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Synthetic Biology, A New Tool for Biological System Engineering Discipline - An Overview

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COLUMN ARTICLE

Introduction

Genetic engineering (GE) term was introduced by a novelist - Jack Williamson in 1951. Since then, GE has widely been accepted with key progress - ranging from gene therapy to genetically engineered crops and microorganisms. Though the term fits into the American Engineers Council for Professional Development engineering definition, there lies a fundamental difference between conventional and GE. For instance, conventional engineering is well defined by mathematical principles and are modular in nature. The lack of well-established design principles makes GE a trial and error process. Understanding the dynamic function of a biological system has become easier with successful completion of diverse genome projects [1]. However, during the pre-genomic age, research approaches that were categorized as GE were mostly restricted to cloning and recom¬binant gene expression. In short, GE was not yet fortified with tools/knowledge necessary to create biological systems that display in-depth regulatory behaviour found in microorganisms [2].

Synthetic biology [SB] is rapidly evolving biological system engineering at molecular level which displays functions that do not exist in the nature. This engineering view can be applied at all levels of biological arrangements from individual molecules to whole cells, tissues and organisms. In principle, SB allows the design of biological systems in a systematic way. Now after a decade, SB has experienced considerable growth in scope and has become a widely acknowledged branch of life science [3]. The origin of SB can be marked out in 1961 where by the study on lac operon led to postulate the existence of regulatory circuits which support the cells to response to its environment [4]. The size and scope of SB began to increase intensely in the mid-2000s bringing together researchers from numerous disciplines at the first international conference, SB 1.0. The meeting was widely praised and for the first time, scientific community began to make strong efforts to improve the engineering of genetic systems by creating modular parts and developing methods to construct and tune particular circuit designs [5]. Initially in 2008, scientific news began to appear describing broader array of better characterized parts which exhibited diverse behaviours. High-throughput DNA assembly systems with decline in gene synthesis costs, fur¬ther accelerated the engineering of genetic circuits [6-8]. Taking advantage of the dramatic increase in genome sequencing data's along with DNA assembly and decline gene synthesis costs, researchers started to develop syn¬thetic pathway to identify favourable metabolic routes based not only on the metabolic system of the host but also on all known and predicted enzymatic functions. Recent high profile success that uses these approaches in *E. coli* includes biosynthesis of bioplastic [9], fatty-acid-derived fuels [10], gasoline [11] and isobutanol [12,13]. Possibly, the highest profile SB success during this period is the heterologous production of antimalarial drug artemisinin precursors [14-16]. Similarly, the promising work on the rational

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design of complex polyketides/non ribosomal peptide led to an increased appreciation for the scope and potential of SB [17,18]. As a result, SB emerged as a new generation of interdisciplinary branch of life sciences in which the construction aspect exceeds the traditional view of biology. It is one of the few fields where the entire main scientific disciplines namely biology, chemistry, physics, mathematics and engineering are equally important for success. (Figure 1).

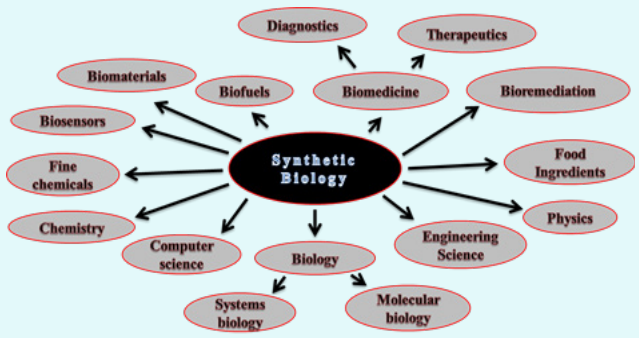

Figure 1: Interdisciplinary branches of synthetic biology.

Synthetic biology for metabolic engineering

SB is an emerging field with the juncture of biology and engineering possessing the potential to revolutionize the way we view and work with biotechnology today. By applying the toolbox of engineering disciplines to biology, an entirely new set of applications become possible. Potential benefits of SB include the development of low cost drugs and the production of chemicals and energy by engineered microorganisms. Generally, it is often difficult to achieve the desired phenotype with metabolic engineering (ME) approach alone due to the complex nature of cellular environment. Hence, SBaims at creating novel biological parts, modules, genetic circuits or organisms by using various molecular biology tools together with mathematical approaches [19,20]. Several synthetic functions and modules have been developed to redirect metabolic pathways to produce novel metabolites [21]; regulate metabolic fluxes in response to environmental changes [22]; perform specific biological behavior such as on/off switch and oscillation [23,24]; and allow communication among cells [25]. In particular, SB has critically contributed to ME by decreasing the capacity of the production host and thereby producing various platform chemicals [26-28].

Use of SB in ME has mainly focused on constructing synthetic pathways for producing non-native/unnatural chemicals by modulating genetic circuits. For producing these chemicals, the genes that convert an existing cellular metabolite are synthesized/assembled from various sources and introduced into the preferred host strain [6,7,20,29,30-32]. This strategy is often useful for enhanced production of a given product using a host strain that is more suitable for industrial applications. For instance, the discovery of ePathBrick: a synthetic platform for engineering *E. coli* helped in the assembly of individual pathway components into three different configurations like operon; -pseudo operon and -monocistronic using different isocaudamer pairs [32-34]. Many such successful applications of constructing synthetic pathways have been reported for the production of fatty-acid-derived fuels [10], L-homoalanine [35], levopimaradiene [36], non-natural alcohols [37] and methyl halides [38]. Nevertheless, designing and construction of synthetic small regulatory RNAs for ME is also one of the successful applications for constructing synthetic pathways for improved production of desired products [39-43]. Similarly, a plasmid-free chemically induced chromosomal evolution (CIChE) for high gene expression is another way to increase the yields of biochemical products [44].

Taking together, SB makes it possible to construct synthetic enzymes and pathways in a desired host strain for the production of a wide range of chemicals ranging from pharmaceuticals to biofuels and to increase the efficiency of flux optimization by fine-tuning the expression levels of multiple target genes that are to be manipulated. The creative features of SB are expected to expand the spectrum of bio-products that can be produced by fermentationand improve the performance of microorganisms beyond the level of conventional ME, through the synthesis and optimization of novel and existing pathways. This approach can become even more powerful when combined with systems biology because the whole cell metabolic characteristics can be analyzed and implemented during design of the enzymes, metabolic pathways and other cellular networks by SB.

A future perspective of Synthetic biology

Since the beginning, SB has grown significantly and has achieved many notable achievementsprovidingplentiful opportunities for biotechnologistfor developing novel processes for large scale production of platform chemicals and therapeutic proteins. However, the crucialchallenges in SB are the modularization/standardization of biological parts andits integration into devices with desired functions. Modularization/standardization of biological parts is similar to modularization/standardization of electronic parts such as inverters, switches, counters, and amplifiers which helps to assemble any part into genetic devices [45,46]. Severalcomputational and experimental tools have been advanced to address these challenges, creating numerous scientific and technological prospects. In general, SBwill rely less on the theory and practice of other engineering disciplines and will instead continue to build its own identity and culture. In addition, new technologies such as CRISPR/Cas mediated genome editing will enable synthetic biologists to take a more holistic engineering approach for modifying synthetic circuits and the host genome with relative ease [47]. The development of cell based therapeutic strategies in which engineered microorganisms interface with the human gut microbiota to fight infection and chronic disease is another challenge [48,49].

Despite the proliferation of circuit design and construction methods, there are still very fewallocation of constructed circuits between groups, as most synthetic networks are developed and then never been used outside the home laboratory. To some extent, this is expected as many of these circuits are proof of principle designs but as the field expands, an important cultural shift will occur. Therefore, the continued fostering of an inclusive and collaborative community is essential.

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