

JB Special Issue - Review

Fifty years of Protein Data Bank in the Journal of Biochemistry

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Protein Data Bank (PDB), jointly founded in 1971 by Brookhaven National Laboratory, USA, and the Cambridge Crystallographic Data Centre, UK, is the single global archive of experimentally determined biological macromolecular structures. PDB deposition is mandatory for publication in most scientific journals, which means ‘no PDB deposition, no structural publication’. The current PDB archive contains more than 180,000 entries and includes many structures from Asian institutions. The first protein structure from Japan was that of cytochrome *c* determined by Prof Masao Kakudo’s group at the Institute for Protein Research, Osaka University, in 1971 at a resolution of 4 Å, and a subsequent atomic structure at 2.3 Å resolution was deposited to PDB in 1976 as the 1st Asian and 21st entry of the entire PDB archive. Since then, 317 protein structures whose primary citation was the *Journal of Biochemistry* (*J. Biochem.*) have been deposited to PDB. Based on this long history between PDB and *J. Biochem.*, a statistical analysis of all structural reports in *J. Biochem.* has been carried out using the relational database system at PDBj (<https://pdbj.org>) and reviewed the yearly distribution, resolution, quality of structure, type of target protein, number of citations and comparison against other major journals.

Keywords: X-ray crystallography; The Journal of Biochemistry; Protein Data Bank Japan; Protein Data Bank; nuclear magnetic resonance.

Protein Data Bank (PDB) is the global archive of experimentally determined biological macromolecular structures (1). The core of each PDB entry is the listed XYZ coordinates of atoms that make up the polypeptides, prosthetic groups, ligands and bound water molecules. The initial release of PDB archive accompanied only seven PDB coordinates, although later datasets of PDB included standardized coordinate files with metadata year by year. Until 1976, the initial layout of PDB entries was a 132-column Diamond format used in the real space refinement programme developed by Diamond (2). In 1976, Brookhaven National Laboratory (BNL) changed the standard format to a compact 80-column format named ‘PDB format’ suitable for punch cards commonly used at that time.

Graphical Abstract



Since 2013, the master format of PDB is PDBx/mmCIF based on the STAR framework. Prior to the internet era, PDB data were distributed physically on magnetic tapes and then later by CD-ROM. Duplicated copies of the PDB files were maintained at BNL (USA; master), the Cambridge Crystallographic Data Centre (UK) and Tokyo (Japan) (3). In 1979, the Japanese site moved from the University of Tokyo to the Institute for Protein Research (IPR), Osaka University. BNL started the worldwide web service in 1995 and set up several official mirror sites at the European Bioinformatics Institute (EMBL-EBI), IPR Osaka University, etc (4). In the early days of PDB, data curation and annotation were carried out solely by BNL, but in 1996 EMBL-EBI established the PDB in Europe (initially as the Macromolecular Structure Database) led by Prof Kim Henrick, collaborating with the PDB team at BNL, and started local data processing of PDB depositions from Europe (5). During this period, the number of PDB depositions increased dramatically, primarily as a result of the widespread adoption of recombinant protein production in structural laboratories, the establishment of third generation synchrotron facilities (ESRF, APS and SPring-8), and the initiation of structural genomics projects in USA, Europe and Japan. At about the same time, the management of PDB in USA moved from BNL to Research Collaboratory for Structural Bioinformatics PDB at Rutgers University (RCSB PDB) led by Prof Helen Berman in 1999. IPR Osaka University established the Protein Data Bank Japan (PDBj) led by Prof Haruki Nakamura in 2000, which started local data processing in Japan with strong technical support from RCSB PDB. In 2003, all the principle investigators from three regional PDB data centres established the formation of the worldwide Protein Data Bank (wwPDB) to maintain a single archive by a global collaborative effort. As a result, the identical PDB datasets were distributed from each regional web/ftp server

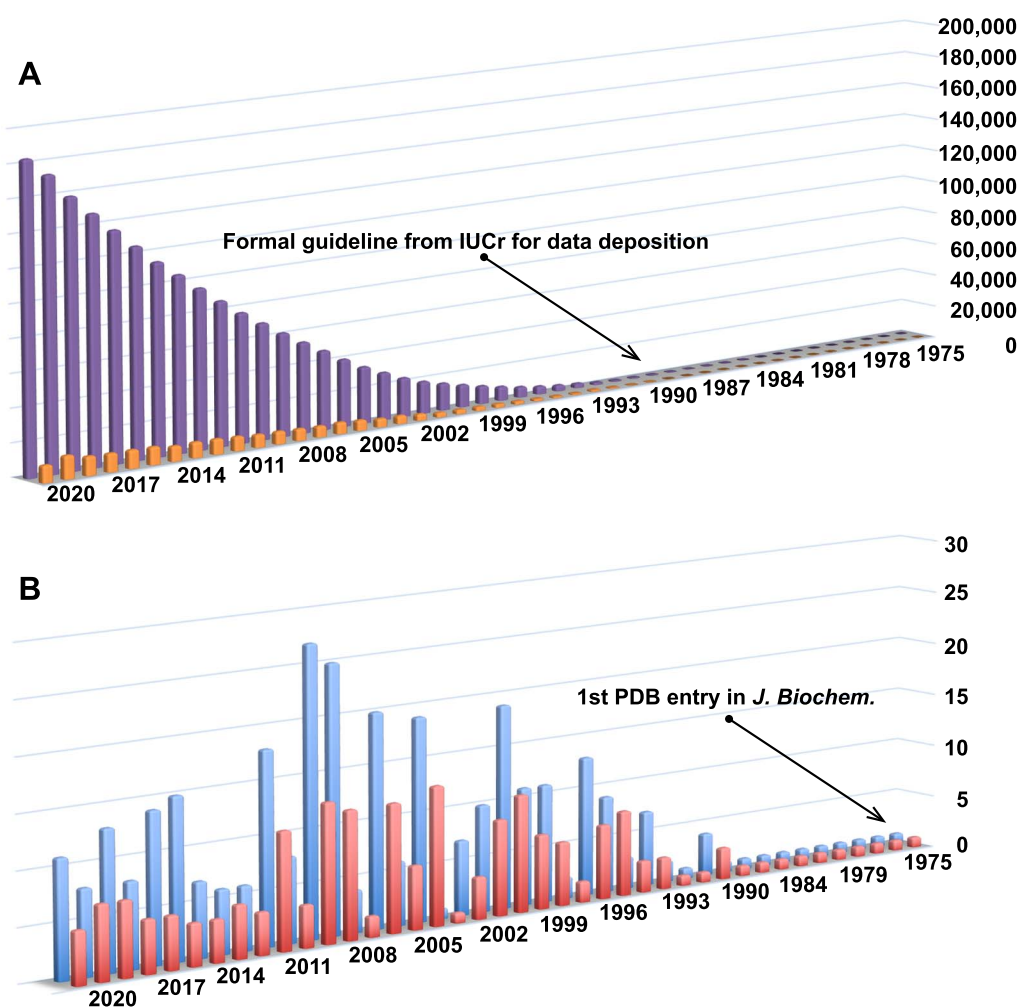


Fig. 1. Statistics of PDB depositions. (A) Total number of PDB entries coloured in purple and annual depositions coloured in orange. (B) The yearly number of PDB entries deposited to the *Journal of Biochemistry* is shown in blue along with the yearly number of published structure papers in red.

in a standard format. Since then, PDB has been managed by the wwPDB organization composed originally of three regional data centres (RCSB-PDB: American PDB (6); PDBe: European PDB (7); and PDBj: Asian PDB (8)) and later expanded to two method-based data centres (the Biological Magnetic Resonance Data Bank (BMRB) in charge of nuclear magnetic resonance, NMR, experimental data and the Electron Microscopy Data Bank (EMDB) in charge of EM experimental maps) (9).

Mandatory PDB deposition prior to publication was guided by the International Union of Crystallography in 1989, which means ‘no PDB deposition, no structural publication’. The structural biology community has maintained this policy up to the present day. Currently, most of the scientific journals request not only a coordinate file submission but also an official validation report during manuscript submission, which is provided by the wwPDB based on the associated structure factors deposited by authors. The current PDB archive contains more than 180,000 entries (Fig. 1) and includes ground-breaking structures directly related to eight Nobel prizes (myoglobin, haemoglobin, insulin, photosynthetic reaction centre, ATP synthase, ribosome, RNA polymerase and G-protein Coupled Receptor). The metadata of PDB written in the PDBx/mmCIF format

are so rich and well categorized in controlled vocabularies of 568 data items that they can support very detailed data queries and find specific data/statistics directly linked to the core PDB entries. Even a non-specialist of Relational Data Base (RDB) system can search the entire PDB archive using the RDB Query Builder of PDBj without any informatics background (8). Using this newly implemented query builder, I carried out statistical analysis of all structural reports in the *Journal of Biochemistry* (*J. Biochem.*) through the PDBj Mine2 service available at PDBj (<https://pdj.org>) and reviewed yearly distribution, resolution, quality of structure, type of target protein, number of citations of PDB entries in *J. Biochem.* as well as a comparison against other major scientific journals [*Journal of Biological Chemistry* (*J. Biol. Chem.*) and *Biochemistry* in USA, *FEBS Journal* (*FEBS J.*, formerly *European Journal of Biochemistry*) and *FEBS Letters* (*FEBS Lett.*) in Europe] published by non-profit scientific societies.

The First Milestone Structure in the *Journal of Biochemistry*

The first structure published in *J. Biochem.* was that of cytochrome (Cyt.) *c* from Bonito (Katsuo) heart (10)

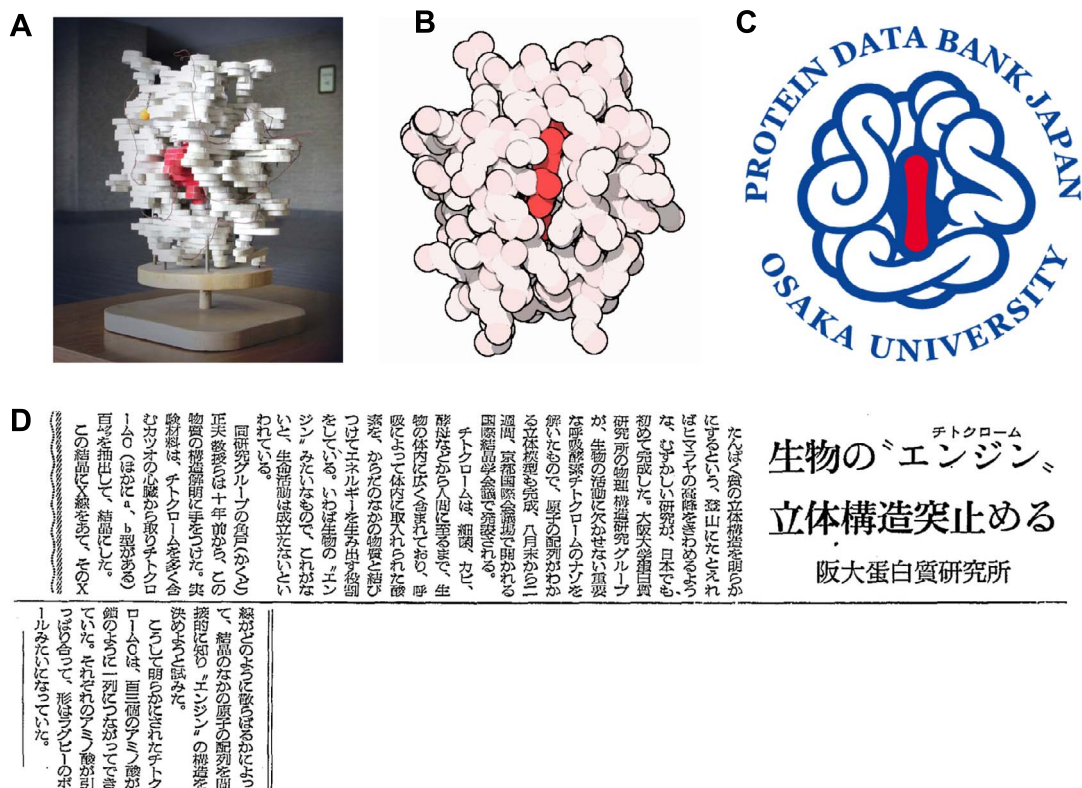


Fig. 2. X-ray structure of Cytochrome *c* from Bonito (Katsuo) heart. (A) 4 Å resolution structure of Cyt. *c* made from Japanese wood. (B) Cartoon representation of Cyt. *c* as a molecule of the month by David S. Goodsell available in the PDB-101 of RCSB PDB and PDBj numon pages. (C) A new logo of Protein Data Bank Japan based on the structure of Cyt. *c*. (D) Article from the *Asahi Shinbun Newspaper* on August 1, 1972, reporting the atomic structure of Cyt. *c* was reported in IUCr 1972, shown with permission from the Asahi Shinbun Co.

determined by Prof Masao Kakudo's group from IPR Osaka University in 1971 at a resolution of 4 Å, which was also one of the early protein structures from Asian research institution (Fig. 2). A model of the structure made from Japanese wood was exhibited in the main entrance hall of IPR as a commemorative scientific achievement (Fig. 2A). A subsequent atomic structure at 2.3 Å resolution (PDB ID: 1CYC) (11) was deposited to PDB in 1976 as the 1st Asian and 21st entry of the entire PDB archive. All these historical structural reports were published in *J. Biochem.* (Ashida *et al.*, *J. Biochem.*, **70**, 913–924, 1971; Ashida *et al.*, *J. Biochem.*, **73**, 463–465, 1973; Tanaka *et al.*, *J. Biochem.*, **77**, 147–162, 1975). A structure of Cyt. *c* was featured as molecule of the month by David S. Goodsell in PDB-101 of RCSB PDB and PDBj numon pages (Fig. 2B), which was also used as the new PDBj logo (Fig. 2C). Elucidation of the structure of Cyt. *c* was headline news in Japan at that time. Indeed, an article appeared in *Asahi Shinbun*, a major Japanese newspaper, announcing 'The 1st Japanese protein structure solved by Prof Masao Kakudo's group would be reported in the 9th IUCr congress held at Kyoto, Japan, in 1972'. In this article, Prof. Kakudo said 'The crystallization and X-ray data collection required 100 g of purified Cyt. *c*. The obtained structure of a single polypeptide chain composed of 108 amino acids resembled the shape of a rugby ball' (Fig. 2D). A historical perspective of the structural analysis of Cyt. *c* and further expanded research work was reviewed

by Emeritus Prof Tomitake Tsukihira of Osaka University, a former graduate student of Prof Masao Kakudo, in a special issue of *J. Biochem.* celebrating the 50th anniversary of PDB (12).

Most Cited Structure in the Journal of Biochemistry

After the first protein structure was published in *J. Biochem.*, 317 further protein structures in total whose primary citation was *J. Biochem.* were deposited to PDB. In order to quantify the long and eventful history between PDB and *J. Biochem.*, I have searched the citation indices of each publication with the help of Oxford University Press and ranked the top 10 most highly cited structure papers in *J. Biochem.* (Table 1). The most cited paper by far was the structural report of Taka-amylase A (PDB ID: 2TAA) (13) determined by Prof Masao Kakudo's group in 1984. The number of citations for this paper was 633 at the end of June 2021. A crystal of Taka-amylase A contained three molecules related by non-crystallographic symmetry in the crystallographic asymmetric unit, whose molecular weight in the asymmetric unit was bigger than most of the PDB archive at that time (Fig. 3). Taka-amylase A was a symbolic enzyme for IPR because the founder of IPR, Prof Shiro Akabori, the seventh president of Osaka University, extracted and purified that enzyme in the 1950s from *Aspergillus oryzae* (14) used for brewing

Table 1. Top 10 citations of PDB structures published in the *Journal of Biochemistry*

PDB ID	Authors	Title	Year	Vol.	Pages	Citations
2TAA	Matsuura <i>et al.</i> (13)	Structure and possible catalytic residues of Taka-amylase A.	1984	95	697–702	633
4FXC	Tsukihira <i>et al.</i> (15)	X-Ray Analysis of a [2Fe-2S] Ferredoxin from <i>Spirulina Platensis</i> . Main Chain Fold and Location of Side Chains at 2.5 Å resolution.	1981	90	1763–1773	198
2E2R	Matsushima <i>et al.</i> (16)	Structural evidence for endocrine disruptor bisphenol a binding to human nuclear receptor ERRγ.	2007	142	517–524	167
1ARS	Okamoto <i>et al.</i> (17)	X-ray crystallographic study of pyridoxal 5'-phosphate-type aspartate aminotransferases from <i>Escherichia coli</i> in open and closed form.	1994	116	95–107	143
1AN9	Mizutani <i>et al.</i> (18)	Three-Dimensional structure of porcine kidney D-amino acid oxidase at 3.0 Å resolution	1996	120	14–17	119
1SRD	Kitagawa <i>et al.</i> (29)	Three-dimensional structure of Cu,Zn-superoxide dismutase from spinach at 2.0 Å resolution.	1991	109	477–185	98
1CYC	Tanaka <i>et al.</i> (11)	The crystal structure of bonito (Katsuo) ferrocyanochrome c at 2.3 Å resolution. II. Structure and function.	1975	77	147–162	88
1JVS	Yajima. <i>et al.</i> (30)	Crystal structure of 1-deoxy-D-xylulose 5-phosphate reductoisomerase complexed with cofactors: implications of a flexible loop movement upon substrate binding.	2002	131	313–317	88
2EIQ	Yamaguchi <i>et al.</i> (31)	Human xanthine oxidase changes its substrate specificity to aldehyde oxidase type upon mutation of amino acid residues in the active site: roles of active site residues in binding and activation of purine substrate.	2007	141	513–524	82
1BFG	Ago <i>et al.</i> (32)	Crystal structure of basic fibroblast growth factor at 1.6 Å resolution.	1991	110	360–363	81

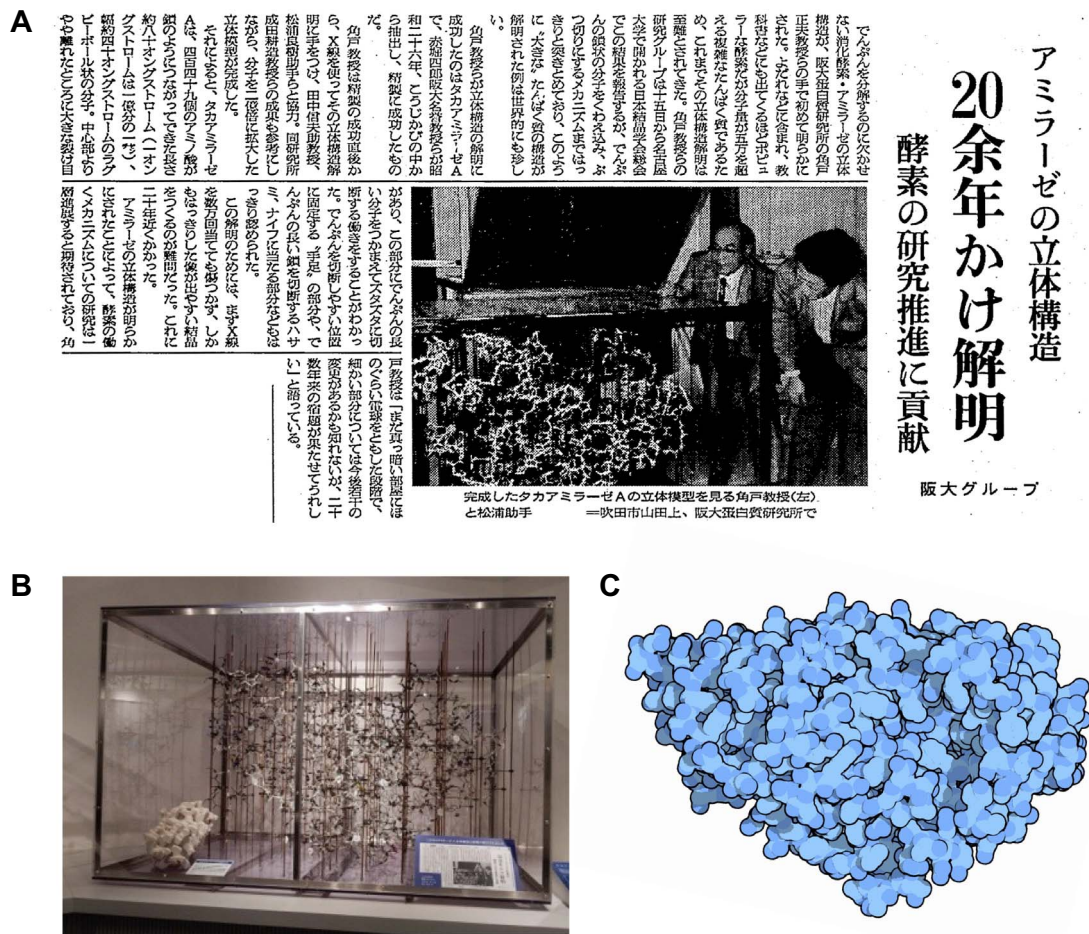


Fig. 3. X-ray structure of Taka-amylase A from *Aspergillus oryzae*. (A) Article from the *Asahi Shinbun* Newspaper on November 14, 1979, reporting a newly determined mainchain structure of Taka-amylase A, shown with permission from the Asahi Shinbun Co. (B) Kendrew model of Taka-amylase A. (C) Cartoon representation of Taka-amylase A as a molecule of the month by David S. Goodsell available in the PDB-101 of RCSB PDB and PDBj numon web pages.

Japanese sake. The news of the structural determination was again announced in an article that appeared in *Asahi Shinbun* (Fig. 3A). In this news article, Prof Masao Kakudo was quoted as saying ‘It takes more than 20 years to determine the structure after Prof Shiro Akabori succeed in purification of Taka-amylase A. It consists of 449 amino acids and has a big cleft for catalytic activity. Most time-consuming process was a successful crystallization showing the good quality of diffraction pattern without any significant radiation damage.’ The Kendrew model of Taka-amylase A built with brass parts using a half-mirror device was archived in the University Museum of Osaka University (Fig. 3B). Taka-amylase A was also featured in PDB-101 of RCSB PDB and PDBj numon pages (Fig. 3C). Emeritus Prof Masami Kusunoki of Yamanashi University, a former PhD student of Prof Masao Kakudo, wrote another historical perspective of the structural work on Taka-amylase A in the same PDB 50th anniversary issue.

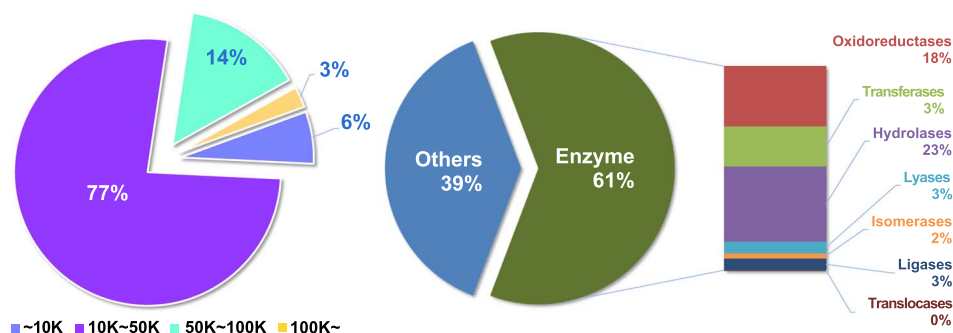
Other Milestone Structures from the Journal of Biochemistry

The top five most cited structure reports in *J. Biochem.* include an X-ray structure of plant-type [2Fe-2] ferredoxin from *Spirulina platensis* (PDB ID: 4FXC) by

Tsukihira *et al.* (15), Structural evidence for bisphenol A binding to human nuclear receptor ERR γ (PDB ID: 2E2R) by Matsushima *et al.* (16), X-ray studies of pyridoxal 5'-phosphate-type aspartate aminotransferase from *Escherichia coli* (PDB ID: 1ARS) by Okamoto *et al.* (17) and the 3D structure of porcine kidney D-amino acid oxidase (PDB ID: 1AN9) by Mizutani *et al.* (18). Except for that on aspartate aminotransferase, the other three reports were reviewed as a JB commentary written by one of the original co-authors in this PDB50 anniversary issue. Amongst all 317 PDB entries published in *J. Biochem.*, a structure with the highest resolution limit was that of a [2Fe-2S] type ferredoxin from *Chlamydomonas reinhardtii* (PDB ID: 6LK1) by Ohnishi *et al.* (19) in my research group, whose resolution was 0.90 Å (Table 2). In that paper, my group analyzed the quantitative radiation damage by X-ray irradiation and published the least damaged high-resolution X-ray structure obtained using the minimum X-ray dose. There are 18 NMR structure entries published in *J. Biochem.*, and the first NMR structure reported in *J. Biochem.* was an RNA structure of SPR19 binding domain in human SRP (PDB ID: 1L1W) (20) by Prof G. Kawai's group in 2002. Unfortunately, there is no report in *J. Biochem.* for structure obtained by 3D electron microscopy, fibre diffraction and neutron diffraction.

Table 2. PDB-related statistics of five academic journals by biological/biochemical societies

Journal name	PDB entries as a Primary citation	PDB entries with any related citations	Oldest date of deposition to PDB	Highest resolution structure appearing in the Journal
<i>J. Biochem.</i>	317	457	August 1, 1976	0.90 Å
<i>J. Biol. Chem.</i>	12,945	15,031	April 1, 1975	0.80 Å
<i>Biochemistry</i>	10,747	12,552	March 1, 1975	0.78 Å
<i>FEBS J.</i>	1688	2,156	June 11, 1985	0.95 Å
<i>FEBS Letter</i>	834	1,395	June 9, 1986	1.00 Å

**Fig. 4. Distribution of molecular weights and type of proteins whose structures were published in the Journal of Biochemistry.**

Distribution of Molecular Weights and Characteristics of Target Proteins

In the early days of protein crystallography, a target protein with a large molecular size was more challenging in terms of crystallization, X-ray diffraction experiments, model building and crystallographic refinement. However, most of these difficulties have been overcome by using modern biotechnological approaches, developments in software and the establishment of state-of-the-art synchrotron facilities. The molecular weight of the target protein structure is an important parameter to be considered in the history of structural biology. Here, the distribution of molecular weights of published structures in *J. Biochem.* was analyzed (Fig. 4, left panel). A total of 77% of published structures have a molecular weight ranging between 10 K and 50 K. Fourteen percent of these structures have a higher molecular weight from 50 K to 100 K, and 3% of them have a much higher molecular weight of over 100 K. I also analyzed the type of target proteins published in *J. Biochem.* (Fig. 4, right panel). A total of 61% of reported structures were those of enzymes, which could explain why the majority of target proteins have a molecular weight range of between 10 K and 50 K. The type of enzyme, based on the enzyme code numbers in the metadata of PDB, and their occupancies are shown in the side panel of Fig. 4. The majority of these enzymes are hydrolases, such as proteases or amylases, with 23% occupancy. The next most common type of enzyme are oxidoreductases (18% occupancy) followed by transferases (12% occupancy). The percentage occupancies for lyases, ligases and translocases are quite small, ranging from 0 to 3%.

Comparison with Other Academic Journals Published by Biochemical Societies

In the structural biology community, researchers are publishing their structures in many different journals. The journal reporting the largest number of PDB entries is

J. Biol. Chem., which is published by the American Society for Biochemistry and Molecular Biology (Table 2). There are two PDB entries deposited in 1975 as the first protein structure with a primary citation of *J. Biol. Chem.* One was the structure of high potential iron protein from *Chromatium* (PDB ID: 1HIP) (21), whose resolution was 2.0 Å, deposited by Prof Joseph Kraut in USA, and the other was the structure of concanavalin A (PDB ID: 2CNA) (22) at 2.0 Å resolution, deposited by Prof Gerald M. Edelman also in USA. *Biochemistry* is also one of the top journals reporting many PDB structures, published by the American Chemical Society. The oldest structure whose primary citation is that of chymotrypsinogen (PDB ID: 1CHG) (23) at 2.5 Å resolution deposited by Prof J. Kraut in March 1975. In Europe, the Federation of European Biochemical Societies (FEBS) also publishes two journals named *FEBS J.* (formerly the European Journal of Biochemistry), and *FEBS Lett.*, which also published many PDB structures. The three oldest depositions to PDB with a primary citation of *FEBS J.* were glutathione peroxidase at 2 Å resolution (PDB ID: 1GP1) (24) and third domain of silver pheasant ovomucoid (OMSVP3) at 1.5 Å resolution (PDB ID: 2OVO) (25) both deposited by Prof O. Epp, and bovine trypsinogen at 2.2 Å resolution (PDB ID: 4TPI) (26) by Prof R. Huber's group. All three PDB entries were deposited from Germany on June 11, 1985. The oldest deposition to PDB in *FEBS Lett.* was the structure of aspartic proteinases (PDB ID: 4APE) (27) solved by Prof T.L. Blundell in UK, whose resolution limit was 2.1 Å. Interestingly, early PDB entries related to the major society-based journals, including *J. Biochem.*, were deposited by leading structural biologists across the world. This was probably because in the early days of protein crystallography there were only a limited number of large crystallography laboratories that could perform the time-consuming machine-dependent crystallographic research on macromolecules.

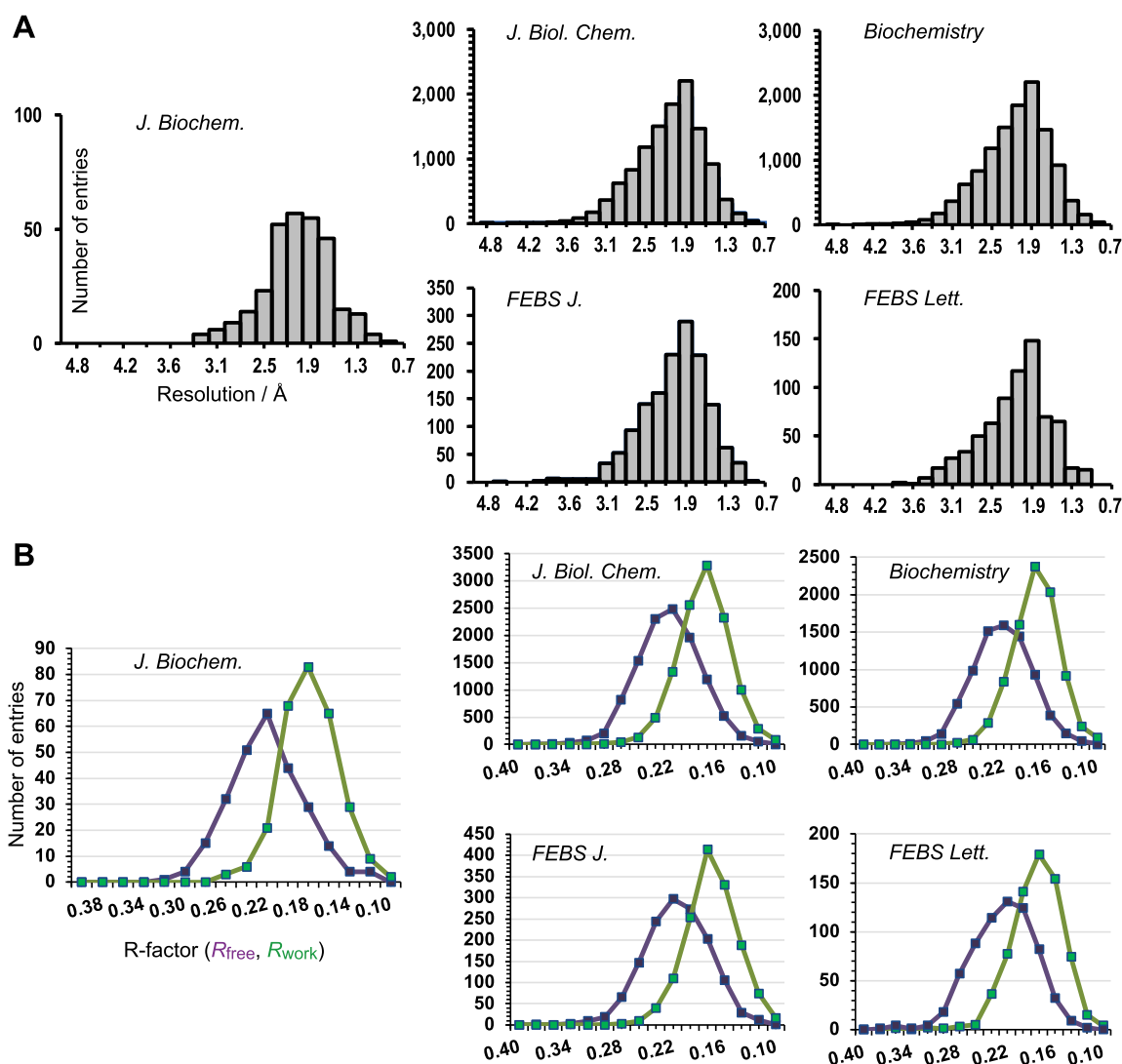


Fig. 5. Histograms of resolution and R-factors reported in the published PDB structures. (A) Distribution of resolution limits of structures published in the *Journal of Biochemistry*, *Journal of Biological Chemistry*, *Biochemistry*, *FEBS Journal* and *FEBS Letters*. (B) Distribution of free and working R factors of structures published in the same journals shown in panel A. Please note that the old PDB entries that did not use free R factor were excluded from this analysis.

Resolution and R-Factor Distribution of PDB Entries Published in Five Journals by the Societies

Important parameters used to evaluate the quality of crystallographic structures include the resolution limit of Bragg diffractions and R-factors representing the consistency between the structure factors observed by X-ray experiments and those calculated from the refined coordinates (Fig. 5). Within the entire PDB archive, a peak of resolution limit distribution exists between 1.8 and 2.0 Å resolution. In total, 23,248 of 183,387 entries in the PDB archive have a resolution limit in this range. Among the five journals by the societies, only *J. Biochem.* showed a broad peak from 1.6 to 2.2 Å resolution (Fig. 5A). The other American and European journals followed the tendency of the entire PDB archive. Why only *J. Biochem.* displays this kind of broad resolution distribution? One

possible reason may be the ratio of PDB entries with a resolution range between 1.6 and 1.8 Å in *J. Biochem.*, which is 15% and higher than that of other journals. If one-third of these entries move to the next lower resolution range, the distribution will resemble that of the others. Although my own first structural report published in *J. Biochem.* (28) was included in this resolution range, I have no idea why the ratio of PDB entries between 1.6 and 1.8 Å resolution was relatively high in *J. Biochem.* More detailed analysis will be needed to answer this question. Usually, the free R-factors to check overfitting during crystallographic refinement showed ~5% higher values against the working R-factors (Fig. 5B). In all five journals, this general rule was observed, which is unsurprising. The peak of free R-factor distribution in *J. Biochem.* was slightly sharper than those of other journals, which may represent careful crystallographic refinement to minimize the difference between free and working R-factors. A peak of working

R-factors in *Biochemistry* was shifted slightly to the lower value range. This observation may imply that the structures reported in *Biochemistry* showed better working R-factors than those of other journals, probably because the focus of the journal was much more chemistry oriented. The total number of articles reporting structures in *J. Biochem.* is not as great as those of other American and European journals, but the resolution of the structures in *J. Biochem.* are comparable to those of the others and the quality of the structures is rather better owing to careful crystallographic refinement.

In 2021, all wwPDB partner data centres, RCSB PDB, PDBe, PDBj, BMRB and EMDB, are celebrating the 50th anniversary of PDB. Here, I have tried to unravel the long and distinguished history of PDB and *J. Biochem.* based on the archived empirical data. As a head of PDBj, I hope that more high quality structural reports will be published in *J. Biochem.*, as the legendary pioneers of structural biology in Japan did at the very beginning of this field of research.

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Conflict of Interest

None declared.

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