



The Evolution of C-Technologies: Trends, Impact, and Future Directions

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ABSTRACT:

The organization of chromosomes in three dimensions is crucial for gene regulation and genome stability. Over the years, various methods have been developed to study chromosome conformation. The advent of chromosome conformation capture (3C) and its high-throughput derivatives revolutionized genome architecture studies by enabling detailed interaction mapping at different scales. These methods, including 3C, 4C, 5C, Hi-C, and advanced techniques like ChIA-PET and Micro-C, have provided insights into chromatin organization, compartments, and topologically associating domains (TADs). This study presents a comprehensive bibliometric analysis of research on C-technologies from 2002 to 2021, using the Scopus database. A total of 2,587 publications were analyzed to track trends, geographical distribution, citation impact, collaborations, and technological advancements. The results indicate a steady growth in publications, with a sharp increase after 2019. Highly cited papers, published in journals like Science, Nature, and Cell, highlight key methodological developments and applications. Co-citation analysis revealed three major research clusters focused on chromosome conformation methods, computational tools, and chromatin topology. The findings underscore the growing significance of C-technologies in genomics and highlight emerging research directions in functional genomics, structural variations, and gene regulation.

Introduction:

The three-dimensional organization of chromosomes plays a fundamental role in gene regulation and genome stability [1–9]. Over the years, various techniques have been developed to study genome architecture, with early methods relying on cytological approaches such as fluorescence in situ hybridization (FISH). While FISH enables the visualization of genetic loci proximity using probes, its low throughput, limited resolution, and sequence specificity constraints make it less suitable for genome-wide studies [10–13].

The advent of chromosome conformation capture (3C) and its derivatives revolutionized the study of spatial genome organization, providing high-throughput insights at local, chromosomal, and genome-wide levels [14–16]. These methods involve five core steps: formaldehyde fixation, chromatin digestion, proximity ligation, molecular detection, and computational analysis. The C-technologies, including 3C, 4C, 5C, and Hi-C, vary in their capabilities—ranging from analyzing

specific locus interactions (one vs. one in 3C) to comprehensive genome-wide contact profiling (all vs. all in Hi-C) [17–19]. These approaches have facilitated the discovery of chromatin compartments, topologically associating domains (TADs), and various polymer models that describe chromatin packing dynamics [20,21]. Further refinements, such as ChIA-PET, Capture-C, and Micro-C, integrate additional steps like protein precipitation or nucleosome-resolution fragmentation to enhance specificity and resolution [22–24]. The choice of method depends on the research question, sample availability, and desired resolution.

Bibliometric analysis is a powerful tool for evaluating research trends by analyzing publication patterns, citation networks, and collaborative efforts within a field [25]. While bibliometric studies have been widely used in research evaluation and policy-making [26–28], there is currently a lack of systematic bibliometric analyses focusing on C-technologies. This study aims to fill that gap by conducting a comprehensive bibliometric



assessment of research on C-technologies since their inception in 2002. The analysis will explore temporal trends, geographical distribution, topical and emerging research areas, journal and citation impact, author collaborations, and technological advancements, providing valuable insights into the evolution and influence of these methodologies.

Methodology:

Database Selection:

This study utilized SciVerse Scopus, a bibliographic database developed by Elsevier, to collect publications on C-technologies, including chromosome conformation capture (3C) and its high-throughput sequencing-based variants. Scopus was chosen over other databases such as Web of Science, Medline, and Google Scholar due to its comprehensive coverage, ease of bibliometric analysis, and integration with Medline [29,30]. Since Medline is fully indexed within Scopus, its inclusion ensured a broad representation of relevant literature. The study focused exclusively on peer-reviewed journal articles, excluding conference proceedings, books, book chapters, and grey literature. The study period spanned from 2002 to 2021, covering two decades of research on chromosome conformation capture technologies.

Search Strategy:

The search strategy was developed based on widely cited review articles on C-technologies. Relevant keywords were identified and refined through trial and error to ensure comprehensive retrieval of publications related to chromosome conformation capture and its associated techniques. The final search query was applied to the title, abstract, and keywords fields in Scopus using the following criteria:

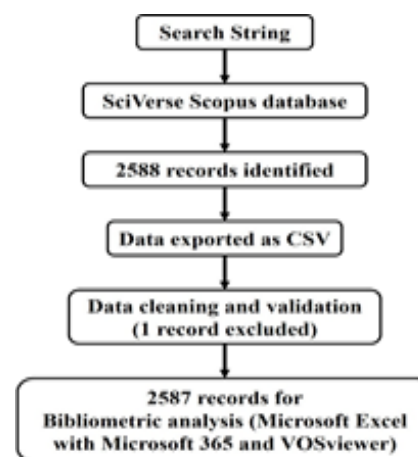
((TITLE-ABS-KEY ("Chromosome Conformation Capture") OR TITLE-ABS-KEY ("Chromatin Conformation Capture") OR TITLE-ABS-KEY ("Capturing Chromosome Conformation") OR TITLE-ABS-KEY ({ChIA-PET}) OR TITLE-ABS-KEY ({ChIP-loop}) OR TITLE-ABS-KEY ({capture-C}) OR TITLE-ABS-KEY ({4c-seq}) OR TITLE-ABS-KEY ({DNase Hi-C}) OR TITLE-ABS-KEY ({micro-C XL}))) AND PUBYEAR > 2001 AND PUBYEAR < 2022) OR (TITLE-ABS-KEY ({Hi-c}) AND PUBYEAR > 2008 AND PUBYEAR < 2022) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (PUBSTAGE ,

"final")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "AGRI") OR LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "NEUR") OR LIMIT-TO (SUBJAREA , "MULT")) AND (LIMIT-TO (LANGUAGE , "English"))

The search was restricted to English-language articles and reviews published in peer-reviewed journals between 2002 and 2021. To minimize false positives, the search was limited to specific subject areas, including Biochemistry, Genetics, Molecular Biology, Medicine, Agricultural and Biological Sciences, Multidisciplinary, Immunology, Microbiology, and Neuroscience. The bibliometric dataset was retrieved from Scopus on January 25, 2023, in comma-separated values (CSV) format, including citation details, bibliographic metadata, abstracts, keywords, and references (Fig. 1).

Validation of Search Strategy:

To ensure the accuracy of the search results, a two-step validation process was performed:



False Positive Check: The 200 most-cited publications were manually reviewed to confirm their relevance to C-technologies. Titles, abstracts, and full texts (where necessary) were analyzed to eliminate false positives.

False Negative Check: The correlation coefficient ($r = 0.972$, $p < 0.001$) was calculated by comparing the number of publications retrieved for the top ten most active researchers with their actual publication records in Scopus (Sweileh 2021). The strong correlation validated the completeness of the dataset.



Data Cleaning and Scientometric Analysis:

The search query initially retrieved 2,588 documents published between January 1, 2002, and December 31, 2021. After data cleaning, one document was removed due to being published in French, leaving 2,587 documents for the final analysis.

Bibliometric and scientometric analyses were conducted using Microsoft Excel (Microsoft 365) and VOSviewer (version 1.6.20) [31]. VOSviewer, developed by the Center for Science and Technology Studies (CWTS) at Leiden University, is widely recognized for its advanced graphical capabilities and ability to process large-scale bibliometric data.

RESULTS AND DISCUSSIONS:

Overview of Publication Status:

Table 1 presents the number of publications retrieved on C-technologies from 2002 to 2021 across various subject areas. The overwhelming dominance of Biochemistry, Genetics, and Molecular Biology (2,114 publications; 81.72%) suggests that C-technologies are crucial in life sciences, potentially for applications like computational biology, bioinformatics, and genetic sequencing. The significant presence in Medicine (21.80%) and Agricultural and Biological Sciences (18.59%) further highlights the relevance of C-technologies in health and biological research. The relatively high contribution from Computer Science (9.39%) and Mathematics (7.69%) indicates the role of computational approaches in advancing C technology applications. Conversely, the low presence in Engineering (0.54%), Health Professions (0.19%), and Materials Science (0.15%) suggests limited integration of C-technologies in these areas. The focus remains heavily skewed towards life sciences.

Table 1: Number of publications retrieved on C-technologies (2002-2021) according to the subject areas

S. No	Subject area	Number of documents	Percentage
1	Biochemistry, Genetics and Molecular Biology	2114	81.72 %
2	Medicine	564	21.80 %
3	Agricultural and Biological Sciences	481	18.59 %
4	Multidisciplinary	246	9.51 %

5	Computer Science	243	9.39 %
6	Mathematics	199	7.69 %
7	Immunology and Microbiology	172	6.65 %
8	Chemistry	155	5.99 %
9	Physics and Astronomy	132	5.10 %
10	Neuroscience	124	4.79 %
11	Environmental Science	55	2.13 %
12	Chemical Engineering	51	1.97 %
13	Pharmacology, Toxicology and Pharmaceutics	44	1.70 %
14	Engineering	14	0.54 %
15	Health Professions	5	0.19 %
16	Materials Science	4	0.15 %
17	Nursing	3	0.12 %
18	Energy	1	0.04 %
19	Veterinary	1	0.04 %

Extracted from Scopus as Scopus_exported_refine_values.csv

Annual growth of publications and citation analysis:

Fig.2 shows the annual growth of publications during the study period along with year wise total citations. The concept of chromosome conformation capture was first introduced in 2002 by Dekker [16]. It is therefore around the same year that we witness the academic publication concerning the same. Thereafter, since 2004 there is a steady growth in the number of pertinent publications. A significant rise in the number of publications on C-technology has been recorded since 2019. More than half of the retrieved documents (n=1324; 51.18%) were published in the last three years (2019-2021) of the study period. According to this study, the linear regression analysis showed a strong positive correlation between the number of publications per year and the year of publication ($R^2 = 0.89$, $p < 0.001$).

The retrieved 2587 documents garnered a total of 172620 citations, averaging 66.7 citations per document. Total citation count showed significant peaks in the year 2002, 2006, 2009, and 2012 (Fig.2). In 2002, only one document was published launching the chromosome conformation capture technique gathering total citation of 2706. In 2006, total citation for 15 documents was 4737 with an average of 315.8. The top cited document



of 2006 [17] introduced the 4C technology, the next version of C-technologies, having a total citation of 1052. The second top cited document for the year 2006 was about the development of 5C technology; another evolved version of C-technologies, with total citation of 900 [32]. In 2009, 37 documents were published with total citation of 9229. The most cited document of the year 2009 is also ranked first in the total citation for the

two-decades of study. The document introduced Hi-C method, the most popular version of C-technologies, with total citation of 5676 [19]. In 2012, 90 documents were published with total citation of 17354. The top four [20,33–35] most cited documents for the year accounted for more than 50% (n=9056) of the total citations for the year. These documents are about the applications of various C-technologies.

Table 2: Top ten most cited articles in C-technologies (2002-2021)

Rank	Title	Authors	Year	Journal	Citations
1 st	Comprehensive mapping of long-range interactions reveals folding principles of the human genome [19]	Lieberman <i>et al.</i>	2009	Science	5676
2 nd	A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping [21]	Rao <i>et al.</i>	2014	Cell	4567
3 rd	Topological domains in mammalian genomes identified by analysis of chromatin interactions [20]	Dixon <i>et al.</i>	2012	Nature	4507
4 th	Capturing chromosome conformation [16]	Dekker <i>et al.</i>	2002	Science	2706
5 th	Spatial partitioning of the regulatory landscape of the X-inactivation centre [33]	Nora <i>et al.</i>	2012	Nature	2032
6 th	Juicer Provides a One-Click System for Analyzing Loop-Resolution Hi-C Experiments [36]	Durand <i>et al.</i>	2016	Cell Systems	1546
7 th	Three-dimensional folding and functional organization principles of the Drosophila genome [34]	Sexton <i>et al.</i>	2012	Cell	1410
8 th	An oestrogen-receptor- α -bound human chromatin interactome [22]	Fullwood <i>et al.</i>	2009	Nature	1328
9 th	HiC-Pro: An optimized and flexible pipeline for Hi-C data processing [37]	Servant <i>et al.</i>	2015	Genome Biology	1274
10 th	De novo assembly of the Aedes aegypti genome using Hi-C yields chromosome-length scaffolds [38]	Dudchenko <i>et al.</i>	2017	Science	1192

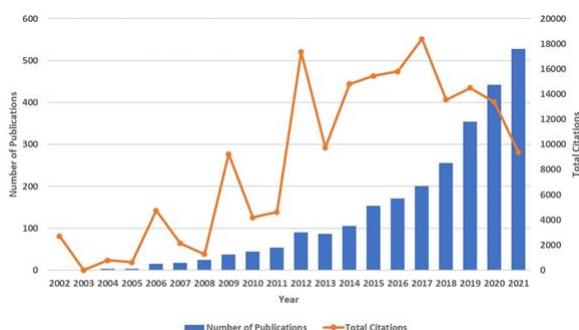


Fig. 2: Yearly publications and total citations regarding C-technologies (2002-2021).

A significant drop in total citation was found at the end of the study period. It is common for more recent works to have fewer citations. This phenomenon is known as

the citation lag, where it takes time for new publications to be read, reviewed, and cited in subsequent works. Older publications generally have had more opportunities to be cited over the years, which is why they often have higher citation counts [39].

Influential articles:

Highly cited research papers often signify significant influence and impact within a particular domain, introducing groundbreaking methodologies, novel concepts, or critical solutions that shape the trajectory of future research. Table 2 presents the top ten most cited articles on C-technologies from 2002 to 2021. Among these, three articles were published in *Science*, three in



Nature, two in *Cell*, and one each in *Cell Systems* and *Genome Biology*.

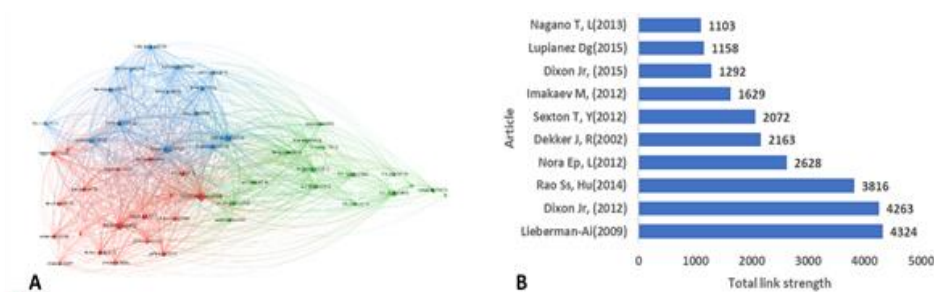


Fig. 3: (a) Co-citation network map of references with at least 50 citations for a cited reference; (b) Top ten cited references with highest co-citation link strength in C-technology (2002-2021).

The most cited paper, Lieberman-Aiden et al. [19], published in *Science*, introduced the Hi-C method, a widely recognized approach for chromosome conformation capture. Similarly, Sexton et al. [34], ranking seventh, discusses an improved and modified version of this technique. The pioneering work of Dekker et al. [16], which launched the chromosome conformation capture (3C) strategy, is ranked fourth, while the introduction of the ChIA-PET method by Fullwood et al. [22] secured the eighth position. The second [21], third [20], and tenth [38] most cited papers focus on various Hi-C applications, whereas the fifth-ranked paper [33] explores the application of 5C technology. Additionally, the sixth [36] and ninth [37] ranked papers introduce software tools for Hi-C data processing and analysis.

Reference co-citation analysis is commonly employed to identify key research themes within a field, where co-citation relationships indicate that two papers are frequently cited together. Fig 3a provides a graphical representation of the co-citation network analysis using VOSviewer, applying the association strength network approach with a minimum threshold of 50 citations per reference. After consolidating multiple entries using a thesaurus file, 50 out of 105,864 cited references met the criteria. The network map revealed three major clusters, 2,226 links, and a total link strength (TLS) of 47,388.

The largest cluster (Red) comprises 19 cited references with 863 links and a TLS of 17,170. The most influential papers in this cluster include Lieberman-Aiden et al. [19] (TLS 4,324), Dekker et al. [16] (TLS 2,163), Nagano et

al. [40] (TLS 1,103), and Jin et al. [41] (TLS 901), collectively accounting for 50% of the cluster's total link strength. Notably, Lieberman-Aiden et al. (2009) and Dekker et al. (2002) were published in *Science*, while Nagano et al. (2013) and Jin et al. (2013) appeared in *Nature*. This cluster primarily focuses on the introduction and enhancement of chromosome conformation capture methodologies and their applications in understanding chromatin interactions and genome organization.

The second-largest cluster (Green) contains 16 cited references with 665 links and a TLS of 7,792. The top-cited works in this cluster are Quinlan & Hall [42] (TLS 1,004) and Langmead & Salzberg [43] (TLS 947). This group emphasizes bioinformatics algorithms and software essential for processing and analyzing C-technology-generated data.

The third cluster (Blue) includes 15 cited references, 698 links, and a total link strength of 22,426. The most cited references here are Dixon et al. [20] (TLS 4,263) and Rao et al. [21] (TLS 3,816). This cluster primarily investigates chromatin topology, regulatory landscapes, and genome functional organization.

Fig 3b highlights the top 10 references ranked by co-citation link strength. *Nature* leads with the highest TLS (535,787), followed by *Cell* (477,481) and *Science* (338,007). Among these top 10 co-cited references, four were published in *Nature*, three in *Cell*, two in *Science*, and one in *Nature Methods*. These highly co-cited works underscore the foundational role of C-technologies in genome research, spanning methodological innovations,



computational advancements, and biological applications.

Author Keywords, Hotspots, and Future Conduits:

Co-occurrence analysis of author keywords for C-technologies was conducted using VOSviewer software. With a threshold value of 10 minimum number of occurrence of a keyword, 91 keywords met the threshold limit out of total 3913 keywords. After re-labelling synonymous words and phrases, the final list comprised 79 keywords. Most prominent key words obtained from VOSviewer include “Hi-C” with 77 links, 834 link strength and 441 occurrences; followed by “3C (chromosome conformation capture)” with 58 links, 363 link strength and 208 occurrences; and “Chromosome conformation” (54 links, 289 link strength and 155 occurrence). The bibliometric network map in Fig. 4a illustrate 5 clusters. The largest cluster (red) has 26 key words. The top key words of this cluster are “3d architecture” (TLS 234); followed by “enhancer” (TLS 206); “epigenomics” (TLS 178); “gene regulation” (TLS 152); and “chromatin interaction” (TLS 100). This cluster represents significance of three-dimensional genome conformation in gene regulation [44] and association of chromatin interaction with enhancers [45], promoters [46], transcription factors [47] and epigenomics [48] etc. The second cluster, represented in green, has 24 keywords. The most prominent keywords in this cluster are “Hi-C” (TLS 834); followed by “genome assembly” (TLS 115). The core concept of this cluster revolves around the significance of Hi-C, the most popular version of C-technologies, in metagenomics, transcriptomics, structural variations and chromosome level genome assembly etc [49–53]. The third cluster (blue) has 22 keywords with “3c” (TLS 363) at the top, followed by “chromosome conformation” (TLS 289); and “tad (Topologically associating domain)” (TLS 294). This cluster focusses on genome architecture, nuclear organization, chromosome territory, long-range interactions, and topologically associating domains [17,54–56]. The fourth cluster (yellow) has 6 keywords with “gwas (genome wide association studies)” (TLS 75) at the top. The clustering is based on advanced technology and functional genomics [57–59]. The fifth cluster has a single key word “transcription regulation” (TLS 70) [60].

VOSviewer overlay visualisation map represents shift in trend in C-technologies over the period (Fig. 4b). The early phase witnessed the development and evolution of chromosome conformation capture techniques, shifting to its application to study chromosome conformation, chromosome looping and gene expression and transcription regulation. By 2019, the Hi-C technique and its application in functional genomics, GWAS, TAD etc. was gaining popularity. By the end of the study period, advanced computational technologies like machine learning and artificial intelligence are making pave into the C-technologies. The coming era in C-technologies is about single cell genome architecture and use of advanced machine learning and artificial intelligence for better understanding [61–63].

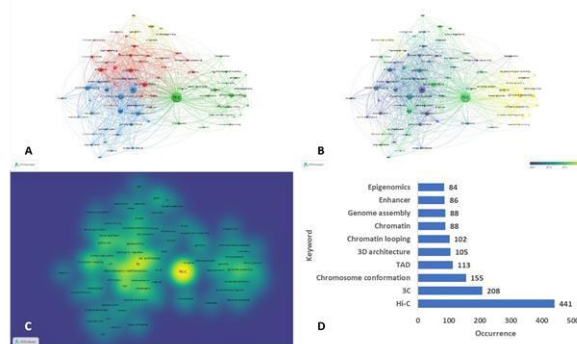


Fig. 4: (a) Co-occurrence network map of most frequently used author keywords for C-technologies (2002-2021); (b) Overlay visualisation map representing shift in trend in C-technologies over the period and their co-occurrence with other relevant keywords.; (c) The density visualization map delineates authors keyword co-occurrence analysis.; (d) List of the ten most frequently used authors keywords for C-technologies (2002-2021).

Fig. 4c shows the density map of keywords related to C-technologies and their co-occurrence with other relevant keywords. The knowledge map indicates dense regions around "Hi-C" and extends towards "3C," "Chromosome conformation," etc. Smaller density regions are visible around keywords like "genome assembly," "3C," "TAD," and "chromatin looping". In the visualizations, brighter yellow hues highlight the most active research areas with frequent keyword co-occurrences. On the other hand, lighter green hues represent less active fields with fewer keyword connections. Fig. 4d displays the top ten keywords sorted by frequency, with “Hi-C” being the most frequently used keyword, appearing 441 times, followed by “3C” (N=208) and “Chromosome conformation” (N=155).



Strengths And Limitations:

This study offers valuable insights into the evolution of chromosome conformation capture (C) technologies through a detailed bibliometric analysis. A major strength lies in its comprehensive approach, covering two decades of research and using Scopus, a well-regarded database, to ensure a broad yet relevant dataset. The systematic search strategy, along with rigorous validation methods, enhances the reliability of findings. Additionally, the use of advanced bibliometric tools like VOSviewer allows for in-depth visualization of research trends, author collaborations, and key thematic clusters, providing a clear picture of how the field has developed over time.

However, there are some limitations to consider. Despite Scopus' extensive coverage, some relevant studies indexed in other databases, such as Web of Science or PubMed, may have been overlooked. The exclusion of conference proceedings, books, and grey literature might also limit the scope, potentially missing emerging research in its early stages. Furthermore, while citation analysis highlights influential works, newer studies may appear underrepresented due to citation lag. Lastly, while bibliometric analysis identifies trends and research gaps, it does not assess the scientific quality or biological impact of individual studies, which would require a more qualitative approach.

Conclusion:

The evolution of chromosome conformation capture (C) technologies has significantly advanced our understanding of genome architecture, gene regulation, and chromatin interactions. The increasing volume of research in this domain underscores its growing importance in life sciences, medicine, and computational biology. Artificial intelligence (AI) is playing a transformative role in this field, particularly in analyzing vast Hi-C datasets, identifying structural variations, and predicting chromatin interactions with higher accuracy. Machine learning models are enabling automated feature extraction, enhancing data visualization, and improving genome assembly techniques. As AI-driven methodologies continue to evolve, they will further accelerate discoveries in genome organization and functional genomics.

Conflict Of Interest:

The authors have no relevant financial or non-financial interests to disclose.

Author Contribution:

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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