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Exploring the Future of Synthetic Biology in India and its Probable Pathways from Infancy to Maturity

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Abstract

Synthetic biology is an engineering inspired approach for ground-up construction of biological systems leading to a preferred phenotypic outcome. Given that the rules of constructing biological systems are unknown, the synthetic biology approach of constructing a genome or pathways or networks is a novel effort and merits careful assessment. Though synthetic biology has made rapid strides in the US and Europe, in India the field is at an early stage. This Delphi study explores the institutional structure and investment scenarios of the evolving Indian Synthetic Biology sector. Comparisons are drawn with the global initiatives with a hope to identify probable future pathways. Here we have attempted to make a general assessment of the field using publications, patents, venture capital sources, legal provisions and a direct community opinion. This is the first Delphi study on synthetic biology in India and attempts to present various synthetic biology sub-domains. The study has potential to help policy makers and scientists on governing, prioritising, planning and funding of the sector and choosing the relevant research themes. The key challenge of governance, accountability and social inclusion vis-à-vis this sector is important in the context of emerging situation in the country. The accuracy of the predictions is dependent upon respondents understanding of synthetic biology, technological breakthroughs, observational and experimental errors both in pre and post-facto scenarios of this exercise. Though interesting observations have been made in this work, there is a need to regularly conduct such studies in India and forecast the evolution of the field in future.

Introduction

The latter half of the 20th century has seen many revolutionary developments in the field of science and technology – the internet and the microprocessor being the two most shining examples. Though it wasn't initially appreciated, the widespread social adoption of these two technologies turned out to be complementary in nature. For example, one can't imagine a hand held device or a notebook without the internet or fast wireless connectivity and vice-versa.

Likewise, in the field of biology the emergence of technology and a reductionist view of biological systems, evolved in parallel. This led to emergence of genetics and molecular biology and their applied counterpart – biotechnology. Due to emergence of high throughput analytical technologies, enormous data generated and emergence of massive computational power and storage, a new field of systems biology was born. Systems biology is about studying nature's biological designs and understanding how a group of molecules/cells generate a certain phenotypic outcome. Synthetic biology deals with ground up construction of biological systems to install novel behaviours. All these fields, either directly or indirectly, complement each other.

The novelty of modern science and technology domains exists in the interdependence and blurring of disciplinary boundaries, making the spectrum of applications much vaster than ever before. This has instilled a new vision and approach for futuristic thinking that departs from the notion of last century i.e. "in the organic world, once two lineages have diverged for some time, they cannot re-join". In the field of engineering, two inventions, first developed to perform different functions in different kinds of machine, can be brought together in a single machine; the trolley-bus being a good example of a "hybrid" between a bus and a tram" [1].

With the arrival of synthetic biology, the monopoly of reconfiguring the existing operational systems (the privilege of which until now existed with engineering sciences) has been broken. There are concrete evidences of engineering design of functions and interactions of macromolecules, design of signalling and regulatory networks and also metabolic networks [2]. It has been observed [2] that "many of the failures that biotechnology suffered can be understood from this new perspective. We adapt our technologies—e.g. in fabrication—and methodologies—such as design—to the new system-scale of the task through adopting the crucial elements of classical, non-life science related engineering disciplines".

Since, a certain action has a potential to result in an unexpected outcome, synthetic biology also comes with its own excitement, limitations and potential areas of fallibility. Presently, key challenges to the global governance of synthetic biology seem to be (a) managing the unknown space b) the need for creating accountability external to the system and c) the fragmentation of social authority [3].

In order to address all these issues, different bodies, agents and organizations have started discussions on the optimum ways to minimize risks associated with Synthetic Biology. Propositions ranging from self-regulation of the scientists to government-imposed regulations have been put forward [4].

Synthetic biology may be in its infancy in India, however, the institutional, regulatory and research ecosystem is well knitted and in place (Figure 1). Nevertheless, there are certain issues which require attention e.g., demarcation of duties and responsibilities among various

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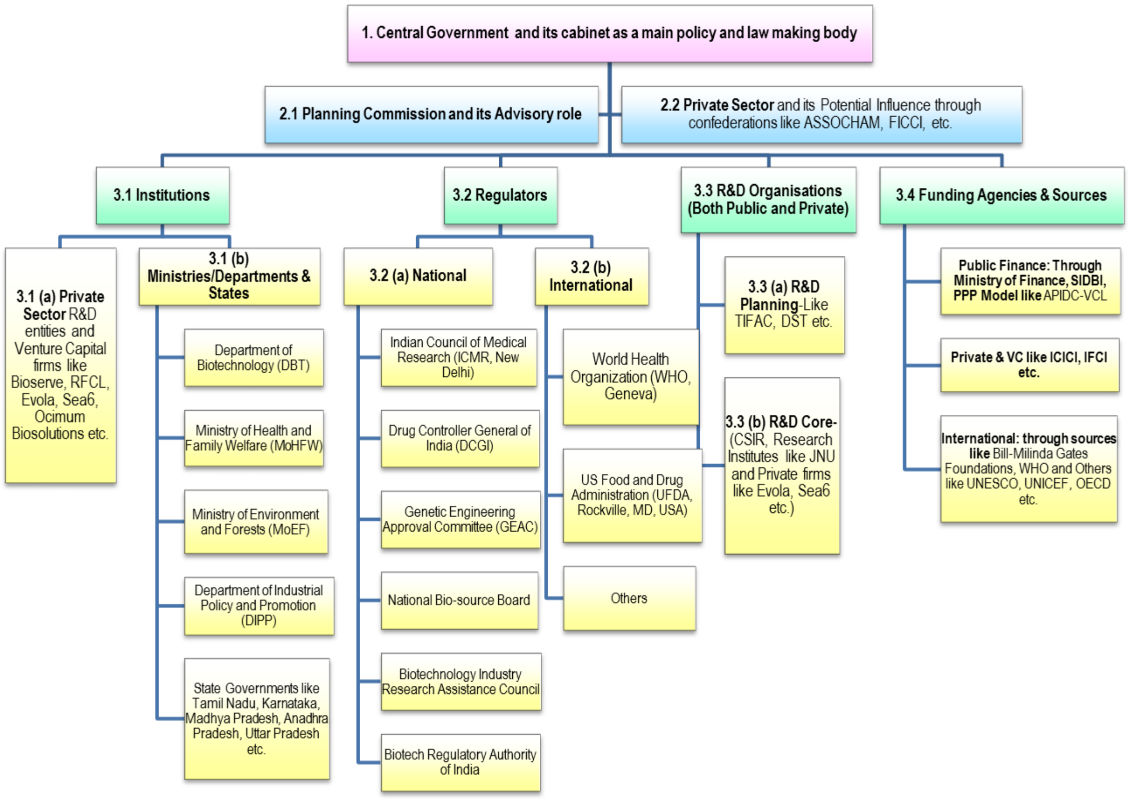


Source: Compiled by the Authors

Figure 1: Organisational Chart representing the Institutional, Regulatory and Research Ecosystem for the Synthetic Biology Sector in India.

spheres of influence within the institutional ecosystem and clearly defining legal standards and definitions. These issues have been dealt in detail in *Regulation and Governance of Synthetic Biology in India* of this essay.

Rationale and Objective(s) of the Study

The world is in conflict with problems ranging from climate change, environmental degradation, water scarcity, lowered agricultural productivity to alarming spread of life threatening diseases like malaria, swine flu, HIV-AIDS etc. Further, there are issues of improving the quality of life and community interactions through technological advancements. For instance, internet has proven to be a potent tool in bridging the rural-urban divide, women empowerment or building a knowledge society [5].

The 'Synthetic Biology' Sector produces a ray of hope when proponents predict future developments of applications ranging from synthetic fuel, food crops, bio-electronic devices, synthetically made body parts and so on. The list is long and produces a sense of both hope and incertitude vis-à-vis the fulfilment of such objectives. One needs to groom this discipline like a gifted child. Therefore, all the intricacies must be defined, implemented and followed rigorously. The rationale of this paper is to assess and compare existing performance of the Indian synthetic biology sector with the global situation and identify four key sub-domains (a) techno-economic,(b) health and environment, (c) social and human resources development, and (d) legal and administrative) that are likely to nourish the sector in future. We hope that this study will help scientists and policy makers in identifying and key research areas for future funding.

The key objectives of this study are:

• To explore the existing position of the institutional structure (both Public and Private) and the atmosphere for investments in the Synthetic Biology sector in India.

• To measure the research efficacy and output of Indian synthetic biology sector and also draw a comparison with the global situation.

• To conduct a technological assessment of existing technologies or choices (if any).

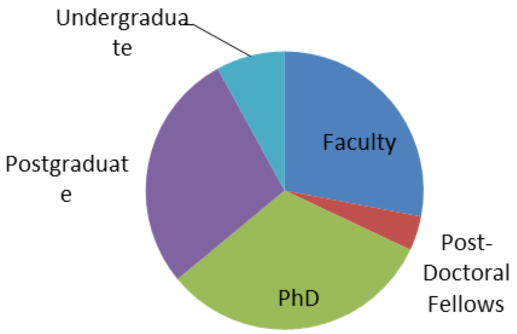
• To identify through Delphi study, probable future pathways under techno-economic, health and environment, social and human resources development, and legal and administrative sub domains.

• To identify the administrative and regulatory issues concerning synthetic biology sector in India.

Data and Methodology

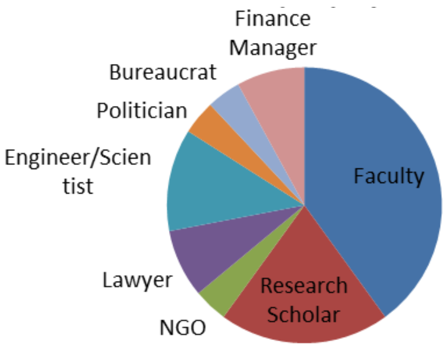
Apart from the review of the literature, the data sources assessed were mainly of two kinds i.e. secondary and primary. The secondary data was sought through important online database repositories like the web of science (for publication related data), Thomson and innovations (for patents information), Dow Jones Venture Source and legal provisions. Extraction of each of this secondary information required a specific keyword search, which has been specifically appended under the concerned tables/data extracted. Furthermore, a review of existing legal provisions and issues vis-à-vis Synthetic Biology has also been performed and elaborated at the *Regulation and Governance of Synthetic Biology in India* in this essay.

A rigorous attempt was made to generate primary data through an online Delphi survey. The Delphi exercise was designed to identify the major challenges and objectives to the sector by 2050. We invited professionals from academics (Biotech and life sciences) and from fields including law, engineering, politics, NGO, bureaucracy, finance etc. This survey comprised of twenty-seven questions mainly within four specific domains under focus viz. Techno-Economic, Health and Environmental, Social and Human Resources Development, Legal and Administrative. The respondents (Seventy-one in first round and twenty-five in the second round) were asked to choose the corresponding year by which certain objectives shall be reached. After two rounds of polling, the data were statistically analysed (software SPSS 17.0, Software Package for Social Sciences) and the results were generated (Figure 5). This exercise helped identify potential key areas and priorities for nourishing, cultivating and grooming synthetic biology sector towards useful outcomes. Care was taken in the research design, formulation of research questions and the Delphi questionnaire, covering both convergent and divergent sub-domains of synthetic biology.

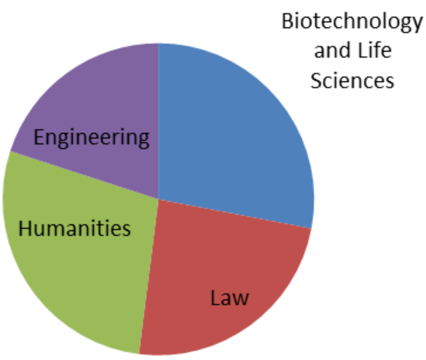


Source: Compiled by the Authors from the Delphi Survey

Figure 2: Composition of the Respondents in Round-1 of Delphi.



Source: Compiled by the Authors from the Delphi Survey
Figure 3: Composition of the Respondents in the Round 2 of the Delphi (According to the Profession/Employment).



Source: Compiled by the Authors from the Delphi Survey
Figure 4: Composition of the Respondents in the Round 2 of the Delphi (According to the Field of Study).

Synthetic Biology in India: An Overview

Response towards Investments and Research and Development (R&D)

Private sector's response towards investments and R&D: Based on findings of this survey, an unclear demarcation seems to exist between investments made for synthetic biology and investments made for the parent disciplines like Biotechnology. In our opinion, Venture Capital (VC) is one of the key indicators of the innovation potential of a certain field [6].

The '*innovation capital*'[1] in the biotech industry has shown a decline by almost 20% from 2009 to 2010 (Ernst and Young, 2012). The impact of declining innovation capital on biotech's traditional innovation role is exacerbated by the extremely polarized distribution of the invested capital. We now have a division into "haves" and "have-nots," where a very small number of companies can afford to invest in the innovation while the large majority continue to work for mere survival [7]. However, India shows encouraging signs given that all VC firms investing in India for biotech stand at 24.24 per cent investment (Table 1), which is at par with some of the leading countries in the world. Likewise, in this study the sub-sectoral investments in Biotech and its associated segments also indicate significant investments in Biopharma, BioServices and Bioagriculture (Table 2). In our survey, at least two Chennai based companies: 'Evolva Biotech Private Limited' and 'Sea 6' have declared their investments in synthetic biology research.

Evolva Biotech Private Limited (EBPL) is a majority-owned subsidiary of the Swiss based Evolva Holding SA. Evolva Holding SA is an international synthetic biology group that works on the discovery and development of novel, differentiated pharmaceutical products that target significant unmet medical needs and on products with applications in Consumer Health, Nutrition & Food Chain. The company is headquartered in Switzerland and has operations in Switzerland, Denmark, India and the United States.

EBPL uses biosynthetic and evolutionary technologies to create and optimise small molecule compounds and their production routes. EBPL hopes to commercially produce saffron using yeast system by 2015. Further, the vanilla synthesis pipeline is at an advanced stage of research. Evolva intends to produce several wellness food ingredients with unique flavour and tries to address existing supply chain bottlenecks in these areas.

Sea6 Company: This new start-up company was launched by a group of graduate students and researchers at IIT Madras. Their initial synthetic biology work led to developing technology for convert seaweeds into biofuel. The company has signed an agreement with Novozymes to convert seaweed carbohydrates into sugar, which can then be fermented to produce ethanol.

Looking through the investment background and the available human resource potential in India, there are initial indicators of continued private investment in synthetic biology in future. Such a

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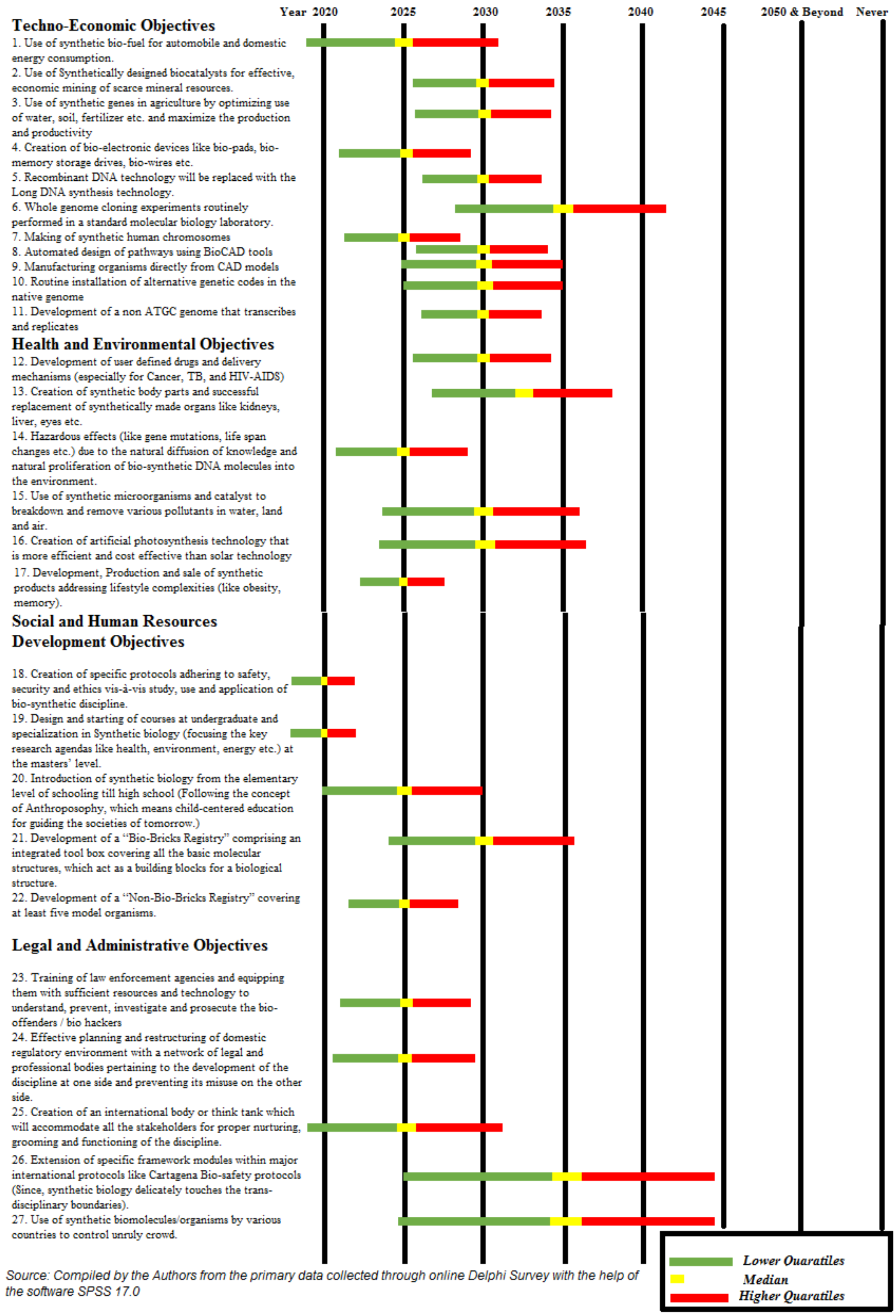

Figure 5: Results from the Delphi survey depicting the probable time of occurance of variou events vis-a-vis the development of Synthetic Biology Sector.

trend will be realistic if a favourable atmosphere for investments and channelization of human resource is created at right time and in right direction (i.e., in important areas).

To fill in this unmet need of the community, current survey was organized to understand where Indian scientific and funding community was moving towards. To our best knowledge this is the first Delphi study organized in this segment in India.

Public sector's response towards investments and R&D

Of several government funding agencies, currently Department of Biotechnology (DBT), New Delhi and Council of Scientific and Industrial Research (CSIR), New Delhi are working towards funding synthetic biology in a significant way.

Recently, DBT has funded the creation of new research centres at DBT-ICT Centre for Energy Biosciences, Mumbai, DBT-IOC Centre for Advance Bioenergy Research, Faridabad and DBT-ICGEB Centre for Advance Bioenergy Research, New Delhi. These centres are focusing on making Biodiesel, Bioethanol, Biobutanol and Biohydrogen.

Some of the recent unconfirmed reports suggest that CSIR may setup a centre for excellence on this theme in future. However, DBT has already taken a lead by announcing competitive funding in synthetic biology for biofuel research. Recently, Department of Biotechnology (New Delhi) and Academy of Finland launched joint funding programs (FINSynBio) to promote Indo-Finnish research cooperation in synthetic biology.

S.No	Country	Total No of VCs	Net VC investment for Biotechnology@	% of VC Firms Supporting Biotechnology
1.	USA	784	168	21.43
2.	China	62	13	20.97
3.	UK	27	9	33.33
4.	India	33	8	24.24
5.	Israel	15	4	26.62
6.	Germany	10	3	30
7.	Australia	2	1	50
8.	Canada	10	1	10
9.	Brazil	3	0	0
10.	Japan	7	0	0
11.	South Korea	4	0	0
12.	World Total	1041	214	20.56

Source: Online web http://venture-capital-firms.findthebest.com/d/c/Biotechnology [Assessed on 15th February, 2013]
@It covers all types of ventures viz. Seed, Early Stage, Growth, Expansion and Later Stage.
#Source: Dow Jones VentureSource, 2012.

Table 1: Operational Venture Capital (VC) Firms funding Biotechnology Projects in different countries.

S.No	Sub-sector	Investment (in Million $)
1.	Biopharma	1,900
2.	BioServices	573
3.	Bioagriculture	420.4
4.	Bio-industrials	122.5
5.	Bioinformatics	50.2
Total	3,066	

Source: Dow Jones VentureSource, 2012

Table 2: Sub-sector wise Total Investments made in Biotech Sector for India (Year 2009-10).

Patents and publications

A number of studies have documented publications in the field of synthetic biology per country. For instance, Europe-North America Comparative Assessment done by 'Synbiology' and PATHFINDER Program by European Commission seem to be prominent ones.

Currently, USA is the leader in both the publications (Table 3 and Figures A1, A2 and A3) and patents[2] in synthetic biology while India's performance statistics look dwarf in comparison. Though Sea6, a company oriented towards synthetic biology, has applied for a provision patent for developing a marine polymer mesh structure to anchor seaweed for aqua-farming, it is a technology based patent. However, numbers must be considered with caution, as many groups often do not label their field of research with the latest buzzword and therefore might be underrepresented [4] (Serrano, 2007). For instance, according to the IPC Codes[3] (International Patent Classification Codes by WIPO) Applied in Inspection Records by WIPO, the classification houses some candid and some subsidiary products based on the application of synthetic biology.

- C12: Biochemistry; Beer; Spirits; Wine; Vinegar; Microbiology; Enzymology; Mutation or genetic engineering.
- C12M: Apparatus for enzymology or microbiology.
- C10L: Fuels not otherwise provided for; Natural gas; Synthetic natural gas obtained by processes not covered by subclasses c10g to or c10k; Liquefied petroleum gas; use of additives to fuels or fires; fire-lighters.
- C10L3/00: Gaseous fuels; Natural gas; Synthetic natural gas obtained by processes not covered by subclasses c10g, c10k; Liquefied petroleum gas.

While looking into the publication and patent databases with above mentioned IPC Codes we find a total of 2,121 documents[4] and 16 patents between the period of 2007-12 (Assessed through Scopus Database, Tables 3-5). In which the following countries were leading (Table 3), while the Table 4 shows the subject wise diversity of publications and Table 5 shows significant Indian institutes contributing through their research.

Publications by Indian scientists: India's current contribution to synthetic biology is in the infancy (Tables 3 and 5) however, the momentum seems to be building up slowly.

S.No	Country	No of Publications#
1.	**United States**	**918**
2.	United Kingdom	244
3.	Germany	182
4.	France	121
5.	**China**	**108**
6.	Switzerland	97
7.	Spain	76
8.	Italy	74
9.	Japan	73
10.	Canada	56
11.	**India**	**29**

Source: Compiled by Authors from the Scopus Database (Assessed on 14 March, 2013)
#Keywords used for the search: TITLE-ABS-KEY("synthetic biology" OR "synthetic Genome") AND PUBYEAR > 2006 AND PUBYEAR < 2013

Table 3: Country wise list of total Publications (2007-12).

S.No	Subjects	No of Publications#
1.	Biochemistry, Genetics and Molecular Biology	**1,326**
2.	Chemical Engineering	419
3.	Immunology and Microbiology	331
4.	Engineering	323
5.	Medicine	**321**
6.	Computer Science	230
7.	Agricultural and Biological Sciences	210
8.	Chemistry	201
9.	Mathematics	188
10.	Multidisciplinary and Others	165

Source: Compiled by Authors from the Scopus Database (Assessed on 14 March, 2013)
#Keywords used for the search: TITLE-ABS-KEY("synthetic biology" OR "synthetic Genome") AND PUBYEAR > 2006 AND PUBYEAR < 2013

Table 4: Subject wise list of total Publications (2007-12).

S.No	Subjects	No of Publications#
1.	Centre for Systems and Synthetic Biology, University of Kerala, Trivandrum	5
2.	National Centre for Biological Sciences, Bangalore	4
3.	Indian Institute of Technology, New Delhi	4
4.	Indian Institute of Technology, Kharagpur	3
5.	Institute of Genomics and Integrative Biology, New Delhi	2
6.	Pondicherry University	2

Source: Compiled by Authors largely from the Scopus Database (Assessed on September 02, 2013). It is quite possible that the coverage may not be 100% complete across various labs in India
#Keywords used for the search: TITLE-ABS-KEY("synthetic biology" OR "synthetic Genome") AND PUBYEAR > 2006 AND PUBYEAR < 2013 AND (LIMIT-TO(AFFILCOUNTRY, "India"))

Table 5: Indian Institutes contributing significant no. of Publications (2007-12).

• Synthetic biology publications by Indian scientists (alphabetical order).

1. Dhar PK, Thwin CS, Tun K, Tsumoto Y, Maurer-Stroh S, et al. (2009) Synthesizing non-natural parts from natural genomic template. J Biol Eng 3: 2. [8]

2. Dhar PK (2012) Designing organisms - the new science of synthetic biology. Biospectrum. [9]

3. Dhar PK (2011) Hacking the genetic code. Nature India. [10]

4. Dhar PK (2011) Making a genome. Nature India. [11]

5. Dhar PK (2012) Will recombinant DNA technology become obsolete? Nature India. [12]

6. Gopal V, Guruprasad K (2010) Structure prediction and validation of an affibody engineered for cell-specific nucleic acid targeting. Syst Synth Biol 4: 293-297. [13]

7. Grover A, Pande A, Choudhary K, Gupta K, Sundar D (2010) Re-programming DNA-binding specificity in zinc finger proteins for targeting unique address in a genome. Syst Synth Biol 4: 323-329. [14]

8. Krishnan R, Manjaly-Antony LA, Dhar PK (2010) Building momentum for systems and synthetic biology in India. Syst Synth Biol 4: 237-240. [15]

9. Kulkarni VV, Paranjape A, Ghusinga KR, Hovakimyan N (2010) Synthesis of robust tunable oscillators using mitogen activated protein kinase cascades. Syst Synth Biol 4: 331-341. [16]

Qualification/Expertise Level	Weightage for the Response
Faculty and Post-Doctorates	4
PhD/Doctoral Candidates	3
Post-graduate Scholars	2
Undergraduate Students	1
Not at all familiar with the field	0

Source: Compiled by the Authors from the Delphi Survey
The qualification data was used to provide a scaled weight to the responses as follows:

Table 6: Weightage for the Level of Expertise of the Delphi Respondents.

10. Kumar A, Ramakrishnan V (2010) Creating novel protein scripts beyond natural alphabets. Syst Synth Biol 4: 247-256. [17]

11. Munjal N, Mattam AJ, Pramanik D, Srivastava PS, Yazdani SS (2012) Modulation of endogenous pathways enhances bioethanol yield and productivity in Escherichia coli. Microb Cell Fact 11: 145. [18]

12. Namboodiri S, Verma C, Dhar PK, Giuliani A, Nair AS (2010) Sequence signatures of allosteric proteins towards rational design. Syst Synth Biol 4: 271-280. [19]

13. Rai N, Anand R, Ramkumar K, Sreenivasan V, Dabholkar S, et al. (2012) Prediction by promoter logic in bacterial quorum sensing. PLoS Comput Biol 8: e1002361. [20]

14. Ramadas R, Thattai M (2010) Flipping DNA to generate and regulate microbial consortia. Genetics 184: 285-293. [21]

15. Saukshmya T, Chugh A (2009) Commercializing synthetic biology: Socio-ethical concerns and challenges under intellectual property regime. Journal of Commercial Biotechnology 16: 135-158. [22]

16. Saukshmya T, Chugh A (2010) Intellectual property rights in synthetic biology: an anti-thesis to open access to research? Syst Synth Biol 4: 241-245. [23]

17. Shankar S, Pillai MR (2011) Translating cancer research by synthetic biology. Mol Biosyst 7: 1802-1810. [24]

18. Sivaraman P, Mattegunta S, Subbaraju GV, Satyanarayana C, Padmanabhan B (2010) Design of a novel nucleoside analog as potent inhibitor of the NAD dependent deacetylase, SIRT2. Syst Synth Biol 4: 257-263. [25]

19. Umesh P, Naveen F, Rao CU, Nair AS (2010) Programming languages for synthetic biology. Syst Synth Biol 4: 265-269. [26]

Products in the market

Currently, there aren't any products ready to serve the market. However, the on-going thrust in investments seen in the Tables 1 and 2 and with the Delphi survey, one can probably expect that in future the situation could change.

Assessment of dual use technologies

The biggest concern in the field of synthetic biology has been the untapped potential to create user-defined organisms towards life threatening applications. There are at least two dual use technologies that have potential for misuse.

• Making user-defined microbes with health and environment implications

• Long DNA synthesis leading to rapid assembly of harmful designs

S.No	Delphi Statements	Median	Quartile		Never (%)
Techno-Economic Objectives					
1.	Use of synthetic bio-fuel for automobile and domestic energy consumption.	2	2	2	0
2.	Use of Synthetically designed biocatalysts for effective, economic mining of scarce mineral resources.	3	1	2	2.94
3.	Use of synthetic genes in agriculture by optimizing use of water, soil, fertilizer etc. and maximize the production and productivity	3	2	3	0
4.	Creation of bio-electronic devices like bio-pads, bio-memory storage drives, bio-wires etc.	2	1	3	0
5.	Recombinant DNA technology will be replaced with the Long DNA synthesis technology.	3	1.5	2	1.47
6.	Whole genome cloning experiments routinely performed in a standard molecular biology laboratory	4	2	3	0
7.	Making of synthetic human chromosomes	2	1	4	0
8.	Automated design of pathways using Bio-CAD tools	3	2	2	0
9.	Manufacturing organisms directly from CAD models	3	2	4	0
10.	Routine installation of alternative genetic codes in the native genome	3	2	5	3.7
11.	Development of a non ATGC genome that transcribes and replicates	3	3	5	5
Health and Environmental Objectives					
12.	Development of user defined drugs and delivery mechanisms (especially for Cancer, TB, and HIV-AIDS)	3	2	3	2.78
13.	Creation of synthetic body parts and successful replacement of synthetically made organs like kidneys, liver, eyes etc.	3.5	2	5	0
14.	Hazardous effects (like gene mutations, life span changes etc.) due to the natural diffusion of knowledge and natural proliferation of bio-synthetic DNA molecules into the environment.	2	2.25	6.5	0
15.	Use of synthetic microorganisms and catalyst to breakdown and remove various pollutants in water, land and air.	3	1	5	0
16.	Creation of artificial photosynthesis technology that is more efficient and cost effective than solar technology	3	1.25	5	4.41
17.	Development, Production and sale of synthetic products addressing lifestyle complexities (like obesity, memory).	2	1.5	4	11.1
Social and Human Resources Development Objectives					
18.	Creation of specific protocols adhering to safety, security and ethics vis-à-vis study, use and application of bio-synthetic discipline.	1	1	2	0
19.	Design and starting of courses at undergraduate and specialization in Synthetic biology (focusing the key research agendas like health, environment, energy etc.) at the masters' level.	1	1	1.75	0
20.	Introduction of synthetic biology from the elementary level of schooling till high school (Following the concept of Anthroposophy, which means child-centred education for guiding the societies of tomorrow.)	2	1	3	4.2
21.	Development of a Bio-Bricks Registry comprising an integrated tool box covering all the basic molecular structures, which act as building blocks for a biological structure.	3	1	3	0
22.	Development of a Non-Bio-Bricks Registry covering at least five model organisms.	2	2	3.5	0
Legal and Administrative Objectives					
23.	Training of law enforcement agencies and equipping them with sufficient resources and technology to understand, prevent, investigate and prosecute the bio-offenders / bio hackers	2	2	3	2.9
24.	Effective planning and restructuring of domestic regulatory environment with a network of legal and professional bodies pertaining to the development of the discipline at one side and preventing its misuse on the other side.	2	1	3	8.3
25.	Creation of an international body or think tank which will accommodate all the stakeholders for proper nurturing, grooming and functioning of the discipline.	2	1	3	0
26.	Extension of specific framework modules within major international protocols like Cartagena Bio-safety protocols (Since, synthetic biology delicately touches the trans-disciplinary boundaries).	4	3	3	2.8
27.	Use of synthetic biomolecules/organisms by various countries to control unruly crowd.	4	3	5.5	12.5

Source: Compiled by the Authors from the primary data collected through online Delphi Survey with the help of the software SPSS 17.0
The data was standardized as '1' for the year '2020', '2' for the year '2025', '3' for the year '2030', '4' for the year '2035', '5' for the year '2040', '6' for the year '2045', '7' for the year '2050 and Beyond', and '0' for the year 'Never',

Table 7: Delphi Statement Statistical Analysis.

Currently, in India both these possibilities have not evolved to the point where such a concern would seem threatening. In our view, the rapid construction of user-defined microbes would be accelerated once a standard parts registry and rules of composition are in place. However, given that interactions are heavily contextual and based on complex interactions, it is unlikely that organisms shall be assembled straight out of a computer model!

Further, DNA synthesis technology needs to extensively evolve to make it error-free and affordable leading to the synthesis of sufficiently long DNA (e.g. chromosome) for causing concern. In our view, given enormous technical challenges in synthesizing long DNA sequences and prohibitive costs involved, such a scenario looks less likely in the near future. However, situation is expected to change if the cost of synthesis touches the sequencing price-point and the mass-scale synthesis of chromosomes becomes common place.

Technological Choices

Synthetic biology community is rapidly developing technologies for faster and simpler engineering of parts, networks and strains towards useful industrial output. Currently, the community is largely focusing on genome engineering, whole transcriptome engineering, pathway engineering, long DNA synthesis and bioCAD platforms. There are significant possibilities for the development of synthetic fuel, bio-electronic devices, and CAD biology tools for health applications and addressing the future environmental and energy challenges of the planet [24].

Exploring the Future: Actual and Potential Technological Pathways

Actual pathway

Bioserve, a Hyderabad based Contract Research Organization

Consensus Build about the Occurrence of Various Questions		
Year/Time of Objective	**First Round Delphi**	**First Round Delphi**
By the year 2020	18, 19	19
By the year 2025	1,4,7,14,17,20,22,23,24,25	1,2,5,8,18,20,21,23,24,25,26,
By the year 2030	2,3,5,8,9,10,11,12,15,16,21	3,4,6,10,11,12,13,16,17,22,27
By the year 2035	6,13,26,27	14,7,9
By the year 2040		
By the year 2045		
By the year 2050 & beyond		
Never		

These round-wise consensus are been mentioned in the Table 8 as follows.

Table 8: Consensus Build on the Time of Events (in two rounds of Delphi).

(established 1995) in the area of clinical research, also seems to be one of the first Indian DNA synthesis company. Based on the information gathered from their website, the company claims an in-house capability of synthesizing short strands of DNA sequences with an aim towards synthesizing longer DNA sequences in future. RFCL, Faridabad, an international distributor of the US based IDT companies, offers long DNA synthesis services.

Potential pathways

The field of synthetic biology seems to be promising at this stage and can lead to potential applications in Biotechnology & Biochemistry and interfacing engineering sciences. However, this requires rigorous prospective thinking from the community who can participate in building a general idea of key targets achievable through synthetic biology approach. As Synthetic Biology touches the boundaries of disciplines like life-sciences, computer science, electrical engineering; it is useful to bring experts from different fields on one platform, to plan future thinking exercise of social relevance. Apart from finding a common ground among experts, the big challenge is the quantification of really good ideas into a consensus. The classic Delphi method has addressed the problem of heterogeneity and proved to be a reliable, comprehensive, and visionary tool for futuristic thinking and planning.

The what, why and how of Delphi: The word Delphi refers to the hallowed site of the most revered oracle in ancient Greece. Apollo, the son of Zeus and Leto, used to transmit forecasts through intermediaries, women known as pythia. In the modern times, the technique of Delphi was developed by the Rand Corporation in 1950s [27]. During the initial stage, its main focus was development of optimal U.S. industrial target system and estimate the number of A-bombs required to reduce the munitions output by a prescribed amount. The Delphi technique gained its popularity by the end of year 1964 with RANDs "Report on a Long-Range Forecasting Study", which aimed to assess long-range trends, with special emphasis on science and technology. Since, then a swarm of important studies have been carried out using this technique to assess the socio-economic, techno-economic impact of evolving frontiers of S&T, energy sector, agro-biotech sectors etc. [28-30].

The Delphi technique is intended to extract an expert opinion through a scientifically proven questionnaire. The novelty of this technique is that it minimizes the vagaries of open/common room discussions and leaves bleak possibility of influence through psychological factors emerging from dominant academic personalities or pressure groups, specious persuasion, rigidity of members or innate tendency of some to get carried away with majority opinion (bandwagon effect) [31]. In the Delphi method, if the consensus is not been attained during the first round of the exercise, the feedback is sent back to the respondents on the questions that require a careful review. If a general consensus emerges in the first round itself, after all the checks and balances, the results are communicated to the participants. Delphi is designed to consolidate individual judgments systematically and obtain a reasonable consensus. The basic features of this technique are anonymity, iteration, controlled feedback and statistical projection of the group response [31].

After a careful literature review of on-going research and future research agendas of various institutes across the globe, a Delphi questionnaire was prepared in this study. The major objective of the Delphi survey was to generate a probable time of occurrence of the various possible scientific developments in future. The respondents were asked to assess the probable time of occurrence using the following seven time intervals with one additional response for indicating an impossible development.

1. By the year 2020
2. By the year 2025
3. By the year 2030
4. By the year 2035
5. By the year 2040
6. By the year 2045
7. By the year 2050 and beyond
8. Never

Here Delphi was used to reach a consensus on futures application and issues concerning synthetic biology within four key thematic category viz. (i) techno-economic, (ii) Health and Environmental, (iii) Social and Human Resources Development, and (iv) Legal and Administrative. The questionnaire comprised of twenty-seven questions with the responses categorized into eight segments as outlined above. The respondents were asked to indicate the most probable year by which such objective is attainable or indicate 'Never' for an impossible event. Apart from general questions and responses the respondents were also asked to state their level of expertise (through education/profession). The composition of the expertise level (Table 6) of the respondents is represented by the following Figure 2.

The first round of Delphi: The Delphi questionnaire[5] was sent through email to two important groups dedicated and working on the areas of synthetic Biology viz. sanjeevani@JNU, New Delhi and Bioclues@Bangalore. In order, to make the representation widespread and visible from the other disciplines directly or indirectly associated with the field of Synthetic Biology, the questionnaire was also sent to a number of experts working in the field of engineering, law, finance,

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bureaucracy, politics, NGOs (working on Bio-Safety issues) and academic groups working on Policy Issues (CSSP@JNU).

The first call generated 150 responses out of which only 71 responses were found valid. Incomplete and improperly filled responses were filtered out. Though the number is not high, probably this may be considered as a first step towards a more comprehensive Delphi study in future. Of 71 validated respondents (Appendix-II) nearly 64% of the respondents (Figure 2) were either from the Faculty, Post-Doctoral Fellow or a PhD student, indicating a scholarly input in the data generated.

A strong convergence (realisation of objectives within the decade of 2020-30) was seen towards twenty-one goals (Tables 7 and 8). A total of 92% of the respondents in this round were either working or were actively associated with the Life Sciences and Biotechnology fields. Though this may sound statistically encouraging - from the Delphi perspective a non-uniform presence of all the stakeholders introduces a minor degree of bias.

In the first round, many of the respondents (especially from non-biotechnology and non-life sciences background), submitted their partial response probably due to technical nature of many questions. When we contacted those respondents about the reason, they confirmed non-familiarity with those concepts.

Based on our experience, probably another way of conducting such surveys may be through a workshop that involves experts who discuss and educate community, comprises of all the stakeholders from the community. Though such an approach is not entirely error-free, it can rectify certain biasness and skewedness in the trends and develop even an informed consensus on the issues/objectives.

The second round Delphi: The first round not only gave a rough idea of the emerging consensus but also helped in identifying twenty-five key respondents who stated their level of expertise as the highest. The questionnaire was resent to these twenty-five respondents for a second round of participation. The respondents came from divergent fields like Biotechnology, Life sciences, law, engineering, politics, NGO, bureaucracy, finance etc. (Figure 3). The only change in the second round was to redesign the questionnaire and address issues of methodology, biases and content validity. The distribution of the second round respondents according to their field of study is shown in Figure 4.

The statistical results of both the first and the second round are shown in the Appendix-II, while, the analysis of the results of the Round-II are presented in the Table 7. We considered median as the nearest probable year of attainment, while, the lower (25%) and higher quartiles (75%) marked the lower and upper limits of the sought objectives of this survey. The composition of the first and the second rounds of the Delphi Survey produced a series of consensus (Table 8) on various goals covered under the Delphi Statement (Table 7).

Inference(s) from the Delphi exercise: The conclusion from the statistical analysis (Table 7 and Figure 5, performed using SPSS 17.0) of the survey is indicative of the fact that although the majority of objectives seem to be achievable, very few were predicted to be achievable by the year 2020. Only two objectives i.e., developing synthetic biology specific protocol and including synthetic biology as a part of standard academic curriculum are expected to be achieved by the year 2020. Similarly, only three objectives were expected to be achieved on a longer timescale i.e. complete genome cloning experiments within the labs; development of a comprehensive international protocol to govern synthetic biology and use of biomolecules for crowd control. However, all other 22 objectives are expected to reach their set standards within the decade of 2020-2030.

From this study, it appears that issues that appear ambiguous to the respondents have generated a middle path response. For instance, since, the routine installation of alternative genetic codes in the native genome has not yet been demonstrated, the respondents chose to keep away from predicting its future evolution until it becomes a standard practice. The majority of the respondents saw near future introduction of a synthetic biology curriculum at the undergraduate level leading to specialization in Synthetic biology in key research agendas like health, environment and energy and at the Master's level. Even the respondents were in favour of introducing the basic concepts of synthetic biology at the elementary level of schooling till high school as this would motivate the younger generation to pursue these advanced disciplines and prepare them better in a highly competitive environment.

The statistically significant (more than 10 per cent) negative response was seen only with two possible goals i.e. development of synthetic products addressing life style complexities and use of biomolecules for unruly crowd control. However, the former is already showing some presence in the market of supplementary beauty products. The dislike with latter goal is probably the result of respondents respect for human ethics.

Irrespective of this seminal study in India on the topic of synthetic biology, the accuracy of the survey rests on factors like respondents' interest and understanding of the subject, knowledge of major technological breakthroughs and the observational and experimental errors both in pre and post-facto scenarios of this exercise.

Socio-Economic Impact Assessment of the Technology

Synthetic biology is catching up in India particularly in the space of biofuels. However, the possibility of commercially available biofuels competing with the petrol and diesel in terms of price point will take time. Competing with compressed gas based fuels will be still tougher. Though several good examples of synthetic biology research are emerging, the key challenges to the global governance of synthetic biology are (i) the governance of non-knowing players and their research space; (ii) the cultivation of external accountability and (iii) the fragmentation of social authority [3].

Hence, to make stable, safe and long term ventures in synthetic biology a properly planned regulatory and governing framework is required. This will not only lead to a positive directed evolution of the field but also prevent misuse. Due to nascent stage of the field, the socio-economic benefits of the field are not yet visible. However, with research targeted at designing innovative products that compete with the existing solutions, it is hoped that synthetic biology may show a significant presence in the socio-economic space in future.

Regulation and Governance of Synthetic Biology in India

The Indian Government has laid down clear rules for people/organizations attempting to apply for patents over life forms. The Section 3(j) of the Patents Act, 1970 states that "plants and animals in whole or in part thereof (other than microorganisms), including essentially biological processes for production or propagation of plants and animals shall not be considered as patentable subject matter".

However, from it is unclear how the current patent laws plan to treat "natural genetic modules" that is part of artificially constructed systems designed at the boundary of life sciences and engineering? Probably artificially constructed live cells that are generated by the combination of standard elements would be barred by Section 3(f) that refers to "mere arrangement, rearrangement or duplication" of independently functioning devices. However, in our view this statement is open for interpretation.

The Indian Patent Act, 1970, Section 3(b) states that, 'an invention, the primary or intended use or commercial exploitation of which, could be contrary to public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment ' is not eligible for patent protection.

From the study and given the rapidly evolving situation, it would be relevant for government to bring clear guidelines and regulations on biosafety and biosecurity concerns emerging from synthetic biology research in the country. Recommendations proposed in a recent paper on this issue are noteworthy [22,23]. Some of the key points made in this important paper were: (a) making public aware of the potential use of Synthetic Biology (b) developing stringent regulations for accessing the synthetic bio-components and products (c) evolving the existing legal framework to incorporate additional security and safety concerns emerging from synthetic biology research while balancing social interests (d) development and enforcement of stringent risk assessment and containment protocols to avoid hazards (e) involving all the stakeholders e.g., government, funding organizations, scientific community and public interest groups to evolve a national consensus

Community Outreach and Engagement with the Technology

In the fall of 2010, the first Synthetic Biology event in the University of Kerala led to identifying synthetic biology interest group and devising synthetic biology curriculum by the academic community. The following year saw another synthetic biology event at Jawaharlal Nehru University, New Delhi with an aim to build synthetic biology research community in India. As a result of these meetings and discussions with the community, formal academic programs are expected to be launched in the country. Synthetic biology is one of the key interest areas of DBT and CSIR and it is hoped that significant activity in the space of educational training and research funding will be visible in the near future.

The Delphi Survey elucidates a wide spectrum of public understanding of Synthetic Biology. Apart from highlighting the community understanding of Synthetic Biology, the Delphi exercise was also successful in getting a general hint of the space where things are likely to evolve in the future. The survey questions were able to find out difference between perceptions, expectations and pragmatic speculation when the data was statistically analysed. This not only gave a sense of what the experts conceived about the questions but also how they want the future to appear. For instance, one of the common questions was whether one can use this discipline to maintain the flora & fauna in the country?

On a larger scale, the scientific and academic fraternity is now concerned with much bigger questions concerning trans-disciplinary boundaries. For instance, can two different methods or disciplines like Synthetic Biology and Nanotechnology be integrated and cultivated to achieve goals of climate change mitigation, enhancement in agricultural production etc.?

A general curiosity was visible in the open-ended comments where the merger or blurring of inter-disciplinary boundaries was speculated by some respondents. A few respondents believed that disciplines shall maintain their orthodox sanctity and seldom cross their boundaries. In their view, it is not the disciplines but the tools that will cross boundaries among several seemingly independent domains. Further, some of the respondents raised the concern that how these emerging disciplines will be groomed, cultivated and managed while avoiding disciplinary, legal or socio-environmental friction. From this study, although the public expectation from synthetic biology was high, the major concern was about its regulation pathways. This trend was clearly visible.

Conclusion

Synthetic Biology as a formal discipline appeared less than a decade ago. Normally, a field takes time to register in domains of scientists, policy makers and funding managers. However, the intellectual penetrance rate of synthetic biology has shown a much higher value than expected. This is probably due to its game changing nature, potential for good industrial applications and its life threatening implications. It remains to be seen if the field was over-hyped and if the promises were oversold. Also, it is unclear if the community will get saturated with promises never delivered or will the research change the quality of human life significantly.

In the context of Indian science, the story has just begun. More useful collisions between scientists, community and funding managers are needed to bring out bright ideas and take them to the market. At this time, a clear perception of what is synthetic biology, its success stories, boundary conditions and regulatory issues, does not seem to have registered very strongly in minds of stakeholders. With more public and private funding, academic training programs and events, things are bound to change within the next 10 years. Though the awareness is rapidly increasing, in our view India has miles to go, to reach a critical mass and make a globally impactful contribution.

Websites and Online Databases

- http://www.biodesignindia.org
- http://ccbb.jnu.ac.in/synjeevani/
- http://www.evolva.com
- http://sea6energy.com/
- http://2007.igem.org/Bangalore
- http://www.che.iitb.ac.in/
- http://dbtindia.nic.in/
- http://www.bioserveindia.com/
- http://venture-capital-firms.findthebest.com/d/c/Biotechnology
- [Online: web] Accessed on 14 March, 2013 URL: http://scopus.com
- [Online: web] Accessed on 19 March, 2013 URL: http://www.synthetic-biology.info/statistics.html
- [Online: Web] Assessed on 21st March, 2013 URL: http://thomsoninnovation.com
- [Online: Web] Assessed on 17th March, 2013 URL: http://www.synbioproject.org/topics/synbio101/definition/

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Foot Notes

[1]It means all equity capital (VC, IPO, follow-on) that is the traditional source of financing for an industry sector heavily involved in start-ups or generating innovation (Ernst and Young, 2012).
[2]For instance USA has in total 17203 Patents alone for IPC classification C10L while India's tally for this is at 432. (Source: [Online: Web] Assessed on 21st March, 2013 URL: http://thomsoninnovation.com).
[3]IPC Codes Applied in Inspec Records (2011) WIPO: http://www.theiet.org/resources/inspec/support/docs/ipccodes.cfm?type=pdf [Online Web: Assessed on 19th February, 2013].
[4]This data included policy briefs, conference proceedings and journal articles by the researchers working within the domain of synthetic biology.
[5]Available online: https://docs.google.com/forms/d/1SKndl5T9-_ZGnYoj07NcQN_Q7GfDtrLAxo_a58vVsnU/viewform.