and Rambachan, 2025), the body of empirical evidence remains relatively limited. Existing empirical work primarily examines AI's impact on product innovation within firms (Lou and Wu, 2021; Bessen et al., 2022; Babina et al., 2024) or on knowledge created in online communities such as StackOverflow and Wikipedia (Burtch et al., 2024; Lyu et al., 2025; Shan and Qiu, 2025). By contrast, this paper focuses the production of scientific knowledge, the upstream input for product innovation, with a strong public good property as well. Whereas some previous studies have raised concerns that prediction technologies could induce inefficient research herding toward targets where predictions are most accurate (Khurana, 2023; Kim, 2023; Hoelzemann et al., 2024), my results point to the opposite direction: research effort shifts away from the best predicted regions and towards not well predicted ones. Moreover, this paper also contributes to the literature on how access to research tools impacts knowledge production (Furman and Stern, 2011; Murray et al., 2016; Helmers and Overman, 2017; Teodoridis, 2018; Furman and Teodoridis, 2020), by showing that AI-based predictions may shift scientists' target choice differently based on what experimental method is used.

Lastly, although AlphaFold's impact has garnered substantial attention within the natural science community (Bertoline et al., 2023; Varadi and Velankar, 2023; Kovalevskiy et al., 2024), most discussions focus on evaluating its reliability in different contexts and its poten-

tial integration into future scientific discovery. However, less attention has been given to its effect on knowledge production from human labs in structural biology, an aspect that may be of greater interest to economists and may guide policymakers in designing better science policy. To my knowledge, only two studies have attempted to address this gap. One is Cavalli (2022), who studies the change in lab organization after the emergence of AlphaFold1.[1] Another more relevant one is Yu (2024), who studies the change of citations of structural biologists with respect to other scientists from other fields in life science. My study, by contrast, asks how AI changes what scientists study, which provides more direct evidence of AlphaFold's impact on knowledge production.

The remainder of the paper is organized as follows. Section 2 provides relevant background knowledge on structural biology and introduces how AF2 revolutionized this field of study. Section 3 describes my data sources and the construction of key measures used in analysis. Section 4 provides descriptive statistics on the trend and composition of aggregate knowledge production in structural biology. Section 5 presents the empirical strategy and main findings. Section 6 concludes with a discussion on potential directions for future work.

2 Background

2.1 Development in Structural Biology: Experiment and Prediction

Structural biology is the study of the three-dimensional (3D) structures of biological macromolecules, including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and, most commonly, proteins. Proteins are often described as the "building blocks of life" because they perform essential roles at every stage of biological processes—providing nutrients for embryonic development (e.g., albumin), catalyzing chemical reactions in living organisms (e.g.,

[1] AlphaFold1 was the first version of AlphaFold that was introduced in 2018 as DeepMind's entry to the CASP13 protein-structure prediction competition. Unlike AlphaFold2, only the competition results and a high-level description of this early version was made public. Meanwhile, its accuracy still fell well short of experimental methods.

enzymes), and defending against foreign pathogens (e.g., antibodies). As these diverse functions are fundamentally determined by the unique 3D structures of proteins, structural biology has emerged as a cornerstone of the life sciences, providing the essential foundation for research that connects molecular functions to practical applications. Since 1901, dozens of Nobel Prizes have been awarded to studies related to structural biology (PDB-101, 2024).

Several different experimental methods have been developed over the history to study the 3D structure since proteins are too small to be directly observed. Among these, X-ray crystallography has been widely accepted as the mainstream. This method involves three main steps: crystallization (growing a suitable protein crystal), data collection (recording X-ray diffraction patterns), and structure solution (analyzing the diffraction data to determine atomic positions in 3D). However, solving protein's structure following this method can be a laborious process with lots of uncertainty. First, growing protein crystals suitable for X-ray diffraction is a slow and highly unpredictable, trial-and-error process. Some structures may take years before crystals can be obtained, if at all, (Gorrec, 2021) and the overall success rate from target selection to solved structure is only around 5% (Slabinski et al., 2007). Even after the crystal is generated, the refinement on structure can also be a "tedious" process (Strasser, 2019). Scientists may go back-and-forth fitting the structural model with experimental data until they decide the result is "good enough" (Brown and Ramaswamy, 2007).

In recent years, Cryo-electron microscopy (Cryo-EM) has become a popular alternative to X-ray crystallography. Cryo-EM flash-freezes biological samples in a thin layer of vitreous ice, which preserves their native structures without the need for crystallization (Doerr, 2016).[2] As Figure 1 illustrates, the remaining steps are largely similar to X-ray crystallography (Goodsell, 2019) though specimen preparation and data analysis still requires several days to months of computation and expert curation (Grassucci et al., 2007; Thompson et al., 2019). Moreover, Cryo-EM is a costly method: the installation can cost around $8 million, with annual operating expenses of about $400,000, compared to just $200–$500 per X-ray

[2]Cryo-EM is particularly useful for proteins that are difficult to crystallize, such as large complexes and membrane proteins (Wang and Wang, 2017; Shoemaker and Ando, 2018).

sample,[3] making it prohibitively expensive for many scientists.

Alongside advances in experimental methods, scientists have also pursued an alternative path: developing automation tools to predict a protein's 3D structure directly from its one-dimensional amino acid sequence. Since sequencing methods had been standardized by the 1970s (Sanger and Thompson, 1953; Edman and Begg, 1967), such tools in principle could allow scientists to bypass the costly and time-consuming experimental process altogether. However, prior to 2018, even the most advanced models remained far from achieving accuracy comparable to experimental methods (Kryshtafovych et al., 2019). The introduction of AF2 marks a major breakthrough in this direction. Leveraging deep learning algorithms, AF2 is the first method that achieves prediction accuracy comparable to laboratory experiments for a substantial share of proteins (Callaway, 2020). In July 2021, DeepMind published a paper in *Nature* that open-sourced AF2's algorithm, enabling scientists worldwide freely access to this powerful method (Jumper et al., 2021). That paper quickly became one of the most cited publications, accumulating over 30,000 citations in less than 3 years. In Oct 2024, the main developers of AlphaFold, Demis Hassabis and John M. Jumper were awarded the Nobel Prize in Chemistry for their contributions in protein structure prediction.[4]

2.2 Unique Characteristics of Structural Biology

Structural biology has emerged as a particularly informative setting for studying innovation and the economics of science since the groundbreaking work of Hill and Stein (2025a,b). This field offers several unique advantages. First, experimental projects in this field are highly comparable: scientists worldwide share a common objective—determining molecular structures through standardized experimental procedures, with the structure itself serving as the project's final output. Second, this field is exceptionally well archived: rich, standardized

[3]Estimated pricing for services from several representative US institutes including California Institute of Technology, Johns Hopkins University, and The University of Kansas

[4]The advancements of AlphaFold did not stop there. In May 2024, DeepMind released AlphaFold 3, which expanded its predictive capabilities to include the structures and interactions of all of life's molecules—not only proteins, but also DNA, RNA, ligands, and more are included (Abramson et al., 2024).

data are stored in repositories such as the Protein Data Bank (PDB), where each structure's target, timing, method, quality, and outcome are recorded in a consistent and publicly accessible format. Moreover, these structural records can also be linked to complementary datasets, such as the publication records and drug development applications, that provide deeper insight into the direction and progress of scientific innovation.

Combined with the comprehensive coverage of experimental projects, the introduction of AF2 in structural biology offers a unique context to study the impact of AI on scientific knowledge production following a difference-in-differences analysis. The public release of AF2 constitutes a sharp, exogenous technological shock with clearly defined timing. Moreover, variation in the confidence of AF2's predictions across proteins creates natural heterogeneity in exposure: some proteins are predicted with near-perfect accuracy, comparable to the most precise laboratory results,[5] while others remain relatively poorly predicted. This variation enables the construction of treatment and control groups.

3 Data

3.1 Data Sources

The Protein Data Bank (PDB) Established in 1971, the Protein Data Bank (PDB) is a comprehensive repository in structural biology that archives experimental projects worldwide. These projects primarily focus on determining the structures of large biological molecules, 92% of which are proteins.[6] When the exploration is completed, depositing the structure in the PDB has become a necessary step, as the scientific community has required this practice for anyone before submitting publications or grant applications since the 1990s. In this process, a unique PDB ID is assigned to a certain structure deposited and a wide range of information about the structure is recorded. I mainly leverage the following aspects:

[5] According to Tunyasuvunakool et al. (2021), among protein structure prediction for the human proteome, around 36% meet this standard.

[6] PDB Data Distributions, by Polymer Entity Type

target, which includes specific proteins being studied and the corresponding biological features; execution, which includes the timeline (e.g., deposition/release dates), method (e.g., X-ray crystallography/Cryo-EM), quality (e.g., resolution), and personnel (e.g., structure authors/citation authors) involved in the experimental discovery of the target; and citation, which links the structure to the primary academic paper that cites it, if available.

The AlphaFold Protein Structure Database (AFDB) When DeepMind open-sourced AF2 in July 2021, they also launched the AlphaFold Protein Structure Database (AFDB) to make the predicted protein structures publicly accessible.[7] The database aims to lower technical barriers and accelerate scientific discovery by providing ready-to-use predictions without the need for complex software setup.[8] Each prediction has been assigned a unique AFDB ID. AFDB also provides a mean pLDDT score for each prediction, which serves as a global metric indicating its confidence in the average accuracy across all local regions within that predicted structure.[9] I leverage this variation in prediction quality across proteins to construct the treatment indicator. Further details are discussed in Section 3.2.

The UniProt Knowledgebase (UniProtKB) The UniProtKB provides a comprehensive catalog of nearly all publicly known protein sequences and their functional annotations.[10] It is a superset to AFDB, covering both predicted proteins and newly discovered ones not

[7] Case study: AlphaFold uses open data and AI to discover the 3D protein universe

[8] Since the initial launch in July 2021, AFDB experienced several rounds of expansion and by July 2022 it includes over 214 million predicted structures, covering all the known unique protein sequences as of April 2021 (Varadi et al., 2022). See Figure A.1 for an illustration.

[9] The rule of thumb is based on local pLDDT score as each prediction of protein may have certain regions predicted with high-confidence or low-confidence. I follow Jumper et al. (2021) to use the same rule of thumb for global metrics. More details on rule of thumb and how to interpret it can be found in the FAQ of AFDB.

[10] Some sequences are excluded, such as synthetic constructs, patent submissions, or redundant proteomes. Nonetheless, UniProtKB remains the best available proxy for the universe of known proteins. There are two sections in the UniProtKB: a reviewed section called Swiss-Prot, which includes over 570,000 high-quality, non-redundant protein sequences manually annotated by biological experts; and an unreviewed section called TrEMBL, which documents all other protein sequences not yet manually checked by experts. Once a protein has gone through the manually check process, it will be passed from TrEMBL to Swiss-Prot. In this paper, I consider both sections. See details at UniProtKB Coverage.

covered by the AFDB.[11] It also has broader coverage than the PDB, which only records experimentally determined structures. Meanwhile, each UniProtKB entry lists all corresponding PDB IDs, as well as the related AFDB IDs if available. This cross-referencing enables direct linkage between experimental structures and predictions through the same protein being studied.

Other Data Sources To evaluate the downstream scientific and commercial influence of protein structures, I supplement the sample with data from the Web of Science and DrugBank, following Hill and Stein (2025b). The Web of Science provides bibliographic records that allow measurement of publication outcomes if a specific structure is published in a paper that is recorded in the PubMed database.[12] DrugBank further lists PDB IDs associated with drug targets, enzymes, transporters, or carriers, allowing identification of structures with potential commercial applications.

3.2 Measuring and Mapping Key Variables

Treatment Indicator The treatment indicator is built upon the prediction confidence score reported in the AFDB. Following the rule of thumb provided by DeepMind (Jumper et al., 2021; Fleming et al., 2025), predictions are classified into four regions with different levels of prediction confidence based on their mean pLDDT scores:

- Very High (VH) confidence if $pLDDT \geq 90$. This means the prediction is expected to have high accuracy.
- High (H) confidence if $70 \leq pLDDT < 90$. This means the prediction is expected to be good with some misplacement chains.

[11] AFDB only covers around 214 million proteins known as of April 2021. while the number of proteins recorded in the UniProtKB had expanded to roughly 248 million by May 2024.

[12] The linkage between the Web of Science and the PDB is established through PubMed identifiers (PMIDs), unique IDs assigned by the U.S. National Library of Medicine. Each PDB entry is manually linked to the paper that first reports the structure and includes its PMID, while the Web of Science provides a PMID crosswalk.

- Low (L) confidence if pLDDT $50 \leq pLDDT < 70$. This means the prediction should be treated with caution.
- Very Low (VL) confidence if $pLDDT < 50$. This means the prediction should not be interpreted.

When linking predictions to experimental structures in the PDB, it is important to note that the mapping occurs at a more granular level, called "entity". A protein structure in the PDB may represent either a small protein with single entity or a protein complex composed of multiple entities (See Figure 3). To obtain a structure-level measure of prediction quality, I calculate the average prediction confidence $pLDDT_s$ score across all entities within a structure, weighted by each entity's amino acid sequence length. This provides a consistent proxy for how well a structure, on average, is predicted by AF2. For entities without a corresponding prediction, I assign a confidence score of zero, reflecting the absence of predictive information.[13]

In the baseline analysis, a structure is classified as "treated" if its average confidence score falls within the "VH" region ($pLDDT_s \geq 90$), where AF2 predictions are nearly indistinguishable from experimental accuracy. In the sensitivity analysis, I include a second treatment group for those structures in the high-confidence ("H") prediction region ($70 \leq pLDDT_s \leq 90$). The remaining structures, those with lower-confidence predictions or outside AF2 coverage, are grouped into a residual category ("R"). The baseline specification pools the H and R groups into a single "Non-VH" control group.

Quantity of Knowledge Production Quantity measures are constructed to capture the volume and composition of human-produced knowledge. I begin by counting the total number of structure deposits into the PDB each quarter. This provides a baseline measure of total quantity of knowledge produced by structural biologists. To further characterize

[13]Such cases typically involve non-protein entities, missing UniProt identifiers, or proteins discovered after April 2021, which fall outside AFDB's coverage.

the composition of experimental effort, I construct several subgroup measures. First, I identify first-attempt and non–first-attempt structures—those that experimentally determine a protein's structure for the first time versus follow-up studies on previously attempted proteins.[14] This comparison reveals whether the release of AF2 shifted the balance between exploratory projects (first attempts) and exploitative projects (non–first attempts). Second, I distinguish structures targeting human versus non-human proteins to assess whether effort increasingly concentrates on human proteins, which are more likely to have high downstream demand. Third, I also document the composition of these different types of structures varies by experimental method. Together, these measures provide a comprehensive view of how AI has reshaped experimental priorities and research efforts of different types of studies in structural biology.

Quality of Knowledge Production Building on the analysis of quantity, I construct quality measures to evaluate the quality of structures deposited, including informational value and innovation contribution. To measure informational value, I use resolution reported in the PDB which reflects structure's execution precision, where lower values indicate more detailed and reliable determinations. To assess innovation contribution, I examine both the scientific influence and commercial relevance. To measure scientific influence, I rely on each structure's primary citation record in the PDB. I first identify whether the corresponding paper is published and indexed in the PubMed. Conditional on publication, I then record whether the paper appears in the top 10% of journals by Journal Impact Factor (JIF) or Cell, Nature, or Science (CNS), which are viewed as the pinnacle of scientific publication.[15] Because AF2's release is too recent for citation measures to mature at the paper level,

[14]To measure the number of experimental attempts, I use the clustering algorithm provided by the PDB, which groups protein entities based on sequence similarity. Following Brown and Ramaswamy (2007) and Hill and Stein (2025b), entities sharing at least 50 percent sequence similarity are considered to represent the same protein. Within each cluster, I rank entities by their release date and identify whether a given entity corresponds to the first attempt to solve that protein. I then aggregate this information to the structure level, classifying any structure containing at least one first-attempt entity as a first-attempt structure. In the robustness check, I also tested measuring attempt under different thresholds of sequence similarity.

[15]JIF measures the average number of citations received by articles published in a particular journal over a certain period. I use the most recent 2024 JIF for the analysis.

the quality of the publishing journal is used as a short-term proxy to measure a structure's academic influence. Finally, I assess commercial relevance by identifying whether a structure is cross-listed in DrugBank, indicating its potential in drug discovery.

Group Structures by Prediction and Class To account for systematic differences in prediction confidence across protein types, I construct a grouping variable ("bin") that combines two time-invariant characteristics of each structure: AF2 prediction confidence (VH, H, R) and 85 functional classification reported in the PDB (e.g., antibiotic, binding, membrane, transport). This grouping aligns the definition of treatment intensity with biologically meaningful comparisons.

In the following analysis on quantity, I construct a balanced panel with bin as the unit of analysis, which represents a specific domain with a distinct level of AI prediction. In the analysis on quality, which is conducted at the structure level, I include bin fixed effects to absorb unobserved, time-invariant heterogeneity across biological domains that may systematically influence scientific difficulty, demand, or publication outcomes. Together, this design ensures that identification accounts for both time-based trends and time-invariant pre-existing group differences.

3.3 Sample Construction

The sample construction begins with 87,276 structures deposited in the PDB between January 1, 2018, and June 30, 2024 executed either by X-ray crystallography (63,978; 73.3%) or Cryo-EM method (23,298; 26.7%).[16] This window provides a relatively balanced pre- and post- period around the publication of AF2's algorithm in July 2021. It also mitigates the missing-data concern caused by PDB's release policy: deposited structures are not made public until either the associated paper is published or one year has passed since deposi-

[16]Within this period, 97.3% of all deposited structures follow one of these two methods.

tion.[17] I drop 1,172 structures with no protein entities and a few hundred structures for which the author field lists only an institution. When constructing bins, I only keep classes of proteins that have some structures deposited from each of the three prediction regions (VH, H, R) to make sure each bin had at least one deposit within this period of time. Finally, I construct a balanced panel with 255 bins (85 classes $\times$ 3 prediction regions) in 26 quarters (2018Q1-2024Q2) containing 84,154 unique structures.

I provide the baseline summary statistics with involvement in the "VH" prediction region as treated and those in the "H" or "R" as control below. Panel A of Table 1 presents quantity outcomes at the (prediction region $\times$ structure class) bin level. We observe that the magnitude of knowledge produced, either measured by total number of structures deposited or papers published per year-calendar quarter are comparable, suggesting they may share similar level of academic attention. The fraction of first-attempts is similar across groups and the fraction of human structures is slightly higher in the control group. Panel B of Table 1 presents quality outcomes at the structure level by different methods. We see structures in the treatment group are better executed while structures in the control group have better publication records if published.

4 Descriptive Statistics

This section provides a descriptive overview of how the aggregate knowledge production in structural biology evolved around the introduction of AF2. From the empirical trends and cross-sectional distributions, four facts are summarized.

Fact 1: Total deposits keep rising, with a shift towards not-well-predicted proteins.

Figure 4 illustrates both the overall increase in structural depositions and the compositional shift in prediction confidence following AF2's release. As Figure 4a shows, the number of

[17] Once a structure is released, the PDB records both the release date and the original deposit date, when the research team judged the structure to be solved and deposited it. The raw data were downloaded from the PDB on August 26, 2025, and thus include all structures released by that date.

structures deposited per quarter has been rising consistently over this period, from an average of 2,949 in the pre-AF2 period to 3,572 afterward, representing a 21.1% increase. Figure 4b illustrates a compositional shift away from depositing structures in regions with (VH) prediction confidence. The share of total depositions accounted for by VH regions falls by 9.5 percentage points, from 38.0% to 28.5%. Comparing the distribution of prediction scores from experimentally attempted structures with the global distribution of AF2's pLDDT scores across all 214 million proteins covered (Figure 4c), we see only modest changes in the shares from regions where AF2 performs poorly (L and VL) and from regions where predictions are moderately good (H but not VH). Instead, the most pronounced growth comes from underexplored areas outside AF2's coverage: the share of depositions in this out-of-scope region rises by 5.5 percentage points, from 14.8% to 20.3%.

Fact 2: A rise in Cryo-EM use and heterogeneous impact across experimental methods.

Figure 5 presents trends in structure depositions by experimental method. Figure 5a shows that the overall rise in total depositions is mainly driven by the Cryo-EM adoption take-off: quarterly Cryo-EM depositions has more than doubled, increasing from 504 to 1,318, whereas X-ray crystallography depositions declines slightly, from 2,445 to 2,255 (-7.8%). Figure 5b and 5c indicate that AF2's introduction affects research activities unevenly across experimental methods. For X-ray crystallography, there is a clear shift away from targets in regions with very high confidence predictions, where AF2 most effectively substitutes for human experimentation. In contrast, the distribution of prediction confidence among Cryo-EM structures remains largely unchanged before and after AF2's release, suggesting that prediction confidence exerts little influence on scientists' choices of where to exert experimental efforts.

Fact 3: The exploratory deposit remains steady, while the exploitative deposit grows.

Figure 6 compares the composition of exploratory versus exploitative research, measured by whether a structure is identified as "first-attempt". As shown in Figure 6a, the trends in first-

attempt and non–first-attempt structures are largely parallel prior to AF2's introduction. After the release, the production of first-attempt structures remains relatively stable, while the number of non–first-attempt structures rises: average quarterly depositions increase from 2,304 to 2,858 (+24%), indicating an expansion in exploitative work without a corresponding decline in exploratory work. Figures 6b and 6c further show a shift toward less well-predicted areas, with this reorientation more pronounced among first-attempt projects: the share of depositions from moderately well-predicted regions (H but not VH) also declines.

Fact 4: The experimental team size is stable across prediction confidence regions.

In PDB, each structure lists the authors credited with determining and depositing it, and I count the number of authors per structure to measure team size. Because the distribution of team size is highly skewed—with a few structures involving unusually large teams—the interquartile range (IQR) and median of team size in each quarter is used for comparison. Figure 7 shows that structures across prediction regions exhibit similar ranges and temporal patterns in team size, suggesting that AF2 does not meaningfully change the typical organization size of a research team to solve a structure.

These descriptive patterns suggest that the introduction of AF2 is correlated with higher research output, a shift toward targeting less confidently predicted regions—especially those outside AF2's coverage—and a compositional change in the types of structures pursued in structural biology. Taken together, these observations motivate the empirical analysis that follows, where I formally quantify AF2's causal impact on the quantity, composition, and quality of human-produced knowledge in structural biology.

5 Empirical Strategy and Results

5.1 Quantity and Composition of Knowledge Production

This section aims to evaluate how AF2 affects the quantity and composition of human-produced knowledge in structural biology. The estimation equation follows a generalized difference-in-differences model:

$$y_{bt} = \beta(Post_t \times VH_b) + \gamma_b + \delta_t + \epsilon_{bt} \tag{5.1}$$

The outcome variables y_{bt} is the count of certain types of projects deposited from (prediction region $\times$ structure class) bin b at calendar year-quarter t of deposit. The independent variable of interest is the interaction term between two binary indicators: time indicator $Post_t$ that turns 1 since 2021 Q3 when AF2 is published, and treatment indicator VH_b that turns 1 if the prediction branch of a certain bin belongs to the very high confidence region. Bin fixed effects γ_b and calendar quarter fixed effects δ_t are included in all the specifications. ϵ_{bt} is the error term with a conditional mean of 0.

The coefficient of interest is β. If $\beta > 0$, that implies more deposits are produced working on proteins with predictions on par with the experimental results, suggesting AF2 shifts the direction of knowledge production towards areas that are best predicted. However, if $\beta < 0$, that implies scientists have shifted away from producing knowledge in regions that AF2 has the highest prediction confidence.

Table 2 reports the estimates of Equation 5.1 with total count of structure deposits as the outcome. Column (1) reports the result with a Poisson pseudo-maximum likelihood (PPML) estimator. This is used as the main specification since the outcome is a count variable. Column (2) reports the OLS estimator. Estimation results from Column (1)-(2) indicate that bins exposed to the very high confidence prediction region of AF2 experienced a substantial decline in total structure depositions, approximately 34.8% to 42.8% relative

to those that were not. Columns (3)-(4) repeat the estimation under the OLS specification using inverse hyperbolic sine transformed total count as the outcome variable. In column (4), the regression is also weighted by the total number of structures deposited over the pre-treatment period in each class in order to make sure the finding is not driven by classes that account for a small share of total knowledge production. The coefficient of interest is still negative and significant with similar magnitude. Results across columns suggest a reallocation of scientific effort away from regions that AF2 predicts very well towards those it does not.

Moving forward, I evaluate how the composition of human-produced knowledge changed, reflected by the deposit counts of different types of structures. Table 3 reports the results from the PPML specification. The impact on total deposit is listed in Column (1) as a benchmark. Columns (2)-(3) compare deposits of first-attempt (exploratory) versus non–first-attempt (exploitative) structures. Deposits in the VH region declined for both categories, but the drop is larger for first-attempt structures (–39.8% versus -33.7%). This suggests that when AF2 already offers highly accurate predictions, scientists are less likely to experimentally explore unattempted structures in this region. Columns (4)-(5) compare deposits of structures targeting human versus non-human proteins. Deposits for non-human proteins in the VH region fall more steeply, indicating that researchers scaled back on less central, well-predicted proteins while maintaining effort on human targets. Columns (6)–(7) further split human proteins into those that were previously "stuck", historically difficult to resolve, and those that were not.[18] Deposits for stuck human proteins declined by 29.4% in the VH region, whereas the non-stuck ones show smaller 14% change. Although statistically insignificant, this pattern suggests that AF2's predictions may have partially substituted for experimental attempts on the most challenging targets, reducing the incentive to invest in

[18]To identify a set of "stuck" proteins that were poorly resolved experimentally before AF2's release, I follow benchmark standards established by structural biologists: for X-ray crystallography, resolutions above 2.5 Å are generally unsuitable for drug design (Anderson (2003)), while for Cryo-EM, resolutions above 3.5 Å are difficult to interpret (Casanal et al. (2019)). I compute the median pre-AlphaFold resolution for each class–method pair in my sample. If this median exceeds the corresponding benchmark, structures under these class–method pairs are labeled as "stuck".

difficult structural determination when high-quality predictions exist.

Beyond studying how AF2 affects the types of structures scientists study, I further evaluate whether it changes the typical labor intensity of experimental work for the structures that continue to be pursued. I measure labor intensity as the median number of authors involved in solving a given type of structure within each bin–deposit-quarter cell. If AF2 also reduced the labor required for experimentation, we would expect smaller teams for structures with predictions in the VH region. However, the results in Table 4 show only marginal differences in median team size between VH and non-VH bins, with all coefficients close to zero and statistically insignificant.[19]

In order to check the pre-existing trends in structure deposit and explore the dynamic relationship between AF2's prediction and knowledge production, I also estimate the following dynamic difference-in-differences model:

$$y_{bt} = \sum_{\tau \in \Gamma^{Pre}} \beta_\tau (\mathbf{1}\{t = \tau\} \times VH_b) + \sum_{\tau \in \Gamma^{Post}} \beta_\tau (\mathbf{1}\{t = \tau\} \times VH_b) + \gamma_b + \delta_t + \epsilon_{bt} \tag{5.2}$$

In this equation, set Γ^{Pre} includes all the time periods in our sample from the pre-treatment period, except for 2021 Q2, the quarter right before AF2's release. Set Γ^{Post} includes all the time periods in our sample since AF2's release. If the β_τs are not statistically distinguishable from zero when $\tau \in \Gamma^{Pre}$, it supports the parallel trends assumption for our main estimation. When $\tau \in \Gamma^{Post}$ the β_τ identify the dynamic impact of AF2 in year-quarter τ.

Figure 8 presents coefficient estimates from Equation 5.2, under the PPML specification. Overall, pre-treatment coefficients are close to zero and statistically flat for the first-attempts (Figure 8a), lending support to the parallel-trends assumption that production of such types of structures exposed to the VH region or not were on similar trends. For the non first-attempts and total deposits (Figure 8b, 8c), the pre-treatment coefficients display a modest upward trend prior to AF2's release in the earlier periods, suggesting proteins later classi-

[19]For each structure type, the analysis is restricted to bins with at least one deposits each calendar year-quarter over the sample period to ensure consistent within-bin comparisons.

fied as with very high confidence predictions were experiencing a slightly faster growth in experimental activity about two years before AF2's release, but not in the more recent pre-treatment periods. Post-release estimates are all negative for the first-attempts, suggesting a persistent decline in experimental output among the treated group.

To sum up, results above suggest AF2 significantly substituted for experimental efforts in regions where prediction confidence is very high. Such substitution is more pronounced, around a 40% decline, for targets with lower net returns of experimentation, either because the expected cost of experiment is too high (first-attempts) or because there's limited downstream demand (non-human targets). Meanwhile, AF2's impact operates primarily through reallocating efforts away from studying these types of structures experimentally, with little evidence of labor-saving effects within the experiments that scientists continue to pursue.

5.2 Heterogeneity by Experimental Methods

A natural concern with the baseline estimates is that structures solved by different experimental method are pooled together. Because X-ray crystallography and Cryo-EM differ in their workflows, capacity constraints, and the types of proteins they typically tackle, a single aggregate coefficient may mask important heterogeneity across methods. To assess this, I reconstruct the dataset at the method-bin-deposit quarter level and estimate the PPML specification adding a triple interaction between the post-AlphaFold indicator, the very-high confidence group, and a Cryo-EM method indicator:

$$E[y_{mbt}|\cdot] = exp(\beta_1(Post_t \times VH_{mb}) + \beta_2(Post_t \times VH_{mb} \times Cryo_m) + \gamma_{mb} + \delta_{mt}) \tag{5.3}$$

Here y_{mbt} is the count of structure deposit following method m in bin b at deposit quarter t. γ_{mb} are the method $\times$ bin fixed effect. Because Cryo-EM adoption evolves over time, I also allow time shocks to vary by method through including δ_{mt}, the method $\times$ deposit quarter fixed effect. Under this parameterization, β_1 captures the impact of AF2 within the X-ray

crystallography group (the omitted method), while β_2 captures the differential impact for Cryo-EM relative to X-ray crystallography. Accordingly, the impact within Cryo-EM group is captured by $\beta_1 + \beta_2$.

Table 5 reports the heterogeneous effects of AF2 on the composition of experimental knowledge production across methods. Two patterns stand out. First, the decline in first-attempt structures is broadly consistent across methods, as Column (2) indicates. Second, within X-ray crystallography there is a comparable overall contraction in total deposits (Column (1)), accompanied by a reallocation away from non-human proteins and from "stuck" targets (Columns (5)–(6)). This suggests that X-ray crystallography disproportionately scales back work on lower-demand or intrinsically difficult targets once high-quality predictions become available. In contrast, Cryo-EM output appears largely insensitive to AF2's prediction confidence: the treatment coefficients are small and imprecise, and there is little evidence of systematic reallocation across structure types within Cryo-EM, aside from first-attempt deposits. These patterns are suggestive from an inequality perspective: AF2 appears to reallocate efforts most strongly in X-ray crystallography, which is relatively more widely available, while leaving high-end, capital-intensive Cryo-EM capacity largely unchanged.[20]

5.3 Quality of Knowledge Production

In this section, I evaluate the impact of AF2 on the quality of experimentally solved structures. The estimation follows a variant of Equation 5.1 under an OLS specification:

$$y_{ibt} = \beta(Post_{it} \times VH_{ib}) + \gamma_b + \delta_t + \epsilon_{ibt} \tag{5.4}$$

where y_{ibt} denotes the quality measure of structure i belonging to bin b that deposited in calendar year-quarter t. All other terms are defined analogously to those in Equation 5.1,

[20] Meanwhile, the method-specific coefficients are all smaller in magnitude than the baseline pooled estimates. This is expected since the aggregate specification captures the combined response across all methods as well as the expansion of Cryo-EM adoption. More Cryo-EM structures are classified to the control group.

but the unit of analysis is now at the individual structure level. Because each structure is observed only once, the dataset analyzed in this Section is repeated cross-sectional and results in this section should be interpreted with caution. As Section 5.1 documents the compositional shifts in the types of projects deposited after AF2's release, the estimated coefficient here reflects a combination of (i) the causal effect of AF2 on the quality of inframarginal structures—those that continue to be experimentally solved despite receiving accurate predictions—and (ii) selection differences in quality between marginal structures that are no longer attempted and those that remain.

Table 6 reports the estimated impact of AF2 on the execution precision of experimental structures, measured by their resolution. Because resolution is not directly comparable across methods, I estimate the model separately for structures solved by X-ray crystallography and Cryo-EM. Panel A shows limited effect of AF2 on structures determined by X-ray crystallography. Among different types of structures, there's only a modest improvement about 4.6% is observed for treated structures working on human proteins and 4.7% for human proteins that are "non-stuck". For non-human proteins, the quality of resolution decreases by 3.3%. Meanwhile, Panel B shows no significant change in resolution for Cryo-EM structures, suggesting that AF2 had little direct effect on the precision of Cryo-EM based experimental outcomes.

I proceed to examine how AF2 affects a structure's innovation outcome, including both the academic influence and the commercial relevance. For academic influence, it is first measured whether a structure's primary citation is published in an academic paper cross-listed in the PubMed database. Then conditional on publication, I evaluate the corresponding journal's academic influence based on the scientometrics indices introduced earlier. As one paper may include multiple structures, when building the structure-paper link, I only include pairs with papers containing structures originating from a same single bin to ensure that the mapped publication reflects a consistent treatment exposure, avoiding ambiguity from papers that span structures belonging to different prediction-confidence regions or functional

classes. 81.8% of published papers in my sample satisfy this filter. For the commercial relevance, it is measured by whether a structure is cross-listed in the DrugBank.

Table 7 reports the estimation results. Panel A includes all the structures and I observe the introduction of AF2 shows only marginal effects on whether a structure is cross-listed in PubMed, DrugBank, or published in the most prestigious CNS journals. However, Columns (3)-(4) indicate that structures linked to proteins with very high prediction confidence are, on average, 4.9 percentage points less likely to publish in journals within the top decile of the Journal Impact Factor (JIF) distribution. To better understand the source of this publication penalty, I re-estimate the specification separately for first-attempt and non–first-attempt structures which may have different objectives: the first-attempts represent exploratory efforts, aimed at solving previously unknown structures, whereas the non first-attempts reflect follow-up or exploitative research focused on functional characterization or application. Clear heterogeneity is observed: in Panel B, which only includes the first-attempts, all estimated effects are negative and larger in magnitude, with the probability of publication in a top-decile JIF journal decreases by 11.2 percentage points. By contrast, Panel C shows no comparable decline among the non first-attempts. This pattern suggests that AF2 may erode the scientific novelty channel that once reward being the first to experimentally solve some previously unknown protein's structure. For structures with highly accurate predictions, the publication premium of being the first to experimentally solve an unknown structure largely disappears.

5.4 Robustness Checks

In this section, I check the robustness of our main result, the compositional change in knowledge production. First, I evaluate if the impact is driven by other concurrent shocks around the release of AF2 or a small number of protein classes that attract disproportionate attention. Second, I alter how treatment and "first-attempts" are defined and see if we can still observe the similar result. Finally, I incorporate an analysis with multiple treatment

intensities.

Alternative Drivers Around the release of AF2 in 2021Q3, there's also a surge in biomedical research related with COVID-19. In Panel A of Table A.1, I identified the protein entities originating from COVID-19 using the taxonomy ID and drop all the structures including any COVID-19 protein entities. The results are marginally smaller in magnitude as most of COVID-19 protein entities are beyond AF2's coverage and correspondingly structures involved are mainly assigned to the control group. Still a 31.8% decline is observed for total structure depositions and such shrink is more substantial for the first-attempts (-39.6%). Therefore, the surge of COVID-19 studies is ruled out as the main driver of my result. Then, I evaluate if the results are driven by the shift of research interest in a small set of heavily studied protein classes. In Panel B of Table A.1, I report the results after dropping structures from the top five mostly studied classes, each contain more than 5,000 structures.[21] Still, a contraction of experimental activity in the VH region is observed after the most intensively studied classes are removed. This indicates the treatment effects estimated are not mainly driven by the shift of research interest in a few blockbuster classes, but instead reflect a broader reorganization of experimental work across all fields in structural biology.

Verifying Treatment and Outcome Measurement A second major concern is that the treatment variable is not properly measured at the structure level. Because the existence of structures consists of multiple protein entities, the main specification aggregates entity-level pLDDT scores into a structure-level measure using a weighted average with entities' amino acid sequence length as the weight. If alternative aggregation rules lead to materially different classifications of "treated" structures, the estimated effects may reflect measurement choices rather than the differences in how well each structure is predicted by AF2.

To assess whether the main findings are sensitive to how treatment is defined, I implement three complementary robustness exercises and report the results in Table A.2. Panel

[21] Hydrolases, transferases, viral proteins, oxidoreductases, and membrane proteins are excluded.

A restricts the sample to single-entity structures, where treatment assignment is directly observed and no aggregation is required. The estimated effects remain largely unchanged. The main deviation is in Column (6), where the substitution away from "stuck" human proteins becomes weaker. This likely reflects the fact that most structures classified as "stuck" are multi-entity complexes, which are excluded in this exercise. Panel B evaluates an alternative aggregation rule by replacing the baseline length-weighted average pLDDT with the median, giving equal weight to all entities within a complex protein structure. The magnitude of the effects becomes slightly smaller, but the qualitative conclusions remain the same. Finally, Panel C assigns treatment based on the maximum entity-level pLDDT within each structure. This is the most broad definition: structures are considered "treated" if they include any entity with very high prediction confidence. Even under this classification, I continue to observe an overall contraction in deposits, especially for first-attempt structures. Interestingly, this definition yields a relative increase in human proteins and "stuck" targets, suggesting that scientists may proceed with difficult or high-value structures when at least one entity of the structure is very well predicted, even if most of other parts remain challenging.

I also re-evalute the measurement of "first-attempt" structures. In the PDB, proteins are grouped into "clusters" based on sequence similarity, and in the baseline I classify a structure as first-attempt if it contains any entity that is the first release within a 50% similarity cluster. To test whether this definition drives the results, I re-create the indicator using two alternative thresholds: a more permissive 30% similarity cutoff and a stricter 100% identity cutoff. As the similarity threshold increases, clusters become narrower, so more structures are mechanically labeled as first-attempt. Table A.3 shows that the main result persists: the decline in first-attempt structures in the VH region remains large and statistically significant even under the 100% identity threshold. This confirms that the baseline results are not an artifact of missing near-duplicate structures or marginal cases around the similarity cutoff.

Treatment Intensity Finally, I extend the analysis for multiple treatment intensities. In the baseline specification, only structures in the VH region are viewed as "treated", while all others serve as controls. This binary definition may raise two concerns: first, pooling moderately predicted (H) regions with poorly predicted (R) ones as the control group may underestimate the impact if AF2 meaningfully changes scientists' behavior even with intermediate confidence; second, including regions beyond AF2's prediction coverage in the control group may overestimate effects if AF2 induces a positive spillover of experimental effort toward proteins where predictions are unavailable.

To address both concerns, I re-estimate the model with a multi-category treatment design. In addition to the VH group, I introduce (i) an indicator for high-confidence region (H) and (ii) a separate "ZERO" group for deposits outside AF2's prediction scope. Under this case, the low (L)/very-low (VL) confidence regions that covered by AF2 are used as the control group. The resulting specification is shown below.

$$E[y_{bt}|\cdot] = exp(\beta_1(Post_t \times VH_b) + \beta_2(Post_t \times H_b) + \beta_3(Post_t \times ZERO_b) + \gamma_b + \delta_t) \quad (5.5)$$

Table A.4 reports the results. Under this design, the substitution effect remains concentrated in the most intensively treated VH region and is slightly larger than in the baseline (about -39.1%), consistent with very-high-confidence AF2 predictions being viewed as close substitutes for experimentally resolved structures. I also find suggestive evidence of a confidence gradient: outcomes decline in the H region along several margins (especially first-attempt and non-human), but the magnitudes are smaller than in VH, indicating that AF2's impact is not driven by an arbitrary VH threshold. Finally, coefficients for the ZERO region are positive but statistically indistinguishable from zero across outcomes, offering little evidence that the baseline VH effect is mainly driven by spillovers toward targets outside AF2's predictive scope. Taken together, these results reinforce the interpretation that the baseline pattern reflects a genuine substitution response that scales with predictive confidence, con-

sistent with effort being reallocated away from targets where confidently predicted structures are readily available.

6 Conclusion

This paper studies how AI technology affects the quantity, quality and composition of human-produced knowledge, under the context of AlphaFold2's introduction in structural biology. My findings suggest that the volume of knowledge production continues to grow after the introduction of AF2 and there's a clear compositional change: experimental efforts substitute away from solving proteins whose structures AF2 predicts with very high confidence, with a decline in deposition at about 35%. This reallocation is more substantial for targets with lower net expected returns, such as proteins not being experimentally solved before which may be costly to solve from scratch or non-human proteins with limited downstream demand. Meanwhile, I also find little evidence of improvement brought by AF2's prediction within the structure that scientists continue to proceed, either in terms of the team size or the resolution. These patterns imply that AF2 primarily alters what target to be studied experimentally instead of how much more efficient or effective the experiment is carried out. Moreover, I also document a heterogeneity across experimental methods. While the rising popularity of modern Cryo-EM method drives much of the growth in aggregate knowledge production, AF2's prediction shows limited effect on what types of structures to target within Cryo-EM method. Most of AF2's substitution effects are concentrated in the traditional X-ray crystallography method, which disproportionately retreats from hard-to-solve or low-demand targets when high-quality predictions become available. In sum, these findings suggest that AI-based "floodlights" such as AF2 reallocate scientists' effort away from tasks where prediction can substitute for experiment and toward domains where human expertise remains complementary. However, access to experimental tools may be crucial in determining who can fully exploit the newly illuminated search space.

There remains much to be studied in the future. First, while this paper tracks changes in what structures are experimentally solved, it does not incorporate individual scientist level data to answer who drives this change and how scientists with different expertise endowment are affected. Linking structure deposit records to authors' research portfolios and career history would make it possible to measure scientists' differential exposure to AF2 and understand the distributional effects across scientists. Second, the organizational and funding response to AI breakthrough is largely unexplored: Do grant agencies shift resources across fields differently affected by AI? How labs reorganize in response to AF2? And do these adjustments spill over to adjacent scientific domains not directly targeted by AF2? Finally, AF2 represents an earlier generation of AI technologies that automates a single task within a specific domain. Emerging generative AI systems has the potential to automate multiple tasks across the scientific workflow, from hypothesis generation (Ludwig and Mullainathan, 2024) to experimental design (Charness et al., 2023), even generating new theories (Mullainathan and Rambachan, 2025). Understanding the extent to which the patterns documented here generalize to other fields as more components of scientific inquiry become automated is an important avenue for future work.

AlphaFold's success underscores the value of freely accessible, comprehensive mapping initiatives to innovation, such as the earlier Human Genome Project (Williams, 2013). However, it is premature to definitively assess its long-term effect on scientific novelty. Although research effort appears to be shifting toward previously not well-predicted areas, it remains an open question how much this translates into the solution of genuinely novel structures or merely reallocates resources toward commercially viable targets at the expense of pushing the frontier forward. Furthermore, the asymmetric adjustments across experimental methods suggest potential distributional risks on who can continue to participate in the research landscape. Consequently, policy interventions may be required to prioritize complementary investments in theoretical research and ensure that the necessary infrastructure remains accessible to a broad spectrum of researchers.

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Tables

Table 1: Baseline Summary Statistics

Panel A. Quantity

	Treatment Group VH		Control Group Non VH		Two-sided T-Test
	Mean	Std. Dev.	Mean	Std. Dev.	$Pr(\|T\| > t)$
N of Deposit per Calendar Quarter	13.18	37.95	10.76	24.20	0.537
N of Papers Published per Calendar Quarter	10.53	29.33	9.26	20.82	0.690
(%) First-Attempts Fraction	22.43	22.53	27.25	21.64	0.099
(%) Human Structures Fraction	21.95	27.25	30.64	29.56	0.024*
N	85		170		255

Panel B. Quality

	Treatment Group VH		Control Group Non VH		Two-sided T-Test
	Mean	Std. Dev.	Mean	Std. Dev.	$Pr(\|T\| > t)$
Method: X-ray Crystallography					
Resolution (Lower is Better)	2.00	0.53	2.15	0.65	0.000***
(%) PubMed listed	0.02	0.93	0.02	0.41	0.941
Primary Citation's 2024 JIF Score	6.75	8.21	8.16	9.47	0.000***
(%) DrugBank listed	0.00	0.01	0.02	0.40	0.000***
N	14911		19325		34236
Method: Cryo-EM					
Resolution (Lower is Better)	3.61	1.46	3.95	2.16	0.000***
(%) PubMed listed	0.04	0.57	0.01	0.00	0.000***
Primary Citation's 2024 JIF Score	13.65	13.97	19.32	16.40	0.000***
(%) DrugBank listed	0.00	0.00	0.00	0.00	0.000***
N	774		6278		7052

The unit of observation is bin-deposit quarter in Panel A and structure in Panel B. Structures deposited between 2018Q1 and 2021Q3 are included. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2: Impact of AlphaFold2 on the Total Amount of Deposit

	PPML (Count)	OLS (Count)	OLS (Asinh)	
	(1)	(2)	(3)	(4)
POST × VH	-0.427***	-5.439***	-0.242***	-0.334***
	(0.095)	(1.676)	(0.048)	(0.073)
% Δ (VH vs Non VH)	-34.8	-42.8	-24.3	-33.5
Control Mean	12.72	12.72	12.72	12.72
Deposit Quarter FE	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes
Weighting	None	None	None	PreAF2 Size
R-squared	-	0.805	0.811	0.895
N of Bins	255	255	255	255
N of Observations	6630	6630	6630	6630

The unit of observation is bin-deposit quarter. In Columns (1)-(2), the outcome variable is the count of structures deposited in each bin-deposit quarter, estimated using Poisson pseudo-maximum likelihood and OLS, respectively. In Column (3)-(4), OLS is estimated with the outcome count reported in inverse hyperbolic sine transformation. %Δ is computed as $100 * (e^{\hat{\beta}} - 1)$ in column (1), $100 * (\frac{\hat{\beta}}{\bar{y}})$ in column (2) and $100 * (\hat{\beta} * \sqrt{1 + \frac{1}{\bar{y}^2}})$ in column (3), (4) where $\bar{y}$ is the control mean. Column (4) is weighted by the total amount of structures deposited under the same class in the pretreatment period of our sample. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3: Impact of AlphaFold2 on the Deposit Composition

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.427***	-0.508***	-0.412***	-0.239	-0.509***	-0.349	-0.151
	(0.095)	(0.086)	(0.111)	(0.156)	(0.098)	(0.329)	(0.177)
% Δ (VH vs Non VH)	-34.8	-39.8	-33.7	-21.2	-39.9	-29.4	-14.0
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	255	224	250	198	249	125	175
N of Observations	6630	5824	6500	5148	6474	3250	4550

The unit of observation is bin-deposit quarter. Column (1) includes all the structures deposited. In Columns (2)–(3), the outcomes are the counts of first-attempt and non–first-attempt structures. In Columns (4)–(5), the outcomes are the counts of structures from human and non-human proteins. In Columns (6)–(7), the outcomes are the counts of human structures originating from classes that were "stuck" versus those that were not. Bins with no deposits of certain type of structures are dropped in each regression. The specification follows Poisson pseudo- maximum likelihood and %Δ is computed as $100 * (e^{\hat{\beta}} - 1)$. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4: Impact of AlphaFold2 on the Size of Experiment Team

	Total Deposits	Attempt Status		Origin Status	
	(1)	(2)	(3)	(4)	(5)
Outcome: Size of Team	-	First	Non First	Human	Non Human
POST × VH	0.018	-0.019	-0.005	0.044	0.016
	(0.075)	(0.056)	(0.077)	(0.088)	(0.080)
% Δ (VH vs Non VH)	1.8	-1.9	-0.5	4.5	1.6
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes
N of Bins	71	28	57	31	57
N of Observations	1846	728	1482	806	1482

The unit of observation is bin-deposit quarter. Column (1) includes all the structures deposited. In Columns (2)–(3), the outcomes are the counts of first-attempt and non–first-attempt structures. In Columns (4)–(5), the outcomes are the counts of structures from human and non-human proteins. %Δ is computed as $100 * (e^{\hat{\beta}} - 1)$. Each column includes only bins with continuous deposits of the corresponding type of structure over the sample period. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 5: Heterogeneity of Impact by Experimental Methods

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.196**	-0.242***	-0.186	0.002	-0.312**	-0.361	0.013
	(0.095)	(0.083)	(0.113)	(0.146)	(0.123)	(0.287)	(0.151)
POST × VH × Cryo-EM	0.198	-0.001	0.223	0.079	0.314	0.452	0.049
	(0.168)	(0.161)	(0.194)	(0.226)	(0.200)	(0.337)	(0.380)
% ΔX (VH vs Non VH)	-17.8	-21.5	-17.0	0.2	-26.8	-30.3	1.3
% ΔC (VH vs Non VH)	0.2	-21.6	3.7	8.4	0.2	9.6	6.4
Method × Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method × Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Method-Bins	456	377	437	345	433	133	212
N of Observations	11856	9802	11362	8970	11258	3458	5512

The unit of observation is method-bin-deposit quarter. Column (1) includes all the structures deposited. In Columns (2)–(3), the outcomes are the counts of first-attempt and non–first-attempt structures. In Columns (4)–(5), the outcomes are the counts of structures from human and non-human proteins. In Columns (6)–(7), the outcomes are the counts of human structures originating from classes that were "stuck" versus those that were not. Bins with no deposits of certain type of structures are dropped in each regression. Specifications of both panels follow the Poisson pseudo- maximum likelihood. %ΔX (X-ray Crystallography) is computed as $100 * (e^{\hat{\beta}_1} - 1)$, %ΔC (Cryo-EM) is computed as $100 * (e^{\hat{\beta}_1 + \hat{\beta}_2} - 1)$. Clustered standard errors at the method-bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 6: Impact of AlphaFold2 on the Resolution of Structures

Panel A. Structures by X-ray Crystallography

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Resolution	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	0.020	0.010	0.018	-0.098**	0.070**	-0.056	-0.100**
	(0.030)	(0.021)	(0.034)	(0.046)	(0.034)	(0.140)	(0.047)
% Δ (VH vs Non VH)	-0.9	-0.4	-0.9	4.6	-3.3	2.2	4.7
Control Mean	2.13	2.24	2.10	2.12	2.14	2.59	2.11
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
R-Squared	0.1155	0.0927	0.1341	0.1814	0.1251	0.2440	0.1658
N of Bins	236	189	227	168	229	21	147
N of Observations	61276	12084	49167	20154	41107	574	19580

Panel B. Structures by Cyro-EM

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Resolution	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	0.080	-0.002	0.122	0.180	0.008	0.155	0.359
	(0.124)	(0.123)	(0.153)	(0.183)	(0.143)	(0.334)	(0.227)
% Δ (VH vs Non VH)	-2.2	0.1	-3.4	-5.0	-0.2	-4.1	-10.9
Control Mean	3.62	3.59	3.62	3.57	3.64	3.82	3.31
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
R-Squared	0.0954	0.1291	0.1129	0.1395	0.1101	0.1397	0.1348
N of Bins	192	144	182	137	176	93	44
N of Observations	22847	5466	17362	6748	16074	3584	3164

The unit of observation each structure deposited. In Column (1), all structures are included. In Columns (2)–(3), first-attempt and non–first-attempt structures are included. In Columns (4)-(5), structures from human and non-human proteins are included. In Columns (6)-(7), stuck human proteins and non stuck human proteins are included. Specifications of both panels follow the OLS regression. As less the resolution is, higher the quality of execution, $\%\Delta$ is computed as $-100 * (\frac{\hat{\beta}}{\bar{y}})$ where $\bar{y}$ is the control mean. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 7: Impact of AlphaFold2 on the Innovation Outcomes of Structures

Panel A. All Structures

	PubMed		Top JIF Decile		CNS		DrugBank	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Outcome: [Event] (0/1)								
POST × VH	-0.012	-0.011	-0.049**	-0.046**	-0.017	-0.014	0.018	0.019
	(0.021)	(0.021)	(0.022)	(0.022)	(0.012)	(0.012)	(0.018)	(0.018)
Control Mean	0.83	0.83	0.50	0.50	0.11	0.11	0.23	0.23
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	No	Yes	No	Yes	No	Yes
R-squared	0.065	0.067	0.092	0.099	0.094	0.114	0.152	0.153
N of Bins	249	249	227	227	227	227	249	249
N of Observations	84148	84148	55224	55224	55224	55224	84148	84148

Panel B. First-Attempts

	PubMed		Top JIF Decile		CNS		DrugBank	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Outcome: [Event] (0/1)								
POST × VH	-0.038*	-0.038*	-0.112***	-0.110***	-0.027	-0.025	-0.014	-0.014
	(0.020)	(0.020)	(0.032)	(0.033)	(0.018)	(0.018)	(0.015)	(0.015)
Control Mean	0.87	0.87	0.51	0.51	0.13	0.13	0.14	0.14
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	No	Yes	No	Yes	No	Yes
R-squared	0.082	0.084	0.129	0.136	0.106	0.134	0.180	0.185
N of Bins	205	205	187	187	187	187	205	205
N of Observations	17577	17577	11664	11664	11664	11664	17577	17577

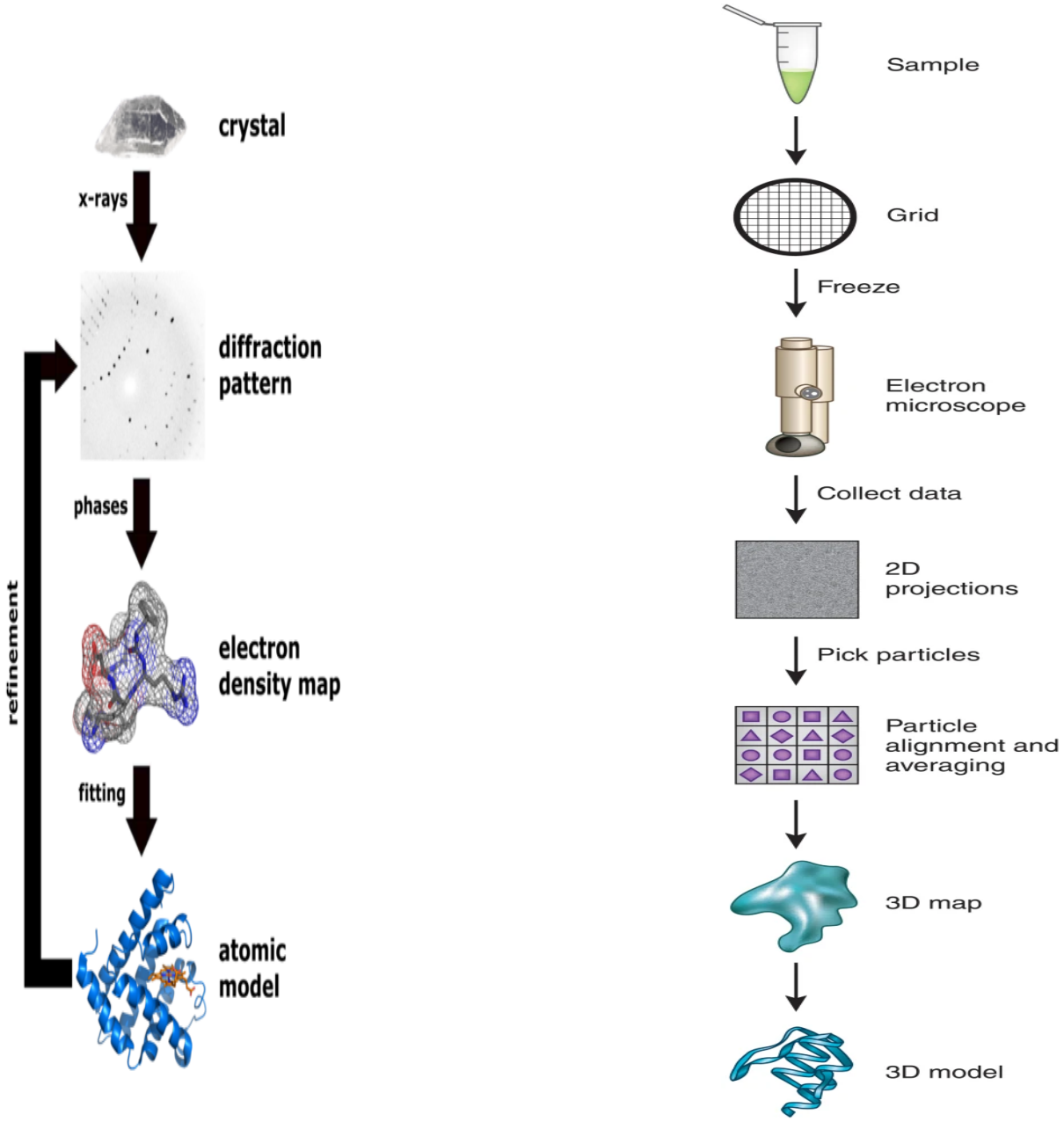
Panel C. Non First-Attempts

	PubMed		Top JIF Decile		CNS		DrugBank	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Outcome: [Event] (0/1)								
POST × VH	-0.006	-0.004	-0.029	-0.025	-0.013	-0.009	0.029	0.030
	(0.024)	(0.024)	(0.025)	(0.025)	(0.012)	(0.012)	(0.020)	(0.020)
Control Mean	0.82	0.82	0.50	0.50	0.10	0.10	0.25	0.25
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controls	No	Yes	No	Yes	No	Yes	No	Yes
R-squared	0.073	0.075	0.097	0.104	0.112	0.128	0.174	0.174
N of Bins	239	239	221	221	221	221	239	239
N of Observations	66547	66547	43543	43543	43543	43543	66547	66547

The unit of observation each structure deposited. The specification follows a linear probability model. Controls included are biological features measuring the complexity of structures including the number of entities, molecular weight, total number of polymer residues and number of non-hydrogen atoms. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

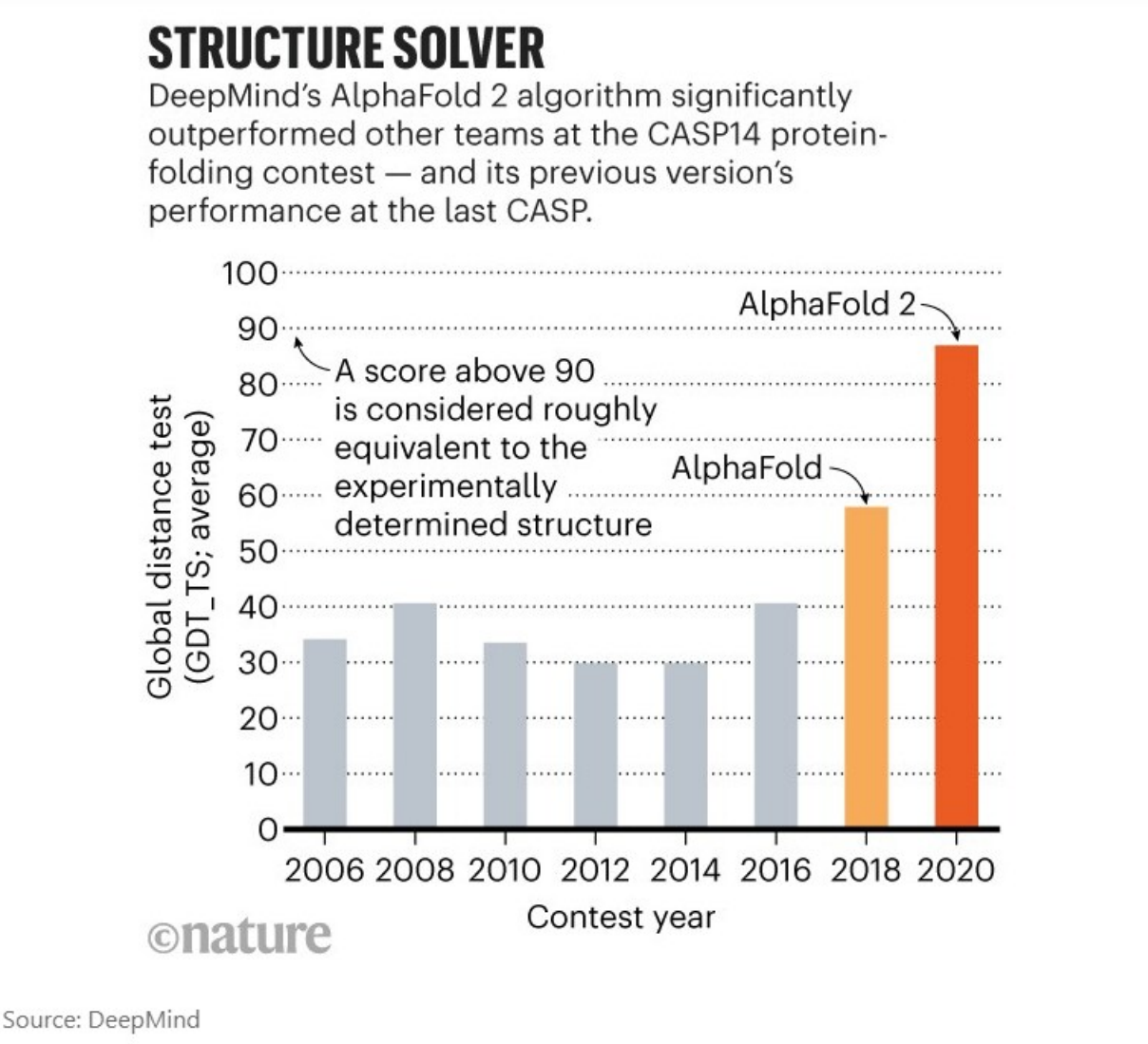
Figures

Figure 1: Experimental Methods: X-ray Crystallography vs. Cryo Electron Microscopy



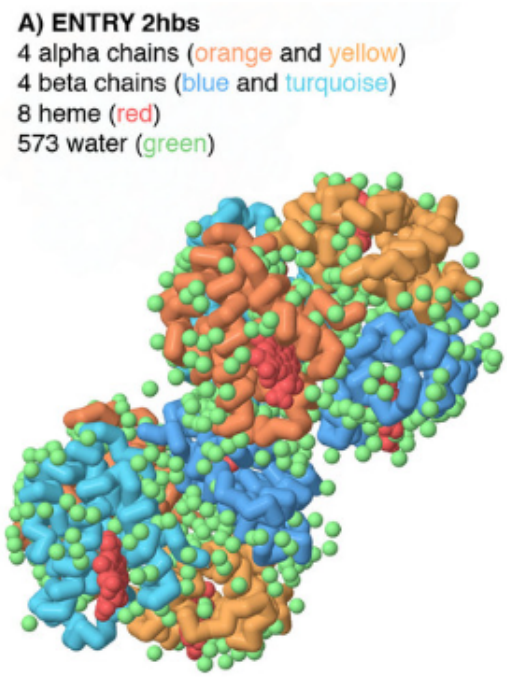
Source: Left: Wikipedia: X-ray crystallography; Right: (Doerr, 2016)

Figure 2: Average Global Test Score Across Target Proteins in CASP Contests



Source: (Callaway, 2020)

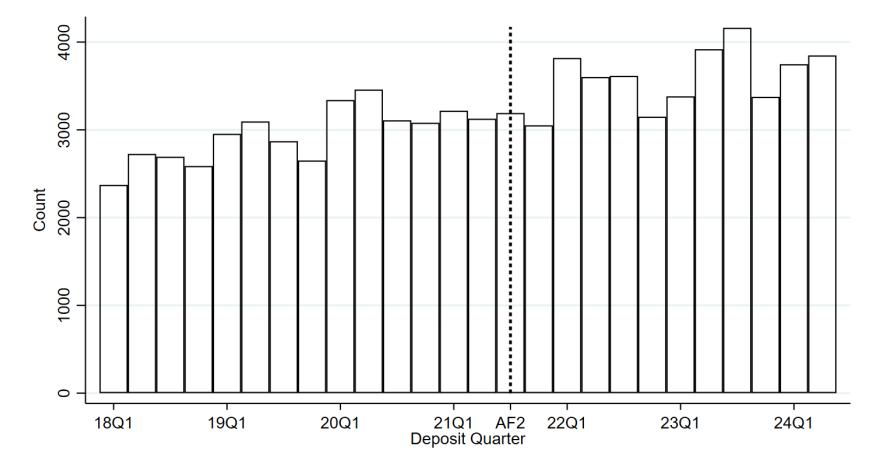
Figure 3: An Example of Protein Structure with Multiple Entities



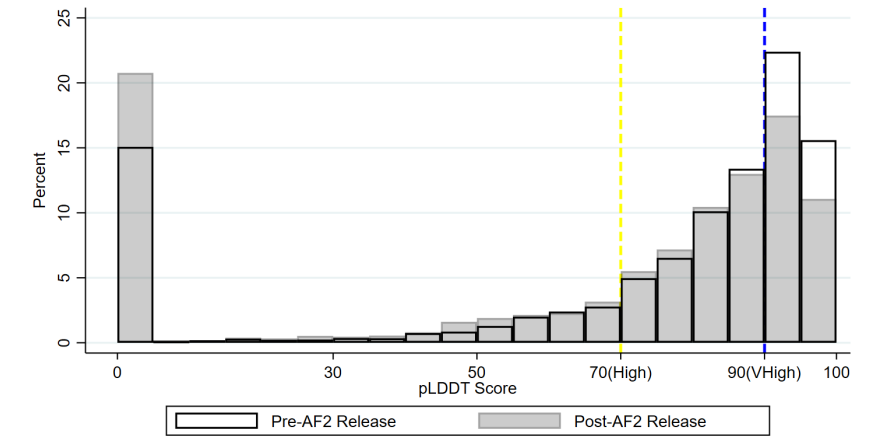
Source: Organization of 3D Structures in the Protein Data Bank

Figure 4: The Evolution of Aggregate Structure Deposit by Prediction Confidence

(a) Quarterly Count of Structure Deposits in the PDB



(b) Histogram of Structures' Average pLDDT Score



(c) Histogram of Proteins' Average pLDDT Score Covered by AF2

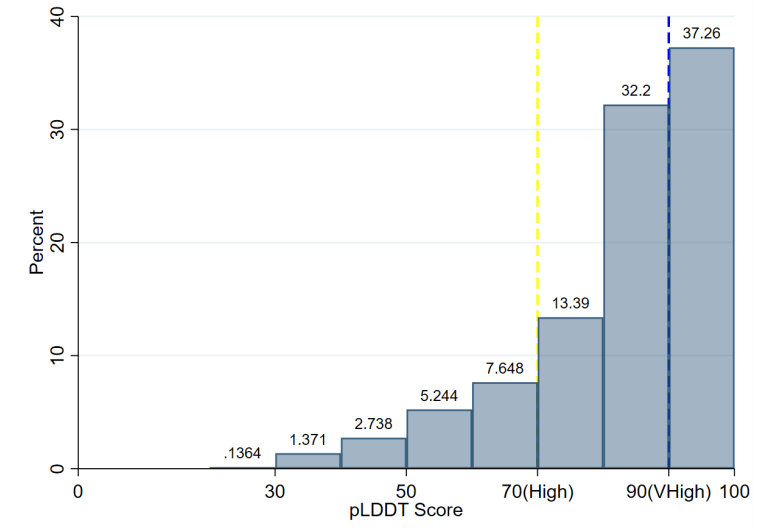
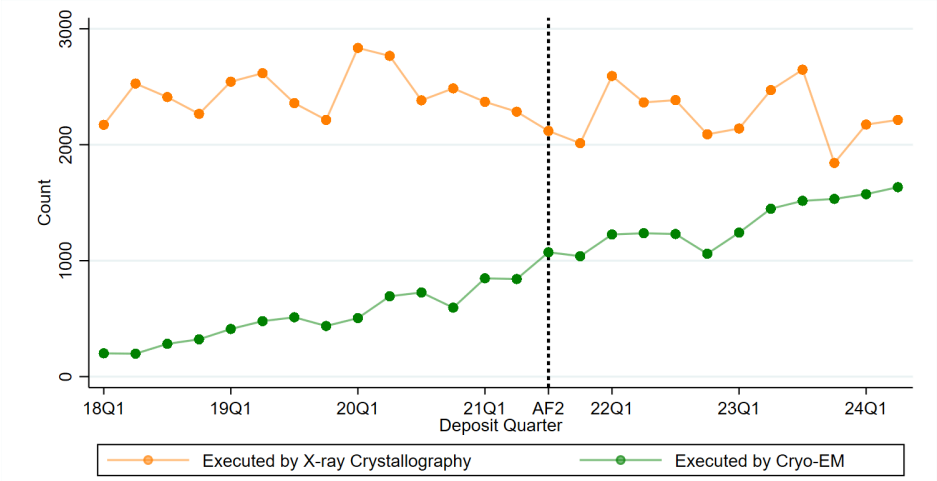
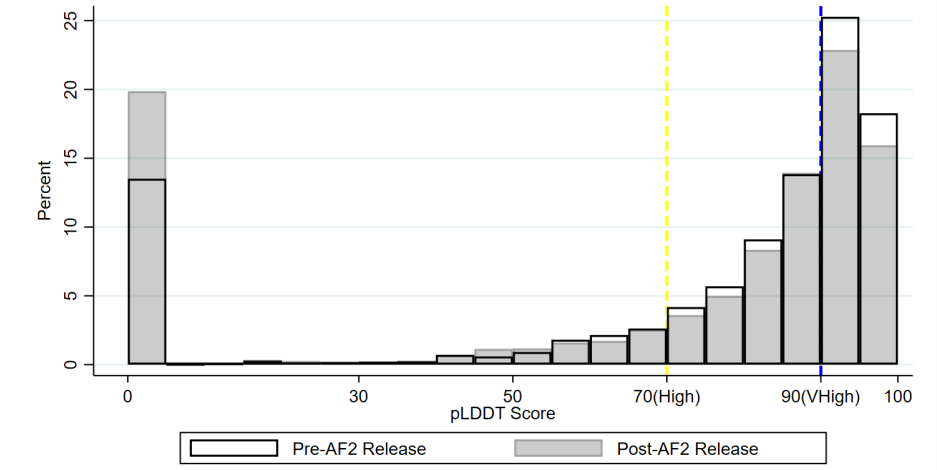


Figure 5: The Evolution of Aggregate Structure Deposit by Experimental Methods

(a) Quarterly Count of Structure Deposits in the PDB



(b) Histogram of Structures' Average pLDDT Score (By X-ray Crystallography)



(c) Histogram of Structures' Average pLDDT Score (By Cryo-EM)

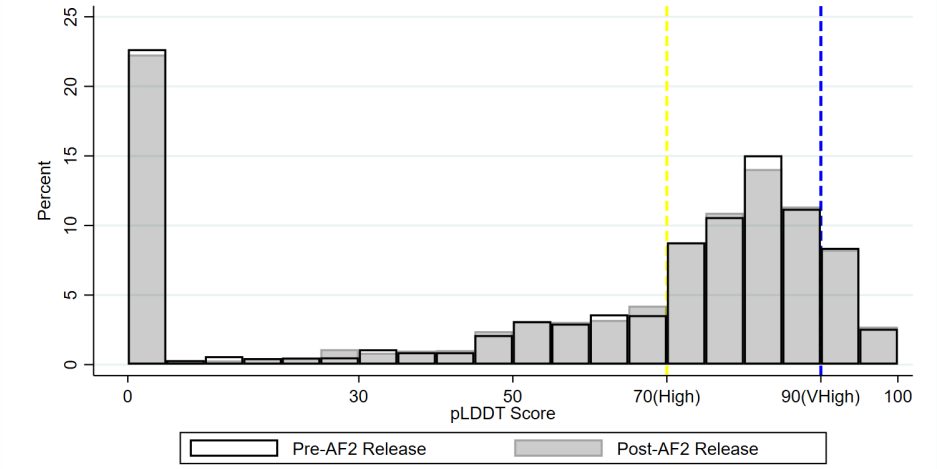
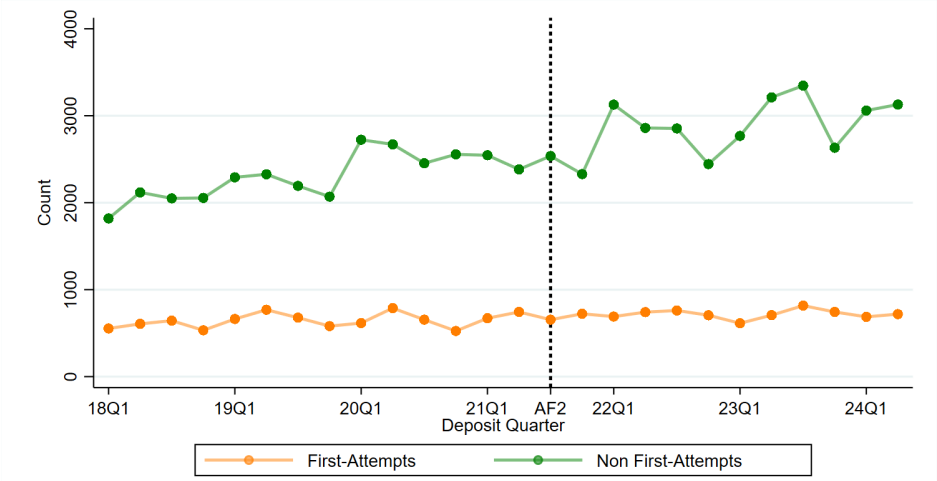
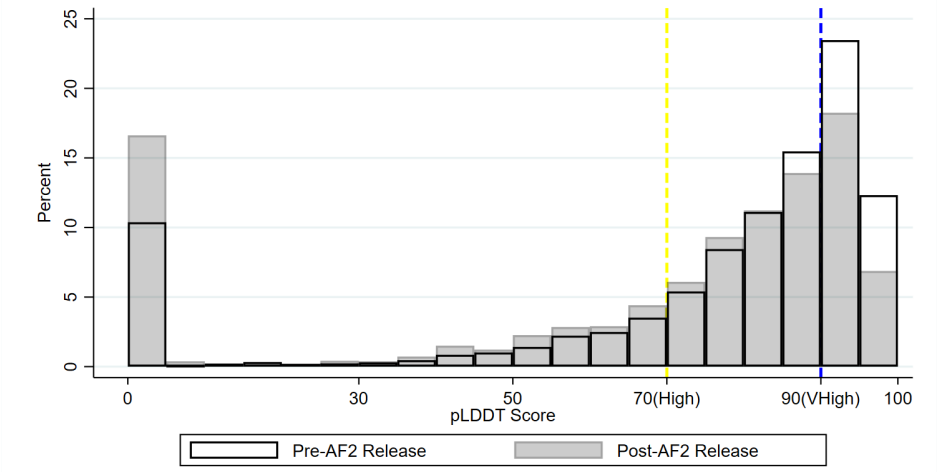


Figure 6: The Evolution of Exploratory Versus Exploitative Structure Deposit

(a) Deposit Count Trend: First-Attempts vs. Non First-Attempts



(b) Histogram of Structures' Average pLDDT Score (First-Attempts)



(c) Histogram of Structures' Average pLDDT Score (Non First-Attempts)

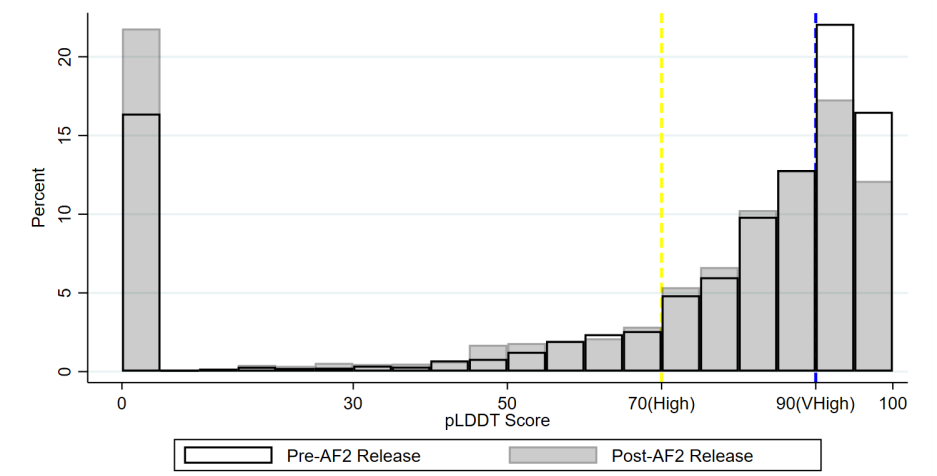
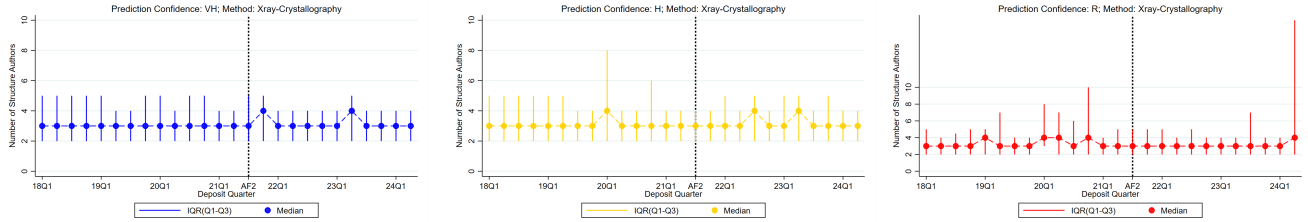
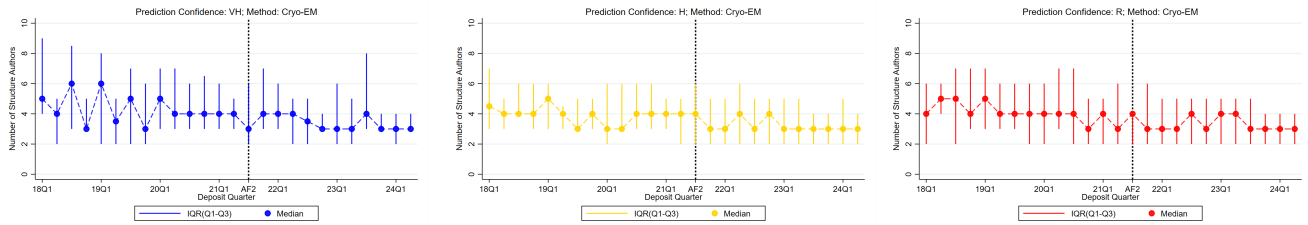


Figure 7: Experimental Team Size Across Prediction Confidence Regions

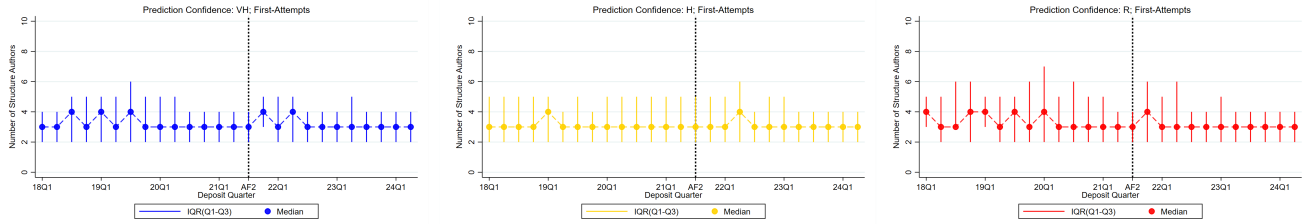
(a) Structures executed by X-ray crystallography



(b) Structures executed by Cyro-EM



(c) First-Attempts



(d) Non First-Attempts

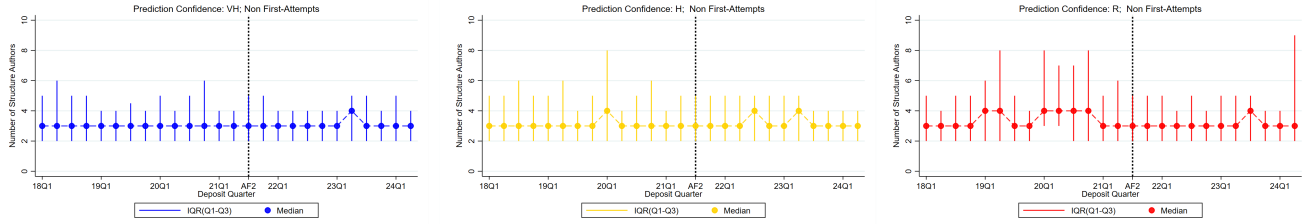
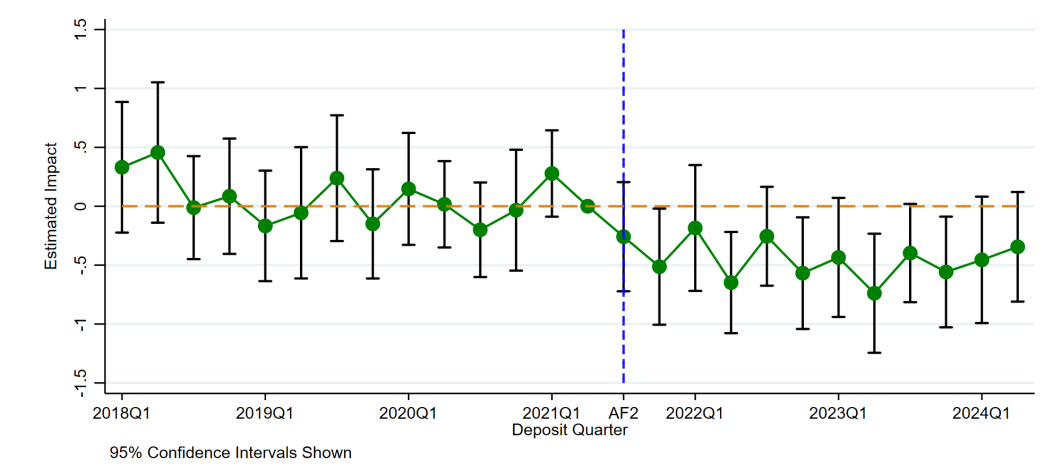
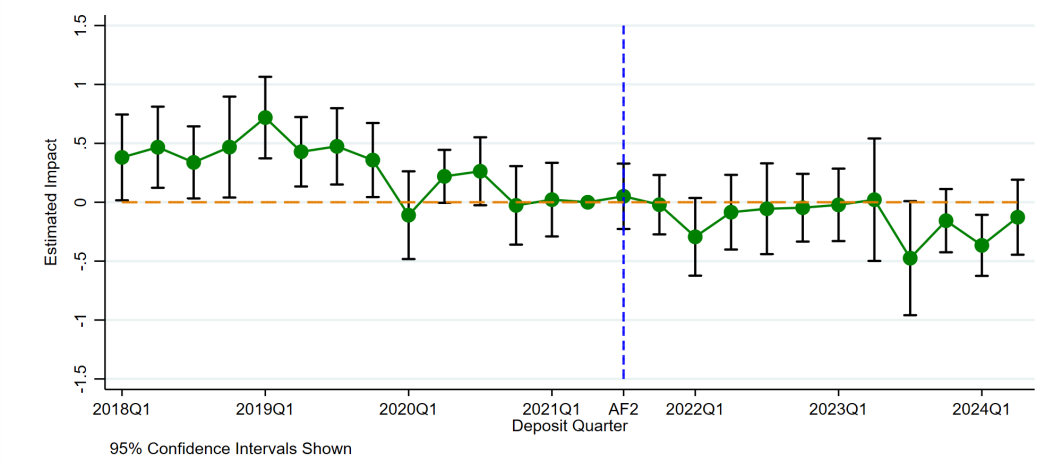


Figure 8: Event Study: Impact of AF2 on Structure Deposit Count (PPML)

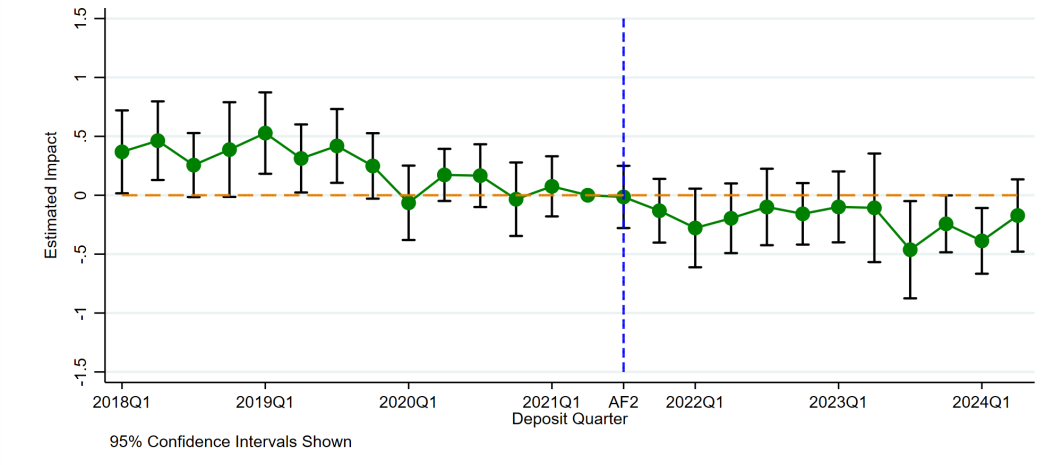
(a) First-Attempts



(b) Non First-Attempts

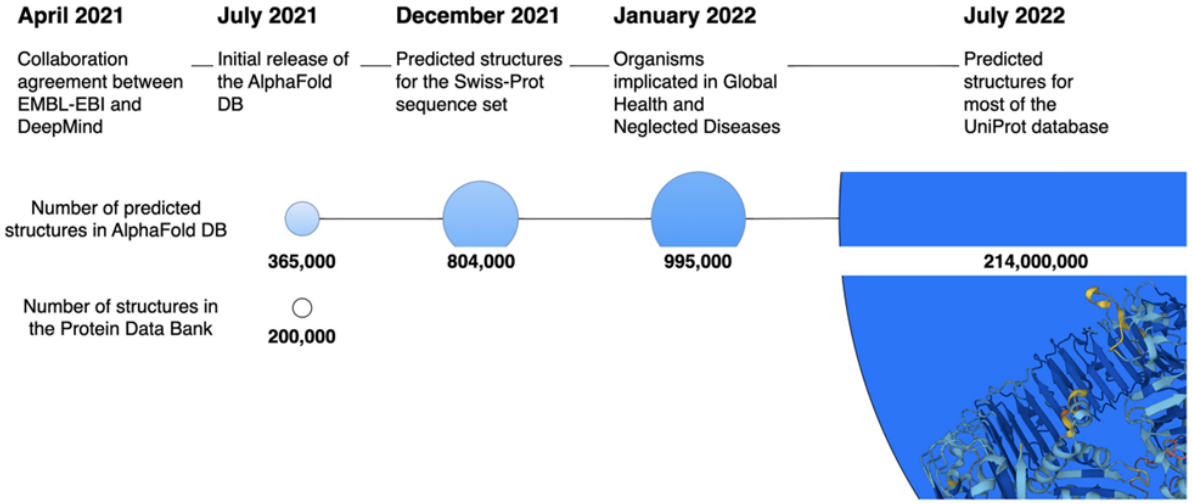


(c) Total Deposit



7 Appendix

Figure A.1: The Expansion of AlphaFold DataBase



Source: (Varadi et al., 2024)

Table A.1: Robustness: Potential Alternative Drivers

Panel A. Drop Structures Related with COVID-19

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.382***	-0.505***	-0.356***	-0.221	-0.451***	-0.332	-0.119
	(0.078)	(0.087)	(0.090)	(0.156)	(0.069)	(0.331)	(0.176)
% Δ (VH vs Non VH)	-31.8	-39.6	-29.9	-19.9	-36.3	-28.2	-11.2
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	255	224	250	198	249	126	174
N of Observations	6630	5824	6500	5148	6474	3276	4524

Panel B. Drop Structures from the Top Five Most Studied Classes

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.364***	-0.616***	-0.306***	-0.225	-0.416***	-0.275	-0.066
	(0.093)	(0.120)	(0.115)	(0.231)	(0.071)	(0.252)	(0.251)
% Δ (VH vs Non VH)	-30.5	-46.0	-26.3	-20.2	-34.0	-24.0	-6.4
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	240	209	235	183	234	116	160
N of Observations	6240	5434	6110	4758	6084	3016	4160

The unit of observation is bin-deposit quarter. Panel A drops all the structures including any protein entity origin from COVID-19 by the taxonomy ID. Panel B drops all structures from the most studied five classes, including hydrolase, transferase, viral protein, oxidoreductase, membrane protein. Column (1) includes all the structures deposited. In Columns (2)–(3), the outcomes are the counts of first-attempt and non–first-attempt structures. In Columns (4)–(5), the outcomes are the counts of structures from human and non-human proteins. In Columns (6)–(7), the outcomes are the counts of human structures originating from classes that were "stuck" versus those that were not. Bins with no deposits of certain type of structures are dropped in each regression. The specification follows Poisson pseudo- maximum likelihood and %Δ is computed as $100 * (e^{\hat{\beta}} - 1)$. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table A.2: Robustness: Treatment Measurement

Panel A. Structures with Single Entity Only

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.332***	-0.343***	-0.329***	-0.111	-0.439***	-0.070	-0.108
	(0.110)	(0.084)	(0.128)	(0.180)	(0.131)	(0.751)	(0.191)
% Δ (VH vs Non VH)	-28.2	-29.0	-28.1	-10.5	-35.5	-6.7	-10.3
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	237	198	229	171	233	63	163
N of Observations	6162	5148	5954	4446	6058	1638	4238

Panel B. Aggregate by Structure's Median pLDDT

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.388***	-0.379***	-0.396***	-0.157	-0.484***	-0.184	-0.105
	(0.099)	(0.085)	(0.115)	(0.155)	(0.104)	(0.338)	(0.177)
% Δ (VH vs Non VH)	-32.2	-31.5	-32.7	-14.5	-38.4	-16.8	-10.0
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	267	229	259	202	261	126	179
N of Observations	6942	5954	6734	5252	6786	3276	4654

Panel C. Aggregate by Structure's Max pLDDT

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.210*	-0.242**	-0.200	0.105	-0.352***	0.121	0.045
	(0.117)	(0.098)	(0.132)	(0.152)	(0.124)	(0.244)	(0.179)
% Δ (VH vs Non VH)	-18.9	-21.5	-18.1	11.1	-29.7	12.9	4.6
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	261	229	257	202	253	119	182
N of Observations	6786	5954	6682	5252	6578	3094	4732

The unit of observation is bin-deposit quarter. Panel A keeps structures with single entity only. Panel B aggregates the pLDDT score to the structure level using the median among entities within the structure. Panel C aggregates using the max. Column (1) includes all the structures deposited. In Columns (2)–(3), the outcomes are the counts of first-attempt and non–first-attempt structures. In Columns (4)–(5), the outcomes are the counts of structures from human and non-human proteins. In Columns (6)–(7), the outcomes are the counts of human structures originating from classes that were "stuck" versus those that were not. Bins with no deposits of certain type of structures are dropped in each regression. The specification follows Poisson pseudo- maximum likelihood and %Δ is computed as $100*(e^{\hat{\beta}}-1)$. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table A.3: Robustness: "First-Attempt" Measurement

	First-Attempts			Non First-Attempts		
	(1)	(2)	(3)	(4)	(5)	(6)
Outcome: Count						
Cluster Standard:	30 %	50 % (Main)	100 %	30 %	50 % (Main)	100 %
POST × VH	-0.621***	-0.508***	-0.439***	-0.410***	-0.412***	-0.417***
	(0.102)	(0.086)	(0.086)	(0.105)	(0.111)	(0.121)
% Δ (VH vs Non VH)	-46.3	-39.8	-35.6	-33.6	-33.7	-34.1
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	217	224	245	250	250	246
N of Observations	5642	5824	6370	6500	6500	6396

The unit of observation is bin-deposit quarter. In column (1)-(3) the outcome variable is the count of "first-attempt" structures defined by different threshold of sequence similarity cluster. In column (4)-(6) the outcome variable is the count of "non first-attempt" structures defined by different threshold of sequence similarity cluster. Bins with no deposits of certain type of structures are dropped in each regression. The specification follows Poisson pseudo- maximum likelihood and %Δ is computed as $100*(e^{\hat{\beta}}-1)$. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table A.4: Robustness: Deposit Composition under Multiple Treatment Intensity

	Total Deposits	Attempt Status		Origin Status		Stuck Status	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Outcome: Count	-	First	Non First	Human	Non Human	Stuck	Non Stuck
POST × VH	-0.495***	-0.648***	-0.460***	-0.307*	-0.630***	-0.362	-0.275
	(0.083)	(0.090)	(0.100)	(0.170)	(0.060)	(0.361)	(0.199)
POST × H	-0.178	-0.291***	-0.143	-0.097	-0.277***	-0.020	-0.183
	(0.113)	(0.107)	(0.129)	(0.169)	(0.085)	(0.229)	(0.209)
POST × ZERO	0.106	0.174	0.093	-0.086	0.018	0.029	-0.130
	(0.180)	(0.127)	(0.208)	(0.238)	(0.171)	(0.549)	(0.230)
% Δ (VH vs VL, L)	-39.1	-47.7	-36.9	-26.4	-46.8	-30.4	-24.0
% Δ (H vs VL, L)	-16.3	-25.3	-13.3	-9.3	-24.2	-2.0	-16.7
% Δ (ZERO vs VL, L)	11.1	19.0	9.7	-8.3	1.8	3.0	-12.2
Deposit Quarter FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bin FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N of Bins	327	283	320	239	319	143	212
N of Observations	8502	7358	8320	6214	8294	3718	5512

The unit of observation is bin-deposit quarter. Column (1) includes all the structures deposited. In Columns (2)–(3), the outcomes are the counts of first-attempt and non–first-attempt structures. In Columns (4)–(5), the outcomes are the counts of structures from human and non-human proteins. In Columns (6)–(7), the outcomes are the counts of human structures originating from classes that were "stuck" versus those that were not. Prediction regions VH, H and ZERO are included as three separate treatment groups and region VL and L are the control group. Bins with no deposits of certain type of structures are dropped in each regression. The specification follows Poisson pseudo- maximum likelihood and %Δ is computed as $100 * (e^{\hat{\beta}} - 1)$. Clustered standard errors at the bin level are reported in parentheses. Statistical significance is indicated as: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.