

## Synthetic Biology Based Biosensors and the Emerging Governance Issues

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### Abstract

Synthetic biology is a nascent field of applied science that has found applications in diverse areas such as healthcare, energy, agriculture, food additives and industrial chemicals. Its market is estimated to grow to a value of \$4.5 billion in 2015. The role of synthetic biology for development of biosensors for biomedical application and its related governance issues have been considered in the present review. The recent developments in the synthetic biology based biosensors as well as critical factors such as biosafety, standardization and proprietary rights for its socio-economic acceptance have been discussed. Scrutiny of such issues aims to understand the different parameters that can stimulate the growth as well as success of synthetic biology derived biosensors and minimise the associated risk.

**Keywords:** Biosensing; Biosafety; Diagnostics; Standardization; Intellectual property rights

**Abbreviations:** IP: Intellectual Property; IPR: Intellectual Property Rights; FDA: Food and Drug Administration; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; WTO: World Trade Organisation; TRIPS: Trade Related Intellectual Property Rights; CAGR: Compound Annual Growth Rate; COP: Conference of the Parties

### Introduction

The quest to manipulate organisms and to create new organisms as well as molecules with desired bio-attributes has led to the emergence of the field of synthetic biology. Amalgamation of principles of genetics, robotics, nanotechnology, systems biology, engineering and computational biology enables rapid investigation, manipulation and development of an entire genetic circuitry for different applications.

As a result of large demand in respect of security, biodefense, environmental monitoring and diagnostics, according to Thusu, the global revenues for biosensor market are estimated to grow at a Compound Annual Growth Rate (CAGR) of 11.5% over the period 2009 to 2016 [1]. The global synthetic biology market in the year 2011 was worth US\$ 1,537.5 million and the value of the market has reached US\$ 2,120 million in 2012. The market is expected to reach US\$ 16,745 million by 2018 growing at a CAGR of 41.1% from 2010 to 2018 [2]. Although, the market is expected to expand, the extent of use of biosensors is constrained due to issues of sensitivity, variable readout times, short life span of biomolecules and stability of the sensor. Some of the biosensors also need pre-treatment, prior to use while some are too expensive to manufacture. Because of these difficulties, biosensors that are miniaturised, highly specific and sensitive, capable of multiple analyte detection and monitoring are current agenda of research [1].

As widely acknowledged, synthetic biology is a multidisciplinary science that endeavours to develop user defined functionality based organisms for the benefit of mankind [3,4], synthetic biology can play a pivotal role in the development of novel diagnostic methods, prevention strategies and therapeutics. It can pave way for beneficial exploitation of biosensing and monitoring mechanisms in different domains (Figure 1) based on natural mechanisms of regulations occurring in living systems. Biosensors are constructed of whole cells, antibodies, nucleic acids, enzymes or receptor proteins or a combination of these as the recognition unit, that detect the targets. On recognition, an electrical and/or optical signal in proportion to the target concentration is generated.

Synthetic biology can provide the platform to create such biosensor circuits with input processing modules that read genetically coded readouts, thereby, enabling detection of *in vivo* conditions. Synthetic biology can enable designing of such biosensing systems by connecting diverse sensing parts with information processing modules. For instance libraries usually are screened to identify desired sequences through use of *in vitro* and *in vivo* assays or fluorescence activated cell sorting, however, it is challenging to identify the right module through such means. Synthetic biology has enabled development of a RNA based biosensor that can support high throughput put fluorescence activated cell sorting to detect P450 monooxygenase activity *in vivo* [1] and solve the problem of module detection. An miRNA-based classifier biosensor that integrates logic and sensing modules to detect a pattern of up to six endogenous miRNAs for identifying live mammalian cancer cells (HeLa) in a mixed coculture of HeLa/HEK293 [5,6] is a potential commercial candidate.

Synthetic biology can enable detection of complex environmental conditions via the integration of genetic filters and logic circuits into biosensors. An arsenic sensing biosensor has been developed comprising of AHL-synthase LuxI as a positive-feedback element under the control of a native arsenite-responsive promoter that is repressed by ArsR in the absence of arsenite [7]. However, in the presence of arsenic, the promoter is activated, thereby resulting in production of luminescence. Another example of application of synthetic biology in the field of biosensing is a biosensor based on *Escherichia coli* (*E. coli*) developed for detection of the explosive trinitrotoluene (TNT) on basis of a protein that binds to TNT molecules [8,9]. At present, most of the biosensing systems are designed for detection of environmental pollutants, however, these strategies can also be employed to develop biosensors with application in medical diagnosis.

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**Received** September 19, 2013; **Accepted** November 18, 2013; **Published** November 21, 2013

**Citation:** Bhatia P, Chugh A (2013) Synthetic Biology Based Biosensors and the Emerging Governance Issues. Curr Synthetic Sys Biol 1: 108. doi: [10.4172/2332-0737.1000108](https://doi.org/10.4172/2332-0737.1000108)

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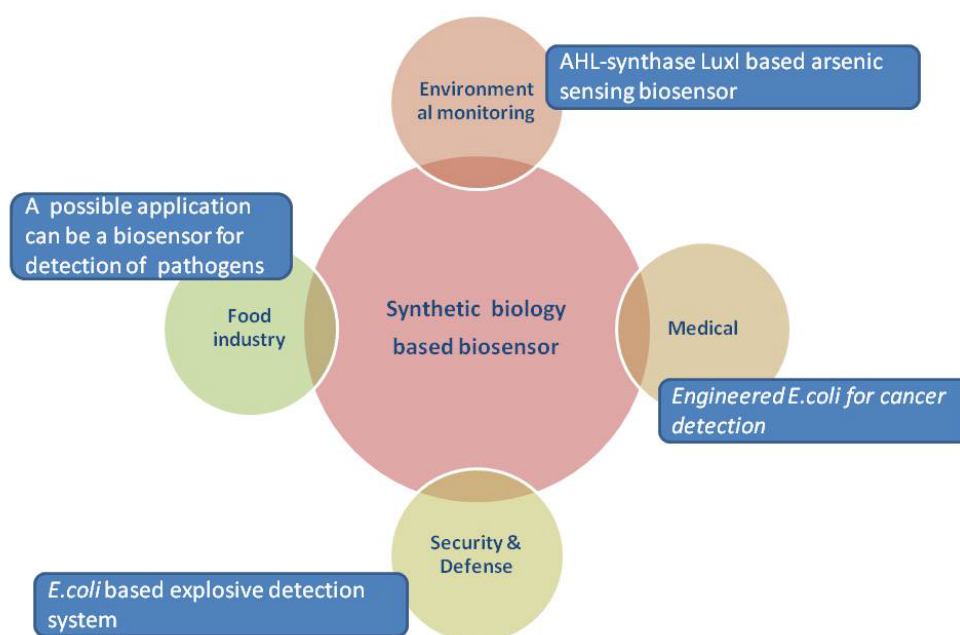


Figure 1: Application areas of synthetic biology based biosensors.

As indicated above, synthetic biology as a transformative technology is gaining recognition and is being explored to find solutions for human benefit. Through synthetic biology tools, it is possible to construct unnatural molecules that may have excellent sensing capabilities; toxicity assessment of these molecules is imperative. Schmidt and Pei [10] caution that such synthetic biology based biosensors also raise the fear of misuse, dual use and biosecurity [10]. Therefore, synthetic biology derived biosensors have to address social as well as economic challenges so as to gain public acceptability and commercial viability. Although, allied regulatory frameworks do exist, these are not synthetic biology specific nor sufficient to address the issues of the emerging synthetic biology based biosensors. Also it is notable that there is a lack of efficient toxicological assessment methods to assess the biosensors derived via synthetic biology [10].

Besides assessments and testing methods, a harmonized standardization of components and parts can accelerate effective commercialization of synthetic biology based biosensors. At the current stage of lifecycle, a flexible form of regulation for synthetic biology based biosensors can provide a good solution for its effective and success growth. Most of the technologies including life sciences thrive on innovation and generation of intellectual property (IP) in the process of innovating. Protection of intellectual property right (IPR) serves as an incentive for both the creator and the society. As is the case with other life science technologies, IP protection is crucial for commercialization of synthetic biology too. An essential tool for enhancing collaborations and commercialization of synthetic biology based biosensors is creation of a strong IP regimen. As mentioned earlier, synthetic biology derived biosensors are created by making use of engineering principles, involving diverse technology and design elements, due to which multiple forms of protection are possible under IP regime. Despite the fact that all members of World Trade Organisation (WTO) are Trade Related Intellectual Property rights (TRIPS) Agreement compliant, yet there are differences in the laws at the national level as IPRs are territorial. Therefore, for the protection

of commercial interest in respect of synthetic biology based biosensors, a plethora of strategies is being pursued. Moreover, as the biosensing circuits would be designed using well characterised standard parts, the question of ownership, availability of these parts and mode of protection needs to be resolved. Increase in significant investments and launch of commercial synthetic biology derived biosensors products will depend on the addressal of the said issues of governance.

The present review describes the recent advances made in the field of synthetic biology based biosensors. Various emerging regulatory issues with the evolution of synthetic biology based applications have been also pointed. The later sections present issues related to commercialization of synthetic biology based biosensors such as standardization, regulatory pathway, intellectual property rights and biosafety.

## Application of Synthetic Biology in Diagnostic Biosensors

There is a shift in demand from conventional methods of diagnosis that are tedious and time consuming to the use of biosensors that offer rapid and onsite monitoring. The shift has triggered tremendous research aiming at exploring mechanisms to improve functionality and sensitivity. A biosensor is made up of biomolecules as the sensing unit to identify or detect cells, organism or other biomolecules [11]. Different biomolecules such as nucleic acids (both DNA and RNA), proteins, lipids, antibodies and cells have been used to identify a specific condition of a tissue or cell. Different strategies are currently being employed for developing biosensing systems given their relevance in healthcare, environment monitoring, agriculture and especially in disease diagnosis. The three critical parameters for biosensor technology are specificity, sensitivity and rapidity. Synthetic biology offers the capability to engineer organisms and develop biomolecule based biosensors for detection of metabolites, pathogens and disease states. Synthetic biology mimicking the natural biological circuits which regulate cellular functions provides a tool to develop

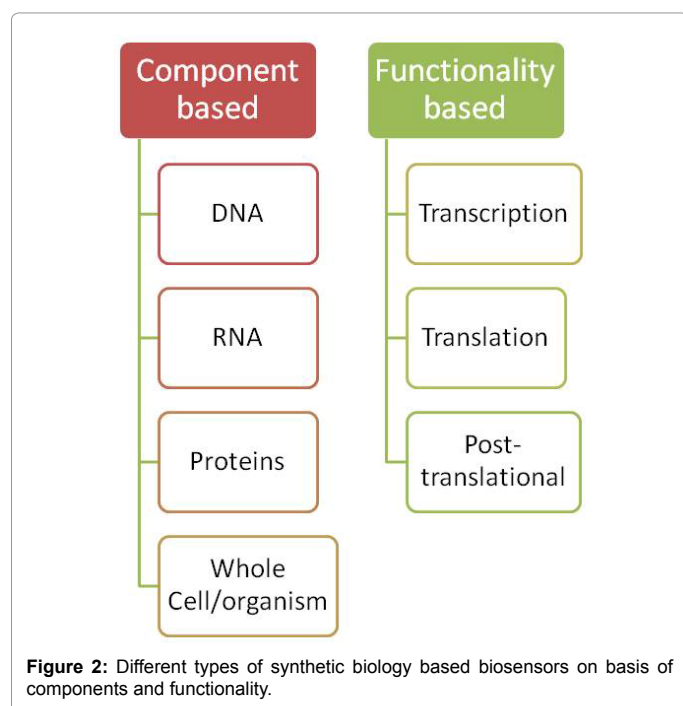
biosensors that identify the analytes and ascertain their levels. As described above, employing synthetic biology strategies, it becomes convenient to construct or modulate the signal output, selectivity and sensitivity in comparison to conventional diagnostic methods. Figure 2 illustrates different types of synthetic biology based biosensors. Most of the bacterial biosensing systems are comprised of three components that are a sensitive unit to detect the input signal, a transducer which transmits the obtained signal to processing unit to provide an output. Based on this modularity, synthetic biology can be adopted to develop systems that can respond to diverse environmental conditions with desired input and output units [12]. For instance, a digital to analog converter circuit with constitutive promoters of different strengths has been developed that processes two different inducer inputs to generate four stable analog gene expression output levels when there is toggling of gene expression [13].

One of the mechanisms by which cells respond to environment is transcription and this mechanism along with transcription factors, promoters, etc can be exploited to create transcriptional biosensing systems [14]. For example a biosensor based on CrkII adaptor protein that detects the tyrosine kinase activity of Bcr-Abl in cells of CML patients has been developed to study the response of therapy and to detect drug resistant cells within heterogeneous population [15]. A two component tracking strategy involving green fluorescent protein and red fluorescent protein based two stage amplifying protein cascade construct for biosensing DNA damage exhibited increased sensitivity [16]. Quorum sensing in microorganisms is a one of the attributes used by transcriptional biosensors in which small signalling molecules are used to determine their population. This approach has been used to design biosensing systems for detection of microorganisms. Saeidi et al. [17] describe a synthetic genetic system developed using *Escherichia coli* to sense and kill pathogenic *Pseudomonas aeruginosa* strain, comprising of quorum sensing, killer unit, and lysing unit. *Pseudomonas aeruginosa* is a bacteria that causes fatal infection in patients suffering from cystic fibrosis and cancer. The system enabled modified *E. coli* to detect the pathogenic bacteria and kill it on release of

pyocin. The biosensor enabled *E. coli* to sense acyl homoserine lactones produced by the pathogenic bacteria, thereby triggering production and release of pyocin *via* its own lysis. This strategy can use the commensal microbial population as a chassis for synthetic biology based biomedical research as it has an advantage of easy administration, and also as these micro-organisms reside naturally in the gut microbiota, they can be administered as probiotic formulations. However, it would be essential to study the effect of such engineered organisms on the other resident organisms of the body.

Gene expression at translational level is regulated by non-coding RNAs. For instance, riboswitches that bind to small molecules through aptamer domains result in conformational change in the messenger RNA's 5' non-coding region and thereby modulate gene expression. These aptamers are naturally occurring sensors with high specificity. These naturally occurring sensors can be used as a component to make biosensors along with transducers. A biosensor with engineered riboswitches was developed for detection of overdose of theophylline, an antiasthmatic drug [18]. Monitoring of over dose of theophylline is crucial as the overdose results in serious consequences. The concentration of theophylline was detected by the theophylline-dependent growth of *E. coli* using thymidylate synthase, an essential enzyme for cell growth that was linked with an anti-theophylline aptamer. The sensing construct was made using theophylline binding aptamer which was inserted in the 5' proximal coding region of GFP that was used as a reporter gene. In presence of the theophylline there was a structural change leading to reduced ribosomal accessibility [18].

Another approach that has been used to constitute biosensing system is through copying the post translational control systems. Using temperature sensitive RNA biosensors or aptamers as explained above or ribozymes, different analytes can be detected. The structural switching biomolecules can serve as components for development of biosensors [19]. Genetically encoded biosensors are simple devices and they either use transcription regulators to identify analytes translational controlling molecules such as aptamers. However, purification of these biosensors will be costly and tedious affair. An alternative to these are whole cells that are easy to manipulate and are more stable than biomolecules even under harsh conditions [20]. An *E. coli* based system was developed by Anderson et al. [21] to invade cancer cells only, based on hypoxia detection in cancer cells using the lux quorum sensing circuit and hypoxia responsive promoter. Thus, engineering of mixture of components using synthetic biology approaches, a specific, sensitive and rapid diagnostic system can be created. However, it also necessitates the assessment of these engineered biosensing circuits in biological systems. Besides bacteria, other organisms can also be used for development of a biosensor. Bacteriophages, because of their inherent attraction for bacteria are an interesting model for microbial diagnostics. Due to their specificities and capabilities of replicating only in the presence of specific bacteria, they offer a unique advantage. As a result, bacteriophages have been explored to circumvent disadvantages of conventional methods of diagnostics which are time consuming, laborious and often yield false results. Natural and genetically modified bacteriophages standalone or in conjugation with other sensing mechanisms have been proposed [22]. One such genetically engineered bioluminescent reporter phage for plague diagnostic has been developed that encodes bacterial *Vibrio harveyi* luciferase on infecting *Yersinia pestis*, which is detected by addition of an aldehyde substrate whereby light is produced signalling presence of *Y. pestis*. However, absolute quantification of number of target bacteria is not possible through this method. Another FDA approved  $\gamma$  phage assay for detection of *B. anthracis* based on *luxAB* genes encoding bacterial





luciferase. However, signal amplification is required for its detection [23]. Both the examples illustrate engineering of bacteriophages to create role specific biosensing systems, indirectly indicating role of synthetic biology in bacteriophage based microbial diagnostics. To overcome the limitations of quantification and signal amplification, the principles of synthetic biology come handy. Multiple bacterial identifying circuits can also be built using different modules for rapid diagnosis of different bacteria. All the same, although, bacteriophages seem to be a good model for development of biosensors via synthetic biology, they need to be extensively engineered and the developers have to address safety challenges to make commercializable [24].

As described in the earlier sections, synthetic biology based biosensors have a strong potential in medical diagnostics. Biosensors can be used for identifying cancer cells; therefore, their production needs to be scaled up, which is possible only on availability of standardised protocols and parts. Therefore, a close scrutiny of standardization, proprietary rights and Biosafety is essential for effective commercialization of synthetic biology based biosensors. These issues have been examined in the sections ahead.

## Governance of Synthetic Biology Based Biosensors

Owing to development of synthetic biology in diverse spheres such as biomedicine, biofuels, biomaterials and industrial chemicals, the global synthetic biology market is estimated to reach \$4.5 billion over the year 2015 [5]. As discussed in previous section, i.e. section 2, different strategies based on nucleic acid, protein or organisms have been deployed to develop biosensors using synthetic biology approaches. For example, quorum sensing has been used to create a biosensing circuit to sense and kill *Pseudomonas aeruginosa*. Adoption of this strategy for large scale production and commercialization would significantly depend on reproducibility elucidating the relevance of standardization of the whole spectrum of tools, programming languages, biological parts and devices for apt development of biosensors via synthetic biology. Balancing freedom of research and minimizing risks associated is important to ensure growth of this field. To commercialise biosensors derived via synthetic biology approaches, it is pertinent that the various aspects related to biosafety, intellectual property, standardisation, and regulatory are dealt with, in a timely manner. The present section deals with the above mentioned issues pertaining to the use of synthetic biology based biosensors.

## Biosafety of synthetic biology derived biosensors

The most essential step at this stage of research is to assess risk of synthetic biology based biosensors in terms of biosafety and how the anticipated associated risks can be mitigated. Microorganisms and biomolecules such as proteins as well as nucleic acids can be engineered as biosensing systems employing synthetic biology. They are proposed for use as pathogen detection or disease detection in living systems. These strategies raise serious questions with respect to the outcome of interactions of engineered microorganisms and biomolecules with the commensal microorganisms, non-target organisms and other neighbouring biological molecules. This uncertainty of impact of these engineered organisms and biomolecules with biosensing capabilities on environment or living systems makes risk assessment and mitigation an important area of research [25]. Also novel methods to assess the impact of synthetic molecules created with sensing and deactivating modules on the biological systems are required. Therefore, there is an urgency to have a governance system in place that regulates the use and release of such manipulated organisms. The International Civil Society Working Group on Synthetic Biology realising these concerns has submitted a

report to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) on the 'Potential Impacts of Synthetic Biology'. The report holds that, at the present there is no intergovernmental body with a mandate to regulate the impact of synthetic biology on land, biodiversity and humans [26]. The emerging issues of synthetic biology and their impact on biodiversity on the basis of the SBSTTA's report were discussed in India during Convention on Biological Diversity's Conference of the Parties (COP) 11 meeting held on October 12, 2012 at Hyderabad. Impact assessment of synthetic biology on conservation and sustainable use of biological diversity and associated social, economic and cultural considerations were the major point of discussion [27]. Realising the importance, three Scientific Committees - Committee on Emerging and Newly Identified Health Risks (SCENIHR), the Committee on Consumer Safety (SCCS) and the Committee on Health and Environmental Risks (SCHER) have been constituted by the EU Commission to study the risk [28].

Recognising the need to control these self-replicating engineered organisms and thereby to combat the fear of negative impact on the environment, synthetic biology is being explored to identify the solutions. Host-circuit based dependencies such as using toxin-antitoxin complementarily and metabolite dependency can be a strategy to restrict interaction with nature. Another mechanism may involve containment of these biosensors through encapsulation. Tracking of microorganisms in the environment is possible by using DNA barcodes. The most interesting and appropriate approach can be the use of self-destruction property in the biosensing microorganisms or low rate of survival or plasmids that are lost with the number of replication [29]. All these strategies would aid to alleviate the fear of harm to human beings, animals and the ecosystem.

There are other factors besides issues of biosafety that determine commercial success of synthetic biology derived products. One such tool which will play a considerable role in synthetic biology research is intellectual property especially patents. The next section discusses the intellectual property regime for synthetic biology based biosensors.

## Intellectual property rights: freedom to research and incentives

Synthetic biology offers a platform for developing such tools that have the capacity to reduce waiting time and at the same time enhance accuracy of sensing as well. A factor that can serve as an impetus for its economic growth and effective commercialization is the ease of generation of IP. The following section examines the scope of protection available under the current intellectual property regimen for the synthetic biology based biosensors. Although, IPR comprises of different forms such as patents, copyrights, trademarks, designs, however, the current section focuses on patents as the major IP tool as they are the prime trade currency for commercialisation.

Saukshmya and Chugh [4] have observed over a period from 1990 to 2008 there is an exponential increase in synthetic biology based patent application filing claiming methods of developing synthetic DNA strands, compositions, genes or parts of genes. Till late there was stifling ambiguity on patentability of isolated human DNA sequences. The recent judgement of the Supreme Court of United States of America in the *Association for Molecular Pathology v. Myriad Genetics* case clarifies that the isolated DNA sequences being products of nature, are not considered as patentable; however, cDNA is patentable [30]. Association for Molecular Pathology had opposed patents on *BRCA1* and *BRCA2* human genes filed by Myriad genetics, on the basis, that both genes and the method of detection of

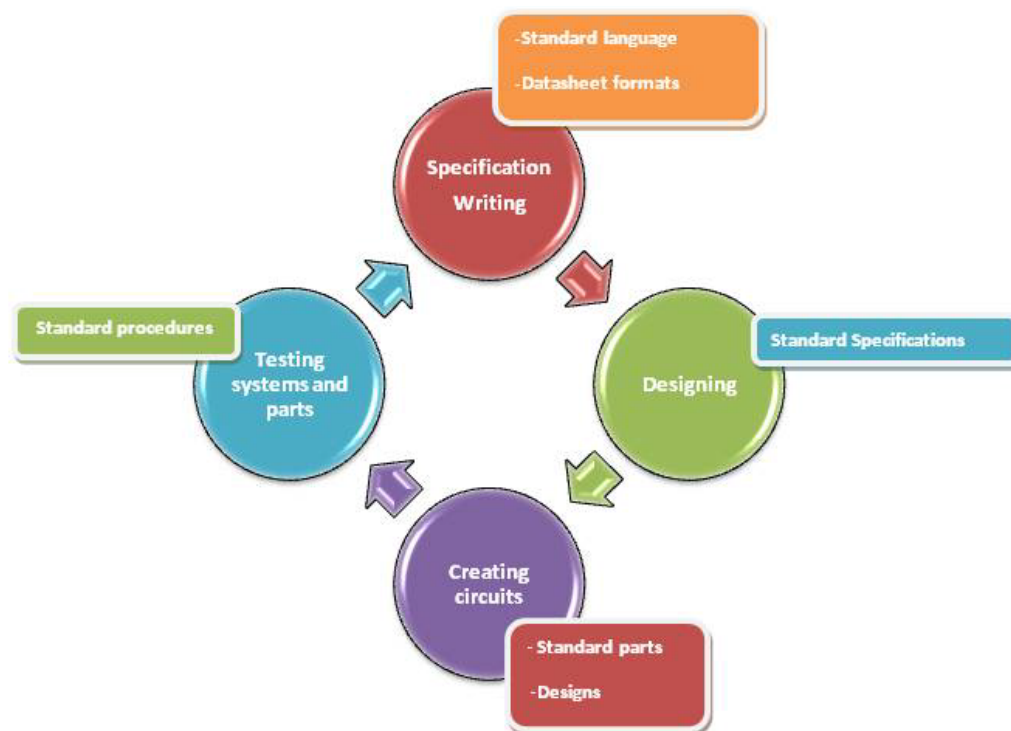
these genes, do not fall under the purview of patentability criteria. The district court in 2010 had held both genes and the method of detecting as non-patentable; later this judgement was partly reversed by the US Supreme Court in 2012 allowing genes to be patentable. However, in June 2013 this judgement too was reversed rendering only cDNA only patentable [30]. This judgement would render the genetic circuits as non-patentable, however, the techniques involved in engineering the organisms using genetic circuits may be considered patentable in case they meet the patentability criteria. The method of detection was held non-patentable in 2010 by the district court and the decision was affirmed by the Federal Court stating that the method of detection does not involve any transformative step [31]. Similarly in Europe and India in accordance with the flexibility conferred by Article 27(3) of TRIPS diagnostic methods have been excluded from the purview of patentable inventions. In Europe, in respect to method of diagnosis of human diseases, patents cannot be granted as per the Article 53(c) EPC (32). Section 3(i) of the Indian Patent (Amendment) Act, 2005, diagnostic methods are rendered as non-patentable inventions and the Section states that “any process for the medicinal, surgical, curative, prophylactic [diagnostic therapeutic] or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products”. In light of the judgement and respective legislations the various parts and modules of a biosensor as well as the steps involved in diagnosis may not be patentable in many countries. The national patent laws have excluded some inventions from the scope of protection, for example, in case of India, the Section 3(f) states that “The mere arrangement or re-arrangement or duplication of known devices each functioning independently of one another in a known way is not an invention”. Creation of a biosensor with different known properties and parts may not be patentable in India in light of Section 3(f).

Although, as discussed above, under certain circumstances the gene sequences and genetic circuits may not be patentable, genetically modified microorganisms are patentable, provided they are novel and involve inventive step. The US Supreme court decision in the *Diamond v. Chakrabarty* case was responsible for initiating patenting of life forms – microorganisms. Such judgements have paved way for patenting novel microorganism through biotechnological interventions. In Europe and India, both being WTO members had implemented the TRIPS Agreement and allowed genetically modified microorganisms as patentable inventions. Patentability of microorganisms in USA, Europe and India has been discussed in detail by Jain et al. [3]. In India, one of landmark judgement in case of microorganisms is the Calcutta High Court decision in *Dimminaco AG v. Controller of Patents and Designs*, 2002. A patent was applied for protecting the process of preparation of a live vaccine for Bursitis and the vaccine itself in 2002 by the Swiss company Dimminaco A.G. However, the patent application was rejected with a remark ‘not patentable’ by the Controller of Patents, as the invention involved processing of microbes which are living organisms and the invention does not involve any manufacturing process. The company appealed against the decision of the Controller in the Calcutta High Court and the Court reversed the decision of the Controller stating that the Indian Patent Act does not bar ‘processes’ from being patentable if the end-product is living organism. The Court also clarified that the microorganisms in laboratories under controlled environment are patentable [32,33]. Currently post amendments in the Indian Patent Act in 2005, although naturally occurring microorganisms are not patentable synthetically developed or genetically engineered microorganisms are patentable in India. Under the described circumstances, the synthetic biology based

biosensing microorganisms also meet the patentability criteria. Another essential requirement for patenting of microorganisms across the globe is that the microorganisms need to be deposited in an International Depository Authority. The same rule also extends to synthetic biology based whole cell biosensors; however, along with the deposition of the microorganisms, deposition of the datasheet detailing the modules used should be made mandatory. This would ensure that the microorganism is available to the public and it is reproducible. For production of biosensors accessibility to diverse tools, parts and databases is required. However, interoperability is the key for successful development, which in turn depends on standardization. The following section assesses the relevance of standardization and efforts made towards standardization in synthetic biology.

### **Standardization of parts, registries and methods for development of biosensors**

Synthetic biology is founded on the principle of engineering pertaining to division of tasks with the objective of creating tools or organisms as per human needs, which in turn depends on readily available and well described components [34] as well as methods [35]. To achieve this objective, the most important factor is standardization. Developing a standard is technically and socially challenging. Standardization is required at each step from specification to design and building of a synthetic biology biosensing circuit to its testing (Figure 3). For the development of various genetic circuits in synthetic biology with biosensing capabilities, exchange of information and interoperability of parts is crucial. Also standardisation is required to enable accurate reproducibility and testing of the synthetic biology based biosensors. The first initiative in this regard was creation of ‘The Registry of Standard Biological Parts’ at MIT, however the Registry does not guarantee that many such parts can exhibit the same activity in different assemblages [36]. Another open source Registry is the Joint Bio Energy Institute Inventory of Composable Elements (JBEI-ICEs) which contains information of parts such as plasmids; microbial host strains as well as DNA and can be used to produce a synthetic biology based whole cell organism biosensor [37]. Similar to the Registry of Standard Biological Parts, another Registry is proposed to be created at the Imperial College, UK. Standardization of the format for exchange of information that defines modules, how the parts are interlinked to ensure identification of biomolecules and generation of signals as well as characterization of behaviour can assist in harmonization of this field. Datasheet needs to include information related to these biosensors on characterization of long-term performance, behaviour, stability, and fate of synthetic circuits [38]. Gradually standards are being developed for documentation and effective exchange of information among the synthetic biology community. One such Standard to promote exchange of information related to DNA components employed in synthetic biology is Synthetic Biology Open Language (SBOL). It enables reproducibility through emphasis on preferred terminology for the parts and how the parts are interconnected. Another similar Standard is DICOM-SB pertaining to metadata and images related to a Biological Part [39]. Based on the various standards established under BioBrick, standards such as Bgl Brick Standard for construction of metabolic pathways in various combinations for improved gene expression have been proposed [40]. Such strategic efforts for standardization of parts will pave way for accelerated growth of synthetic biology in the field of biosensors by promoting interactions and collaboration at the international level. Although, steps have been taken towards standardisation of parts and modules, however, the route of interaction among these modules is difficult to standardise [9]. To make these interaction pathways in synthetic biology based biosensors more



**Figure 3:** Steps involved in the development of synthetic biology based biosensors and their relationship with standardization.

predictable and less complex, standardisation of interaction pathway is essential. Although, due to availability of these libraries and standard data sheets, creating a biosensor via synthetic biology would become easy, its commercialization would be subject to regulatory approvals. The following section analyses whether the existing regulatory regime would suffice or it requires amendments for effective governance of synthetic biology based biosensors.

### Harmonization of regulatory regime for engineered biosensors

Biosensors find use in the medical space, through diagnosis of cell states, diseases and regulating the metabolic pathway. As discussed above standardization is one of the essential factors for effective commercialization. However, synthetic biology based biosensors would also require approvals for being marketed. The question arises which regulatory pathway nucleic acid based biosensors will follow, pharmaceutical or medical device or biologics? And whether whole cell biosensors be regulated as genetically modified organisms? It is not clear at the present and these issues needs to be addressed for effective governance of synthetic biology in this field. In this regard, the European Commission has requested its three Scientific Committees which are Committee on Emerging and Newly Identified Health Risks (SCENIHR), the Committee on Consumer Safety (SCCS) and the Committee on Health and Environmental Risks (SCHER) to analyse and provide their joint opinion with respect to the relationship between Synthetic Biology and genetically modified organisms in general. As the potential application of synthetic biology is in the field of biosensing, it calls for review of existing regulatory frameworks and laws to accommodate the issues related to it. There are inherent differences in the scope of each of the legislation with law being territorial in nature. Therefore, on a global platform a harmonized

regulatory regime can enable effective commercialization of synthetic biology based biosensors. The work is still in progress.

### Conclusions

Synthetic biology holds immense potential towards providing solutions related to different spheres surrounding human lives. Earlier, synthetic biology based bioenergy and bioremediation solutions were prime loci of focus, however, now strategies towards biomedicine are being adopted. Other than drugs, synthetic biology is also being explored for creation of biosensors for diagnosis. Synthetic biology based on engineering principle has a key role to play in development of biosensing systems. One of the examples of biosensors based on synthetic biology approach is the bacterial system that identifies and eventually leads to death of pathogenic bacteria through quorum sensing.

The intellectual property assets, especially patents would determine the freedom to operate available for an enterprise for commercialization of synthetic biology based biosensing systems. Safety and standardization of the parts used for the development of synthetic biology based biosensors would also form essential catalyst for commercialization of research and scaling up of the research. Standardization is critical to ensure harmonised procedures for scaling up production of biosensors and their testing. Creating robust and efficient biosensors with added feature of safety are the major challenges for a synthetic biologist that can be addressed using principles of engineering. It is interesting to know that synthetic biology has the potential to address the biosafety fears and is being explored to devise 'self-destruction' or tracking strategies in microorganisms. Currently most of the biosensors for medical diagnosis are at research level and at concept stage. For growth of synthetic biology derived biosensors, a regulatory pathway that governs use and safety of the product would

be crucial. It remains to ascertain how nucleic acid and organism based biosensors are regulated and to ascertain whether Convention on Biological Diversity play a role and to what extent? Asynthetic biology specific framework to regulate research and commercialization at a global level will enhance the growth of synthetic biology based bio-economy.

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