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A Bibliometric Analysis of Scholarly Publication on Protein Folding From 2018 to 2022

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Abstract

The paper investigates the research output of protein folding published in the last five years, from 2018-2022. The source data are retrieved from the SCOPUS database and analyzed using MS Excel and VOS Viewer software. The VOSViewer software is mainly used for networking and visualization to understand the research pattern. A total of 12515 documents on protein folding are retrieved and considered for the study. The research finds that Uversky, V.N. was the most prolific protein folding author with the highest 42 publications and top 2560 global citations. The most productive countries in this field is the USA (4443 publications), followed by China (1791 publications), and Germany (1197 publications). The four hot keywords in protein folding research are protein binding, protein conformation, and metabolism, but protein folding is a burning author keyword. Most articles have been published by the CNRS (Centre National de la RechercheScientifique). This study will benefit future researchers worldwide in understanding the research pattern of protein folding.

Keywords: Protein folding, Bibliometrics, Bibliometrix, Protein conformation,Chaperon

Introduction

Proteins are large complex biomolecules that play many vital roles in our bodies (1). This complex organic compound makes hormones and enzymes and plays an essential role in building and repairing muscles, bones, cartilage, skin, etc. The basic building blocks of proteins are called amino acids (2) Protein comprises twenty-plus basic chains of amino acids, each called a polypeptide (3). To perform the biological function, these chains adopt the termed structure (native shape) through a physicochemical process known as protein folding (2,4).

The protein folding mechanism goes through 4 steps of a structural process that are primary, secondary, tertiary and quaternary (5). The first structure of the protein is the primary structure, the nascent protein. Then folding occurs in the primary structures, giving the secondary structure like the α-helix and the β-pleated sheet. This is not a well-stabilized protein structure. This secondary structure is three-dimensional in nature but nonfunctional. From the secondary structure, tertiary functional protein structures are formed through a process called hydrophobic effect or hydrophobic collapse (3). Most of the cases, the protein stabilizes at the tertiary structure, but this is not the final conformation of the protein through protein folding. Sometimes the tertiary structure transforms into the quaternary structure (6). In this process, the nonfunctional nascent protein is transformed into a final stabilized functional form called a native protein (7). To fold the nascent protein to its native state, the favorable interactions are Hydrophobic effect, Electrostatic effects, Enthalpy from Vander walls packing interaction, and gain of protein-protein H bonds, whereas protein conformational entropy and loss of protein-water H-bonding are the unfavorable interactions (6,8).

Protein folding is crucial for normal physiology, including development and healthy ageing, and failure of this process is related to the pathology (9). Sometimes molten globule (compact intermediate tertiary structure of a protein) aggregates and debates from the folding pattern, and the protein remains unfolded (10). Due to the failure of native structures,inactive proteins are formed (11). Inactive protein functions raise various diseases like Huntington's disease (8), Alzheimer's disease (12), Cystic fibrosis (13), Parkinson's disease (14), Gaucher's disease followed by allergies (15). Chaperon helps to keep the protein on the right path if the protein debate from the holding pattern.Now a days,various experimental techniques are used for protein folding such as Circular dichroism (16), X-ray crystallography, Fluorescence spectroscopy,X-ray crystallography etc. (17); However, Kubelka et al., reported that the time scale of the protein folding depends on its size and topology (18).

Figure 1 shows that Protein folding has been an emerging area of research in the last few decades. To understanddomain-specificresearch trends, hotspots and their interrelationships with other research areas, we analyzed the global literature on 'protein folding' published in the last 5 years, from 2018 to 2022, using bibliometric methods.

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Bibliometrics methods are quantitative approaches for evaluating and monitoring written and published research (19). It is *a* valuable tool for tracing a specific research field’s intellectual structure. Pritchard first introduced itin 1996, comprising mathematical and statistical approaches.Itencompasses a set of methods thatmeasure the various aspects of literature like subject, author, citations, affiliation, country, sources etc (20). (Zyoud et al., 2022). Bibliometrics has been considered a standard science policy and research management tool (21)technological innovations like artificial intelligence (AI. Ithelps to monitor the literature growth and research pattern. The science indicators such aspublication trend, authorships, citation statistics, keyword analysis etc., are some of the bibliometric techniques useful for tracking the evolution of science and technology and decision-making (22,23,24). Citation analysis is the most conventional method to measure the scientific quality of individual researchers. Author co-citation analysis was developed by White & Griffith, and this method provides the intellectual structure in sciencedisciplines (25,26). It has also been stated (27) state that this quantitative analysis helps to identify the authorship pattern and literature growth followed by institutional collaboration. Several researchers have tested the bibliometric and scientometric approaches in different subject areas to understand the research patterns.

Research objectives

The study aims to analyze the protein folding research output between 2018 and 2022by employing the bibliometrics methods based on information retrieved from the Scopes database. Thefollowing are the main objectives:

To study the year-wise distribution and growth of the publications, To analyze the author’s productivity and identify the most prolific researcher in the field, To evaluate the country-wise research trends globally and examine the highly productive organizations and most cited documents in protein folding research, To establish a network of Co-citation and Co-authorship and, To plotnetwork visualization of the co-occurrence of keywords in protein folding global research outputs.

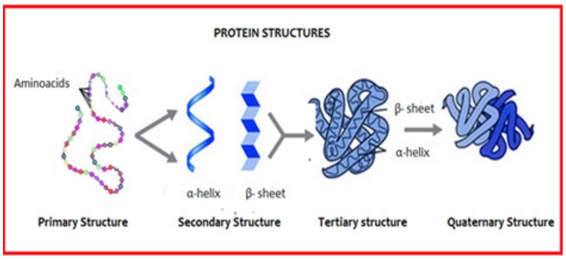

Figure 1:—Protein folding stages (https://www.researchgate.net/publication/298786402_Principles_of_Protein_Folding)

Materials and Methods

The sample dataset was collected from the Scopus Database,the largest international bibliographic and citation database and is used primarily for bibliometrics research in all parts of the World. The word'proteinfolding'was used as the search string and qualified with the Scopus search criteria 'Article title, Abstract, Keywords'. The instant result is thenlimited to the last 5-year publications data covering 2018 to 2022. The result found 12515 publications during the study period that included all types of documents' erratum' and 'retracted'.We analyzed the collected data using MS Excel andVOSViewer software. This study analyses the number of publications, citations, and productivity of authors, organizations, countries and journals/articles. We also analyzed the quality of the author's and organization's academic production using the H-index. We constructed the co-authorship, co-citation, and keyword occurrence network to study the relationship and visualise the datausing the VOSViewer.

Results and Discussion

The study discussed the entire results in two parts: (a) performance analysis and (b) science mapping. The performance analysis examines the characteristics of the publications and the perception of quality using different tools and techniques. It accounts for the research's publication patterns, contribution and productivity in the given field. In contrast, science mapping focuses on the relationship between research constituents such as keywords, citations and authorships. It identifies how authors andcountries are related and their evolutionary significance (28,29,30).

Performance analysis

Performance analysis is the simplest methodin the bibliometric study toanalyze the performances of different research constituents, such as articles, authors, institutes, countries, and journals,over a period of time (31,32). We performed all these analyses in this study to present the research trends.

Annual publications analysis

Ofthe total number of 12515 publications on protein folding retrieved from the Scopus database between 2018 and 2022,the highest number of 2674 (21.37%) papers were published in 2018 with most h-index, followed by 2666(21.30%) papers in 2020, 2623 (20.96%) papers in 2019, 2494 (19.93%) papers in 2021 and a comparatively lowest number of 258(16.44%) of papers in 2022 as shown in Table 1.

In contrast,the citation analysis column shows the highest number of citations received in2019, followed by 2018, during the study period. The data show that the annual publication growth slightly decreased from 2018-2022.

Bibliometric analysis of authors,institutions and countries/regions

Table 2 analyses the distribution of the ten mostprolific authors. The author with the most published papers (42) is Uversky, V.N. from the University of South Florida, Tampa, USA, followed by Gianni, S.(36) and Hassan, M.I.(29). The highest 1125citations isreceived by Vendruscolo, M., from University of Cambridge, UK withmaximum 17 h-index followed by Best, R.B. from NIH, USA having 770 citations with 14 h-index.The author's productivity analysis also shows that the most creativeauthors are from USA and INDIA in protein folding.

Table 1: Distribution of annual growth of scientific publications

Sr. No	Year	No. of Publications	Citations	h-index
1	2018	2674	65697	152
2	2019	2623	70494	133
3	2020	2666	43109	108
4	2021	2494	31935	80
5	2022	2058	8558	42

Table 2: Distribution of most prolific authors

Authors	TP	CT	h-index	Institution	Country
Uversky, V.N	42	560	14	University of South Florida, Tampa	USA
Gianni, S.	36	332	10	Sapienza Università di Roma	Italy
Hassan, M.I.	29	313	11	JamiaMilliaIslamia, New Delhi	India
Vendruscolo, M.	28	1125	17	University of Cambridge	UK
Islam, A.	27	275	10	JamiaMilliaIslamia, New Delhi	India
Ahmad, F.	25	270	10	JamiaMilliaIslamia, New Delhi	India
Wolynes, P.G.	24	424	13	Rice University	USA
Toto, A.	24	172	8	Sapienza Università di Roma	Italy
Gruebele, M.	23	310	10	University of Illinois Urbana-Champaign	USA
Best, R.B.	23	770	14	National Institutes of Health (NIH)	USA
Note: TP-Total no. of publications, CT-Citations					

Figure 2 shows the top ten countries in terms of scientific research publications on Protein folding. The data reflects that the USA has published the highest number of 4443 papers, which is 35.5% of total publications, followed by China with 1791(14.32%) papers and Germany with 1197(9.56%) papers.

This studyalso investigated institute-wise scientific researchpublications and their productivity. Table 3 presents the ten most highly productive institutions/organizations in protein folding research. The Institute with the most publications is 'CNRS Centre National de la RechercheScientifique' which is in France and has published the highest 325 publications, followed by the Chinese Academy of Sciences (245) and the National Institutes of Health (231). In contrast, the Howard Hughes Medical Institute, USA has received the highest 8189 number of citations with 42 h-index, followed by the University of Cambridge, UK, with 6643 citations and 36 h-index. The analysisaslo shows that the USA has participated the most, followed by China in protein folding research globally.

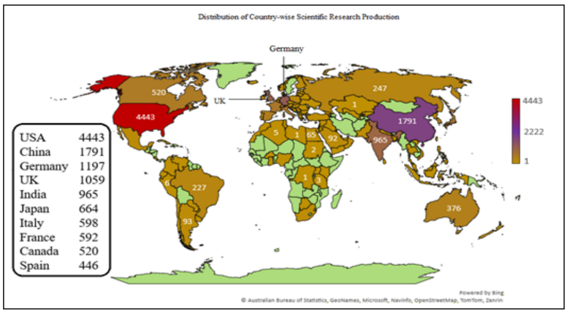

Figure 2 Distribution of County-wise scientific research publications

Bibliometric analysis of most cited papers

Table 4 provides the top ten highly cited papers. The paper entitled "Highly accurate protein structure prediction with AlphaFold" published in Nature in 2021 received a maximum of 7366 total citations, followed by "Reactive oxygen species (ROS) as pleiotropic physiological signalling agents" published in Nature Reviews Molecular Cell Biologyin 2020 with 1583 citationsand "Accurate prediction of protein structures and interactions using a three-track neural network"published in science in 2021 with 1384 citations, respectively. Naturejournals were taking leadership in producinghighly citedpapers in protein folding research. Science Mapping

Table 3: Distribution of highly productive organizations

Affiliations	TP	CT	h-index	Country
CNRS Centre National de la RechercheScientifique	325	4911	35	France
Chinese Academy of Sciences	245	3596	29	China
National Institutes of Health (NIH)	231	5024	37	USA
Ministry of Education China	218	3076	28	China
University of Cambridge	175	6634	36	UK
Inserm	168	3239	25	France
Howard Hughes Medical Institute	155	8189	42	USA
Harvard Medical School	142	4602	35	USA
ConsiglioNazionaledelleRicerche	137	1726	22	Italy
University of Chinese Academy of Sciences	133	1850	22	China
Note: TP-Total no. of publications, CT-Citations				

Science mapping is a multifaceted-bibliometric tool to analyze and examine scientific output (28). Thisbibliometrics method uses computational techniquesto analyze the citation data quantitatively, classify them, and visualize the interrelationships between bibliographic objects, and also establish the network links, clusters, overarching structure, evolution of research themes and research fronts, and geographic spread of the body image research (33). In this study, we used VOSviewer software to study the network visualization ofco-authorship in relationships with countries, co-occurrence of keywords, and co-citation analysis of documents, authors and organizations.

Co-authorship network analysis

The co-authorship method is one of the most verifiable methods to quantify and examine scientific collaboration (34). Figure 3 shows the network visualization of co-authorship analysis with the countries. The circle signifies a country/region, and the size of each circle symbolizes the number of publications of each country, indicating the activity of the country/region. The lines between circles represent the cooperative relationship between two countries/regions. The study considered the criteria of a minimum of 5 papers with 5 citations. As a result, 76 countries met the threshold of 175 countries.These are grouped into 8 clusters,forming8256 total link strength.TheUSAhasthe highest link strength (2713), followed by the UK(1362), Germany (1342), China (884) and France (804).

Table 4: Highly Cited Documents

Title/Authors	Year	Source Title	Cited by
Highly accurate protein structure prediction with AlphaFold by Jumper J.; Evans R.; Pritzel A.; Green T.; Figurnov M.; Ronneberger O.; Tunyasuvunakool K.; Bates R.; Žídek A.; Potapenko A.; Bridgland A.; Meyer C.; Kohl S.A.A.; Ballard A.J.; Cowie A.; Romera-Paredes B.; Nikolov S.; Jain R.; Adler J.; Back T.; Petersen S.; Reiman D.; Clancy E.; Zielinski M.; Steinegger M.; Pacholska M.; Berghammer T.; Bodenstein S.; Silver D.; Vinyals O.; Senior A.W.; Kavukcuoglu K.; Kohli P.; Hassabis D.	2021	Nature	7366
Reactive oxygen species (ROS) as pleiotropic physiological signalling agents by Sies H.; Jones D.P.	2020	Nature Reviews Molecular Cell Biology	1583
Accurate prediction of protein structures and interactions using a three-track neural network by Baek M.; DiMaio F.; Anishchenko I.; Dauparas J.; Ovchinnikov S.; Lee G.R.; Wang J.; Cong Q.; Kinch L.N.; Dustin Schaeffer R.; Millán C.; Park H.; Adams C.; Glassman C.R.; DeGiovanni A.; Pereira J.H.; Rodrigues A.V.; Van Dijk A.A.; Ebrecht A.C.; Opperman D.J.; Sagmeister T.; Buhlheller C.; Pavkov-Keller T.; Rathinaswamy M.K.; Dalwadi U.; Yip C.K.; Burke J.E.; Christopher Garcia K.; Grishin N.V.; Adams P.D.; Read R.J.; Baker D.	2021	Science	1364
AlphaFold Protein Structure Database: Massively expanding the structural coverage of protein-sequence space with high-accuracy models by Varadi M.; Anyango S.; Deshpande M.; Nair S.; Natassia C.; Yordanova G.; Yuan D.; Stroe O.; Wood G.; Laydon A.; Zídek A.; Green T.; Tunyasuvunakool K.; Petersen S.; Jumper J.; Clancy E.; Green R.; Vora A.; Lutfi M.; Figurnov M.; Cowie A.; Hobbs N.; Kohli P.; Kleywegt G.; Birney E.; Hassabis D.; Velankar S.	2022	Nucleic Acids Research	1278

Cellular Senescence: Defining a Path Forward by Gorgoulis V.; Adams P.D.; Alimonti A.; Bennett D.C.; Bischof O.; Bishop C.; Campisi J.; Collado M.; Evangelou K.; Ferbeyre G.; Gil J.; Hara E.; Krizhanovsky V.; Jurk D.; Maier A.B.; Narita M.; Niedernhofer L.; Passos J.F.; Robbins P.D.; Schmitt C.A.; Sedivy J.; Vougas K.; von Zglinicki T.; Zhou D.; Serrano M.; Demaria M.	2019	Cell	995
Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding by Starr T.N.; Greaney A.J.; Hilton S.K.; Ellis D.; Crawford K.H.D.; Dingens A.S.; Navarro M.J.; Bowen J.E.; Tortorici M.A.; Walls A.C.; King N.P.; Veesler D.; Bloom J.D.	2020	Cell	978
Highly accurate protein structure prediction for the human proteome by Tunyasuvunakool K.; Adler J.; Wu Z.; Green T.; Zielinski M.; Žídek A.; Bridgland A.; Cowie A.; Meyer C.; Laydon A.; Velankar S.; Kleywegt G.J.; Bateman A.; Evans R.; Pritzel A.; Figurnov M.; Ronneberger O.; Bates R.; Kohl S.A.A.; Potapenko A.; Ballard A.J.; Romera-Paredes B.; Nikolov S.; Jain R.; Clancy E.; Reiman D.; Petersen S.; Senior A.W.; Kavukcuoglu K.; Birney E.; Kohli P.; Jumper J.; Hassabis D.	2021	Nature	914
Site-specific glycan analysis of the SARS-CoV-2 spike by Watanabe Y.; Allen J.D.; Wrapp D.; McLellan J.S.; Crispin M.	2020	Science	866
ColabFold: making protein folding accessible to all by Mirdita M.; Schütze K.; Moriwaki Y.; Heo L.; Ovchinnikov S.; Steinegger M.	2022	Nature Methods	811
The Unfolded Protein Response and Cell Fate Control by Hetz C.; Papa F.R.	2018	Molecular Cell	802

Co-citation network analysis

Figure 3: Co-authorship network analysis

The co-citation analysis discloses the frequency at which other scholarly articles have cited two publications together, presenting important information regarding the interconnectedness within the literature(Ki, 2023). In this study, the co-citation map includes at least fifty references that appear in the bibliographies of the 12515 publications focused on protein folding. 370cited references met the established co-citation frequency threshold.We found 6 clusters indicated in colours with a total link strength is 22875. Figure 4 shows the network map of the co-citation of references. The circle size represents the number of times the cited references collaborate,as appears commonlyin the number of citing papers. The larger a circle, the more often vital co-citation seems. The author Walter P. received the highest number of citations (204) with top link strength of 754, followed by Hartl F.U., having 181 citations with 663 link strength. Authors such asAnfisenC.B.andKabsch W. secured 3rdand 4th positions in co-citation network analysis, having 177 and 170 citations with 569 and 488 link strengths, respectively.

Co-occurrence of keywords network analysis

Keywords were grouped into 5clusters with total link strength of 189379. Figure 5depicts a network map of all keywords within the research papersselected for the study. The width of the network lines reflects the intra-relationship among the keywords, i.e., the thicker the network line, the stronger the association. The keywords that appeared most were 'Protein folding'with an occurrence of 10687 and a total link strength of 258779, followed by 'metabolism' (112155;7222), protein expression (72061;2363) and 'protein confirmation'(67249;2642). Other frequently used keywords which are thematically associated are protein structure, protein binding, protein function, protein domain, aminoacid sequence, molecular dynamics, chaperone, gene expression, protein-protein interaction, gene expression, protein aggregation, physiology, protein secondary structure, binding site, protein misfoldinganddrug effect.

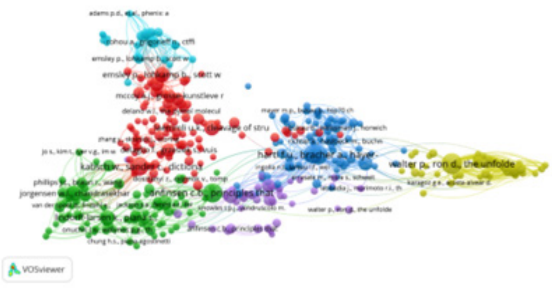

Figure 4: Co-citation network analysis

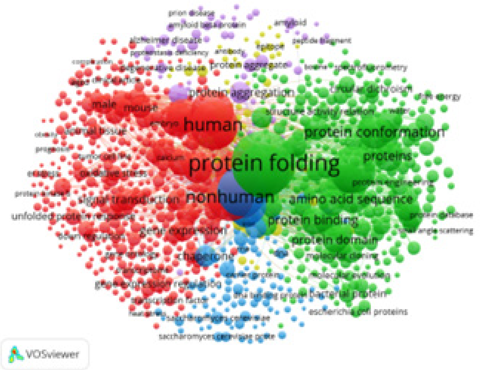

Figure 5: Co-occurrence network of keywords

Conclusion

Here, we employed both quantitative and qualitative approaches to describe the research trend in protein folding,covering data from 2018 to 2022.The study examined 12515 scientific productions retrieved from the Scopus database. The finding of the study reveals that although a good number of papers published during the study, but the number of publications has been decreasing from 2018 to 2022. The USA has contributed the most papers during the study, and an author named Uversky, V.N from the country has contributed the most. In contrast, the highest number of papers has been published by a France-affiliated organization called CNRS. The co-author network analysis tells that the total strength of the co-authorship links of a given researcher with other researchers was highest in the case of the USA, followed by UK, Germany and China. The most used keyword is 'protein folding',asreportedduring the study period.

Strengths and limitations

Here we have provided an overview of the current literature on 'Protein folding', by analyzingthe information about authors, publishers, publication year, and the number of citations and predicted the current hot topics and the trendsfrom them. In this study, we collected the data only from Scopus and a specific period. However, there is enough scope for further studies using different metrics on this emerging study area. Even results representation will be different if other databases are also considered.

Conflicts of Interest

The author declares no conflict of interest.

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