From a word to a world: the current situation in the interdisciplinary field of synthetic biology

Xiaojun Hu and Ronald Rousseau

ABSTRACT

Using a carefully designed search query, we describe the field of synthetic biology in terms of leading countries, organizations and funding sources. Besides articles we also paid some attention to patents. The USA is the leading country in this field, followed by China. There is a clear exponential growth in the field of synthetic biology over the latest 14 years. Keywords were analyzed using the notion of year-based h-indices, core gap and relative core gap. We conclude that the term “synthetic biology” hides a large world ready to be explored by interdisciplinary research.

INTRODUCTION

Synthetic biology can be defined as the application of engineering principles to the fundamental components of biology. More precisely The Royal Society (2014) describes synthetic biology as follows:

"Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."

The European NEST High-Level Expert Group (2005) defines synthetic biology as follows:

"Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures—from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of biological systems’ in a rational and systematic way."

The title of this article is derived from De Lorenzo & Danchin (2008) who described the current state at that time.

The purpose of this investigation in descriptive informetrics is to explain the current situation of this emerging field. In order to extract the necessary information, we performed a topic mining exercise in the Web of Science (WoS). The main step in this exercise is the
construction of a search query in order to catch the essential components of the field. Our query is more comprehensive and leads to better results than that used by Oldham, Hall & Burton (2012), described in the next section. The results of this query enable the detection of the most active countries/regions, continents and organizations. In order to broaden the set of retrieved articles, we performed an additional search in PubMed and MEDLINE.

Not surprisingly, the USA is the most active country while Mainland China is moving up the ranks to become second in the last year. We further determine the WoS categories and areas to which articles on synthetic biology belong. It is shown that the growth in terms of number of published articles per year follows an exponential curve. These aspects are of interest and form an essential part of the study of any emerging field, but they do not use any new technique. Yet for the study of the distribution of topic keywords we apply a recently introduced approach (Hu & Rousseau, 2014a) based on the idea of year-based h-indices (Mahbuba & Rousseau, 2013). Details of the method are provided in the ‘Methods’ section. It is found that protein engineering, metabolic engineering and protein design are the overall hot topics in synthetic biology.

This article is an extended and reworked version of a preprint deposited in the arXiv (Hu & Rousseau, 2014b).

A SHORT HISTORY AND REVIEW OF THE FIELD

The term “synthetic biology” was first introduced by the French scientist Stéphane Leduc (1912) although with a different meaning than today’s version, and according to Wikipedia in modern times by the Polish geneticist Waclaw Szybalski (Szybalski, 1974). Although Wikipedia provides a quote, we were unable to find this quote in Szybalski (1974). To be precise, Szybalski describes what we would nowadays call synthetic biology and writes: “we enter the synthetic phase of research in the field” (i.e., of molecular biology). Putting aside the question of who was first, it is true that the term gained popularity and usage in mainstream science only in the year 2004 when the first international meeting, called Synthetic Biology 1.0, was held at the Massachusetts Institute of Technology (Jain, Bhatia & Chugh, 2012). Going back to Fleming’s discovery of penicillin (the first antibiotic with wide-spread use) Jain and her collaborators discuss the scope of synthetic biology for developing novel drugs. Envisaging many other applications, scientists nowadays declare that they can do better than evolution (Schuster, 2013). Schuster points to promising aspects for information storage, recalling a pilot study (Church, Gao & Kosuri, 2012) in which an entire book, including figures and Javascript, totalling more than five megabits, were stored on a single DNA molecule. Goldman (2014) points out that the near-completion of the Human Genome Project provided the impetus for significant disciplinary progress. Reviews on synthetic biology, from a field-specialist technical point of view, can be found in Li & Vederas (2009), Purnick & Weiss (2009) and Esvelt & Wang (2013). Moreover, Purnick & Weiss (2009) as well as Esvelt & Wang (2013) provide a timeline of milestones in synthetic biology.

The main article to use informetric techniques to study the field of synthetic biology is by Oldham, Hall & Burton (2012). They explore the field to inform debates on the
governance (related to the United Nations Convention on Biological Diversity) of the field. For this reason they focus on different visualizations. Based on WoS data they distinguish between two groups of articles: the core consisting of 1,255 publications and a group of articles citing the core leading to another 5,995 items. Searches were conducted in January 2012. Their core was obtained by a topic search for “synthetic biology,” “synthetic genomics,” “synthetic genome” or “synthetic genomes.” Details are discussed later in this article when comparing their results with ours. We note that Oldham, Hall & Burton (2012) observed the incipient diversification of synthetic biology into mammalian synthetic biology, cell free synthetic biology, chemical synthetic biology, genome engineering, genome-scale synthetic biology, and even more. They point out that this diversification is important for policy debates, as synthetic biology may cease to be a ‘unitary’ object for policy action.

Recently Goldman (2014) studied the related field of systems biology, using it as an empirical example to explore changes in the disciplinary structure of a field. She works under the assumption that concepts from systems biology are transmitted by papers linked via journals to various disciplines (in practice WoS subject categories). Following Liu & Rousseau (2010) she notes that the subject categories of the journals publishing on a topic can be indicators of the breadth of disciplinary diffusion. The author used a bipartite network to explore connectivity and concretely betweenness centrality among subject categories and journals. From 2000–2011 the number of subject categories and the number of journals both increased, while the percentage of subject categories with betweenness centrality equal to zero decreased. Such a decrease did not occur for the percentage of journals with betweenness centrality equal to zero. By 2011 subject categories formed a single large component. The whole structure can be characterized as a core/semi-periphery/periphery structure. Biotechnology & Applied Microbiology, Biochemistry & Molecular Biology, Computer Science, Mathematical & Computational Biology, Biophysics, and Genetic & Heredity form the core. Pharmacology & Pharmacy, Toxicology, Immunology, Nutrition & Dietetics, and Neurosciences & Neurology are examples of intermediary fields belonging to the semi-periphery. She notes that growth at the periphery occurs largely through interdisciplinary journals. Goldman (2014) performed a study which revealed that, over time, several clinical disciplines move toward the core. Immunology, healthcare sciences & services and oncology are examples of such categories. This movement illustrates the progress made by systems biology in translating theory to practice. As a specific example of the efforts to bridge theory and practice, she mentions the creation of the human diseases linking genotype and phenotype (Goh et al., 2007). Finally, she proposes a typology of journal roles in core bridges, intermediary bridges and reinforcers.

**METHODS**

**Construction of a search query**

As the retrieval language for the WoS is a keyword language and not based on a controlled vocabulary or a thesaurus, we have to construct a specific search query similar to what has been done for the field of nanotechnology (Kostoff et al., 2006).
The following methodology (synthesized in Fig. 1) has been employed.

1. Essential records were retrieved using the term “synthetic biology” as a topic search in the Web of Science (in short: WoS):
   
   \[ \text{TS} = \text{"synthetic biology"} \quad \text{and document type} = \text{article} \]
   
   Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = 2000–2013.

   This search retrieved 1,333 records (date of retrieval: January 11, 2014). These were downloaded using the full record option.

2. Next, we extracted the “Keywords” and “Keywords Plus” from all 1,333 records, and obtained their frequencies. In this way 6,054 terms were found and ranked in descending order of occurrence.
Table 1  Search results by different interfaces.

| Search query                                      | Time span   | Records |
|---------------------------------------------------|-------------|---------|
| PubMed/MeSH Synthetic biology as MeSH term        | 2011–       | 821     |
| PubMed/advanced Search string applied to title/abstract | 2000–2013   | 12,028  |
| MEDLINE/WoK Search string as a topic search       | 2000–2013   | 27,208  |
| WoS Search string as a topic search               | 2000–2013   | 13,836  |

(3) We sought the precise meanings of the terms in this list making use of MeSH (Medical Subject Headings) definitions and descriptions in Wikipedia (http://en.wikipedia.org/).

This led to a list of most-used content terms related specifically to synthetic biology. The resulting list has been verified by a field expert.

(4) We then used these content terms related to synthetic biology to expand the original query, leading to the final search string:

\[
\text{TS} = (\text{“synthetic biology” OR “synthetic gene network*” OR biobrick* OR “protein design*” OR “genetic circuit*” OR “gene regulatory network*” OR “cell-free protein synthesis*” OR “metabolic engineering” OR “protein engineering” OR “promoter engineering” OR “DNA assembly” OR “RNA engineering biosensors” OR “multipart DNA assembly” OR “sequential circuits” OR “benchmark synthetic circuits” OR “DNA nanotechnology” OR “human artificial chromosome” OR “synthetic promoters” OR “transcriptional circuits” OR “abstract genetic regulatory network*” OR “gene assembly” OR “post-transcriptional regulation” OR “engineered proteins” OR “cell-free gene circuits”) AND Document Types: (Article).}

Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH

Timespan = 2000–2013.

In this way, 13,836 records were obtained. This set is the main focus of this article. In order to broaden the view on the field of synthetic biology we also performed three other searches (in December 2014), starting with a search in PubMed with “synthetic biology” as a MeSH term. However, since this term was only introduced since the year 2011, this search only led to a small set of 821 journal articles. For this reason, we used the search string constructed for the WoS in the “advance search” of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/advanced). This led to a search in the title/abstract field. In this way, we retrieved 12,028 journal articles published during the period 2000–2013. Finally, we queried MEDLINE via the Web of Knowledge (WoK) (https://apps.webofknowledge.com/MEDLINE_GeneralSearch). This approach has a better search interface and provides a search field for “topic search.” Using the same search string and restricting to the article type, we retrieved 27,208 journal articles published in the time span 2000–2013. All records were downloaded for further analysis. Table 1 synthesizes our search results.
We note that Goldman (2014) only used the topic search term “systems biology” in the WoS and included all publication types, leading to 4,446 publications over the period 2000 through 2011. This is a major difference between our approach and that of Goldman.

As the field of synthetic biology is said to hold great promise for commercialization, we also performed a search for patents in the Derwent Innovations Index (DII) using a similar search query as in the WoS. The search was performed on January 24, 2014 in CDerwent, EDerwent and MDerwent, and the timespan = 2000–2013. This resulted in 788 patent records.

Data processing
- Topic keyword counting. We determined the keyword frequency based on the retrieved 13,836 records from the WoS search and their yearly distribution.
- Dynamic study of keyword use. To find out the major keywords in this field and their changes in frequency over the period 2000–2013, we calculate the value for the highly frequent keywords using the recently introduced “year based h-type indices” (Mahbuba & Rousseau, 2013; Hu & Rousseau, 2014a; Hu & Rousseau, 2014b).

RESULTS AND BASIC DATA
In this section we show basic results: most active countries/regions, continents and organizations; WoS categories and areas to which articles on synthetic biology belong; number of articles per year and aspects of growth. Most data were obtained by using the WOS analyze function. Table 2 shows a list of most-cited articles in the field of synthetic biology according to the WoS.

We abbreviated the term Synthetic Biology, referring to the set of articles retrieved by our WoS query as SB.

The most-active countries/regions over the period 2000–2013 are shown in Table 3. We added the leading country in Africa (South Africa) and Bangladesh as an example of a developing country and because of previous interest in it (Mahbuba & Rousseau, 2010). The WOS assigns an article to each country with at least one participating author as shown by his/her institutional address. In addition to rankings over the whole period, we also...
Table 3  Most-active countries/regions over the period 2000–2013: data from the WoS.

| Rank | Country               | # Articles | % SB and ranking | # Publications and ranking 2000–2007 | # Publications and ranking 2008–2013 |
|------|-----------------------|------------|------------------|--------------------------------------|-------------------------------------|
| 1    | USA                   | 5,973      | 0.144 (2)        | 2,419 (1)                            | 3,554 (1)                           |
| 2    | Germany               | 1,392      | 0.129 (5)        | 504 (3)                              | 888 (3)                             |
| 3    | Japan                 | 1,294      | 0.125 (7)        | 630 (2)                              | 664 (4)                             |
| 4    | People’s Republic of China | 1,258    | 0.092 (16)      | 263 (5)                              | 995 (2)                             |
| 5    | England               | 966        | 0.101 (13)       | 347 (4)                              | 619 (5)                             |
| 6    | France                | 621        | 0.080 (19)       | 244 (6)                              | 377 (6)                             |
| 7    | Canada                | 553        | 0.088 (17)       | 224 (7)                              | 329 (8)                             |
| 8    | South Korea           | 508        | 0.119 (8)        | 164 (9)                              | 344 (7)                             |
| 9    | Italy                 | 442        | 0.074 (21)       | 182 (8)                              | 442 (10)                            |
| 10   | Spain                 | 410        | 0.083 (18)       | 128 (12)                             | 282 (9)                             |
| 11   | Netherlands           | 385        | 0.110 (11)       | 164 (9)                              | 221 (11)                            |
| 12   | Switzerland           | 346        | 0.136 (3)        | 143 (11)                             | 203 (12)                            |
| 13   | Australia             | 301        | 0.069 (23)       | 109 (14)                             | 192 (14)                            |
| 14   | India                 | 300        | 0.069 (24)       | 105 (15)                             | 195 (13)                            |
| 15   | Sweden                | 279        | 0.113 (9)        | 110 (13)                             | 169 (15)                            |
| 16   | Denmark               | 208        | 0.149 (1)        | 83 (16)                              | 125 (18)                            |
| 17   | Israel                | 195        | 0.129 (4)        | 57 (19)                              | 138 (17)                            |
| 18   | Taiwan                | 184        | 0.070 (22)       | 41 (20)                              | 143 (16)                            |
| 19   | Scotland              | 158        | 0.106 (12)       | 35 (22)                              | 123 (19)                            |
| 20   | Finland               | 156        | 0.126 (6)        | 75 (17)                              | 81 (22)                             |
| 21   | Belgium               | 147        | 0.076 (20)       | 64 (18)                              | 83 (21)                             |
| 22   | Austria               | 128        | 0.096 (14)       | 40 (21)                              | 88 (20)                             |
| 23   | Singapore             | 109        | 0.112 (10)       | 31 (27)                              | 78 (23)                             |
| 24   | Russia                | 102        | 0.028 (27)       | 35 (22)                              | 67 (24)                             |
| 25   | Brazil                | 99         | 0.031 (26)       | 38 (22)                              | 61 (27)                             |
|      | South Africa (38)     | 28         | 0.033 (25)       | 12 (36)                              | 16 (41)                             |
|      | Bangladesh (52)       | 10         | 0.096 (15)       | 3 (49)                               | 7 (53)                              |

showed the number of publications and rankings for the first and the second half of the period. Moreover, we calculated the percentage of articles about synthetic biology among all articles (over the same period) and the ranking (restricted to the 27 countries/regions studied here) according to this parameter.

China (and to a lesser extent Singapore, South Korea, Taiwan and Austria) moved up in the rankings when comparing the second period to the first one. Among the top countries, Japan lost two positions in the rankings. The ranking according to the percentage of articles devoted to Synthetic Biology shows that, on the one hand, Denmark, Israel, Finland and Singapore have a high percentage of articles on SB, and even Bangladesh ranks 15th. On the other hand China, although ranking second in the second period, is only 16th in the ranking per percentage devoted to SB, illustrating the fact that China has many other priorities. Also, Canada, France, Italy and Spain have other priorities. Compared with the results of Oldham, Hall & Burton (2012) we notice several differences: the UK is second
Table 4 Shares per continent.

| Continent   | Share (in %) |
|-------------|--------------|
| Europe      | 37           |
| North America | 37         |
| Asia        | 22           |
| Latin America | 2          |
| Oceania     | 2            |

Table 5 Most-active organizations.

| Organization                                           | # Articles |
|-------------------------------------------------------|------------|
| Massachusetts Institute of Technology (USA)            | 244        |
| Chinese Academy of Science (P.R. China)                | 242        |
| Harvard University (USA)                              | 242        |
| Caltech (USA)                                         | 228        |
| Stanford University (USA)                             | 221        |
| University of Tokyo (JPN)                             | 203        |
| University of California Berkeley (USA)                | 197        |
| Duke University (USA)                                 | 148        |
| University of Washington (USA)                         | 147        |
| University of Illinois (USA)                           | 138        |

in their core group, Switzerland 5th, Spain 6th, Japan 8th and China 10th. However in the citing articles group China becomes 4th.

We divided by continent and obtained the results shown in Table 4. Note that because whole counting has been used, the sum (17,648) is more than the real total (13,836), hence we show results as percentages of the total (and even then results should be interpreted as approximations). Russia is considered to be a part of Europe, not for geographical reasons (then it would be part of Asia) but because most research is performed in the European part of Russia. North America consists of Canada and the USA, while the other countries of the Americas are referred to as Latin America. Compared with the total output of the world, Africa’s share is smaller than 1%. Clearly, Europe and North America keep each other in balance while Asia is the upcoming third.

Most active organizations are shown in Table 5. This list is clearly dominated by American universities, but since the day we collected the data CAS has overthrown MIT as the most-active organization. Yet, this list has no clear top university or small group of top organizations but numbers decrease slowly. We further note that the first company in this list is Genentech Inc. on rank 185 with 27 articles. This seems to indicate that, although synthetic biology can be considered an applied field it is not yet a field which is ripe for large scale commercialization.

Again Oldham, Hall & Burton (2012) obtain different results. Their list of most-active organizations consists of the University of California Berkeley, the Swiss Federal Institute of Technology (ETH), Harvard and MIT. We found 121 articles for ETH. Clearly, as already
Table 6  Most-active assignees (from the DII search).

| Assignee name                                                                 | # Patents |
|------------------------------------------------------------------------------|-----------|
| Cellfree SCI KK (= CO LTD) (JP)                                               | 25        |
| Macrogen Co Ltd (Korea)                                                      | 23        |
| Dokuritsu Gyosei Hoin Rikagaku Kenkyush (JP)                                 | 17        |
| Shimadzu Corp (JP)                                                           | 17        |
| Toyoboeki KK (JP)                                                            | 17        |
| Massachusetts Institute of Technology (MIT) (USA)                            | 12        |
| NEC Electronics Corp (JP)                                                     | 12        |
| University of Louisiana State University and Agricultural & Mechanical College (USA) | 10        |
| Riken KK (JP)                                                                | 10        |
| University of California (USA)                                                | 9         |

shown on country level, China and Japan are underrepresented in their investigation, while, moreover, our results are more recent.

Delving somewhat deeper into this, we also performed a search for patents in the Derwent Innovations Index (DII) using a similar search query as in the WoS. Contrary to article publishing institutions, patent assignees are mostly Japanese and Korean (see Table 6). However, the numbers of assigned patents are of an order of magnitude less than numbers of publications, confirming the observation that the field is not yet ripe for large-scale commercialization. No Chinese company belongs to this list.

The multidisciplinary aspects of SB are clearly shown by the WoS categories involved in its research. Table 7 shows the top-10 categories which together cover about 63% of all articles. However in total 173 WoS categories were involved. As many journals belong to more than one category, the ten categories shown in Table 7 already add up to more than 100%. Also, Oldham, Hall & Burton (2012) have Biochemistry & Molecular Biology as leading subject category (core and citing articles), followed by Chemistry (for the citing articles group) and Biotechnology & Applied Microbiology (second in the core). We observe that Chemistry and Goldman’s (2014) core category Computer Science are not included in our list. The reason is that we used Web of Science categories, while Oldham, Hall & Burton (2012) and Goldman probably used so-called research areas (but write that they use subject categories). Computer Science as a research area consists of several Web of Science categories such as: Computer Science Interdisciplinary Applications; Computer Science Hardware Architecture and Computer Science Theory & Methods. A similar observation holds for Chemistry. Moreover, a different approach was used: we and Oldham, Hall & Burton (2012) counted articles, while Goldman applied network centrality indicators. Finally, we used a more inclusive search query.

Using the five main research domains of the Web of Science, we obtain the following percentages per domain: see Table 8.

As MEDLINE covers more journals in medicine and the life sciences than the WoS, be it that more journals are not peer-reviewed (Hu, 2005), we derived a list of journals from this database publishing the most articles within the field of synthetic biology (see Table 9).
Research in synthetic biology is often supported by grants from large funding bodies. The WoS yields a list of 8,455 names, although there are many funds occurring under several names. Table 10 shows the most-important ones: NIH USA has more than 1,000 supported articles, while the other ones have at least 200 supported articles each. Oldham, Hall & Burton’s (2012) list of funding institutes is dominated by the National Institutes of Health (NIH), the National Science Foundation (US) and the European Programs. Again, China’s research (funded by NSFC) is underrepresented in their study.

Doing better than evolution has a touch of “playing God” and certainly entails moral obligations and ethical problems, see e.g., Renn & Roco (2006) for a discussion of similar problems in the field of nanotechnology. Adding the topic terms “ethic*” OR “moral*” to the main query led to 54 articles. The largest group (17) is in the WoS Category Ethics, followed by Social Sciences Biomedical (12). Six articles are published in Environmental Values and five in Bioethics. More than half were published in the latest two years.

**Growth in the number of articles on synthetic biology**

The yearly growth curve based on the WoS query is shown in Fig. 2. This curve can best be described as exponential growth. Giving the year 2000 the x-value 0 (and hence 2013 the x-value 13) a best-fitting curve is given by \( y = 454.3 \times e^{0.105x} \) \( R^2 = 0.97 \), where \( y \) denotes the yearly number of published articles on synthetic biology.

This analysis provides an opportunity to compare WoS data with MEDLINE data. Figure 3 shows the growth in number of published articles according to MEDLINE/WoK.
Table 9 Twenty journals publishing the most articles on synthetic biology (period 2000–2013); data from MEDLINE/WoK.

| Source                                                | # records |
|-------------------------------------------------------|-----------|
| PLoS ONE                                              | 1,202     |
| Proceedings of the National Academy of Sciences of the United States of America | 716       |
| The Journal of Biological Chemistry                   | 562       |
| Nucleic Acids Research                                | 532       |
| Methods in Molecular Biology                          | 449       |
| Biotechnology and Bioengineering                       | 410       |
| Applied Microbiology and Biotechnology                 | 409       |
| Journal of Biotechnology                               | 400       |
| Journal of Molecular Biology                          | 399       |
| Bioinformatics Oxford England                          | 345       |
| Protein Engineering Design Selection Peds              | 333       |
| Metabolic Engineering                                 | 325       |
| BMC Systems Biology                                   | 313       |
| BMC Bioinformatics                                     | 308       |
| BMC Genomics                                           | 301       |
| Biochemistry                                           | 294       |
| Biochemical and Biophysical Research Communications    | 288       |
| Applied and Environmental Microbiology                 | 266       |
| Journal of the American Chemical Society              | 259       |
| Current Opinion in Biotechnology                       | 259       |

Table 10 Most important funding organizations.

| Funding Organization                                             | # records |
|-----------------------------------------------------------------|-----------|
| National Institutes of Health (NIH)—USA                        |           |
| National Science Foundation (NSF)—USA                          |           |
| National (Natural) Science Foundation China                     |           |
| European Union (EU)/European Commission (EC)                   |           |
| Deutsche Forschungsgemeinschaft (DFG)                          |           |

Also these data lead to an exponential growth with a best-fitting curve given by $y = 535.1 \cdot e^{0.148x} (R^2 = 0.99)$. Although our MEDLINE search retrieved considerably more records than the WoS search, the corresponding growth curves show a similar trend.

Distribution of topic keywords, year-based h-indices

We found a total of 22,253 keywords in the retrieved WoS records. Keywords-PLUS were not included as they are in most cases too general, i.e., not specific for the field of synthetic biology. However, the majority of the keywords (16,905 terms or 76%) occurred just once, reflecting the broadness of the field as well as the fact that, being in an emerging stage, terminology has not yet settled. Remarkably, the term “synthetic biology” (and related terms) occurred just 28 times (in the period of 2000–2013) proving that we had to look into the field’s “world” rather than just considering the “word.” Focusing on major topics,
we brought keywords and related forms together under one name. In this way we obtained 35 highly frequent topic-related keywords each occurring at least 100 times. We removed general topics such as cell, enzyme, genetic, gene, protein, *Escherichia coli* and their related terms, leading to 28 keywords representing the hot, specific topics in the field of synthetic biology. These keywords were analyzed using a recently introduced approach based on year-based h-indices (*Mahbuba & Rousseau, 2013*).

We recall the following definitions from *Hu & Rousseau (2014a)* and *Hu & Rousseau (2014b)*. Consider a given topic term T and assume that years (here restricted to the period 2000–2013) are ranked according to the number of articles published dealing with this
Table 11: Hot topic keywords in the research field of synthetic biology and their year-based activity h-type indices during the period 2000–2013.

| Topic keywords                | Year-based h-index | Core interval      | Top year | Core gap | Relative core gap |
|-------------------------------|--------------------|--------------------|----------|----------|------------------|
| Protein engineering           | 14                 | 2000–2013          | 2011     | 0        | 0                |
| Metabolic engineering         | 14                 | 2000–2013          | 2013     | 0        | 0                |
| Protein design+               | 14                 | 2000–2013          | 2012     | 0        | 0                |
| DNA+                          | 11                 | 2002–2013          | 2013     | 1        | 0.09             |
| MicroRNA+                     | 10                 | 2002–2013          | 2013     | 2        | 0.2              |
| Cell-free protein synthesis+  | 10                 | 2004–2013          | 2007     | 0        | 0                |
| Protein folding+              | 10                 | 2000–2011          | 2004     | 2        | 0.2              |
| RNA+                          | 9                  | 2003–2013          | 2012     | 2        | 0.22             |
| Mutagenesis+                  | 9                  | 2004–2013          | 2002     | 1        | 0.11             |
| Gene expression+              | 9                  | 2002–2013          | 2013     | 3        | 0.33             |
| Stability+                    | 9                  | 2004–2015          | 2013     | 1        | 0.11             |
| Fluorescence+                 | 9                  | 2001–2013          | 2013     | 4        | 0.44             |
| Protein stability+            | 9                  | 2001–2013          | 2004     | 4        | 0.44             |
| Gene regulatory network+       | 8                  | 2006–2013          | 2012     | 0        | 0                |
| Directed evolution+           | 8                  | 2005–2013          | 2012     | 1        | 0.125            |
| Nano+                         | 8                  | 2005–2013          | 2013     | 1        | 0.125            |
| Evolution+                    | 8                  | 2003–2013          | 2013     | 1        | 0.125            |
| Systems biology+              | 8                  | 2004–2013          | 2012     | 2        | 0.25             |
| Microarray+                   | 8                  | 2006–2013          | 2012     | 0        | 0                |
| Sequential circuit+           | 8                  | 2000–2008          | 2000     | 1        | 0.125            |
| Biocatalysis+                 | 7                  | 2005–2013          | 2013     | 2        | 0.29             |
| Combination+                  | 7                  | 2002–2013          | 2013     | 5        | 0.71             |
| Gene regulation+              | 7                  | 2005–2013          | 2013     | 2        | 0.29             |
| Self-assembly+                | 7                  | 2007–2013          | 2012     | 0        | 0                |
| Antibody+                     | 7                  | 2002–2013          | 2013     | 5        | 0.71             |
| Dynamics+                     | 7                  | 2007–2013          | 2012     | 0        | 0                |
| Protein–protein interaction+  | 7                  | 2006–2013          | 2013     | 1        | 0.14             |
| Genome+                       | 6                  | 2006–2013          | 2012     | 2        | 0.33             |

Notes.
* The symbol “+” indicates a keyword and its related terms.

The symbol “t” indicates a keyword and its related terms. Then this topic’s year-based h-index is equal to t if t is the highest rank such that in the first t years t articles were published dealing with this topic (because of the period used, this h-index can at most be equal to 14). Let Z and Y be the latest and the oldest years included in the topic’s h-core, then the period [Y, Z] is called the core interval. If Z − Y + 1 = t then there is no gap in the core. The core gap is defined as Z − Y + 1 − t, or informally: the number of missing years in the core. Finally, the relative core gap for topic T is defined as: (core gap/t). In Hu & Rousseau (2014a) and Hu & Rousseau (2014b) we have shown how using these notions may provide an easy-to-use overview of a field concretely: molecular research in nervous system diseases. Table 11 shows the results of the analysis of the SB set, based on year-based h-indices.
Clearly, protein engineering, metabolic engineering and protein design are the overall hot topics in synthetic biology. Oldham, Hall & Burton (2012) found the following top terms: synthetic biology, E. coli (a term we removed), gene expression, systems biology and metabolic engineering. Table 10 shows that the core interval of most topics extends to the latest year (namely 2013). Moreover, the top year (the year in which the most articles on this topic were published) is often 2012 or 2013, indicating that interest in these topics is still growing. Interest in sequential circuits seems to have passed its peak.

**CONCLUSION**

We believe that the innovative domain of synthetic biology may become a bigger interdisciplinary domain than nanoscience and nanotechnology. Clearly it is one of the battlefields where leading countries fight for the supremacy in science (Joyce, Mazza & Kendall, 2013). In terms of countries and institutes, the USA is still leading the field, but Mainland China is a strong and upcoming second. The term “synthetic biology” hide a large world ready to be explored by interdisciplinary research collaborations. We hope that this informetric study brings a new perspective to the study of synthetic biology.

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**ADDITIONAL INFORMATION AND DECLARATIONS**

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**Competing Interests**

The authors declare there are no competing interests.

**Author Contributions**

- Xiaojun Hu and Ronald Rousseau conceived and designed the experiments, performed the experiments, analyzed the data, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.
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