

12TH FIVE YEAR PLAN

*REPORT OF THE PLANNING
COMMISSION CONSTITUTED
TASK FORCE ON*

*SYNTHETIC AND SYSTEMS
BIOLOGY RESOURCE NETWORK
(SSBRN)*

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Executive Summary

- Synthetic and Systems biology is a new area of biological research that combines science and engineering. It encompasses a variety of different approaches, methodologies and disciplines. Synthetic and Systems biology lies at the interface of many different biological research areas such as functional genomics, protein engineering, chemical biology, metabolic engineering, systems biology and bioinformatics.
- From programmable systems, the scale of these attempts grew to creating small modules or networks, with inherent properties. Currently, an emerging trend is the ambitious attempt to use these modules to engineer whole cells. Several groups across the US and EU are actively engaged in the Synthetic and Systems Biology research.
- In India the Synthetic and Systems Biology is at a nascent stage. The institutions involved in the research in this area include CSIR Laboratories, IISc, NCBS, IIT-Kharagpur, Bose Institute, University of Kerala and a couple of companies.
- The timing is suitable for a well supported 'push' into synthetic biology, both from the point of view of enabling technologies as well as to look towards practical applications. The immediate goal should be to build a base of research expertise and infrastructure in Synthetic and Systems Biology. In terms of human resources, there is little debate that India's potential remains untapped. As an indicator of future growth in Synthetic and Systems Biology, it is useful to examine the role of MIT's International Genetically Engineered Machines Competition (iGEM) and create such environment in the country.
- It is emphasized that investment in broad undergraduate education, as opposed to narrow technical training, related to Synthetic and Systems Biology will have strongly positive effects in many disciplines, ranging from traditional biology, to engineering, chemistry, and even the practice of medicine. In this context, the correct steps

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forward will be the development of a broad-based engineering curriculum that allows students to maintain their basic engineering and quantitative skills while exposing them as early as possible to exciting new directions in biology.

- India has the opportunity to be a world leader in playing a role as a protector and supporter of open source biological platforms, by providing the correct legal environment in which small biotechnology players can compete on a level field along with pharmaceutical and petroleum giants. Through this route Synthetic and Systems Biology could also be focussed to create desired niches.
- Task Force recommendations cover augmenting Capacity through Creation of Institutions, augmenting Human Resource Development, building Translational Capabilities, evolving Multi-Modal and Fast Track Funding Options, building International Linkages, creation of Training Centre, Network Centres, dedicated seminar circuits for Synthetic and Systems Biology research, creation of fellowships in the area and facilities for micro-fluidics, high-throughput genome sequencing, and engineering and omics scale data generation; creation of plug-and-play facilities and creation of open knowledgeware. It is also recommended that the Task Force may be converted into a Standing Committee with a new set of members for creation of National Document and coordination of Synthetic and Systems Biology Research Network in the country. It was further recommended that the funding for Synthetic and Systems Biology initiatives under the aegis of the Task Force could be restricted to those domains where funding was not available elsewhere.
- The budget for the project is estimated at about Rs1970 Crores during the 12th Five Year Plan. Implementation of the project in its form and shape, and execution in a specific location will largely depend on the champion that CSIR is currently in pursuit of. The activities will need a high throughput environment for successful realization.

1. Macro Overview of Synthetic and Systems Biology

1.1. Introduction

Building on the achievements in basic biological sciences during the early part of the century, several new bio-technologies have been emerging in the recent past. Molecular biology was the study of the components of a living system, while genomics targeted generation of data of the whole system. “Systems biology” is the understanding of biology at the systems level by integrating parts of the molecular biology and information of genomics, and applying engineering principles for understanding the system. “Synthetic biology” refers to the creation of new artificial systems from the understanding of the biological systems, by designing and integrating parts to create a whole system.

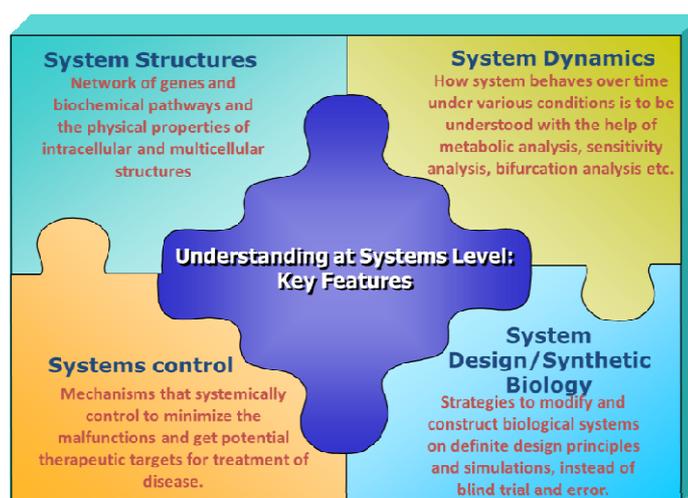


Figure 1: Synthetic and systems biology are multi-disciplinary fields that integrate the knowledge of different scientific disciplines and needs the skill sets of academics, entrepreneurs and researchers

Understanding of (1) system structures, (2) dynamics, (3) control methods, and (4) design methods are major four milestones of systems biology research. Systems Biology is the integrated approach to studying biological systems— intracellular networks, cells, organs, and any biological entity—by measuring and integrating genetic, proteomic and metabolic data. This approach involves cellular and pathway events that are in flux and interdependent. Its application to drug discovery includes utilizing clinical samples from diseased and healthy (normal) patients to uncover System Biology Markers and Pathways Targets, which are indicators of

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disease and potential targets for therapeutic intervention. The field of systems biology is expected to mature in the next few years, and be characterized as a field of biology at the system level with extensive use of cutting-edge technologies and highly automated high-throughput precision measurement combined with sophisticated computational tools and analysis.

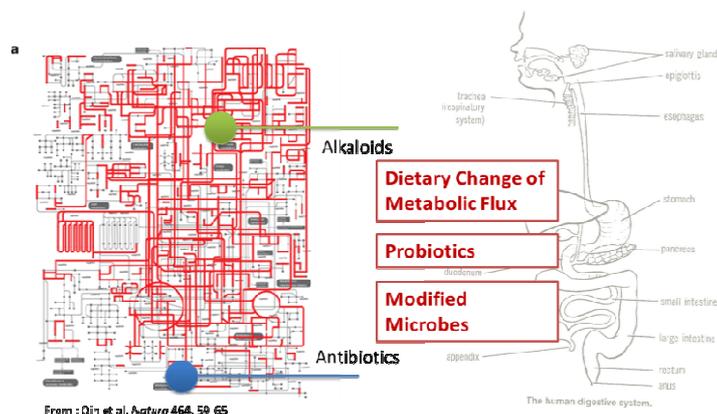


Figure 2: A synthetic biology approach to Engineering Human Gut as a Biofactory for Drugs and Drug-Like Molecules

Synthetic biology refers to both:

- the design and fabrication of biological components and systems that do not already exist in the natural world ; and
- the re-design and fabrication of existing biological systems.

Synthetic biology is different from Systems biology. Systems biology studies naturally occurring complex biological systems as a whole often with some medical significance. Synthetic biology however, is focussed on how to build artificial biological systems for engineering applications, using many of the same tools and experimental techniques.

Mostly driven by the advances and developments in systems biology, synthetic biology has become a field of its own only recently. Besides providing an understanding of basic life sciences, synthetic biology has great promise in medical, chemical, food, and agricultural industries. It has the potential to fabricate practical organisms that could clean hazardous waste in inaccessible places, to use plants to sense chemicals and respond accordingly, to produce clean fuel in an efficient and sustainable fashion, or to recognize and destroy tumours. Currently, synthetic biology is at a very early stage of development, and the risks associated with it remain unknown. Therefore, techniques for risk assessment and risk reduction should also be followed-up alongside the innovation path.

1.2. Origin and Evolution of Synthetic and Systems Biology

The term ‘synthetic biology’ was first used by Barbara Hobomin 1980, to describe bacteria (biological) that had been genetically engineered (synthetic) using recombinant DNA technology. Synthetic biology was largely synonymous with ‘bio-engineering’. In 2000, the term ‘synthetic biology’ was again introduced by Eric Kool and other speakers at the annual meeting of the American Chemical Society in San Francisco. Here, the term was used to describe the synthesis of unnatural organic molecules that function in living systems. More broadly in this sense, the term has been used with reference to efforts to ‘redesign life’.

Systems biology finds its roots in the quantitative modelling of enzyme kinetics, a discipline that flourished between 1900 and 1970; the mathematical modelling of population growth; the simulations developed to study neurophysiology; and control theory and cybernetics. The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology". Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. An often stated ambition of systems biology is the modelling and discovery of emergent properties, properties of a system whose theoretical description is only possible using techniques which fall under the remit of systems biology.

In its ‘first wave’, synthetic biology focused on creating and perfecting genetic devices and small modules. Currently, modules include switches, cascades, pulse generators, time-delayed circuits, oscillators, spatial patterning and logic formulas. These and other modules can be used to regulate gene expression, protein function, metabolism and cell–cell communication. The on-going phase is the ‘second wave’ of synthetic biology, in which basic parts and modules need to be integrated to create systems-level circuitry. Based on an analysis of publications in this space, it is understood that although the overall number of synthetic systems has increased over a 9 year span, the complexity of published systems seems to have reached a plateau, at least for now.

A major challenge for synthetic biologists is designing multi-cellular systems to exhibit finely tuned coordinated behaviour, as the precise details of most biological environments are poorly understood. The uncertain and intricate nature of biology makes standardization in the synthetic biology field difficult. Thus, engineering biological systems probably requires both new design principles and the simultaneous advance of scientific understanding. Synthetic biologists will need to formulate new and effective bioengineering design principles to address these challenges. Newer designs should permit combining modules into complex synthetic pathways and thereby create sophisticated cellular behaviours. Such *systems-level bioengineering* can synergistically target multiple pathways, symptoms or targets — such as multiple cell populations or organs — creating the potential for innovative environmental and therapeutic applications.

1.3. International Status

Synthetic biology is a nascent field, and there is currently no systematic, global effort to coordinate the developments in synthetic and systems biology research. Much of the research so far has been pioneered by individual groups in the US, and the European Union. Despite the lack of concerted efforts, there are several groups across the US and EU who are actively engaged in this field. The initial focus of researchers attempting to create programmable systems was to develop modular parts that can be decoupled from the cellular system and integrated at will into networks to produce predictable effects. Gradually, the scale of these attempts grew from creating components to small modules or networks, with inherent properties. Currently, an emerging trend is the ambitious attempt to use these modules to engineer whole cells.

Most of the excellent work comes from a few leading research groups in the world. Annexure 1 provides a summary of leading scientists in the area and their research interests that allow us to benchmark the international level of research in the area and the leading centres in the world. Institutions with a research ambience that encourages inter-disciplinary science are uniquely positioned to host synthetic biology projects. A conscious and laudable community effort with the aim of creating a generation of scientists, selected from today's students, who are familiar with the inter-disciplinary nature of the field, is the international genetically engineered machine contest or iGEM. Groups of students, with an advisor, design machines, engineer them and display them at an iGEM annual jamboree of sorts. The iGEM contest has over the years gathered momentum, impact and popularity, ensuring a crop of future synthetic biologists. At the same time, synthetic biology has already seen the other end of scientific enterprise, with scientists taking up projects that address a commercially important problem, like the engineered production of a plant derived drug at reduced cost or the engineering of microbes for production of environment friendly fuel. An attempt has been made to highlight a landmark achievement and also benchmark the current trend as defined by the aspirations of majority of scientists in the area. (See Annexure 2 for details). Figure 3 explains the measures and milestones towards a successful European synthetic biology.

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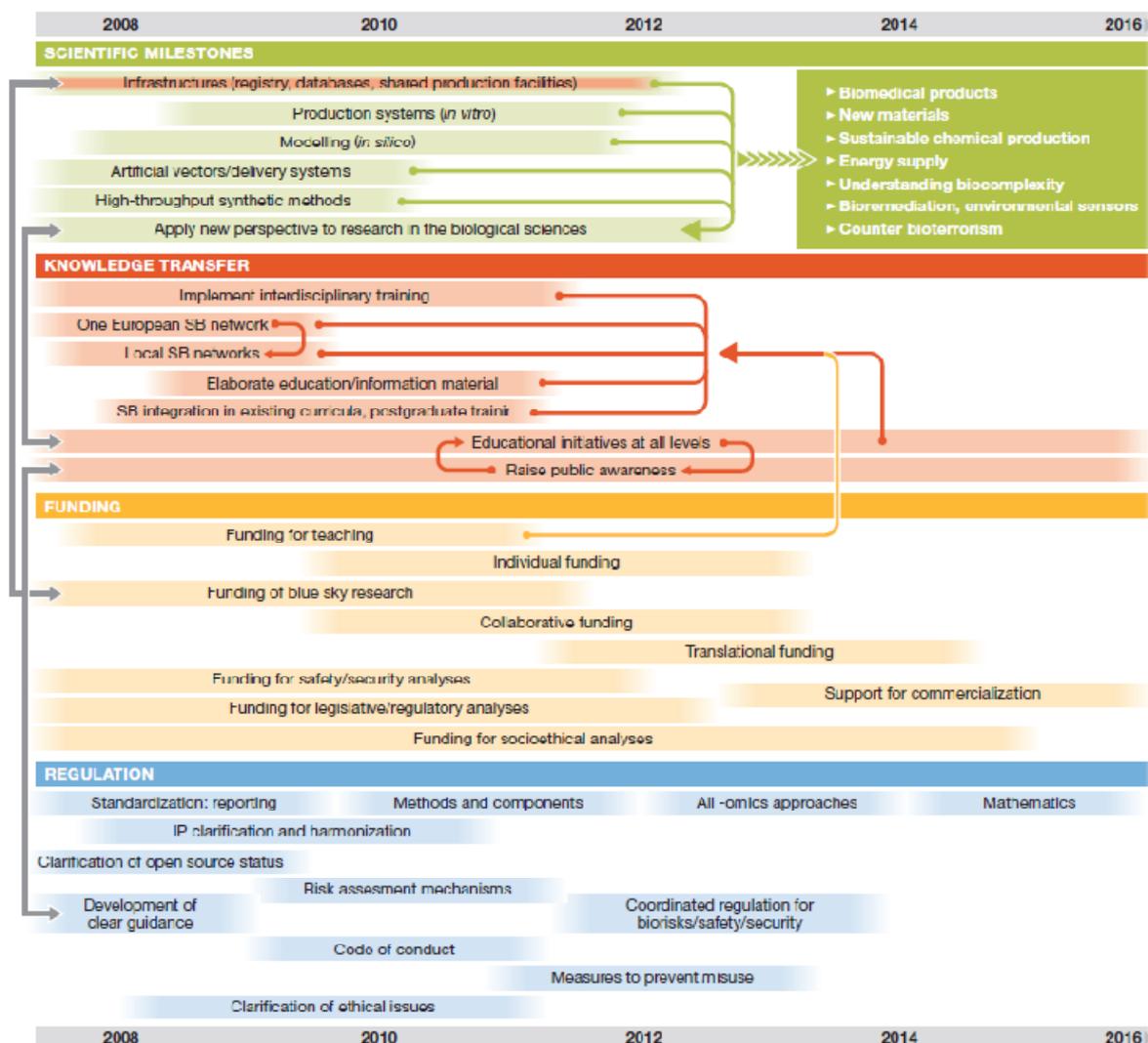


Figure 3: Roadmap of measures and milestones towards a successful European synthetic biology. IP, intellectual property; SB, synthetic biology. Source: [EMBO Rep. 2009 August; 10\(S1\): S5-S8](#)

1.4. National Status

Synthetic and systems biology is a relatively new field and isolated efforts are being undertaken in India. However India is well poised to take up the challenge to build up this field and become globally recognized player. Annexure 3 provides a list of Synthetic and Systems Biology Research organization gives an overview of research in the field of systems biology in India.

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There is no specific institution for Synthetic and Systems Biology in India. Scattered activities in this field from specific groups across national institutes have been supported by Government agencies such as CSIR, and DST. Besides, companies such as Cell Works Research India Pvt. Limited and BioCOS Life Sciences Pvt. Limited have common interests in this specialized field.(Please see Annexure 3 more details). The Centre for Systems and Synthetic Biology, University of Kerala is also engaged in systems and synthetic biology research.

At the CSIR, two synthetic biology and metabolic engineering related projects have been formulated, namely 'Synthetic biology and metabolic engineering of azadirachtin biosynthesis pathway' and 'Metabolic engineering of vinca alkaloid pathway' with national relevance. Azadirachtin is absolutely an eco-friendly insecticide (biodegradable and not toxic to humans) mainly present in fruits/leaves of neem tree (our national plant). On the other hand, vinblastine and vincristine alkaloids are very powerful antitumor drugs, which are used for human cancer therapy and are present in *Catharanthus roseus* plant (widely available in India) have high commercial demand and are used worldwide. Azadirachtin, vinblastine and vincristine are produced in small amount within the respective plants, which make them expensive to produce commercially. Furthermore, these biomolecules have very complex chemical structures; as a result synthesis of each of them in the laboratory is economically not viable. Therefore, combination of synthetic biology and metabolic engineering approaches will be the best solution to get bulk quantities of these molecules using microbial organism as a living chemical factory. At present eight CSIR laboratories are actively involved in these projects. Apart from these activities at CSIR, a few national laboratories/university are also initiated synthetic biology related work.

One of the immediate impacts of systems biology would be on the implementation of personalized medicine in human healthcare. Keeping this in view, at CSIR, a project on "Multi agent therapy of cancer: a systems biology approach" has been initiated at XI the plan. There has been a paradigm shift in drug discovery. The concept of one-drug one-target is being replaced by the present strategy to discover drugs that affect multiple targets at the level of disease network. The emerging principle of multi-target anti-cancer drug design is to reconstruct disease related networks at a global and systems level, analyze the network properties to find potential drug targets and finally evaluate the effect of single- or multi-agent on the disease network. A CSIR-IGIB led Team India initiative, with a large number of colleges and universities across India, worked on the systems biology of MTb, in its OSDD program. Several other laboratories in India are also applying systems approach to solve different biological problems.

1.5. Patterns of Investment

With a large potential for research and development, and future benefits for economy and society, synthetic and systems biology presents an opportunistic area for investment. The field is still nascent with scattered research activities among

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small working groups, across both the US and EU. The US presents a more advanced region for synthetic and systems biology in terms of activity and networking within the scientific community. As the field is still in its infancy, funding for synthetic biology projects was identified as one of the main bottlenecks to progress.

In the EU, recommendations included funding activities that should predominantly support so-called 'blue sky' research or basic research projects. In the EU, the introduction of a more unconventional approach, that of an additional two-step 'evolutionary' funding scheme, was thought to be more appropriate for this emerging field. In the first step, projects were to be supported on their specified contribution to creating an innovative outcome. No strict selection procedures were applied at this stage. In the second step, all projects after a defined period were reviewed by an expert panel with respect to their actual contribution to the desired outcome. This led to a selection of projects for further funding. The scheme was believed to allow the pursuit and testing of unconventional and creative ideas at the initial stage, so all projects would have a chance to demonstrate their quality.

Since 2005, the U.S. government has spent approximately \$430 million on research related to synthetic biology, with the Department of Energy (DOE) funding a majority of this research. Approximately 4% of the total has been allocated to examine the ethical, legal and social implications of synthetic biology and is funded through DOE, the National Science Foundation and the Department of Agriculture. By comparison, the European Union and three European countries – the Netherlands, the United Kingdom and Germany – have spent approximately \$160 million on synthetic biology research with around 2% going toward implications research. In the EU, there has a decrease in the funding in 2010 mainly owing to the discontinuation of the NEST programme. The NEST programme was meant to stimulate a research community in Europe, with the aim that national funding agencies should later continue to fund scientific projects in that area.

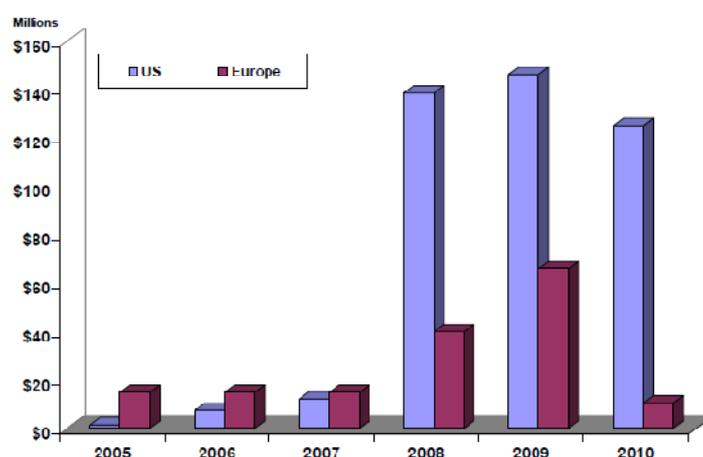


Figure 4 depicts the annual spending of the U.S. government agencies, the European Commission and individual European countries; Source: [Woodrow Wilson International Center for Scholars, June, 2010](#)

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It is suggested that the Genomic Sciences Program and the Joint Genome Institute could be classified as synthetic biology research and the budgets of these two programs alone total more than \$230 million a year for fiscal years 2008, 2009 and 2010. (Also see Table 2, Annexure 4 for greater details).

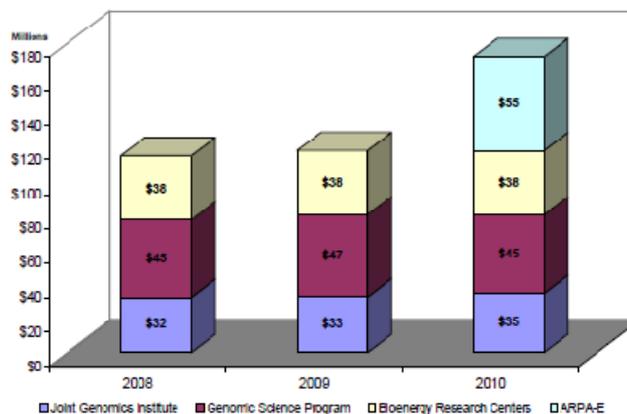


Figure 5 DOE Funding; Source: [Woodrow Wilson International Center for Scholars, June, 2010](#)

Since 2005, Europe has allocated around \$160 million to synthetic biology research. This includes funding provided by the European Commission along with the individual country budgets of the United Kingdom, the Netherlands and Germany. The European Commission spent close to \$45 million between 2005 and 2007 on synthetic biology as part of the Sixth Framework Program for Research and Technological Development. The Seventh Framework Program, which runs from 2007 to 2013, has allocated approximately \$8 million until 2010, including \$2 million for implications research. (Also see Annexure 5 for funding that were supported by the European Commission's 6th framework programme NEST)

Among the EU countries, UK is the only country with an established funding scheme for R&D and ELSI that successfully integrates these research communities. Estimated funding of synthetic biology in the United Kingdom is estimated at between \$30 million and \$53 million since 2005. Research funding is divided among three programs: Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council and the Wellcome Trust.

In Germany, the Deutsche Forschungsgemeinschaft (DFG, or German Research Foundation), acatech (the German Academy of Science and Engineering), the German Academy of Scientists Leopoldina and the National Academy of Sciences consider synthetic biology a funding priority. The DFG is planning to invest approximately \$3.5 million in synthetic biology.

Besides the US and EU, several other countries such as Japan, Brazil, Israel, China, Singapore and Taiwan have invested in this field; details of the fundings are unavailable in the public domain. Synthetic biology is still in an early developmental

stage in China. The need to fulfil agricultural demands and enhance industrial production, and to provide health care to the 1.3 billion people, is the key force driving Chinese biotechnology research. Early biotechnology developments in China emphasized more on research for agricultural applications but less for medical and pharmaceutical ones. The launch of funding projects 863 and 973 Programs, has seen a surge of activities towards the development and utilization of molecular techniques in life science.

In India, on the subject some activities have been funded by Government agencies such as CSIR and DBT for specific projects. The current recommendation on promoting activities in this space will pave way for a great enablement of the area.

2. Synthetic and Systems Biology as an Enabling R&D Domain

2.1. Exploiting Biological Sources for Value Added Products

Synthetic biology represents a powerful new direction of bio-engineering that brings together the following components: (a) The goal: to construct novel biological entities (cells, tissues, whole organisms) that bring together diverse biological components (genes, proteins, architectures) to achieve desired functions. (b) The substrate: the entire diversity of the biosphere, which represents an essentially infinite resource of novel and useful molecules and designs. (c) The method: a systems-level approach to the design and testing of engineered, multi-component, modular biological entities. This approach has generated proof-of-concept systems ranging from engineered gene-regulatory networks to customized metabolic pathways and synthetic bio-sensors. The discipline is now at that difficult juncture in which advances in the laboratory must be converted into widely distributed applications. Here we list potential applications; current limitations that represent immediate research goals; and new research directions that are expected to emerge; all on a ten-year horizon.

Potential applications areas, known limitations, probability of successful deployment at 10Y:

Biofuels

In the race to biofuel development, synthetic biology appears as a natural partner. The main thrust is on the use of engineered photosynthetic organisms (e.g. algae) as biofuel sources. Key research directions include reactor designs to maximize photo absorption, and metabolic engineering to maximize flux through relevant pathways without compromising overall cell viability. At current scales, these engineered systems do not compete with fossil-fuel resources, alternative carbon-

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reduction techniques, or even process-driven biofuel techniques such as cellulosic ethanol from non-food plant sources. Probability at 10Y: Low.

Bioremediation

There are already field-scale studies on the use of microbes to process toxic or hazardous materials, ranging from oil spills to nuclear radioactive waste. These applications typically rely on discovering natural populations of microbes that colonize contaminated areas. New directions involve actively engineering these microbes to more efficiently carry out the desired breakdown processes. The current limitation is a regulatory one: the uncertainty in the consequences of releasing engineered microbes at large scale in the open environment. Probability at 10Y: Medium.

Biosensors

The use of engineered biosensors has revolutionized laboratory studies of cells and organisms. At the level of protein engineering, medical diagnostic applications are also growing. However, the specific applications of the broad synthetic biology approach to this area are still in test stages. The applications of biosensors could include: detection of low level chemicals in the environment; detection of molecules within the human body; design of diagnostic kits. Probability at 10Y: Medium–high.

Food

The debate and discussions that surround GMO (genetically modified organism) crops is familiar. Synthetic biology enters as the next-level genetic engineering technique, moving beyond the single-gene and two-gene modified crop variants into massively re-organized plant genomes. Unlike the synthetic biology of microbes, or even animal cell lines, the field of plant synthetic biology is in its infancy, with both technical as well as regulatory barriers to overcome. Probability at 10Y: Low.

Health

This is arguably the most important problem to which the power of synthetic biology may be brought to bear. Extensive applications relate to the more ‘traditional’ protein engineering approaches. The applications of new synthetic systems to human health include: biosensor-based diagnostics, engineered bacteria to target specific pathogens, enhancing the production of bio-pharmaceuticals, understanding and regulating commensal microbial consortia, and the use of live biological agents for drug delivery or immune modulation. The regulatory barriers for live-cell therapies remain high. Probability at 10Y: High (biopharma); Low (live-cell therapies).

2.2. Technological Issues

Research in synthetic biology to date has focussed on using cells (bacterial or eukaryotic) as platforms within which a small group of new components (e.g. on the order of tens of genes) can be assembled and operated. The design cycle involves planning, construction, validation, followed by iterative improvement. New directions involve moving beyond individual cells, moving beyond small groups of genes, and moving beyond predictive design cycles.

Moving beyond individual cells: microbial consortia. Natural microbial populations perform metabolic tasks in tightly coupled inter-species aggregations known as consortia. Mimicking these natural populations using engineered systems represents one of the most promising directions for increasing the capacity of metabolic production in synthetic systems.

Moving beyond small groups of genes: genome-scale engineering. The approach pioneered by Craig Venter envisions the construction of a cell with a minimal genetic repertoire, on top of which large sets of new genes or pathways can be added at will in a single synthetic step, essentially involving direct chemical synthesis of the whole genome. Breakthrough possibilities here involve construction of entire combinatorially synthesized libraries of synthetic cells that, using appropriate screening methodologies (see below) can be selected for desired behaviours.

Moving beyond predictive design cycles: selecting and evolving synthetic constructs. Synthetic biology runs up against a complexity barrier, where unforeseen interactions between components results in the inability to predict the behaviour of new combinations. At the other extreme, bench-top evolution experiments are typically used to select for simple phenotypes (such as the presence or absence of antibiotic resistance). The combination of the two promises to be much more powerful: it is possible that a simple synthetic 'decoding circuit' can be placed on top of a library or mutation screen to convert a complex phenotype into a selectable fitness advantage. Building on top of a genome engineering strategy, it will be possible to screen large numbers of architectures rapidly to select for the desired outcome. A major enabling technology in this area will be the ability to perform high-throughput low-sample screening. Promising options include the use of adaptive microfluidic devices coupled to sensitive single-cell imaging techniques.

2.3. Advantage India

Worldwide, the timing is suitable for a well supported 'push' into synthetic biology, both from the point of view of enabling technologies as well as in looking toward practical applications. India, with its growing base of excellence in life sciences research, is fully capable of entering the fray.

India's needs, ranging from energy security, to improvements in agriculture and health, present challenges to synthetic biologists. The immediate goal should be to

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build a broad base of research expertise in synthetic biology, including: (a) Increasing the number of synthetic biology groups and consortia at research institutes and universities. (b) Supporting the growth of enabling technologies and platforms, including microfluidics and whole-genome techniques. (c) Nurturing a new generation of students engaged in bio-engineering, with strong basic skills in the life sciences as well as the physical sciences, engineering, computation, mathematics, and statistics.

In terms of human resources, there is little debate that India's potential remains untapped. As an indicator of future growth in synthetic biology, it is useful to examine the role of MIT's International Genetically Engineered Machines Competition (iGEM). This event, targeted at undergraduate students, has been running annually since 2005. The first team from India to participate at iGEM was from the National Centre for Biological Sciences, in 2006; in 2011, four teams represent India. While these teams have made a good showing, winning several prizes over the years, over the same period the number of teams based in China has grown from zero to twenty. This gap is partly due to a lack of awareness of the area (which falls between the cracks of traditional disciplines), and a lack of resources to support expensive biology practical training at the undergraduate level. We emphasize that investment in broad undergraduate education (as opposed to narrow technical training) related to synthetic biology will have strongly positive effects in many disciplines, ranging from traditional biology, to engineering, chemistry, and even the practice of medicine. In this context, the correct steps forward will be the development of a broad-based engineering curriculum that allows students to maintain their basic engineering and quantitative skills while exposing them as early as possible to exciting new directions in biology.

India has the opportunity to be a world leader in playing a role as a protector and supporter of open source biological platforms, by providing the correct legal environment in which small biotechnology players can compete on a level field along with pharmaceutical and petroleum giants.

2.4 Ethics and the social context: points of caution

Synthetic biology is a powerful enabling technology, and as such its growth must be matched with introspection and caution. While one should provide synthetic biology research with the broadest possible support, this must occur in an atmosphere of public acceptance and transparency, with an effort to minimize large negative consequences. Looking only at the recent history, it is clear that a premature push to bio-fuels has pitted food crops against fuel crops, leading to global food inflation. While the production of anti-malarial drugs cheaply and efficiently using synthetic biology will be of great benefit, it must be determined whether the current bottleneck involves drug production, or its broad distribution especially in the rural context. The debate over GMO crops need not be reiterated here, suffice to say that unless the public is brought on board the potential of large-scale beneficial outcomes to synthetic biology research will be limited. This new science promises cheap,

abundant, and accessible solutions in terms of food, fuel, and health. These benefits should be made available to the broadest possible population: a problem in which science plays only a small part.

3. Accreting Synthetic and Systems Biology Initiatives in India

3.1. Introduction

It is widely believed that synthetic and systems biology has the potential for major wealth generation by development of new innovative industries. Healthcare, energy and agriculture are accepted to be key beneficiary sectors. Developing countries have been projected to gain substantially from such advances provided adequate emphasis is given to institutionalizing and leveraging the disciplines into higher trajectories of application. This would require policy interventions, strategic planning and sustained fiscal support.

India stands at a cross-road in its policies and focus towards application of biotechnology to social welfare and industrial development. Learning from the past when apprehension into entering the genomics and proteomics revolution had denied the country substantial competitive advantage over peers, it is currently widely felt that judicious and quick decisions are imperative to ensure that India attains commanding heights in the synthetic biology and system biology initiatives. Focus should therefore be towards addressing the lacuna that exists in raising synthetic and systems biology into higher trajectories of application. Capacity buildings, development of adequate human resources, leveraging translational capabilities and putting in place innovative funding options are matters of particular importance. Instead of building new structures and systems *de novo*, it would possibly be judicious to build around existing frameworks through a process of accretion. The envisaged roadmap should concentrate upon tapping the energy of the young students to confront challenges; facilitate the process through transformation of the entire education system for doing things differently, and in the process create both input funds for resources and generate output in the form of results.

3.2. Focus on Capacity Building

In contrast to many developed countries, India has a significantly sub-critical capacity towards pursuing synthetic and system biology R&D. Apart from lack of institutions that are mandated to work towards synthetic and systems biology, an important impediment is the disconnect that exists among scientific and technological domains. Capacity building should therefore be concentrated upon not only increasing the number of institutions engaged in the domain but also to promote

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large scale trans-disciplinary discourse. The following approach could be adopted for the purpose:

- Create “focal centres” within R&D laboratories, universities and academic institutions to undertake well-focused research in synthetic and systems biology;
- Connect institutions across various disciplines to undertake synthetic and systems biology initiatives in a network mode;
- Set up new institutions both in physical and virtual mode;
- Augment information processing, warehousing and analyzing capabilities through establishment of data grids;
- Enable application of open innovation and crowd sourcing approaches to problem handling;
- Develop effective liaison with industries to promote and facilitate participatory technology development.

3.3. Focus on Human Resources

Success of a new discipline in attaining maturity for industrial application depends upon availability of adequate number of trained human resources. Synthetic and system biology being essentially trans-disciplinary domains, require expertise in life sciences (including biotechnology, molecular biology, genetics etc); engineering sciences; chemical sciences and computational sciences (including information technology). Courses taught in our conventional educational systems often fail to bridge the gap in the requirement of trans-disciplinary manpower. The following approach could be adopted for the purpose:

- Develop innovative educational delivery mechanisms that would focus upon trans-disciplinary sciences through newer curriculum and pedagogy;
- Augment conventional courses with ‘project mode learning’ in close cooperation with R&D institutions;
- Facilitate inter-connectivity among university programmes in science and engineering with focus upon synthetic and system biology;
- Facilitate continuing programmes in these areas;
- Leverage capabilities through international collaboration.

3.4. Focus on Translation

Synthetic and system biology fall within the domain of application sciences. Thus, translation of R&D outcomes into creating competitive products and processes would be instrumental towards development of the domain. Leveraging translational capabilities would require development of institutional mechanisms on one hand and effective industrial cross-talk on the other. The following approach could be adopted for the purpose:

- ❖ Create “technology feeder channels” that feed laboratory scale technologies into incubation platforms for appropriate scale-up;
- ❖ Catalyze adaptation of available technologies in synthetic biology and system biology at the global level in tune with Indian needs;
- ❖ Dovetail the synthetic and system biology network with available translational platforms in the country so as to speed-up product delivery;
- ❖ Initiate multi-modal participation with identified industries in the given domain.

3.5. Exploring Innovative Funding Options

Synthetic biology and system biology being pristine domains require adequate fiscal support. Innovative options towards funding could be considered as one of the essential features to jump-start the domains. Such options could include among others tax holidays to industry sectors for engaging in synthetic biology research in association with public R&D laboratories and academic institutions; providing seed money to institutions involved in research; initiate fast-track funding to researchers; earmark significant funds towards research and public discourse on the various policy issues associated with synthetic and system biology; and so on.

3.6 Accretion through International Collaboration:

New domains are amenable to collaborative interplay. Jump-starting capabilities in synthetic and system biology could be achieved effectively through collaborative endeavours involving players from abroad. Institutionalizing joint-initiatives at individual, organizational and country levels could provide significantly useful. European Union, Japan, North America, Israel and the Far East represent prospective partners.

4. Regulatory and Intellectual Property Issues Associated with Synthetic and Systems Biology Initiatives

Synthetic biology holds huge promises for society, in the way we use and modify biological systems; in the way biological knowledge is organized and more importantly the fundamental changes it brings about in the biological processes. However, from its definition of being a discipline that concentrates upon “the engineering of biological components and systems that do not exist in nature and re-engineering existing biological elements”, it is evident that the domain is associated with large potential perils to the society; as also tricky intellectual property issues. As such, utmost attention requires to be paid in devising effective regulatory framework that governs the safe and ethical use of synthetic and system biology.

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Despite the comparatively recent advent the discipline has made into the scientific world (just a decade back in 2000), it has made extraordinary strides. Already the construction of a completely artificial cell is underway; attempts are being made to use synthetic biology to produce carbon-neutral bio-fuels and bio-remediating micro-organisms and so on. Significant volume of knowledge in this area occupies the proprietary domain.

Four major issues are associated with synthetic biology that warrants global concerns:

- **Intellectual Property Issues** – Currently there are raging controversies between those who believe in open access to synthetic biology initiatives and those who promote proprietary knowledge. The provisions of TRIPS have prohibited protection of life forms as such except micro-organisms.
- **Bio-security Issues** – There is a potential peril of synthetic biology being misused by bio-hackers who could use the technology to recreate dangerous viruses to be used in warfare and terrorism.
- **Bio-safety Issues** – There exists a possibility of unintentional release of synthetic organisms to the natural habitats thereby posing serious threat to environment and health. Adopting a preventive policy in this front could forestall the large potential applications synthetic biology initiatives could have.
- **Ethical Issues** – As the discipline is associated with recreation of living organisms, it raises important moral and ethical concerns among several stakeholders who are opposed to interfering with life in its natural form.

Moreover, the safe and efficient promotion of synthetic and systems biology initiatives would also require the regulatory frameworks developed around it to be looked in conjunction with a number of collateral instruments such as Convention of Biological Diversity, TRIPS, Cartagena Protocol and others.

5. Devising Industrial Options with Synthetic and Systems Biology

5.1. The Changing Face of Biotechnology Industries

The Department of Biotechnology (DBT) was set up by the Government of India under the Ministry of Science and Technology in 1986, to give a boost to the Biotech industry in India. The funding and initiatives of DBT have been successful in generating a rich pool of academicians and scientists. India has become a hub of Biotechnology activity in the last decade. It is an ideal ground to set up biotech companies not only by Indian ventures, but also MNCs. India provides a sound

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knowledge base combined with skilled manpower. It is also a great place to set up manufacturing units, not to mention research laboratories.

In India, industries are engaged in following segments:

The field of medicine is making rapid progress and breakthroughs, thanks to new biotechnological processes and products. Traditional medicine treated the symptoms of various diseases. But biotechnological processes, in combination with pharmacology have the capability to develop proteins or molecules, which target the pathway of the disease and provide a cure. India is producing insulin, human growth factors, blood clotting factors, fertility drugs, antibiotics, vaccines and enzymes, which can be used to cure many human disorders. Gene therapy, a gift of biotechnology can cure genetically acquired diseases. It involves replacing defective genes, which may (somatic treatment) or may not (germline treatment) be transmitted to the next generation, as the need may be. A whole range of diseases like AIDS, cancer, sickle cell anemia, hemophilia, cystic fibrosis, diabetes, etc., can be detected and treated using biotechnological procedures developed in the country.

The production of high yielding and disease resistant crops through biotechnological means is a real boon to agriculture. Plants can be engineered with new genes for a favourable trait. They can be induced to form more nutritious fruits and/or vegetables. Their color and size too can be manipulated by altering their genetic constitution, viz. replacing defective genes or incorporating new genes. If clinical trials are successful, we are in for a revolution in biopharmaceuticals. Disease resistance crop varieties can be produced by incorporating Bt (*Bacillus thuringiensis*) gene in the crops, which when expressed produces the Bt toxin. When the insect feeds on the plant, the toxin acts on its metabolism and causes the death of the pest. Crops can also be engineered to tolerate biotic and abiotic stress conditions. Biotechnology has erased the divide of the seasons, allowing us to enjoy our favourite fruits, vegetables and flowers all through the year.

The environment around us is undergoing a lot of change due to increased amounts of pollutants and climatic changes around the globe. To maintain a sustainable environment, it is necessary to cleanse our habitat. Biotechnology helps us to study the existing degradation pathways and improvise on them. For example, the oil spills in coastal regions and petroleum seepage into water bodies, can be controlled by bioengineered microorganisms, which can degrade these harmful pollutants. India has shown this capability. Biotechnology in conjunction with environmental sciences provides valuable insights into the different pathways and networks of important elements in nature, thereby helping in bioremediation.

The Government of India is going all out to embrace the biotech industry and its products. Funds are flowing through Venture Capitalists (VCs) to biotech start-ups. Rebate on R&D, 100% foreign direct investment, excise and customs duty waiver on certain products, etc., are some of the incentives introduced by the government. India has made great strides in all the above biotechnological applications. The

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Indian biotech industry today encompasses 325 companies, some of them including Biocon, Serum Institute of India and Panacea Biotec alone, contributing to 27% of revenues.

Biocon is the first and presently the leading biotech company in India. Initially it brought in revenues by manufacturing enzymes. But it has gradually become more research oriented with the goal of introducing new drugs to the market. Its manufacturing capabilities include microbial and mammalian cell culture fermentation, synthetic chemistry and therapeutic drugs for the treatment of cancer, autoimmune and metabolic diseases. Serum Institute of India, Indian Immunologicals and Bharat Biotech specialize in the production of vaccines. Serum Institute of India is the world's largest producer of measles and DTP vaccines. Panacea Biotec has recently set up a plant in Himachal Pradesh, India, for production of bacterial and viral vaccines. Wockhardt is a biopharma powerhouse with 11 world class manufacturing plants in India. Shantha Biotechnics is located in Hyderabad and its products include Hepatitis B vaccine, Streptokinase drug and Interferon alpha-2b. The big player in agro-biotech, MAHYCO Monsanto has released a number of Bt cotton hybrids, which have been approved for commercial cultivation. The significant reduction in the use of pesticides and higher and better quality yields will result in increased incomes to farmers. Genetically modified field crops like rice, mustard, groundnut, maize, tubers like potato, vegetables like tomato, cabbage, okra, etc., are also under various stages of field trial led by Indian biotech companies. Development of products tailored to the needs of the Indian agricultural sector, will go a long way in making the country self-sufficient.

The above-mentioned achievements of Indian biotech companies have started attracting overseas partners and investors. Indian biotech firms have started scaling up their capabilities to become global players. With proactive government schemes, VC funding, new products and groundbreaking research, India is fast emerging as a biotech leader in the Pacific, alongside Singapore, Japan, Taiwan, Korea and China.

5.2. Technological Innovation as a Competitive Strategy

The 21st-century competitive landscape is characterized by the fundamental nature of globalization and rapid and significant technological changes. In many industries technological innovation is now the most important driver of competitive success. To survive intensive global competition, country must be technologically innovative.

Innovation today is increasingly going beyond the confines of formal R&D to redefine everything. Today innovation can mean new and unique applications of old technologies, using design to develop new products and services, new processes and structures to improve performance in diverse areas, organisational creativity, and public sector initiatives to enhance delivery of services. Innovation is being seen as a means of creating sustainable and cost effective solutions for various problems.

5.3. Leveraging Industries through Synthetic and Systems Biology

What physics was to the 20th century, biology will be to the 21st, and Quantitative Biology (Systems Biology and Synthetic Biology) will be a vital part of it. Systems Biology is about "quantitative, predictive and dynamical biology". The ultimate aim of "quantitative, predictive and dynamical biology" is a reliable computational model of the cell, and an "Integrative Systems Physiology" model of the organism. It has a tremendous economic potential for pharmaceutical, and biotech industry. And in the case of the neuronal cell it also has a tremendous economic potential for computer companies.

The first major commercial applications for synthetic biology will be to produce biofuels and medicines. Eventually, the hope is to create any type of valuable industrial chemicals that would otherwise be produced by petrochemicals. Synthetic biology is being used in two different processes for biofuels production -- first is using synthetic enzymes to break down biomass into sugars for fuel, and second is creating microbes that produce fuel directly. Enzymes, which are proteins that catalyze reactions, are being engineered with synthetic DNA into microbes are tailored to break down certain types of biomass, such as woodchips or corn stalks, and increase the rate at which they are broken down into sugars that can then be fermented into ethanol or other types of fuels.

Synthetic biologists hope to change the organisms so that the oil they produce is chemically similar or identical to the oils that are currently used in today's transportation and energy infrastructure. These microbes would become "living chemical factories" that can be engineered to pump out almost any type of fuel or industrial chemical.

The other major application of synthetic biology that will likely see commercialization soon is to produce medicine. The first of these medications is artemisinic acid – a precursor to the important anti-malarial medicine artemisinin – which is being produced by *E. coli* with synthetic DNA. Proponents claim that vaccines for influenza produced by synthetic organisms are close to commercialization.

Perhaps the most excitement about systems biology lies in the area of predictive, preventive and personalized medicine. Predictive, preventive and personalized medicine has the potential to transform medicine by decreasing morbidity and mortality due to chronic diseases such as cancer, Parkinson's and diabetes.

This distinctive new approach of synthetic biology promises solutions to some of today's most pressing and difficult problems in environmental protection, human health and energy production. It also provides an alternative perspective from which to consider, analyze and ultimately understand our living world.

Synthetic and Systems biology could lead to a large number of applications. Industries can be based on these applications. The Sleeping Beauty transposon system is an example of an engineered enzyme for inserting precise DNA

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sequences into genomes of vertebrate animals. The SB transposon is a synthetic sequence that was created based on deriving a consensus sequence of extinct Tc1/mariner-type transposons that are found as evolutionary relics in the genomes of most, if not all, vertebrates. This enzyme took about a year to engineer and since its creation has been used for gene transfer, gene discovery, and gene therapy applications.

Biosensor technology is another example of cyborg bacteria. One such sensor created in Oak Ridge National Laboratory and named “critter on a chip” used a coating of bioluminescent bacteria on a light sensitive computer chip to detect certain petroleum pollutants. When the bacteria sense the pollutant, it lights up and is then processed or amplified.http://en.wikipedia.org/wiki/Synthetic_biology_-_cite_note-24#cite_note-24 In Australia, biosensors have been created to detect viruses, bacteria, hormones, drugs, and DNA sequences. In the future scientists hope to create chips that can sense toxins such as environmental estrogens and warfare agents. Even more recently chemists at the University of Nebraska created a humidity gauge by using gold plated bacteria on a silicon chip. With a decrease in humidity there was an increase in the circuit flow. One unique feature that separates the chip from the bioluminescent ones is that after it has been assimilated the bacteria no longer needs to be kept alive for the humidity gauge to work.

Nanotechnology also has made advances by using cyborgs. Researchers at the École polytechnique de Montréal in Canada have attached a microscopic bead to swimming bacteria. Using a magnetic resonance imaging machine (MRI) the researchers have been able to use the magnetic properties of the bacteria to direct it to certain locations. The bead has no purpose at the moment but researchers hope store drugs or other viral fighting agents inside so that it may be released at the directed location.

Isoprene is an important commodity chemical used in a variety of applications, including the production of synthetic rubber. Isoprene is naturally produced by nearly all living things (including humans, plants and bacteria); the metabolite dimethylallyl pyrophosphate is converted into isoprene by the enzyme isoprene synthase. But the gene encoding isoprene synthase has only been identified in plants such as rubber trees, making natural rubber a limited resource. Currently, synthetic rubber is derived entirely from petrochemical sources. Genencor®, a Division of Danisco U.S. Inc., together with The Goodyear Tire & Rubber Company, is currently working on the development of a reliable, high-efficiency fermentation-based process for the Biolsoprene™ monomer, and synthetic biology has played an important role in making this undertaking a reality.

5.4. Creating New Industrial Models

Synthetic biology offers alternative pathways to natural products. Genes encoding particular product in certain cases entire pathways can be transferred to microbes and expressed in fermentors in industrial settings. This will obliterate the need of

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aromatic and medicinal plants for producing natural products. Similarly, a whole new set of industry could come up for secondary metabolites for various applications.

Synthetic Biology has potential to replace petroleum with biofuels. This will be based on the use of engineered photosynthetic organisms as biofuel sources. At current scales, these engineered systems do not compete with fossil-fuel resources, alternative carbon-reduction techniques, or even process-driven biofuel techniques such as cellulosic ethanol from non-food plant sources. However, with advances in knowledge and technologies over the years, it may materialize. Current petroleum industry may be replaced with bio-fuel industry.

Advances and Systems and Synthetic biology may lead to various products from biomass which is currently produced from petroleum. A concept of bio-refinery will be established in its true sense.

Predictive, Preventive, Personalized, and Participatory (P4) medicine: It is a medical model emphasizing in general the customization of healthcare, with all decisions and practices being tailored to individual patients in whatever ways possible.

The use of engineered biosensors will replace current diagnostic techniques. Medical diagnostic applications are also growing at the level of protein engineering. However, the specific applications of the broad synthetic biology approach to this area are still in early stages. The applications of biosensors could include: detection of low level chemicals in the environment; detection of molecules within the human body; design of diagnostic kits.

Synthetic biology will lead to next generation of genetic engineering technique, moving beyond the single-gene and two-gene modified crop variants into massively re-organized plant genomes. However, this area has to overcome massive regulatory and ethical barriers.

6. Recommendations

The Task Force on Synthetic and Systems Biology Resource Network (SSBRN) discussed the issues involved at length. It was of the view that as this domain is at a formative stage and other countries have not gone far ahead, it is prime time to take initiatives. The Indian entry into the area should be well-planned and should not be delayed as happened in the case of Genomics. It was also felt that all the concerned departments viz. CSIR, DBT, DST, ICAR and ICMR should participate in this initiative to make a mark in the area. The recommendations of the Task Force are given below:

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- **Building Capacity through Creation of Institutions:**

- The Task Force recommends that the Government adopt adequate measures to build capacity in Synthetic and Systems Biology through creation of institutions. Such institutions could be established both in physical and virtual mode, utilizing multi-modal financial models (i.e. a combination of government funds, industrial funds, international investments and internal revenues).
- CSIR is proposing setting up of an Institute of Synthetic and Systems Biology in the 12th Five Year Plan. The institute would focus on creating comprehensive knowledge base and development of technologies/products. The Task Force endorses CSIR proposal and proposed funding for the same.
- The Task Force recommends creation of “focal centres” within National laboratories and universities to promote R&D in Synthetic and Systems Biology. There should also be efforts to connect institutions across various disciplines particularly those in biological science, chemical science, engineering science and information technology to leverage the identified activities in the domain.
- The Task Force recommends large scale efforts to augment information processing, warehousing and analytical capabilities of laboratories/centres engaged in synthetic and systems biology through establishment of “data grids” and ‘virtual private networks”. Adequate use of the NKN is recommended. CSIR-CMMACS could play a lead role in this endeavour.
- A Facility for Microfluidics and Micro-Devices can be established as experimental Synthetic and Systems Biology is heavily dependent on cell-biological assays. Existing micro-fluidic and related techniques are instrumental in speeding up the development cycle for synthetic biology. Students should be exposed to these techniques as early as possible. Specific possibilities are:
 - ❖ Microfluidic devices for single-cell work in conjunction with imaging
 - ❖ Microfluidic devices for controlling cell microenvironments
 - ❖ Micro devices for tissue scaffolds
 - ❖ Micro devices for force application and measurement at the cellular scale.
- The Task Force also recommends setting up of Centres (or by project mode) to promote cross learning from engineering sciences for biological and bio-inspired design, by developing and borrowing techniques from established engineering disciplines such as control theory, communication technology, systems engineering etc.

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- The Task Force recommends setting up of a National Facility for Genome Scale Engineering, wherein de novo small genome design and synthesis, and assembly of large genomes with hundreds of specific mutations will be pursued. The facility can also be used to make a combinatorial libraries of designed genomes which can then be screened for desired functions.
- The Task Force also recommends a Omics scale data generation and acquisition capacity which would cover domains such as transcriptomics, proteomics, metabolomics, glycomics and lipidomics. Analysis and interpretation of data is very challenging currently, and will require specific capabilities to enhance analytics.
 - ❖ The Task Force recommends setting up of a National Facility for High-throughput Genome Sequencing as knowledge of genome sequences has become indispensable for basic biological research, other research branches utilizing genome sequencing, and in synthetic and systems biology.. Genome sequencing that goes beyond sequencing technologies need to be well supported. These include
 - Surveying biodiversity, identification of new proteins and pathways
 - Assembly/annotation of whole genomes
 - Metagenomics of mixed samples
 - Sequencing as a tool for whole genome designs and selection
 - Pharmagenomics
- The Task Force recommends offering of incentives to projects which involve significant participations from theoretical sciences like physics, applied mathematics, engineering etc., and biologists for multiscale modelling in biological systems. Examples include transport phenomena like convection-reaction-diffusion, constitutive behaviour.
- Thrust areas that need to be strongly supported include
 - ❖ Multi-scale modelling of biological systems including study of transport phenomena, constitutive behaviour, convection-reaction-diffusion
 - ❖ Genome to phenome associations, disease modelling
 - ❖ Tissue and organ systems
 - ❖ Intracellular communication, chemotaxis, quorum sensing, self assembly
 - ❖ Systems pharmacology, pharmaco genomics and systems medicine
- It is recommended to create six Network Centres for Synthetic Biology research at NCBS, Bangalore; IGIB, New Delhi; IICB, Kolkata; Bose Institute, Kolkata; IISc, Bangalore and CMMACS, Bangalore.

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- **Augmenting and Nurturing Human Resource:**
 - The Task Force recommends development of innovative educational delivery mechanisms that would focus upon trans-disciplinary sciences through newer curriculum and pedagogy. Project mode learning and continuing education for practicing scientists, teachers and professionals in diverse domains should be encouraged to augment human resource development in synthetic and systems biology.
 - The Academy of Scientific and Innovative Research (AcSIR) of the CSIR could be identified as the nodal organization for human resource development in synthetic and systems biology in the country. In the process the Academy should network with universities/academic institutions, IITs, IISc, NITs, IISERs, HBNI and industry to achieve seamless interplay of all stakeholders of the academic community.
 - Develop a 'Virtual Training Centre (VTC)' under the umbrella of CSIR operated through hub and spoke model. This should also be accessible to undergraduate engineering students, and run summer programs with heavy emphasis on experimental and quantitative techniques. We should target students from both engineering and biology. Training can include 'fun' topics, but the underlying goal should be to provide students with a broad and stable base of topics in bioengineering. These should include: (i) Experimental topics: modern molecular biology; genomic techniques; protein engineering; bio-processing; engineering topics, e.g. microfluidics, instrumentation, imaging. (ii) Quantitative topics: statistics, model inference, simulations.
 - Task Force recommends creating 100 fellowships per year in the area of Synthetic and Systems Biology on the lines of Ramalingaswamy Fellowship. Each fellowship will carry an amount of Rs.50,000/month plus 20% contingency. The fellowship will be tenable for 3 years duration. Total expenditure under this for 12th plan period will be Rs.90 crore. The fellowship may be named as "SSB Career Development Grant". Details of the scheme will be developed later.
 - Establish a seminar circuit on the lines of the Indian TPSC (Theoretical Physics Seminar Circuit) to initiate frequent interactions both between and among the synthetic and systems biology research communities in the country. This forum also permits engagement with other disciplines, including medicine, computer science, and engineering. Two of the basic aims of this circuit would be: (i) to strongly involve SRF's and postdocs and not just senior faculty; (ii) to enhance interaction among researchers.
 - Organise competition in synthetic and systems biology area on the lines of MIT's International Genetically Engineered Machines Competition (iGEM), and the highly popular IITs' Robotics and Engineering Competition.

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- **Creating Knowledgeware for Synthetic and Systems Biology:**

- The Task Force recommends creation of knowledgeware in Synthetic and Systems Biology in open source mode. It is proposed that a portal for the purpose be created and maintained. The Wikipedia model could be followed for the same. The endeavour should be in participative mode.

- **Developing Translational Capabilities:**

- The Task Force recommends creating “technology feeder channels” that feed laboratory scale technologies into incubation platforms for appropriate scale-up and catalyze adaptation of available technologies in synthetic biology and systems biology at the global level in tune with Indian needs. In the process, attempts should be made to dovetail the synthetic and systems biology network with available translational platforms in the country so as to speed-up product delivery in multi-modal participation with identified industries in the given domain.
- Available translational platforms such as the DBT’s Translational Health Science and Technology Institute, CSIR Innovation Complexes, DST’s Technology Business Incubators in various universities and R&D institutions should be used adequately and their core competencies leveraged to suit the increased translational needs.
- It is recommended that close liaison should be maintained with the National Innovation Council’s Cluster Innovation Centres to the extent applicable.
- The translational endeavours could be augmented through setting up of plug and play facilities.

- **Evolving Multi-Modal and Fast Track Funding Options:**

- Synthetic biology and systems biology being pristine domains require adequate fiscal support. The Task Force is of the opinion that innovative options towards funding should be put in place in order to circumvent the lengthy bureaucratic processes. Such options could include among others tax holidays to industry sectors for engaging in synthetic biology research in association with public R&D laboratories and academic institutions; providing seed money to institutions involved in research; initiate fast-track funding to researchers.
- Significant funds towards research and public discourse on the various policy issues associated with synthetic and system biology; and so on. Such initiatives could be taken up in collaboration with the Indian Institutes of Management; National Institute of Advanced Studies, and so on.

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- **Fostering International Linkages:**

- Large scale international collaboration should be promoted and implemented. Linkages should be built and operationalized through institution of exchange fellowships, including research grants; implementation of visiting faculty schemes; setting up joint centres and so on. Cooperation with South East Asian countries should be given priority although North America, European Union, Japan, Australia, Brazil, Israel and South Africa could also be the important target countries to begin with.

- **Converting Task Force into a High-Powered Standing Committee**

- Task Force with new set of members may be converted into a High Powered Standing Committee for creation of National Document and coordination of Synthetic and Systems Biology Research Network in the country. CSIR offers to do this job in partnership with DBT, DST, ICAR and ICMR to focus on infectious diseases, host pathogen interaction, quorum sensing, and complex diseases, green chemistry etc.

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Recommended Budget for SSBRN during 12th FYP

S No	Head	Budget (Rs in Crore) (2012-17)
1	Synthetic and Systems Biology Capacity Building	1460.00
1.1	Setting up of the CSIR Institute of Synthetic & Systems Biology (CSIR-ISSB)	800.00
1.2	Establishing Network Centre for Synthetic and Systems Biology	50.00
1.3	Synthetic and Systems Biology Focal Centres in National Laboratories	90.00
1.4	ICT Connectivity, Computational Infrastructure, Knowledge Development	50.00
1.5	National Facilities (Microfluidic Facility and High-Throughput Genome Sequencing Facility)	330.00
1.6	Grant-in-aid to Synthetic and System Biology Initiatives	140.00
2	Human Resource Development in Synthetic and Systems Biology	190.00
2.1	SSB Career Development Grant Programme for Young Engineers and Scientists	90.00
2.2	Virtual Training Centres (VTCs)	90.00
2.3	Competition and Seminar Circuits	10.00
3	Translational Capability Development	100.00
3.1	Plug-and-Play Facilities and Incubators	75.00
3.2	Joint Activity with National Innovation Council	25.00
4	International Collaboration (Joint Centres, Overseas Internships etc)	100.00
	GRAND TOTAL	1850.00

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Annexure 1:

A non-exhaustive list of synthetic biologists and their research interests

Scientist/Institute	Research Interests and accomplishments (collected from conference/lab/institutional/wiki websites)
Adam Arkin /Lawrence Berkeley National Laboratory	Director of the Synthetic Biology Institute and of the Physical Biosciences Division at Lawrence Berkeley National Laboratory (LBNL), is also Professor in University of California, Berkeley's Department of Bioengineering. He is also co-director of the Virtual Institute of Microbial Stress and Survival, director of bioinformatics at the Joint Bioenergy Institute, and co-director of BIOFAB (International Open Facility Advancing Biotechnology). His research centers on uncovering the evolutionary design principles of cellular networks and populations and exploiting them for applications.
Caroline Ajo-Franklin /Lawrence Berkeley National Laboratory	Explores and engineers the interface between living organisms and non-living materials at the nanoscale. By programming processes such as electron transfer and biomineralization, she seeks to enable cells to electronically communicate with electrodes and to control the synthesis of inorganic materials. Ultimately, her work aims to create a new class of smart, self-renewing materials based on genetically reconfigured living cells seamlessly integrated with human-made components..
Chris Voigt /MIT	Voigt was earlier in UCSF, named by MIT review as one of the top 35 innovators in the world under the age of 35. His research interests focus on the reprogramming of bacterial organisms to perform coordinated, complex tasks for pharmaceutical and industrial applications. He is a member of the National Science Foundation-funded Synthetic Biology Engineering Research Center, called SynBERC, and works in the developing field of synthetic biology. His recent works include engineering a bacterial two-component system to regulate gene expression in response to red light, engineering bacteria to sense its environment and conditionally invade cancer cells either when the concentration of bacteria is large enough, when the environment has little oxygen (e.g. inside a tumor), or when a specific chemical is present, Constructing a logical gate inside bacteria.
Christina Smolke /Stanford University	Smolke's research program focuses on developing modular genetic platforms for programming information processing and control functions in living systems. She has pioneered the design and application of RNA molecules that process and transmit user-specified input signals to targeted protein outputs, thereby linking molecular computation to gene expression.
Dan Gibson /J. Craig Venter Institute	Gibson led the JCVI efforts to synthesize two complete bacterial genomes. Those projects resulted in creation of the first synthetic bacterial cell and development of an enabling suite of DNA synthesis and assembly methods.

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George Church /Harvard Medical School	Professor of Genetics at Harvard Medical School, Professor of Health Sciences and Technology at Harvard and MIT, and a core faculty member at the Wyss Institute for Biologically Inspired Engineering at Harvard University. Co-inventor of first direct genome sequencing method. Initiated Personal Genomics Project and with others, a company called Codon devices. Current research focuses on integrating biosystems-modeling with Personal Genomics & synthetic biology.
Gurol Suel /UT Southwestern Medical Center	Focuses on understanding cellular decision-making. In particular, his laboratory is investigating the relationship between the dynamics and connectivity pattern of genetic circuits and their role in multipotent differentiation. By utilizing various approaches including systems and synthetic biology his goal is to identify basic principles that underlie cellular decision-making and utilize this insight to alter or engineer novel cellular behavior.
James J. Collins/Centre for Biodynamics, Boston University	He is a founder of the field of synthetic biology, which exploits findings from systems biology to "forward engineer" novel biological circuits. Currently, Collins is tinkering with the circuits of bacteria that are activated when the bugs are exposed to antibiotics and are either killed or deploy protective measures against the drugs.
Jay Keasling/University of California, Berkeley. Lawrence Berkeley National Laboratory, Synthetic Biology Department at UC Berkeley, Joint BioEnergy Institute.	Keasling is considered one of the foremost authorities in synthetic biology, especially in the field of metabolic engineering. Other, related research interests include systems biology and environmental biotechnology. Keasling's current research involves the metabolic engineering of the <i>Escherichia coli</i> bacterium to produce biofuels and of the <i>Saccharomyces cerevisiae</i> yeast to produce the anti-malarial drug artemisinin.
Jeff Gore /MIT	Dr. Jeff Gore is an Assistant Professor in the Department of Physics at the Massachusetts Institute of Technology. His biophysics laboratory studies evolutionary dynamics and quantitative ecology by combining microbial experiments with ideas from physics, mathematics, and economics. As a Pappalardo Postdoctoral Fellow in the MIT Physics Department, he used approaches from game theory to understand how yeast cells cooperate to grow on the sugar sucrose, yielding insight into the conditions required for the evolution of cooperative behaviours. Jeff received his PhD at the University of California, Berkeley as a Hertz Fellow, where he developed new techniques to manipulate individual biological molecules.
Jeff Tabor /Rice University	Dr. Jeff Tabor is an Assistant Professor in the Department of Bioengineering at Rice University. He received his PhD in Molecular Biology from the University of Texas at Austin, and did post doctorate research with Chris Voigt at UCSF. He has previously studied how the expression of heterologous genes can impact gene expression noise and worked with a team to engineer <i>E. coli</i> to function as a one and two color photographic film and a distributed edge detector. His current work involves rebuilding signal transduction networks to understand how multicellular behaviors are coordinated in biology.

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John Glass /J. Craig Venter Institute	At the JCVI he led the mycoplasma minimal genome, and genome transplantation projects, and has been a key scientist in environmental genomics and viral metagenomics work. Glass and his Venter Institute colleagues are now using these and new synthetic genomics approaches to create cells and organelles with redesigned genomes to make microbes that can produce biofuels, pharmaceuticals, and industrially valuable molecules.
Luke Alphey /Oxitec, Ltd and Oxford University	Dr. Luke Alphey is the Chief Scientist at Oxitec Ltd. Oxitec is developing innovative technology to control insect pests, based on the use of engineered sterile males of the pest insect species ('RIDL® males'). These insects carry a simple genetic circuit imparting conditional (repressible) lethality. In the lab - or factory -provision of tetracycline allows the insects to thrive. On release into the wild, the males mate wild female insects, which lay eggs that are unable to develop into adults, due to inheritance of the control circuit and the absence of the repressor 'antidote'.
Matthew Scott /University of Waterloo	Quantitative analysis of Escherichia coli under various modes of growth inhibition led to the formulation of several empirical correlations between growth rate and macromolecular cell composition, called the 'growth laws.'
Nathan Hillson /Joint BioEnergy Institute	Dr. Nathan Hillson is the Director of Synthetic Biology at the Joint BioEnergy Institute (JBEI) in Emeryville, California and Research Scientist at Lawrence Berkeley National Laboratory. In his current role at JBEI, Dr. Hillson coordinates and directs the development of the JBEI-ICE biological parts repository, the characterization and standardization of biological parts, the computer-aided design of biological pathways and circuits invoking the standardized parts, and the automated assembly of the pathways and incorporation thereof into microbial hosts such as E. coli and S. cerevisiae, towards the sustainable production of clean biofuels.
Pamela Silver /Harvard Medical School	Dr. Pamela Silver, Professor of Systems Biology at Harvard Medical School and founding member of the Wyss Institute of Biologically Inspired Engineering at Harvard University is interested in the field of Synthetic Biology. Her interests focus on the predictable and facile engineering of biological systems with applications in both human health and global sustainability. Recent work includes engineering cell-based computers, metabolic pathways for biofuel and commodity production and increased carbon dioxide fixation.
Reshma Shetty /Ginkgo Bioworks	Dr. Reshma Shetty graduated from MIT with a PhD in Biological Engineering in 2008 during which she worked on building digital logic in cells. Reshma has been active in synthetic biology for several years and co-organized SB1.0, the first international conference in synthetic biology in 2004. Her coolest genetically engineered machine to date was engineering E. coli to smell like mint and bananas. In 2008, Forbes magazine named Reshma one of Eight People Inventing the Future and in 2011, Fast Company named her one of 100 Most Creative People in Business. Reshma and colleagues have founded synthetic biology startup Ginkgo BioWorks, Inc. whose mission is to make biology easier to engineer.

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Ron Weiss/MIT	Artificial tissue homeostasis, Assembly and delivery of genetic circuits, Flexible cellular platforms for reconfigurable biocircuits, In vivo biosensors, Mammalian synthetic transcriptional regulation, MicroRNA sensing and processing circuit in mammalian cells, Rapid assembly and delivery of large scale genetic circuits into mammalian cells, Regulatory networks utilizing protein-protein interactions, Retroactivity, Synthetic ecological system for pattern formation
Steven Benner /Westheimer Institute for Science and Technology	Dr. Steven A. Benner is a Distinguished Fellow at the Foundation for Applied Molecular Evolution and The Westheimer Institute of Science & Technology, which he co-founded. His research spans many fields in the physical sciences and natural history. His early work in synthetic biology generated, in 1984, the first synthetic gene encoding an enzyme, strategies for the total synthesis of genes, a redesigned DNA that incorporates twelve nucleotides, expanded genetic systems that encode proteins with more than 20 amino acids, nanostructures that exploit these, and some of the first designed enzymes. From these, his laboratory has constructed artificial chemical systems capable of supporting Darwinian evolution and tools that today help personalize the care of some 400,000 patients annually. His laboratory also helped found the field of paleogenetics, which resurrects ancestral genes and proteins from extinct organisms for study in the laboratory, providing strategies to test historical hypotheses throughout basic and biomedical research and in fields such as mammalian reproduction, hypertension, and alcoholism. In collaboration with Gaston Gonnet, the Benner laboratory developed evolutionary bioinformatics as a field, completing in 1990 the first exhaustive matching of a modern genomic sequence database, developing advanced models for patterns of sequence divergence in genes and proteins, coupling bioinformatics models for protein divergence with protein function, and providing the first successful tools to predict protein folds from sequence data alone. This work also marketed the first evolutionary organized genomic database, the Master Catalog.
Ting Wang /Washington University School of Medicine	He develops algorithms for identifying regulatory motifs, and analytical and visualization methodologies to integrate genomic and epigenomic data. He is a co-inventor of the UCSC Cancer Genomics Browser and a co-investigator of the Epigenome Roadmap Mapping Centers.
Uri Alon/Weizman Institute, Israel; Harward	Authored the textbook, introduction to systems biology, constructs and analyses network motifs in E. coli and yeast
Van Oudernadeen/MIT	Stochastic gene expression and its relevance to systems biology
Vivek Mutalik /BIOFAB	Dr. Mutalik is currently working on Generalized Expression Operating Systems that will be useful for designing and programming gene expression in a predictable manner at genome-scale engineering efforts. He is also directly responsible for managing the efforts in designing, building, and testing a

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	collection of engineered genetic components that control constitutive RNA production, RNA processing and degradation, translation initiation, protein degradation and DNA replication. He received his PhD from the Indian Institute of Technology, Bombay, in Mumbai, India where he worked with Prof. Venkatesh in the area of computational systems biology
Yue Shen /Beijing Genomics Institute, Shenzhen	Yue (Chantal) Shen is the Leader of the Synthetic Biology Unit of the Beijing Genomics Institute, Shenzhen. Her work focuses on metagenomic sequencing, assembly, and characterization of genes found in the human intestinal tract. She also leads international cooperative projects, including the E. coli Central Dogma Project with the BIOFAB and the SC2.0 Project with Johns Hopkins University.
Zhen Xie /MIT	Dr. Zhen Xie helped to pioneer the use of RNAi-based logic circuit for manipulating mammalian cells.
Denis Noble	Systems level modeling of the heart
Leroy Hood	President and co-founder of the Institute for Systems Biology in Seattle, is a pioneer in systems approaches to biology and medicine. Dr. Hood's research has focused on the study of molecular immunology, biotechnology and genomics. His professional career began at Caltech, where he and his colleagues developed the DNA sequencer and synthesizer and the protein synthesizer and sequencer--four instruments that paved the way for the successful mapping of the human genome and lead to his receiving this year's prestigious Russ Prize, awarded by the Academy of Engineering. A pillar in the biotechnology field, Dr. Hood has played a role in founding more than fourteen biotechnology companies, including Amgen, Applied Biosystems, Darwin, The Accelerator and Integrated Diagnostics. He is a member of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine, one of only 10 people in the world to be elected to all three academies. In addition to having published more than 700 peer reviewed articles, he has coauthored textbooks in biochemistry, immunology, molecular biology and genetics, as well as a popular book on the human genome project, The Code of Codes.
Kitano	Japan, pioneer of bio-robotics and systems biology
Chris Myers, Univ of Utah	current research interests are algorithms for the computer-aided analysis and design of real-time concurrent systems, analog error control decoders, formal verification, asynchronous circuit design, and modeling, analysis, and design of genetic circuits.
D. Niopek, Heidelberg	miRNA switches

Annexure 2: Current international benchmarks in synthetic biology

This portion summarizes the current international benchmarks in synthetic biology projects. The projects are classified by scale, into parts, modules, cellular level systems and others. In each section, an attempt has been made to highlight a landmark achievement and also benchmark the current trend as defined by the aspirations of majority of scientists in the area.

Parts: This term basically refers to the smallest building blocks of genes: promoters, terminators, IRES etc, that can be used to achieve desired expression. Engineered receptors, ligands, Hybrid transcriptional activators with predictable, and engineered specificities and strengths are all part of this milieu. The registry of standard biological parts serves as a repository for searching and exchanging parts. The bio-parts are analogous to the standardized nuts, bolts, and connectors in a lego set. Currently, the registry is richer in prokaryotic parts, but many eukaryotic parts, and ncRNA based parts are yet to be included. This area has scope for college students, through summer trainings and short fellowships to rapidly contribute, while enriching their own experience. The genomics revolution was spurred on by the reduction in cost by development of novel technology and the successful commercialization of these tools. In synthetic biology, the need for rapidly synthesize a designed bio-part has spawned companies like DNA2.0 that will one day replace cloning as a staple activity in molecular biology labs. This emerging trend internationally, has tremendous scope for entrepreneurs in India.

Modules or Devices: Modules or Devices achieve the next level of complexity, with the integration of different parts to achieve a predictable behaviour. The repressilator and bacterial toggle switch remain landmarks in this area, although they were originally demonstrated in 2000. Feedback negative regulation can and is often used in biological systems to achieve periodic oscillations. For instance, circadian rhythms, the 24 hour body clocks in our system are achieved by feedback negative regulation, wherein a transcription factor represses itself after its concentration in the cell builds up to a certain level. Without further synthesis of the factor, its level gradually decrease, the auto-repression is relieved resulting in iterative expression and repression and eventually cyclical steady state levels of the protein. The repressilator was built using three well known repressor proteins, none of which are part of a natural oscillator. The three repressors were connected in a manner that induced cyclical expression of a fluorescent protein in bacterial cells. Although, many basic devices like toggle switches, oscillators and cell signaling devices have been created, we are far from this being a routine activity. The reason, is the lack of predictable behaviour, such that, the wiring of these devices to larger networks can vary from cell to cell affected by endogenous factors that may influence stability, turnover and affinities of interacting parts. Nevertheless, we are well past the “proof of concept stage and the engineering of devices accounts for the vast majority of iGEM projects today. Projects in this area are ideally suited for post-graduate education. E.coli and yeast remain the workhorses for synthetic biology, owing to the large number of standardized parts available in these systems and a culture of exchanging reagents.

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Cellular systems: The next level of complexity arises from the engineering of whole organisms that display a predictable behaviour. For instance, the bacterial quorum sensing is a natural phenomenon, where some bacteria use metabolites produced by the other cells in a culture to sense the strength of the population and respond as a community to environmental perturbations. Using synthetic biology, this pathway was wired to the expression of a toxic protein, so that when the cell numbers in a population grow beyond a threshold, the bacteria would sense it and get killed. This sort of self-control of population can be used in fermentation technology.

Minimal organisms: A fundamental question that has fascinated biologists ever since we started getting a glimpse of the genomes of bacteria, is how many genes does an organism need to survive. This has further led to the current question of “Can we engineer a microbe that can survive under laboratory conditions, using a minimal set of genes? Although motivated by a fundamental question, such an organism has tremendous value since these organisms can act as micro-bioreactors taking over from E.coli and yeast which come with a lot of endogenous baggage.

Mycoplasma are bacteria with extremely small genomes highly dependent on the environment for nutrients. One approach to creating a minimal organism is to delete portions of such already small genomes to explore the limit of such a trimming. Three independent leading groups have estimated that with a minimal 100 to 500 genes it will be possible to “run” a minimal cell. Craig Venter’s group further constructed a minimal synthetic genome, assembled it and introduced it into proto-cells. A whole sub-field of synthetic biology involves the development of proto-cells using synthetic liposomal or lipo-peptide structures. However, smart materials – traditionally an area of materials research has not been explored in the development of proto-cells. The minimal organisms of the future may not use the conventional building blocks of natural world, DNA, RNA, proteins and lipids, but may be fabricated from the best suited materials invented by humans.

Applications: The appeal of synthetic biology for young students and the public is largely due to the creative application of design principles to develop systems that are perceived as immediately useful and fascinating at the same time. Two such examples illustrate the potential of this field. Firstly, the synthetic yeast cell that carries out key bio-transformations for the synthesis of artemesin, a promising anti-malarial drug derived from a plant. The low yields of the natural compound were insufficient to meet market demands, resulting in high prices. By engineering a yeast cell that has the key enzymes derived from plants, the compound was synthesized in a fermentor, thus rapidly reducing costs. Another fascinating application that illustrates the potential impact of synthetic biology is the development of a plant that loses chlorophyll and changes color if it detects Tri-nitro-Toulene in the environment. These weeds, dubbed bomb-sniffing plants are far from commercial applications, since it still takes hours of exposure to change color. However, it presents the possibility of a whole new type of environmental detection and management.

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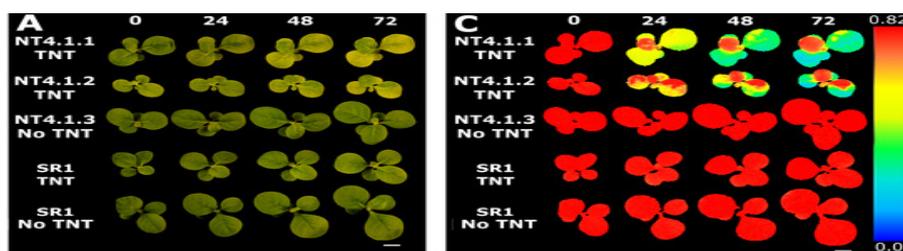


Image Courtesy: PLoS ONE 6(1): e16292

Fig 6: A plant engineered to drain chlorophyll from its leaves when it detects TNT in the environment was developed by the Medford group at Colorado State University.

Annexure 3: Details about National Status

Bose Institute, Kolkata

Systems biology has evolved as a discipline with the growing appreciation that molecules, pathways or cells looked at in isolation and using qualitative bulk measurements, often fail to provide the required insight into the system as a whole. In recent times, much information has been gleaned from studying diseases such as cancer by quantitative, mathematical and network level analysis of the disease. With this in view, a programme was initiated in Bose Institute to (a) apply quantitative and mathematical approaches and (b) unbiased, genome-wide experiments coupled to in silico network analysis, to better understand human disease and disease-causing agents. They are presently expanding into whole organ analysis in the context of diseased states.

National Centre for Biological Sciences

One of the major research areas at NCBS involves the 'Theory and Modelling of Biological Systems'. They currently have seven faculty members who work in related areas.

- Dr. Upinder Bhalla. Dr. Bhalla's group carries out computational and experimental studies of a variety of systems related to brain function. At the molecular level, they carry out single-molecule simulations of synaptic behaviour; at the network level, they study the connectivity of neuronal networks such as the associative memory network of the hippocampus; at the organismal and behavioural levels, they study the basis of learning and adaptation in olfactory response of rodents.
- Dr. Shachi Gosavi. Dr. Gosavi studies models of protein dynamics and protein folding. She studies structure-based models of the protein folding process, and is particularly interested in the conflicting requirements imposed by folding and function. For example, her work on the beta-trefoil

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fold highlighted a slowing down of folding due to a long-distance interaction dictated by the ultimate structure.

- Dr. Sandeep Krishna. Dr. Krishna uses theoretical models to analyse the structure and function of biological feedback loops. His research has shed light into the design of the lambda-phage lysis/lysogeny decision pathway. His current projects include the study of RNA-based regulatory pathways, as well as the study of multi-cellular and tissue level regulatory dynamics.
- Dr. Madan Rao. Dr. Rao's interests cover many areas of soft-matter physics, including the behaviour of driven, out-of-equilibrium systems. His group's research projects include the study of membrane-cytoskeletal interactions, the study of active cytoskeletal networks, and the study of lipid dynamics within the membrane itself.
- Dr. R. Sowdhamini. Dr. Sowdhamini's group studies protein sequence and structure. They are particularly interested in identifying distant protein-homology relationships using structure-based methods, to identify distant members of large protein super families.
- Dr. Mukund Thattai. Dr. Thattai carries out computational and experimental work on bacterial gene regulatory networks and eukaryotic intracellular traffic systems. His recent projects include the study of design principles that govern feedback loops involved in quorum sensing, a form of bacterial cell-to-cell communication. More recently his group has initiated multiple research projects into the evolutionary origins of compartmentalized eukaryotic cells.
- Dr. Madhu Venkadesan. Dr. Venkadesan is interested in organismal mechanics, particularly the problem of walking and locomotion. More generally, his research focuses on questions of control and optimization of biomechanical systems, and ultimately hopes to uncover principles of neural control of muscles.

Indian Institute of Science, Bangalore

The work in the area of Systems and Synthetic Biology carried out at the Indian Institute of Science can be grouped under the following categories: (a) Network Biology- Reconstruction and analysis of biological processes at molecular level detail, metabolic and signaling pathways, genome scale metabolic reconstruction, stress response networks, simulation and perturbation studies using kinetic modeling and constraint based modelling approaches; (b) comparative genomics by analyzing networks in different species using graph theoretical methods, (c) Boolean modeling and rule-based modeling of specific biological processes such as host-pathogen interactions, (d) Mathematical biology of bacterial and viral infections at a variety of levels ranging from the epidemiology level to reaction kinetics. Closely related to this and often directly feeding into systems level studies are a number of

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groups carrying out (e) experimental work to characterize signaling networks, neuronal circuits, gene expression profiling and proteomics, (f) bioinformatics and computational biology analysis and predict promoter regions in genome sequences, characterize kinomes, various protein-protein interactions, proteome scale structure modelling and (g) development of new algorithms, data structures and machine learning methods to enable data mining, systems modeling, analyses and prediction

Indian Institute of Technology, Kharagpur

The Bio-microfluidics research group at IIT Kharagpur utilizes different combinations of microscale actuation techniques and critical system parameters to achieve rapid DNA hybridization, and practically implement the same through the design and fabrication of novel bio-microfluidic devices. The group has developed a microfluidic system that supports growth of cells for significantly longer time without any requirement of incipient flow, and a microfabrication compatible and high resolution force measurement technique termed as Ultrasoft-Polydimethylsiloxane based Traction Force Microscopy (UPTFM), so as to depict the physiological state of the cells, surviving in the micro-confinement. The group has subsequently integrated the technique with a microfluidic platform for evaluating different states of stress in adherent cancer and cells. The group has observed an unknown enhanced stress adaptive response of cells, which may be further exploited in the understanding of tumor progression *in vivo* and designing microfluidics based drug screening platforms.

The group has also been pioneering in India to work on CD based biomicrofluidics. CD-based microfluidics (micro channel networks are embedded into a rotating disk) appears to be ideal for the future of more compact and inexpensive lab-on-a-chip devices for point-of-care diagnostics. Technology developed by this group has led to the simple design and inexpensive fabrication of CD-based systems, in which fluid may be transported in a controllable manner with the aid of forces in the rotating platform. The CD-based system also acts like a mixing platform and reaction chamber for bio-chemical analysis. Such systems may be potentially used for rapid, accurate, inexpensive, and portable bio-diagnostic platforms.

Council of Scientific & Industrial Research (CSIR)

CSIR has initiated two projects in the area of synthetic biology and two in the area of systems biology in the XIth Five Year Plan. Brief about them are given below:

- **Synthetic Biology for Healthcare and Bio-tools development: an Indian Effort:** CSIR-IICB as nodal institute with NCL, IMTECH, NBRI, CIMAP and IHBT as participating institutes

Neem [*Azadirachta indica* A. Juss, Meliaceae (mahogany) family], has long been recognized for its properties both against and in improving human health. Azadirachtin, a complex tetranortriterpenoid limonoid from the neem

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seeds, is the main component responsible for both antifeedant and toxic effects in insects. It is a natural insecticide. The commercial production of huge quantity of azadirachtin is mandatory for the viable world market as pesticide. Azadirachtin can be synthesized chemically but the yield is very low. Therefore, the aim of this project is to give emphasis on the exploration of biotechnological approaches, synthetic biology and genome sequencing to produce azadirachtin, a biopesticide of global demand.

- **Metabolic Engineering of Vinca Alkaloid Pathway:** CSIR-IICB, IMTECH, NCL, NBRI, CIMAP, CDRI & IHBT and non CSIR institutes IMM and University of California at Berkeley

The proposal aims towards the synthesis of high value phytochemicals i.e. vinblastine and vincristine with the help of design and fabrication of biological components and systems by applying synthetic biology approaches. The proposed phytochemicals are used in various types of cancer chemotherapy regimens and have commercial demand of about 5-10 kg/annum and cost is 5 million US dollars/kg. The very low yield of these chemicals from *Catharanthus roseus*, the only natural source to extract these chemicals make them expensive for commercial production. It is proposed that thorough understanding of the metabolic pathway for their synthesis in natural source as well as application of the synthetic biology tools and techniques for synthesis of these chemicals through designer host would help to overcome the low yield problems of these important chemicals.

- **Multi-agent Therapy of Cancer: A Systems Biology Approach:** The project, involving CSIR-IGI and IICB, and JNCR etc, seeks to mine the existing literature and databases to build a preliminary signalling network operating in few cell lines of these two cancer types; experimentally generate the information on genomic changes, epigenetic changes, transcriptome profile, proteome profile and miRNA profile for couple of these cell lines; build the signalling network structures operating in these cell lines by mathematical modelling based on the information obtained from above; subject these thoroughly characterized cell lines to perturbation by different anticancer molecules (novel and known) either singly or in combination to detect the distortions in network structures and to identify the key elements of the network affected by the perturbations; and execute the modelling exercise to discern the most probable chemotherapeutic targets and to assess the efficacy of the treatment.
- **Systems Biology of MTb: A Systems Biology Approach:** This was a CSIR-IGIB led Team India initiative, with a large number of colleges and universities across India.

Cell Works Research India Pvt. Limited

- It is a start-up company in the Life Science/Pharma drug discovery space. Cellworks uses a very novel concept of Virtual Proteomics based disease prototype system, which uses high through put assay techniques to study drug-disease interactions. They are using these prototyping platforms to come up with novel therapies for Arthritis, Oncology, Diabetes and other debilitating disease. It is a completely new way of looking at Pharma Drug Discovery, wherein they are bringing in techniques and disciplines for IC design to create a 'Drug Design' paradigm.

BioCOS Life Sciences Pvt. Limited

- BioCOS is engaged in multi disciplinary computational research in the areas like Systems Biology/ Network Models, Next Generation Sequencing Data, Microarray Data Analysis and Algorithms for Biological Imaging. They have a team of Scientists and Engineers, who are executing and researching multiple R&D activities such as in Diabetes, Metabolic Syndrome Traits, Malaria, Cancer, Plants, and Small RNAs. The team taking up various contract based research programs such as in the areas of Next generation Sequencing Data Analysis Algorithms and Computational Platforms (DNaseq, RNASeq, Chip Seq, methylation patterns and data annotation), Nucleolin, NPM1, CARM-1, P53, Protein Kinases and P300 related R&D. BioCOS also has strong R&D programs being executed internally in the areas of biomedical Image Processing, Proteomics and Metabolic Syndrome Diseases. Apart from product developments, BioCOS focuses to participate (Contract research based) in the R&D development of computational platforms and solutions relevant to diagnosis, prognosis and therapy of various human diseases. The Company has developed and facilitated research solutions and IP in the areas of Metabolic Syndrome Diseases (Diabetes, Obesity, Dyslipidemia, CVD and Hypertension), parasite stage specific diagnosis related markers in Malaria (Severe and cerebral malaria) and some Cancers.

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Annexure 4:

Table 2 U.S. identified funding directed at the study of the ethical, social, or legal implications of synthetic biology; Source: [Woodrow Wilson International Center for Scholars, June, 2010](#)

Agency	Project	FY Start	Amount
NSF	Synthetic Biology: Status, Outlook and Public Perception	2008	\$60,000
NSF	Gordon Research Conference on Science and Technology Policy	2008	\$60,000
NSF	Doctoral Dissertation Research: Crafting Life: A Sensory Ethnography of Constructive Biologies	2009	\$14,929
NSF	"Sandpit" to address grand challenge topics in synthetic biology	2009	\$28,800
NSF	ARS Synthetica - A Multimedia Forum Exploring the Artful Design of Living Things	2009	\$74,902
NSF	Cultural Cognition of Synthetic Biology Risks	2009	\$398,990
NSF	Synthetic Aesthetics: Connecting Synthetic Biology and Creative Design	2009	\$244,580
NSF	Transatlantic Exploratory Workshop on the Implications of Cutting-Edge Biotechnologies for Sustainability Science and Policy	2009	\$53,810
NSF	Prediction Markets - An Experimental Application to Synthetic Biology	2010	\$25,000
DOA	Ethical Issues in Agriculture	2009	NA
DOE	Genomic Science Program-Ethical, Legal, and Societal Issues	2008	\$5,000,000
DOE	Genomic Science Program-Ethical, Legal, and Societal Issues	2009	\$5,000,000
DOE	Genomic Science Program-Ethical, Legal, and Societal Issues	2010	\$5,000,000
	Total		\$15,960,991

Annexure 5:

Table 3 All synthetic biology projects and their funding that were supported by the European Commission's 6th framework programme NEST; Source: [Public Understand. Sci. 2011, 1, 1-14](#)

Project acronym	Total project cost (in €1000)	EC contribution (in €1000)
BIOMODULAR H2	2182	1998
BIONANO-SWITCH	2680	1992
CELLCOMPUT	1716	1716
COBIOS*	2582	2064
EMERGENCE*	1520	1520
EUROBIOSYN	2742	1260
FuSyMEM	1400	1400
HIBLIB	3585	1999
NANOMOT	2100	2250
NEONUCLEI	2464	1949
NETSENSOR	1989	1320
ORTHOHOME	1587	982
PROBACTYS	2541	1900
SYNBIOCOM*	264	264
SYNBIOLOY*	226	226
SYNBIOSAFE*	245	236
SYNTHCELLS	1804	1420
TESSY*	232	232
Total	32459	24728

* Projects that are partly or fully dedicated to societal aspects, technology assessment, education or community building.

Source: EC, 2007.