# Postprint Analysis of Patent Competition Landscape in Synthetic Biology

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## Abstract

Synthetic biology is an emerging field that integrates and converges biology, engineering, chemistry, and information technology. It holds broad application prospects in medicine, pharmaceuticals, agriculture, materials, environment, and energy, and may even create novel organisms that do not exist in nature, being regarded as a disruptive technology in the field of biotechnology. This study analyzes the relevant development strategies, funding programs, and policy measures of major countries and regions in the field of synthetic biology, summarizes the development history of patent technologies in this field, reveals the distribution of patent R&D themes, and conducts a comprehensive comparative analysis of patent outputs from major countries and institutions in this field, aiming to provide reference data for researchers and management decision-makers in China' s synthetic biology sector.

## Full Text

## Preamble

### An Analysis of Patent Competition in the Field of Synthetic Biology

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## Abstract

Synthetic biology is an emerging interdisciplinary field that integrates biology, engineering, chemistry, and information technology. It is regarded as a disruptive technology in biotechnology with vast application prospects in medicine, pharmaceuticals, agriculture, materials, environment, and energy, and may even create novel organisms not found in nature. This study analyzes the development strategies, funding programs, and policy measures related to synthetic biology in major countries and regions, summarizes the evolution of patented technologies in this field, reveals the distribution of research and development themes, and provides a comprehensive comparative analysis of patent outputs from major countries and institutions. The findings aim to offer reference data for researchers and policymakers in China' s synthetic biology community.

**Keywords:** synthetic biology; trend analysis; patentometrics; patent mapping

Synthetic biology is an emerging field formed by the convergence of biology, engineering, chemistry, and information technology. Its research content can be divided into three hierarchical levels: first, constructing novel regulatory networks using natural biological modules with known functions to exhibit new functions; second, artificially synthesizing genomic DNA and reconstructing living organisms through de novo synthesis methods; and third, creating entirely new biological systems and even artificial life forms after the first two research areas have been fully developed [1]. Synthetic biology represents another major innovative revolution in the life sciences following genomics.

In recent years, synthetic biology research has received widespread attention, with numerous international organizations and think tanks recognizing it as a promising emerging or disruptive technology. In 2004, MIT Technology Review published by the Massachusetts Institute of Technology named synthetic biology one of the ten emerging technologies that would change the world [2]. In 2010, Science magazine ranked synthetic biology second among its top ten scientific breakthroughs [3]. In Nature' s list of twelve major scientific events in 2010, synthetic biology ranked fourth, and the journal predicted that synthetic biology would become a research hotspot in 2012 [4]. Additionally, the World Economic Forum, McKinsey & Company, the Atlantic Council, the Organisation for Economic Co-operation and Development, and the Center for Strategic and International Studies have all released reports identifying synthetic biology as one of the most noteworthy technological trends with broad market prospects [5-11].

## 2. Overview of Synthetic Biology Development in Major Countries/Regions

The United States is one of the earliest countries to conduct synthetic biology research. In 2004, the Bill & Melinda Gates Foundation invested $42.5 million in Amyris for artemisinin research, and in 2006, the company successfully synthesized artemisinic acid in microorganisms for the first time [12]. Subsequently, the United States has continuously increased its R&D investment in synthetic biology. According to a 2015 report on U.S. synthetic biology research funding trends released by the Woodrow Wilson Center, the U.S. government invested approximately $820 million in synthetic biology from 2008 to 2014, averaging about $140 million per year [13]. Moreover, with funding from the National Science Foundation (NSF), multiple U.S. universities have jointly established various synthetic biology engineering research centers.

Europe was an early region to promote and draft synthetic biology roadmaps. In 2005, the European Commission released a report under its Sixth Framework Programme, outlining prospects for synthetic biology in biomedicine, energy, and environment [14]. In 2007, it launched 18 synthetic biology-related pilot projects [15]. Since then, the EU has successively established the European Research Area Network for Synthetic Biology (ERASynBio) and formulated a development roadmap for European synthetic biology, aiming to promote the vigorous development of synthetic biology in Europe [16]. The United Kingdom is also among the earliest European countries to conduct synthetic biology research. In 2008, the UK Biotechnology and Biological Sciences Research Council (BBSRC) listed synthetic biology as a priority funding area [17], and the Engineering and Physical Sciences Research Council, Imperial College London, and the London School of Economics jointly invested £8 million to establish the Centre for Synthetic Biology and Innovation [18]. The UK subsequently released its synthetic biology roadmap and related strategic plans [19], charting the course for future development.

China also attaches great importance to synthetic biology research and development. The Xiangshan Science Conference held two academic discussions on synthetic biology in 2014 and 2015, exploring applications in producing active pharmaceutical ingredients from medicinal plants and future development strategies. In China' s third technology foresight exercise, synthetic biology was listed as one of the ten major breakthrough technologies. In China' s 13th Five-Year Plan for Science and Technology Innovation, synthetic biology technology has been designated as a key development direction, with plans to initially establish an innovation system for synthetic biotechnology by 2020. Furthermore, China' s National Basic Research Program (973 Program) and National High-Tech R&D Program (863 Program) have both prioritized synthetic biology, funding numerous projects related to energy, medicine, and agriculture.

## 3. Data Sources and Analysis Methods

This study employs a combination of qualitative and quantitative analysis methods, including expert consultation, literature review, patentometrics, and statistical analysis. For the qualitative research, we tracked and monitored strategic plans, funding programs, and policy measures related to synthetic biology released by representative countries and regions, and conducted inductive analysis. For the quantitative research, we used the Derwent Innovation (DI) patent database from Clarivate Analytics (formerly Thomson Reuters) as the data source, developed search strategies based on title and abstract keywords, and cleaned and statistically analyzed the retrieved datasets.

We retrieved a total of 12,944 patents in the synthetic biology field, with the data retrieval date being July 30, 2017. The analysis process utilized Derwent Data Analyzer (DDA) software to conduct detailed analysis of these patents from perspectives including application dates, countries/regions, competing institutions, research hotspots, and highly cited patents, aiming to reveal the

R&D layout and development trends in synthetic biology both domestically and internationally.

## 4.1 Patent Application Time Trend Analysis

The overall trend of global synthetic biology patent applications can be divided into three stages (Figure 1 [Figure 1: see original paper]).

### 4.1.1 Slow Development Period: 1974-1993

Before 1993, patent applications in this field were relatively scarce, with global annual applications numbering fewer than 100, representing the embryonic stage of technological development. Stanford University contributed the first patent application in this field, US3887698A (preparing immunological compositions using natural or synthetic cells). The patented technologies during this period focused primarily on gene synthesis research, with representative patents including WO1992014843A1 (specific binding DNA aptamers for detecting target molecules) applied for by Gilead Sciences, US5591625A (transfecting human bone marrow mesenchymal stem cells with exogenous gene-encoded proteins) by Case Western Reserve University, and US5436391A (preparation of novel protein genes and vectors for plant disease and pest resistance) by Mitsubishi Chemical Corporation.

### 4.1.2 Rapid Growth Period: 1994-2003

The Human Genome Project, launched in the 1990s, gave rise to genomics and enabled unprecedented comprehensive understanding of the complete genetic coding information of a living system. In 2000, Nature reported research achievements in synthetic gene circuits, including the oscillating synthetic biological circuit completed by Michael B. Elowitz at Princeton University and the first artificial synthetic bistable switch constructed by the TS Gardner research group at Boston University using two mutually inhibitory repressor proteins in E. coli. Since then, synthetic biology research has attracted broader attention and importance worldwide, with international development advancing rapidly. Patent applications in this field showed a very clear growth trend during this period, increasing from 480 in 2000 to 590 in 2001, and forming a small application peak in 2003 (610 applications). Thus, the period from 1994 to 2003 was a rapid technological development phase. During this time, many large enterprises in the field had gradually grown and established their own technological competitive advantages. For example, Netherlands-based Affymax Technologies applied for numerous patents in directed molecular evolution, with representative patents including US5605793A (DNA mutagenesis by random fragmentation and reassembly) and US5811238A (generating polynucleotides with desired characteristics through iterative selection and recombination). The Scripps Research Institute and Maxygen also conducted synthetic biology research during this period and rose rapidly, as evidenced by numerous patents being heavily cited by other institutions.

#### 4.1.3 Steady Development Period: 2004-2017

With the completion of the human genome sequencing project in 2003, various omics technologies became relatively mature, and life sciences research entered a period of steady development, synthetic biology included. During this period, most institutions entering the synthetic biology field were Chinese, while some foreign institutions underwent mergers, reorganizations, or dissolution, and Europe experienced debates on synthetic biology ethics and biosafety, leading to fluctuating but rising patent application trends. For example, Divergence Inc. reorganized to form Verdezyne, and Maxygen dissolved in 2013 after selling its main business divisions multiple times, activities that more or less affected international patent application trends. Patented technologies during this period focused primarily on applications, with representative patents from the UK Medical Research Council (EP239400A) and U.S. Solazyme Company (WO2008151149A2), covering recombinant altered antibodies and cultured microbial populations for producing renewable diesel or jet fuel, respectively.

### 4.2 Patent Theme Analysis

Based on the THEMES thematic analysis function in the Derwent Innovation platform, this study conducted visual analysis of R&D themes in synthetic biology, forming a contour map similar to topographic maps. In the map, points represent individual patents, peaks represent different technical themes formed by similar patents, and white areas indicate concentrated patent fields and research hotspots.

According to the technical themes contained in relevant patent literature (Figure 2 [Figure 2: see original paper]), current global synthetic biology patent activities roughly encompass seven technical themes and one application theme. The technical themes include: (1) gene/genome synthesis; (2) xenobiology; (3) DNA assembly; (4) chassis cells; (5) directed evolution; (6) cell-free synthetic biology; and (7) genetic circuits and components. The application theme is (8) pharmaceutical applications, referring to the application of synthetic biology in the medical field. Among these, pharmaceutical applications, gene/genome synthesis, xenobiology, and genetic circuits and components are currently the hot topics in synthetic biology patent R&D. In pharmaceutical applications, the use of aptamers in disease treatment is a hot research direction; in gene/genome synthesis, gene synthesis and transgenic plants are hot directions; in xenobiology, non-natural amino acids are a research hotspot; and in genetic circuits and components, research involves cell lines and nucleic acid aptamers.

### 4.3 Analysis of Major Applicant Countries

In this study, the patent application country refers to the source country of the patented technology, determined by the nationality of the patent applicant (or inventor) to identify the origin of a particular technology. This indicator can more clearly reflect a country' s actual technological ownership.

#### 4.3.1 Annual Patent Trend Analysis

Nearly 60 countries or regions have applied for patents related to synthetic biology. The United States, China, and Japan rank top three in patent volume, with 4,706, 1,517, and 825 patents respectively. Additionally, Germany, the UK, and France in Europe each have more than 260 patents. The overall patent applications from these countries show a growth trend (Figure 3 [Figure 3: see original paper]), indicating increasing global attention to this technology field.

From the annual patent trend perspective, the United States is the leading country in synthetic biology patent applications, with its application trend synchronized with the global pattern. China' s patent applications in synthetic biology have shown rapid development over the past decade, surpassing the United States in 2015 to rank first globally. The growth in patent volume from European countries is not significant, possibly due to intense debates on bioethical issues in the European research community that have slowed progress [20].

#### 4.3.2 Comparison of Patent Output Among Major Countries

**(1) Patent Quality Comparative Analysis**

Comparative analysis of patent quality among countries shows (Table 1 ) that the United States has the largest number of granted patents, followed by China and Japan. However, in terms of the proportion of granted patents, Japan has the highest rate at 40.2%, followed by the United States (38.0%) and Germany (33.5%). Regarding PCT patent volume and proportion, the United States has the most PCT patents. Although the UK ranks fifth in total patent volume, it has the highest PCT patent proportion at 28.2%, followed by France (25.2%) and the United States (25.1%). In terms of patent citations, U.S. patents have the highest citation frequency, followed by the UK and Germany. In contrast, China' s PCT patent proportion and citation frequency are relatively low, indicating that its influence still needs improvement.

**(2) Patent Protection Strength Comparative Analysis**

Territoriality is generally considered a fundamental characteristic of patent rights, meaning that patent rights are only effective within the legal jurisdiction of the granting country and have no legal binding force on other countries. Therefore, patent territorial protection is highly valued by all countries and is used by scholars as an indicator for innovation evaluation. The average number of protected regions and the proportion of overseas patent applications can both reflect the internationalization level of patent protection to some extent. As shown in Table 2 , Japan has the best patent protection, with an average of over six protected regions and a relatively high proportion of foreign patents (49%), primarily seeking protection in the United States, the European Patent Office, and China. China' s average number of protected regions is less than two, with overseas patent applications accounting for only 6%, indicating significantly insufficient overseas patent protection.

#### 4.3.3 Patent Filing and Application Flow Analysis Among Major Countries

Analysis of patent filing situations and mutual application flows among the three major source countries of synthetic biology patents shows that the United States holds a clear technology export position, Japan also has a relatively large patent export volume, while China is in a technology import position. The proportion of domestic patent applications in the United States and Japan accounts for 54% and 51% of their total applications respectively, while China' s domestic patent applications account for 94% of its total. Specifically, the United States has applied for 298 patents in China, Japan has applied for 137 and 56 patents in the United States and China respectively, and China has only applied for 44 patents in the United States (Figure 4 [Figure 4: see original paper]). Relatively speaking, although China has high patent application volume, its patents are primarily protected domestically, with weak layout in other countries.

As shown in Figure 4, China has accepted 2,109 patents, including 566 patents applied for by foreign applicants in China. The major countries applying for patents in China are the United States (298), Japan (56), Germany (34), Switzerland (29), and the UK (25). Foreign patents applied for in China primarily involve technical themes such as gene/genome synthesis, xenobiology, in vivo directed evolution technology, chassis cells, cell-free synthetic biology, genetic circuits and components, DNA assembly technology, and 3D printing (Figure 5 [Figure 5: see original paper]). The United States has the highest number of patents in China with comprehensive technology layout; although Germany has fewer patents in China than the United States, its patent layout is also extensive; Japan and the UK have relatively more patents in chassis cells, and Switzerland has more patents in xenobiology.

### 4.4 Distribution of Major Patent Application Institutions

#### 4.4.1 Global Distribution of Major Patent Application Institutions

According to the distribution of the top 10 institutions in global synthetic biology patent applications (Table 3 ), U.S. institutions are the most numerous with eight, occupying the top five positions globally; Denmark and Canada each have one institution; no Chinese institution ranks in the global top 10.

The top three institutions in patent volume are Verdezyne (374 patents), The Scripps Research Institute (347 patents), and the University of California (190 patents). Verdezyne was formed through the reorganization of Divergence Inc., with patented technologies primarily involving isolated, synthetic, or recombinant nucleic acids and enzyme design methods. The Scripps Research Institute is the largest life sciences research institute in the United States, with basic research covering immunology, molecular and cell biology, chemistry, neuroscience, autoimmune diseases, cardiovascular disease, virology, and synthetic vaccine development, particularly being one of the world' s few leading centers in fundamental biomolecular structure and biomolecular design. Multiple campuses of the University of California system have made achievements in synthetic biology, such as the Lawrence Berkeley National Laboratory at UC Berkeley establishing the world' s first synthetic biology center in 2003 [21]. Additionally, the U.S. National Science Foundation invested $20 million in 2006 to fund the establishment of the "Synthetic Biology Engineering Research Center" by UC Berkeley, Harvard University, MIT, UC San Francisco, and others [18]; today, similar research centers have been established at multiple U.S. universities, explaining why U.S. institutions rank highly.

Analysis of patent application active periods and recent application volumes can reveal an institution' s technological leadership sustainability and latest technological development trends. Analysis of the top 10 institutions shows (Table 3) that except for U.S.-based SomaLogic, the active patent application periods of other institutions basically exceed 15 years, with those exceeding 25 years being the University of California, Harvard University, MIT, and the National Research Council of Canada. The University of California is the earliest institution to apply for synthetic biology-related patents, with a history of 28 years, and its patent applications have shown continuous growth, with patents from the last five years accounting for 41.6% of its total. SomaLogic entered this field most recently, with an active period of only 10 years, but its proportion of patents from the last five years is relatively high at 45.5%. Maxygen (157 patents) dissolved in 2013 after selling its main business divisions to DuPont and Amgen in 2004 and 2006, thus having no relevant patent applications in the past five years.

#### 4.4.2 Distribution of Major Patent Application Institutions in China

The top 10 institutions in China' s synthetic biology field are primarily research institutes and universities (Table 4 ). Among them, research institutes including the Chinese Academy of Sciences (90 patents), Academy of Military Medical Sciences (53 patents), Chinese Academy of Agricultural Sciences (49 patents), and Shanghai Academy of Agricultural Sciences (23 patents) rank 1st-3rd and 8th; universities including Jiangnan University (38 patents), Shanghai Jiao Tong University (30 patents), Tsinghua University (27 patents), Zhejiang University (25 patents), Peking University (21 patents), and Fudan University (19 patents) rank 4th-7th and 9th-10th.

The Chinese Academy of Sciences is one of the earliest institutions in China to conduct synthetic biology research, with its first related patent applications dating back to the 1980s. Apart from the Chinese Academy of Sciences, most Chinese patent application institutions entered the synthetic biology field in the late 1990s, with low annual patent application volumes that were intermittent, indicating that China' s research was generally in the exploratory stage with technological accumulation significantly lagging behind foreign institutions. After 2000, China' s synthetic biology research developed rapidly, with gradually increasing patent numbers. In recent years, China has achieved major breakthroughs in synthetic biology. For example, in March 2017, Science featured the synthetic yeast genome project (Sc 2.0) on its cover, reporting the synthesis of five chromosomes, four of which were primarily completed by Chinese scholars: Yuan Yingjin' s team (Tianjin University), Yang Huanming' s team (BGI), and Dai Junbiao' s team (Tsinghua University) [22].

#### 4.4.3 Patent Application Institution Cooperation Network Analysis

The patent cooperation network among major institutions shows that foreign top 10 patent application institutions have conducted collaborative research (Figure 6 [Figure 6: see original paper]). Among them, five U.S. institutions—Verdezyne, The Scripps Research Institute, the University of California, Harvard University, and MIT—have formed a relatively dense patent application cooperation circle with broad technical content covering CRISPR-Cas, anti-sigma factors, genetically engineered cells, recombinant nucleic acids encoding enzymatic polypeptides, and non-natural amino acids. Danish company Novozymes and U.S.-based Maxygen formed transnational patent cooperation with technical content involving nucleic acid-encoded polypeptides. In contrast, domestic top 10 patent application institutions primarily conduct independent R&D using their own resources, with relatively little cooperation among them.

## 5. Conclusions and Implications

From its conceptual birth to current development and application, synthetic biology has a history of over one hundred years and has received high-level attention from governments worldwide. European and American countries have strengthened strategic deployment by treating it as a promising emerging/disruptive technology, establishing industrial technology R&D centers, formulating industrial development roadmaps, and increasing R&D investment in related fields. Chinese authorities should formulate an industrial development roadmap for synthetic biology that aligns with China' s national conditions as soon as possible, providing focused support for selected priority areas to ensure sustained and steady development of China' s synthetic biology field.

In recent years, the trend of synthetic biology patent applications has continued to rise, indicating that synthetic biology technology R&D and application are still rapidly developing with broad market prospects. The United States is the leader in synthetic biology research and a typical technology-exporting country, with significantly higher technological influence than other countries. Although China' s patent volume in synthetic biology has grown rapidly, ranking second globally, the quality of patents and strength of patent protection in this field still need improvement and strengthening. Therefore, China should emphasize and strengthen original basic research in synthetic biology in the future, shifting the focus of related outputs from quantity to quality and influence, and achieving independent control of core technologies in key areas.

Currently, China has achieved a series of breakthrough results in genome synthesis and other areas, such as the first completion of chemical synthesis of four yeast chromosomes (chromosomes II, V, X, and XII) [22] and the successful creation of the world' s first artificial single-chromosome eukaryotic cell [23], representing milestone breakthroughs in China' s synthetic biology field. Additionally, China is not lagging behind international mainstream levels in related supporting technologies required for synthetic biology, such as large-scale sequencing, microbiology, and bioinformatics. Therefore, China should integrate its advantageous disciplinary resources, starting with major industrial products in medicine, manufacturing, energy, agriculture, and environment, and timely establish national-level synthetic biology research centers or institutes. Meanwhile, China should consolidate and strengthen research in its advantageous fields, promote the transformation and application of achievements, and boost the vigorous development of China' s synthetic biology industry.

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*Note: Figure translations are in progress. See original paper for figures.*