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Mini-Review

From copying to synthesis - Paradigm shift in Biological engineering - Synthetic Biology

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Abstract

Let's play lego game of blocks on life biomolecules, can we? Yes we can, that's what is the era of translational world of science, where synthetic biology envisions to build novel patterns of cellular function from the available blocks by engineering designs on the biological blocks - DNA and protein. The blocks here are the sequence components that are characterized in their most simple forms and then anchored together as a string of co-regulated genetic parts with desired functions. Synthetic biology dwells on high-throughput biological engineering and rational redesigning of biological substrates that have intricate but partially characterized details posing their unique set of challenges. The conceptual biological engineering includes design patterns, genetic or DNA components as libraries, computational tools for design, circuit design scaffolds, with the final aim of application specific designs. These synthetic genetic circuits possess the capacity to manipulate and probe biological interfaces. The comprehensive review aims to shed light on the progress, challenges and applications of key areas where synthetic biology is impacting biological sciences.

Keywords - Synthetic devices, genetic circuits, engineering designs, rational designing, modeling, simulations, biological engineering

Introduction

Establishment of "omics" trends in the era of scientific discourse in biology has identified plethora of genetic and protein components. Systems biology has furthered ascertained the exclusive details of the biological networks that formed the basis of undertaking engineering of biology using synthetic biology. The field is poised to expedite designing, modification and manufacture of genetic materials in living cells / organisms to allow modulation of living or non-living materials under designated regulatory controls (1). The paradigm shift has occurred where DNA copying has been replaced by DNA synthesis, that combines the fundamental knowledge to synthesise desired attributes using individually standardised genetic components as biology toolboxes (1-2). This is achieved through iterative design patterns inculcating molecular biology and computational skills to assemble programmable devices with controlled functional dynamics in living systems. The structured details of such biological components catalogue are aptly represented through BioBricks collection (parts.igem.org/Main_Page), where individual parts have predictable function. Synthetic genetic circuits thus manoeuvre and manipulate biochemical circuitry at the

DNA/RNA/protein molecular interfaces that can be capitalised on interchangeable designs for a variety of biological outputs.

Engineering Biology - Core principles and applications

The engineering phase of the biological components follow the rule book of professional knowledge and training so as to achieve a well defined task. The engineering approaches thus include i) Design cycles using predictive synthetic parts/modules ii) Hierarchial functional designing iii) Manufacture of functional biological modules with quality control and iv) testing and application of finished devices using standardised biological measurements. The field of electrical engineering has been an inspiration to focus on the engineering goals of the bimolecular and cellular capabilities, with significant progress in designing complex circuits as synthetic biological constructs or gene networks applied in diverse fields as of today (3-5).

Technology and engineering transcended in the biological systems, where the translational sciences leap forth applying engineering principles on fabricating and redesign biological parts or entire systems to allow synthesis of new properties in the living systems (4, 6). Biological engineering consists of bio-molecular engineering of genomes, proteins, metabolites and or entire cells or microbes. Such engineered systems have a wide array of applications that include creation of organisms which can synthesize therapeutic or industrial molecules, engineer to attain biofuels from solar energy or waste, microbes that can both sense and remediate contamination, act as biosensors for environmentally or medically significant systems, and also be able to transmit the modulation desired to neighbouring cells (2, 7-8).

DNA Synthesis - Creating the synthetic parts

Synthetic biology holds promise in potentiating controlled DNA dynamics using advanced gene synthesis technologies having constraint based enzymatic error rectifying and genome assembly parameters. These high-throughput technologies are applied to create DNA de novo through chemical preparation methods (phosphoramidite synthesis) (Fig. 1) and enable the researchers to manufacture catalogued DNA sequences and assemble them as new genomes with altered or desired functions (1, 6). Craig J Venter Institute Scientists have designed and synthesized modified bacterial chromosomes that are designated to allow biofuel production, industry specific pharmaceutical intermediates, food ingredients, fine chemicals and bio-speciality chemicals to be utilized in health industry too.

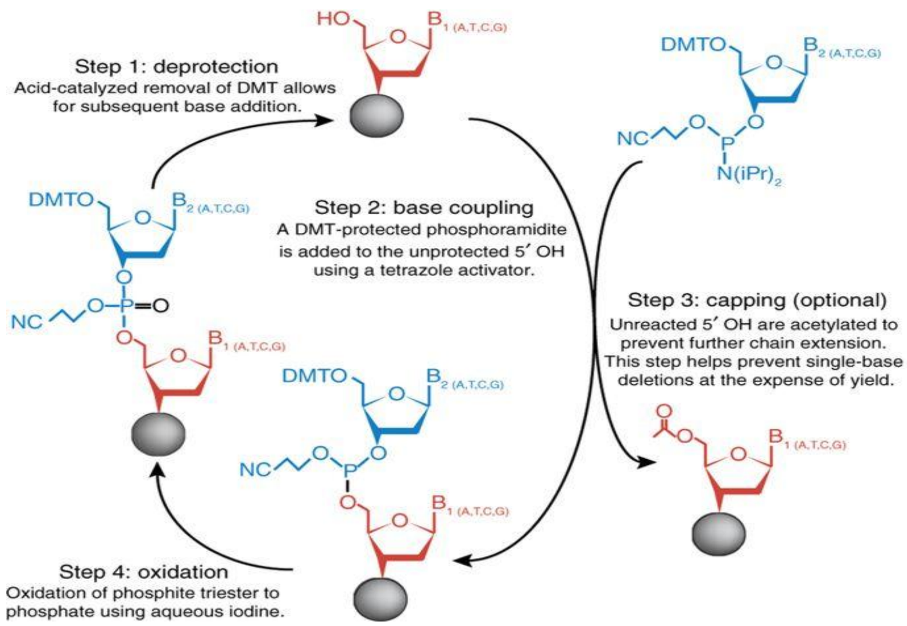

Fig. 1 DNA de novo through chemical preparation method

DNA manipulations began with altering the gene of interest (GOI) or allowing overproduction of the GOI under suitable lab conditions. The overall outcome of the field had limited success rate in Industrial scale applications or in environment (2, 5 & 8). The 21st century in science is the 'century of DNA, where it being the blueprint of life's symphony is tuned to engineering genetic circuits, metabolic pathways, biological systems and even entire organisms. This had been made possible due to advancements in next-generation sequencing (NGS), its applications as in Metagenomics and Microbiome projects that has led to swelling of biological sequence repositories utilised further by improved Bioinformatics algorithms to analyse, manipulate and design engineering components at genetic level (7, 9). The sequence boom from the diversified fields of living systems is allowing the expansion of scientific disciplines such as protein engineering, metabolic engineering and synthetic biology. Scientists are using the novel sequence information and manipulation techniques for developing of theranostic and biosensing devices with the aim for precision medicine. With a string of innovations in instrumentation and technologies connecting the biological sequence data bonanza to construct DNA designs from high fidelity sequences driving the parallel development of methods and instrumentation to produce synthetic DNA at scales for *a priori* testing of engineered biological components hypothesised to create plentitude of multivariate products (10).

Biosystems engineering - Challenges and outputs

Engineered bio-systems combine foundational technologies encompassing DNA synthesis, electrical design patterns and controlled tunable outputs. Synthetic biology impacts academic and industrial arenas with creation of unique / exquisite materials, biosensors, therapeutics and commercially viable bio-enzymes (8, 11). Engineering biological systems is still in its state of infancy due to our inadequacy to functionally characterise components in the intricate network of interrelated sequences. Consequently, such engineering is tethered to heavy dose of empirical trial and error patterns to evaluate novel proteins, expression systems and pathways for the desired function (5, 12). The process here is optimised to include steps of designing a desired synthetic biological pathway or circuit using computer aided simulation and design tools (Bio-CAD). The resulting construct is then divided into smaller overlapping pieces that are easier for synthesis (200-1500 bp typically). The overlapping DNA synthons' thus synthesised after design cycles are assembled into larger DNA pieces that are cloned in expression vector and assayed for function. Iterative designing of the construct (Fig. 2) consists of designing, building. Testing, learning and repeating for the best synthetic system using high throughput methodologies (13-15).

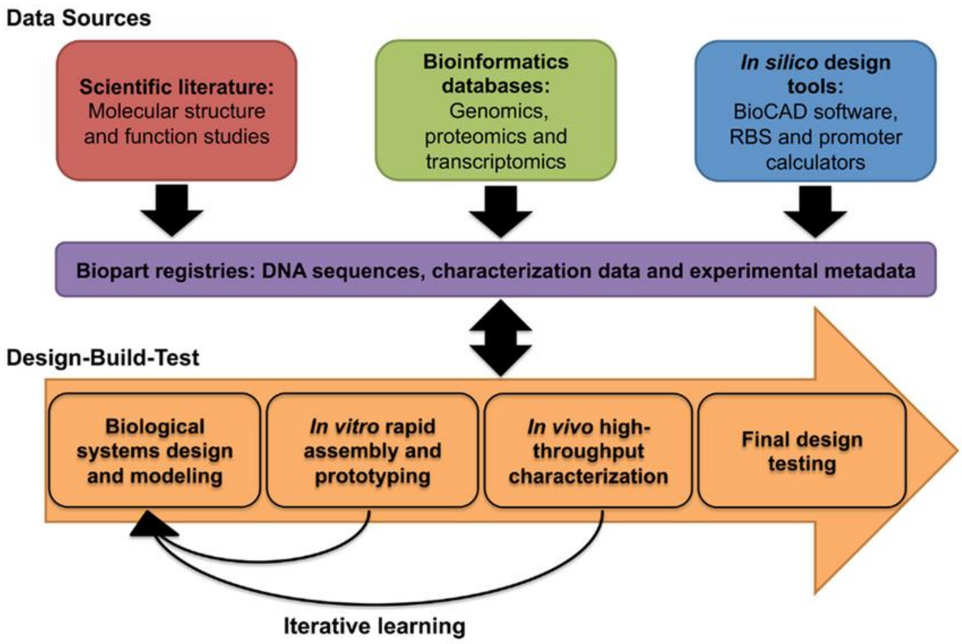

Fig. 2 Iterative designing of DNA construct

The fields systems and synthetic biology studies complex biological systems as integrated wholes, where computational tools such as modelling, simulation, and docking are used in systems biology while experimental techniques to build artificial genetic systems using natural biological components are used in synthetic biology (9, 16). In the aspect of engineering, genetic engineering involved cloning of individual genes and it's overproduction under promoter system while synthetic engineering envisions the assembly of novel pathways, genomes from a set of standardized genetic parts and then allow functional integration in a microbe or cell.

Synthetic Biology Goals:

Identify and catalogue standardized genomic parts that can be used to build novel biological systems (7).

Protein engineering and enzyme engineering designs for diversity in functions (13).

Microbial engineering for biological function performance and optimization for complex multistep production of natural products or metabolites (16).

Synthetic genomes construction and designing desired simple genomes (14).

The fields benefitting from the perspective growth in the field of synthetic gene biology are biomedical engineering, industrial scale engineering and environment monitoring, bioremediation and engineering.

Synthetic Biology Timelines and breakthroughs:

- 2003 - Fully synthetic PhiX174 chromosome, microbe for oil spill clean-up or bioremediation developed at the J.Craig Venter Institute (JCVI) (9).
- 2004 - DNA synthesis multiplex technique developed at Harvard Medical School (3).
- 2006 - Re-engineered yeast containing bacterial and wormwood genes as a chemical factory circuit for producing precursor of anti-malarial drug artemisinin at Berkeley Centre for Synthetic Biology (6).
- 2007 - JVCI designed genome transplantation methods for chromosomal directed complete bacterial transformation (5)
- 2008 - First synthetic bacterial genome of *Mycoplasma genitalium* developed at JVCI representing genome transplantation, synthesis and assembly for fully activated synthetic cell (8)
- 2010 - Scientists at JVCI developed world's first synthetic life form, single celled organism similar to the bacterium causing mastitis in goats with watermarked synthetic genome constructed through chemicals in laboratory (14)
- Genome transcriptional regulatory control through engineered regulators modulating chromatin (transcriptional hotspots) (13).
- Regulating cellular organisation at molecular scales that caters to conducting cell function through gene regulatory networks (1)
- Creating microbes adept for bioremediation, producing biofuels to combat pollution while producing cleaner energy (15-16)

Future Prospects

Technology and techniques are being characterised and standardised to synthesise novel genomes for microbes or cells so as to establish synthetic biology for life usage. Incorporating the diverse capabilities in theoretical mathematics, computational training sets and complex biochemical circuitry, synthetic systems are pitched to achieve versatile and novel engineered functionality. Synthetic biology explores to establish a bio-based economy with emphasis on biological processes replacing chemical reactions to produce cleaner manufacturing operations for a greener technology. The technology thus established aims to provide circuit modules for enhanced natural mechanisms for producing enzymes, vitamins, chemicals and fuel. Protein and metabolic engineering using synthetic biology have been commonly employed in synthetic engineering. iGEM is the worldwide forum where scientists are coming forth with novel formulations of the synthetic biological engineering to create either circuits or entire microbes as genetically enhanced microbes for varied applications. Such platforms have integrated the efforts of young developing brains to put conduct experiments and overcome challenges for exquisite outputs in biology. The coming times would possibly witness the paradigm shift in biological handling of synthetic parts to elucidate, manipulate and create regulated bio-systems.

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Conflict of interest

Authors declares no conflict of interest

Compliance with Ethical Standards

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors

Author contributions

SS: designed the study and prepared manuscript

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