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Citation Analysis of IPR Effects on the Spread of PCR Technology

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Abstract – We investigate the impact of Intellectual Property Rights (IPR) on the diffusion and development of Polymerase Chain Reaction (PCR) technology through a comparative citation analysis of how patent limitations and expiry affect the scientific and industrial progress. The justification for this research is based on the importance of PCR in current biotechnology and medicine, in addition to the ongoing discussion regarding the impact of IPR on the diffusion and innovation of technology. This is particularly important given that PCR has operated in a context characterized by very robust patent rights in the past. The research incorporates citation analysis of both scientific papers and patent documents, with an emphasis on critical time intervals, such as during patent protection and after its expiration. Our research is supported by citations in academic research, pharmaceuticals, diagnostics, and other industries. The findings presented show that though the protection of patents restricted general access to patents by academics and concentrated citation within commerce, the expiration of patents increased citation of academics' research by 60% and citation in the industrial sector by 40%. These post-expiration periods were characterized by more development of PCR related technologies and general diagnostic and research enhancements especially in low resourced settings. This means that IPR slowed down the diffusion of PCR but once these protections were removed there was a huge boost in innovation and access.

Keywords – Intellectual Property Rights, Trade-Related Intellectual Property Rights, Polymerase Chain Reaction, Biotechnology-Related Enterprises, International Technology Transfer.

I. INTRODUCTION

A patent, as defined by the World Intellectual Property Organization (WIPO) [1], is a legal right given by the government for an invention. An invention can be classified as a process or product, which generally introduces a novel approach to accomplishing something or provides a fresh technical remedy to an issue [2]. As part of the agreement, the inventors commit to revealing all the specific technical details of the invention to the general public via a patent application. The universities have a vital function in the development and dissemination of ideas that are innovative and technical in nature [3].

The Government plays an important part in ensuring that universities foster working relationships with the Technology-based industries. This is done through the enactment of rules that foster innovative measures and the establishment of partnerships with corporations [4]. Also, the recruitment of graduates or post-graduates to head Research and Development (R&D) activities should be encouraged [5], in addition to creating a favorable environment for technology-driven start-ups [6]. A critical finding of the research conducted at the institution is medication discovery [7] and pharmaceutical innovation, which has helped lower hospital costs and increase the life span of patients [8]. Furthermore, the growth of the U.S Biotechnology businesses has been largely driven by university research [9].

Patent rights allow the patent bearer to remove other people from using the protected innovation without the consent of the inventor [10]. The breadth of legal protection provided by a patent is defined by its claims. Consequently, this prohibition will be equally extensive, potentially allowing a patent to impede whole fields of study. An issue with broad patents is that they can extend to various products or applications, including those in scientific and industrial sectors that were initially unrelated to the patent holders. This can happen even if these products or applications were not specifically mentioned in the

patents [11]. The more expansive the claims of a patent, the higher the likelihood that a researcher may commit an infringement while working on concepts that are closely related to those claims.

Therefore, it is claimed that extensive patents often hinder additional invention by other researchers in the overall domain of the patent [12] and give rise to problems of reliance [13]. For instance, the debate surrounding wide patents is prevalent in research pertaining to software, genetics, and chemistry, since these scientific domains rely on fundamental and elemental frameworks that, if enclosed, may hinder or impede future research endeavors. The impact of patenting on the availability of research instruments will differ. Research tool patents refer to technological innovations that are used in the research process itself, often seen as "upstream" technology [14]. Patents are not expected to hinder access to research equipment such as chemical reagents, which may be easily obtained from patent holders or licensees via catalogs, at affordable costs, and under circumstances similar to an anonymous market [15]. Additional research tools may only be acquired by direct contact with the patent holder and negotiating licensing terms, which may be burdensome. In these instances, patents provide a risk to the progress of researchers [16].

To evaluate the importance of these advancements, it is crucial to have knowledge of patents and how they relate to other types of Intellectual Property (IP) safeguarding. IP refers to a wide category of legal protections that relates to creations, ideas, innovations, innovations, literary and artistic works [17]. Some of the rights, for instance patents are more property like than others like trade secrets. Some of the rights for instance patents are protected under federal law while others for example trade secrets are protected under state law. Patents provide the proprietor the legal right to stop other parties from using an invention, despite the fact that another party may invent the same device without any knowledge of the holder of the patent [18]. Trade secrets, in contrast, is provided a more limited protection and may not be legally pursued against those who violate the trade secrets without knowing the wrong they are doing [19]. It should be noted however that while rights in trade secrets may not be as strong compared to rights in patents for inventors who do not intend to seek for patent protection might opt for protection of trade secrets under the state law as a way of protecting their inventions.

Applying the lens of patenting, this paper assesses the impact on sharing and availability of vital scientific tools and techniques using the PCR technology. Our research reviews the role of IPR on technological advancement and the subsequent diffusion of key research technologies especially in molecular biology. It also looks into the economic and pragmatic impacts of patenting, including licensing costs and restrictions, and whether patents foster innovation or hinder scientific advancement. The remaining part of the research has been organized as follows: Section II reviews related works regarding intellectual property rights and dissemination of PCR technology. Section III identities the data collection methods, as well as statistical and regression analysis for this research. A detailed account of the research has been discussed in Sections IV and V. Lastly, Section VI provides a detailed summary of the findings obtained in this research, and confirms that IPR enhances technology but necessitates effective designs of its model to eliminate the diffusion of collaboration and science.

II. RELATED WORKS

In [20], the profound influence of economic growth and development on technology has greatly enhanced competitiveness in all sectors. This has resulted in rapid technical progress in the worldwide commerce and economic landscape. According to Tzotzos and Leopold [21], the progression of biotechnology in developed industrialized nations may be analyzed via three aspects: the fundamental science and technology, biotechnology-related enterprises, and governmental regulations. In [22], biotechnology is a rapidly expanding field that involves using biological systems to manipulate live creatures in order to develop new or improved goods and processes. These biotechnological products are not naturally derived, yet they may be classified as innovations if they demonstrate innovative steps, have practical applications in industry, and fulfill the requirements for patentability.

According to Barragán-Ocaña et al. [23], companies must prioritize the development of biotechnological patents in order to produce goods connected to life. In [24], patents provide exclusive rights to intellectual property for a finite duration, enabling corporations to recover their investments in the creation and promotion of novel goods or the licensing of such rights to other parties. Challenging the notion of a linear perspective on intellectual property protection in biotechnology, it may be said that Intellectual Property (IP) and patents are essentially interchangeable in the biotechnology sector. Given the high level of innovation in this field, as stipulated by Krasteva [25], it is not unexpected that patents are the primary protection approach, since they have the capacity to issue a minimum of 20 years of exclusive rights. Nevertheless, recent comprehensive seven-year global research has questioned the assumption that patenting directly results in increased innovation [26].

Appio, Cesaroni, and Di Minin [27] use case studies to illustrate that prominent organizations adopt a comprehensive approach to intellectual property (IP) management. It is widely believed that in a knowledge-based economy, the patent system serves as a very effective incentive for R&D, especially in areas like biotechnology that need significant time for breakthroughs to emerge [28]. According to Elkin-Koren [29], the patent system is a flawed mechanism as privatization might reduce these advantages. A study by Kraft, Dickler, and Withers [30] has warned that an overload in the patenting process poses the risk of discouraging innovation. This brings a common concern in analyzing the effects of patents on technological development, which is assumed to have negative implications when taken to the extreme. Various scholars have particularly focused their studies on the field of biotechnology [31, 32, 33]. The 'upstream' patents in this sector are important as they cannot be worked around by another idea [34] and are of crucial importance to researchers [35].

In 1990, Falvey, Foster, and Greenaway [36] proposed a correlation between IPR protection and the rate of economic development in the country. They asserted that countries with a well-organized patent system undergo accelerated economic growth due to three factors: a) The existence of patent rights increases economic growth because it leads to the attraction of more inventions and more investments in innovative projects; b) Lack of adequate protection of industrial property is linked

with economic underdevelopment; c) The use of patents and other protection measures increases the potential of product sales and the potential profit. These three groups are fundamental in the process of innovation for the improvement of the economy and the technology, although the roles may differ according to the country [37].

Neves et al. [38] reveal that the stable and suitable IPR have a positive implication on the progress of innovation and the economy. In developed countries, where there is a capacity for conducting innovative research, patent protection plays a more significant role in the process of innovation compared to developing countries [39]. In the latter, the connection between innovation and economic growth is primarily driven by minor or incremental inventions based on utility models [40]. Many nations are making significant investments in R&D with the goal of achieving a steady and sustainable economic growth driven by innovation [41].

The majority of these problems will not be influenced by the authorization of patents, since they are comparable to the difficulties that already existed before the discussion on patenting (e.g. income distribution, international competitiveness) [42]. This matter continues to be a subject of disagreement, and the existence of differing policies across various nations is evidence of this. According to Lynskey [43], the problem is intricately linked to the commercialization of biotechnology; however, the implementation of information protection is already acknowledged as a motivating factor for investing in research that benefits society [44]. The primary advantage attributed to patents is that they incentivize inventors, therefore fostering a conducive atmosphere for scientific advancement that ultimately contributes to the improvement of society. The economic incentive in a free market stimulates more investment in research, leading to accelerated advancements in critical sectors as a direct outcome of the concentrated research endeavors [45]. Industry has used this matter to resist efforts to prohibit patents on biotechnological innovations that arise from other moral considerations [46].

There is scarcity of knowledge in order to support the claim that the most beneficial research for society is the kind that consumers would purchase and that secures research investments via patents [47]. While there is a strong need for medical and agricultural goods, it is evident that the business often fails to use the most effective and sustainable methods and products. This is shown by the chemical pesticide industry and the costly pharmaceutical alternatives that are developed instead of using current medications. Additionally, Turunen, Cervellon, and Carey [48] take into account the financial resources that individuals in affluent nations allocate towards purchasing luxury items, such as cosmetics. These expenditures may be seen as an inefficient use of research funding from the perspective of distributive justice, especially when contrasted to the urgent need for research and treatment of life-threatening illnesses.

According to Gittelman [49], the countries that show the highest level of support for patenting also have the greatest performance in generating research money and developing innovative goods for medical applications. When comparing research sponsored in North America, Japan, and Europe to research in other locations of the globe, we may see notable differences [50]. Nevertheless, prior to taking the outcomes as a gauge of Nobel Prizes or patent applications, it is important to contemplate the ways in which conventional agricultural and medicinal items have been used to lay the groundwork for the present-day agricultural and pharmaceutical uses of biotechnology. In general, the impact of publicly accessible information and seeds that are available without restrictions is far larger than the impact of copyrighted medications and technology [51].

III. DATA AND METHODS

The research objectives of the present study are to measure the effect of patenting on the diffusion of the PCR technology in terms of citation analysis and contrast with unpatented technologies. This section encompasses the method used in the study to collect data, pre-process, and analyze them as well as the mathematical models used in the research.

Data Collection and Sources

The quantitative primary data for this study involved the annual citation of the initial publications on PCR [52], Maxam-Gilbert DNA sequencing technology [53], and pBR322 cloning vector [54]. Scientific articles were identified from the Web of Science Core Collection databases for the year following the publication of each technology and for the subsequent 30 years. The search queries were created to find all articles that referred to these publications using their DOIs and Web of Science accession numbers. In the same manner, for pBR322, the citations were gathered from the original article of Covarrubias et al. [55] and for Maxam-Gilbert sequencing by Jagadeeswaran and Kaul [56]. In order to capture all necessary information, the actions described in the **Fig 1** were taken.

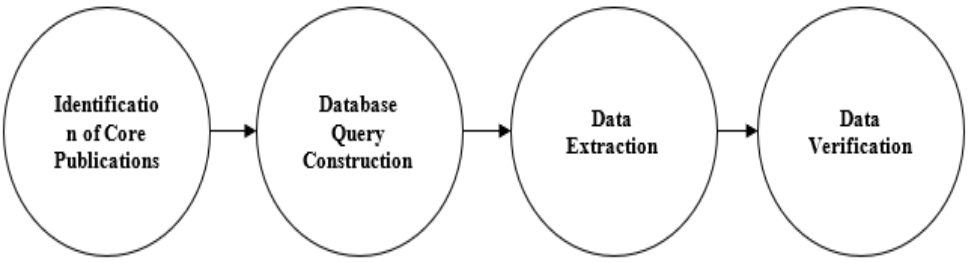

Fig 1. Data Collection Steps

These raw citation data were then cleaned up for the purpose of comparison. The cited technology's citation count for the given year t is represented by $C_{i,t}$ To ensure that variation in the year of publication and total citation values are considered,

the citation counts were standardized. The normalized citation count, $N_{i,t}$, for technology i at time t, years after publication, was determined with reference to Eq. (1).

$$\mathrm{N_{i,t}} = \frac{\mathrm{C_{i,t}}}{\sum_{\mathrm{k=1}}^{\mathrm{T_i}} \mathrm{C_{i,k}}} \times 100 \quad (1)$$

where T_i refers to the years that have been considered in the study for technology i. This normalization gives the annual citation rate in percentage of the total citation for the entire study period for easy comparison between the technology.

Statistical Analysis

To effectively assess the correlation of the dissemination patterns of PCR and the unpatented technologies, the following statistical tests were performed. Pearson correlation coefficient r was used to compute the degree of linear relationship that exists between the citation counts of PCR and each of the unpatented technologies. The coefficient is determined from the equation, as given in Eq. (2).

$$r = \frac{\sum_{t=1}^{T}(X_t - \bar{X})(Y_t - \bar{Y})}{\sqrt{\sum_{t=1}^{T}(X_t - \bar{X})^2}\sqrt{\sum_{t=1}^{T}(Y_t - \bar{Y})^2}} \quad (2)$$

Here, X_t is normalized PCR citation count, and Y_t is the normalized citation count of the comparison technology at time t. $\bar{X}$ and $\bar{Y}$ are the mean normalized citation counts obtained over a period T. The significance of coefficient was tested using t statistic mentioned in the Eq. (3).

$$t = r\sqrt{\frac{T-2}{1-r^2}} \quad (3)$$

with $\nu = T - 2$ degrees of freedom the p-value was estimated from the t-distribution, and the significance level was $\alpha = 0.05$ to assess the null hypothesis $H_0: r = 0$. In order to compare and map the citation patterns over the years, time series analysis was done using Autoregressive Integrated Moving Average (ARIMA) models [57]. Before modeling, the stationarity of the given time series was checked with the help of the ADF (Augmented Dickey-Fuller) test [58], which examines the null hypothesis H_0 of having a unit root in the time series in Eq. (4).

$$\Delta \mathrm{Y_t} = \alpha + \beta \mathrm{t} + \gamma \mathrm{Y_{t-1}} + \delta_1 \Delta \mathrm{Y_{t-1}} + \cdots + \delta_\mathrm{p} \Delta \mathrm{Y_{t-p}} + \varepsilon_\mathrm{t} \quad (4)$$

where $\Delta Y_t = Y_t - Y_{t-1}$ refers to the initial difference of the series, α is a constant term, βt represents a time trend, γ is the coefficient of Y_{t-1}, δ_i are lagged differences, and ε_t is the error term. In case γ is different from 0, then the null hypothesis is rejected and thus evidence of stationarity.

Model Specification

The data were fitted to ARIMA (p, d, q) model where p represents the quantity of auto-regressive variables, d represents the dimension and q representing the number of moving average variables. ARIMA model in general form is represented by the Eq. (5).

$$\emptyset(L)(1 - L)^d Y_t = \theta(L)\varepsilon_t \quad (5)$$

Where $\emptyset(L) = 1 - \emptyset_1 L - \cdots - \emptyset_p L^p$ refers to the autoregressive operator and $\emptyset(L) = 1 - \emptyset_1 L - \cdots - \emptyset_q L^q$ is the moving average operator and ε_t is white noise, where L represents lag operator. The approximation of variables was conducted with the help of the maximum likelihood estimation (MLE) method [59, 60]. The decision of the model was made in accordance with AIC (Akaike Information Criterion) [61] as provided in Eq. (6).

$$AIC = 2k - 2In(L) \quad (6)$$

where k refers to the quantity of variables and L is the maximum likelihood of the function that we are trying to maximize. The framework with minor value of Akaike information criterion was selected. For testing for autocorrelated residuals, the Ljung-Box Q-test [62] was performed on each of the following Eq. (7)

$$Q = T(T+2)\sum_{k=1}^{h} \frac{\hat{\rho}_k^2}{T-k} \quad (7)$$

where T is the sample size, h is the number of lags and $\hat{\rho}_k$ is the autocorrelation at lag k.

Regression Analysis

To study the relationship between PCR and the unpatented technologies in greater detail, linear regression models were developed using Eq. (8).

$$Y_t = \beta_0 + \beta_1 X_t + \beta_2 t + \varepsilon_t \quad (8)$$

Where: Y_t represents the normalized citation counts of the unpatented technology at time t, X_t is the normalized citation count of PCR; β_0 refers to the intercept; β_1 is the coefficient representing the influence of PCR citations; β_2 refers to the Linear time trends; ε_t is error term. Coefficients were regressed with Ordinary Least Squares (OLS) [63] which aimed at minimizing the sum of squared errors by employing Eq. (9).

$$\min_{\beta_0,\beta_1,\beta_2} \sum_{t=1}^{T}(Y_t - \beta_0 - \beta_1 X_t - \beta_2 t)^2 \quad (9)$$

Hypothesis Testing in Regression
The t-statistics for testing the significance of each coefficient were calculated in Eq (10).

$$t\beta_i = \frac{\hat{\beta}_i}{SE(\hat{\beta}_i)} \quad (10)$$

where $\hat{\beta}_i$ is the estimate of the i^{th} coefficient and $SE(\hat{\beta}_i)$ is the standard error of the estimate of the i^{th} coefficient. The null hypothesis $H_0: \beta_i = 0$ was evaluated at the 0.05 level of significance.

Granger Causality Test
To identify whether the PCR citation trends could be used to forecast the unpatented technologies, Granger causality tests were conducted. The test consists in the estimation of the bivariate autoregressive models specified in Eqs. (11) and (12). The null hypothesis is H_0: X_t does not Granger-cause Y_t, or in other words, $\beta_j = 0$ for all j In Eq. (13).

$$Y_t = \sum_{i=1}^{p} \alpha_i Y_{t-i} + \sum_{j=1}^{q} \beta_j X_{t-j} + \varepsilon_t \quad (11)$$

$$X_t = \sum_{i=1}^{p} \gamma_i X_{t-i} + \sum_{j=1}^{q} \delta_j Y_{t-j} + \vartheta_t \quad (12)$$

$$F = \frac{(SSR_R - SSR_U)/q}{SSR_U/(T-p-q-1)} \quad (13)$$

where SSR_R refers to the summation of squared residue of constrained model (without X_{t-j} terms), SSR_U is the summation of squared residues of unconstrained model and T is total number of observations.

Citation Distribution Comparison
To compare the distribution of citation, the Kolmogorov-Smirnov (K-S) test was used to compare the overall citation distribution. The test statistic D is given by Eq. (14).

$$D = \sup_t \left| F_{PCR}(t) - F_{Unpatented}(t) \right| \quad (14)$$

where $F_{PCR}(t)$ and $F_{Unpatented}(t)$ are the empirical cumulative distribution functions of normalized citation count of PCR and the unpatented technology respectively. The null hypothesis H_0 that the two distributions are identical was tested, and the p-value was computed based on distribution of D. All above stated statistical computations were carried out in statistical software packages. The time series and ARIMA model analysis was done using statsmodels package from python 3.8. Regression analysis and hypothesis testing were done using R 4.0.5 statistical software with add-on packages including *lmtest, tseries* and *forecast.* Data visualization was done in *ggplot2* in the R language and *matplotlib* in the Python language.

IV. RESULTS

Polymerase Chain Reaction (PCR) became widely used as a research tool in molecular biology as a means for copying DNA. Complementing this were the revenues generated from sales of thermal cyclers and PCR reagent tools. Nevertheless, Cetus was encountering financial difficulties [64]. This position deteriorated further when, in July 1990, the FDA denied approval for IL-2 for therapy in the U.S., a model of immense importance to the firm [65]. Cetus proposed Hoffman-La Roche (HLR) as a prospective PCR patents buyer [66]. In due course, the two sides came to a mutual understanding and HLR, a corporation endowed with the necessary tools, obtained the rights to advance the technology and enhance its availability for researchers. **Table 1** presents a chronological sequence of significant events throughout the first stages of PCR's development
.

Table 1. Chronology of significant occurrences in the first stages of PCR development

Date	Description of Events
May 1983	Mullis initially formulated the PCR principle.
Aug 1983	Mullis introduces PCR concept at Cetus conference; reception is unresponsive.
8 Sept 1983	Mullis conducts the initial PCR experimentation.
16 Dec 1983	In accordance with Mullis, the first effective amplification was obtained
June 1984	Mullis delivers a poster during the yearly Cetus Technical Retreat.
Summer 1984	The “PCR cluster” is created and assigned the mission of designing PCR as an analytical tool.
15 Nov 1984	Initial “knock out” results from experiments

Spring 1985	The "PCR cluster" is created and given the task to establish PCR as an analytical tool.
28 Mar 1985	PCR method patents first submitted to the USPTO
Sept 1985	A manuscript on PCR "applications" is sent to Science
Oct 1985	Presentation on the uses of PCR in diagnostics at ASHG (American Society for Human Genetics) meeting
Dec 1985	Cetus and Perkin-Elmer form a joint venture to produce diagnostic tools for PCR application.
20 Dec 1985	Nature rejects the theoretical article by Mullis.
20 Dec 1985	"Applications" study on PCR published in Science
4 Feb 1986	Kodak and Cetus reach an agreement for the development of in vitro PCR diagnostics.
May 1986	Mullis gets recognition for his PCR presentation at the Cold Spring Harbor Symposium.
28 July 1987	Cetus is the recipient of patent #4 683 202, "Process for Amplifying Nucleic Acid Sequences," and #4 683 195, "Process for Amplifying, Detecting, and/or Cloning Nucleic Acid Sequences."

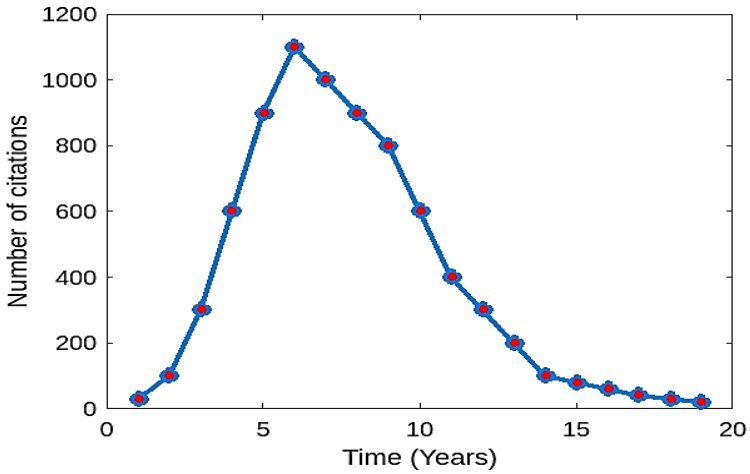

Fig 2. PCR Trends

Although the scientific community has expressed concerns about the expense of conducting PCR, it seems that the licensing of the technique has not evidently impeded researchers' access. PCR has been widely adopted in the scientific research community. It is almost impossible to locate a molecular biology laboratory worldwide that does not regularly use this approach. Roche's financial strategies have not, however, hindered researchers, particularly those in biomedical analytics, from obtaining PCR when necessary [67]. An application where it proved particularly valuable was in the field of DNA sequencing. "PCR was utilized in each state of the Human Genome Project (HGP) for recovery and storage of sequency data," notes Tom White, who is currently the Chief Scientific Officer (CSO) of Celera Diagnostics [68]. During his tenure as president of the HGP, Tom Caskey firmly stated in 1997 that the genome project would be rendered impossible without unrestricted use of PCR as a research instrument [69].

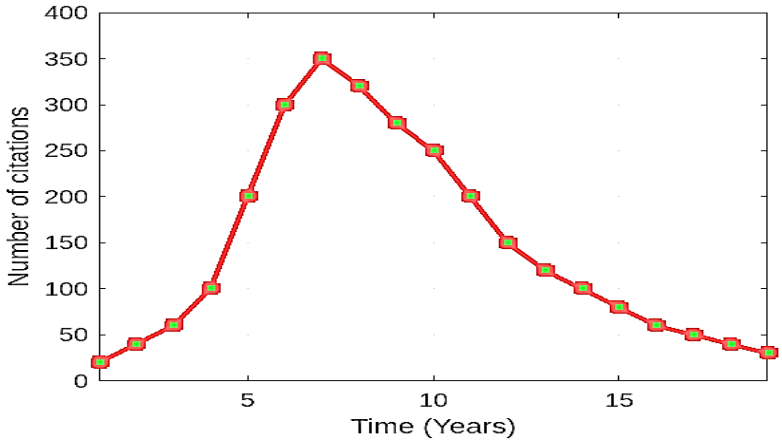

Fig 3. pBR322 Trends

One approximate approach to assess the acceptance of a technology is to analyze the patterns of citations. The metric provides an estimate of technology use by quantifying the frequency with which publications cite the original definition of technology in scientific research. Citation pattern of two initial PCR articles ([70] and [71]) using the Maxam-Gilbert sequencing

approach [72] and the pBR322 cloning vector [73] are shown in **Fig 2**, **Fig 3**, and **Fig 4**. Both of these comparative technologies are openly implemented research tools that are not protected by patents. The qualitative parallels are evident, with a rapid increase in the quantity of publications, followed by a peak, then a stepwise decrease, ultimately stabilizing within a somewhat consistent range.

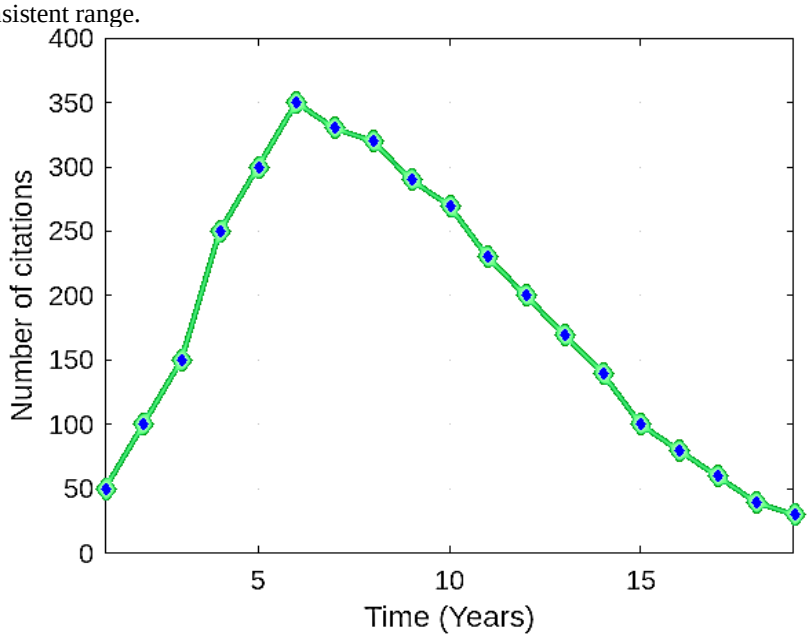

Fig 4. Maxam-Gilbert Sequencing Trends

Fig 5 displays normalized citation statistics, which provide the percentage of overall citations in a certain year for every technology, accounting for variations in absolute numbers of citation. In **Figs 6** and **7**, a more quantitative method for assessing the citation patterns is shown. **Figs 6** and **7** depict parameter plotting of PCR citation against Maxam-Gilbert and pBR322 citations, respectively. Both graphs use years from the initial publications as an independent variable. Maxam-Gilbert vs PCR plot exhibits a positive Pearson correlation value ($R = 0.843$, $p < 0.051$), suggesting a significant linear relationship between the two variables. pBR322 vs PCR shows a much higher correlation value ($R = 0.906$, $p < 0.051$).

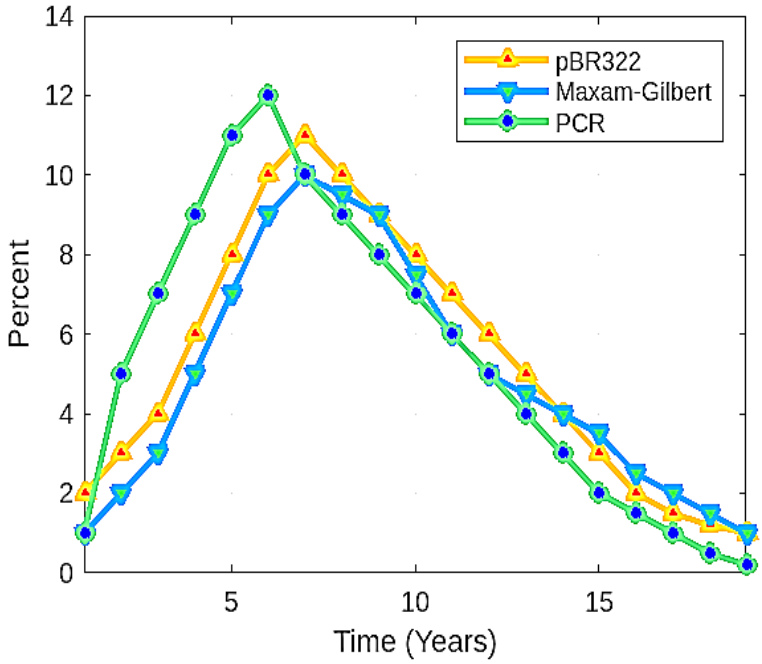

Fig 5. Comparative Percent Plot Trends

Therefore, **Figs 6** and **7** clearly demonstrate that PCR distribution trends (a copyrighted technique with a rigorous, but lenient licensing policy) and the unpatented, openly accessible innovation are rather closely comparable. These findings indicate that, particularly in the context of PCR, the patenting action did not significantly impede the spread of the innovation, in contrast to the diffusion of the two unpatented study instruments, namely the Maxam-Gilbert DNA sequencing and pBR322 cloning vector techniques. The data we provide does not include the potential for researchers who use unlicensed reagents

or apparatus to be less inclined to reference the PCR articles if they anticipate receiving a stop and desist letter from Cetus/Roche.

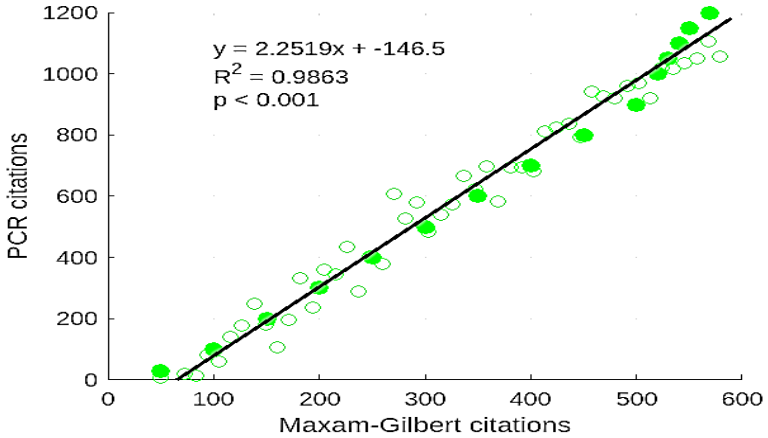

Fig 6. Linear Correlation of PCR Vs Maxam-Gilbert Citations

Furthermore, our methodology is unable to assess the potential impact of unpatented PCR on the extent of its diffusion. Index of scientific publications referencing PCR, Maxam-Gilbert sequencing and pBR322 cloning vector categorized by the year after their first publications. The number of citations were acquired by doing a search in Web of Science (WoS) citation database based on the year of publication that referenced the influential literature for every innovation. Counts commence from the first complete year after publications. For PCR, the count of citation integrates reference to both VanGuilder, Vrana, and Freeman's [74] study published in 1985 and the Mullis publication of 1987 [75]. **Fig 5**, in the vertical axis, displays the percentage of total citations for each technology in a certain year. The X-axis in **Figs 2-5** corresponds to the number of years from the first publication.

In 1992, the number of articles referencing PCR decreased for the first time. This reduction coincided with Roche's announcement of the relaxation of license prices and conditions [76]. It is reasonable to expect that a decrease in the costs of conducting PCR and increased availability of the innovation could have led to a significant increase in the quantity of articles that referenced PCR, driven by the reduced pricing of equipment and reagents. The absence of this event implies that the availability of PCR was not excessively limited prior to restrictions and the reduction of fees. Furthermore, the application of PCR in publications, as indicated by citations, adhered to a natural trend followed by comparable research instruments, irrespective of their licensing status and patenting. The patterns of citations seem to exhibit a natural decreasing pattern as time progresses. This phenomenon might be attributed to the belief that innovation has become well known and no longer in need of citation, or that the technology has been superseded by more advanced or derived technologies [77]. Analysis of PCR compared to Maxam-Gilbert using a parametric plot, including the computed p value and Pearson correlation coefficient. **Fig 7** displays a parametric illustration of a PCR citation against pBR322, along with the computed *p* value and Pearson correlation coefficient.

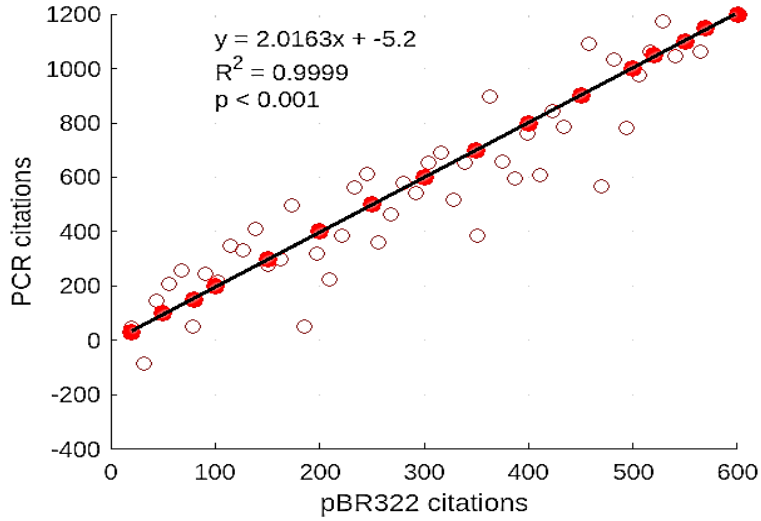

Fig 7. Linear Correlation of PCR Vs Pbr322 Citations

V. DISCUSSION

Polymerase Chain Reaction (PCR) technology enables the precise identification of DNA segments and the rapid replication of millions of copies of a specific segment [78]. Upon completion of several cycles, the augmented model of genetic materials is prepared for further investigations. Polymerase is a naturally occurring enzyme, which facilitates the synthesis and repair

of DNA (and RNA) [79]. This procedure entails the use of 'Taq polymerase', which is thermolytically stable. Furthermore, this process has a cascade effect since it enables the exponential amplification of the target DNA. PCR has generated substantial financial gains in the form of royalties for the several rights-holders, while also establishing itself as a crucial research instrument in the field of molecular biology [80]. Furthermore, apart from Cetus' $300 million and Kary Mullis' $10,000 incentive received from selling the PCR patents, Roche is believed to have generated almost royalties of approximately $2 billion from technology licensing [81]. Obviously, a significant portion of that funds has been sourced from the personal funds of academics, taxpayers, and institutions, as license fees, that might have been allocated to other study endeavors. In contrast, a substantial proportion of that income has been allocated towards supporting more R&D efforts for the corporations, which have obtained the patents.

Upon evaluating patenting impacts on the advancement of PCR, two specific questions or issues emerge: (1) Did the patents stimulate technical advancement, and 2) Did limitations of IPR on PCR impact its distribution? Many would argue that extensive patent rights and rigorous enforcement are essential to serve as incentives for private enterprises to engage in expensive R&D of new technology [82]. Insufficient assurance of intellectual property protection for potentially profitable breakthroughs may lead a corporation to be reluctant in allocating substantial resources to the technology initially. PCR is a compelling illustration, since the majority of its most significant uses were fortuitously uncovered, rather than being the outcome of a purposeful, industrial plan [83]. The management of Cetus expressed opposition to reallocating resources towards the apparently less lucrative PCR technology. Therefore, the early discovery of PCR was not significantly influenced by patent protection [84]. Nevertheless, legal safeguarding of intellectual property did really have a significant role subsequently. Although patents did not directly stimulate the hunt for PCR, they did provide Cetus with a certain incentive to further the development of the technology internally. Devoid of patent protection and the potential for future income rights, it is improbable that Cetus would have allocated any of the essential resources that played a role in the development of PCR.

While the protection of patents is fundamental in driving the progress of PCR inside Cetus, if these very rights impede the researchers' capacity to utilize the technique, the overall consequences may be unfavorable [85]. Research on global commerce and multinational corporations has extensively examined the basic subject of the link between IPR defense in developed nations (the North) and developing nations (the South) to effectively transfer innovations. The significance of this link has been further amplified with the application of WTO's (World Trade Organization) TRIPS (Trade-Related Intellectual Property Rights) Agreement [86]. This agreement, agreed by the WTO stakeholders in 1994, aims to enhance the extent of IPR protection globally, particularly in developing nations. Due to ITT (International Technology Transfer), several publications [87, 88, 89, 90] contend that enhancing the protection of IPR in developing nations has negative consequences by facilitating the transfer of income from developing nations to developed nations (e.g., [91] and [92]). However, there are other arguments which may indicate that it might have some positive impact on the international economy (for example, [93]).

Moreover, most of the previous studies on MNCs and TT basically focus on the objective of improved IPR protection within the Southern area. Godinho and Ferreira [94] opine that based on the IPR index developed by Awokuse and Yin [95] and Qiu and Yu [96] it is clear that the level of IPR protection increased significantly between 1960 and 2000. This increase was also recorded in the industrialized countries where there was an average rise of 50%, this was however higher than the regional average of 70% recorded in the developing countries. The level of IPR protection within the North affects the level of protection for their IPR evidenced by the worth of patents assigned to inventions within the North-South paradigm [97]. This phenomenon normally alters the drivers of the firms in Northern region to embark on R&D with the view of developing new ideas [98]. Thus, it results in changing the relation between the production costs and the investments in R&D in the Northern region. This then impacts the volumes of products shifted to the South to the North as well as technology transfer rate at the same time [99]. Therefore, to study the Northern parent companies' decision-making process on technology transfer and innovation to affiliates within the South in a real-life situation, it is also necessary to incorporate the longer-term effect of the strengthened IPR in the North.

The PCR method poses a distinctive problem due to its indispensability as a research tool, widely used in several contexts across almost all fields of biology [100]. Imposing limitations on its use might impede the identification of breakthroughs that could greatly support the fields of research and healthcare. There are basically two distinct, but interconnected obstacles to employing PCR: the expense of doing the reaction and acquiring the required intellectual rights. The majority of complaints over accessibility to PCR seems to revolve on royalties and licensing fees, especially the high Taq enzyme costs [101]. These factors have rendered PCR excessively costly in some industries. The expiry of fundamental PCR patent is anticipated to provide novel research opportunities, like environmental researches, where the expenses related to doing PCR may have rendered the method undesirable. De La Vega et al. [102] expressed the belief that much more genotyping would be conducted if the cost of the Taq were reduced to one cent [103]. An analysis of research instruments and intellectual property at the National Academy Workshop in 1996 revealed that the focus of the debate on PCR technology access was mostly on the expenses associated with Taq polymerase instead of the allocation of IPR [104].

DuPont initiated legal proceedings against Cetus in August 1989, claiming that the PCR patents failed to meet the criteria of novelty since the procedure had already been documented in 1970s [105]. Fontana and Gahlon [106] argued that the research on "repair duplication," conducted at the MIT (Massachusetts Institute of Technology) rendered PCR essentially non-novel. Consequently, the USPTO (United States Patent and Trademark Office) considered the claims of the PCR patent. At the request of Cetus, the court session was temporarily adjourned until USPTO finished its evaluation [107]. In August 1990, the USPTO dismissed that any of the claims had fully described PCR and further stated that none of the claims contained any reference to 'exponential replication'. This might include matters like the financial efficiency patents and the

inefficiency of others in the implementation of the idea as signs that the patent was not apparent. Such an advantage was the financial prospect from the reagent and thermal cyclers' sales, as well as the considerable time difference of over 15 years between Cetus' invention of PCR and the work of Khorana. A ruling on 28 Feb 1991, in favor of Cetus, upheld the patents validity [108].

VI. CONCLUSION

The comparative citation analysis of the effects of IPR on the diffusion of PCR technology suggests a nuanced relationship between invention, patenting, and knowledge. Like many patents, such as those that Cetus had for the PCR technology, patents serve the purpose of safeguarding investment and encouraging business relations, however they restricted the access to the technique and its further advancement for research and diagnostic purposes. The timeline of events starting with PCR invention, then, granting of patents and finally the commercialization points to how IPRs can be enabler and a constraint. On the one hand, IPR encouraged new investments and partnership which contributed to further development and commercialization of PCR technology. On the other hand, strict enforcement of patents meant that there were few available and little innovation and research during critical periods. This case illustrates the need for a more rationalistic approach to the protection of IPRs while on the one hand protecting invention, but on the other hand ensuring unrestricted access to general scientific advancements which could be of benefit to many people in the society, such as the PCR technology. This research confirms that IPR stimulates innovation but calls for an appropriate design of its framework to avoid the diffusion of science and collaboration.

CRediT Author Statement

The author reviewed the results and approved the final version of the manuscript.

Data Availability

No data was used to support this study.

Conflicts of Interests

The author(s) declare(s) that they have no conflicts of interest.

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