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A Schematic Overview on Computational Methodologies for Designing Synthetically Biological Products

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Abstract

The integration of molecular biology with engineering leads to development of an emerging field in research known as synthetic biology. This work will support the progress in designing and construction of synthetic genetic products. Computational methods would improve the predictability of respective mechanisms and the analysis along with the interpretation of both qualitative and quantitative models will become important. The present review article is a diagrammatic or schematic representation of an overview of synthetic biology, computational methodology, techniques, models and steps involved in designing, components used and tools, softwares and databases used with their applications.

Keywords: Synthetic biology; Computational analysis; Softwares; Models; Genetic products

Introduction

Our biological system is composed of large number of molecular components. Of these components the most important are nucleic acids (DNA & RNA), proteins, carbohydrates, lipids, vitamins and minerals, water and ions. All these components have a specific degree of freedom, conformation and orientation. But the fundamental basic unit of these components is chemicals. It is well said that "Nothing in biology makes its own sense unless or until the evolution of life". This fact explains the application of mathematical concept in biology [1].

Synthetic biology is a branch with combination of biological sciences and engineering sciences. This discipline shares the ideas, principles, concepts, tools, features and objectives of both biology and engineering. It deals with the analysis, investigation, estimation and elucidation of dynamic interaction between genes and proteins in naturally occurring systems [2]. The general aspect of synthetic biology is shown in Figure 1.

Computational Methodologies and Approaches

Molecular modeling and computational methods are mathematical techniques employed to study the natural biological system; their kinetics and dynamics. Using algorithm, statistics and biological datas; these methods could be used for studying synthetic biological products. The types of computational analysis are discussed in Figure 2.

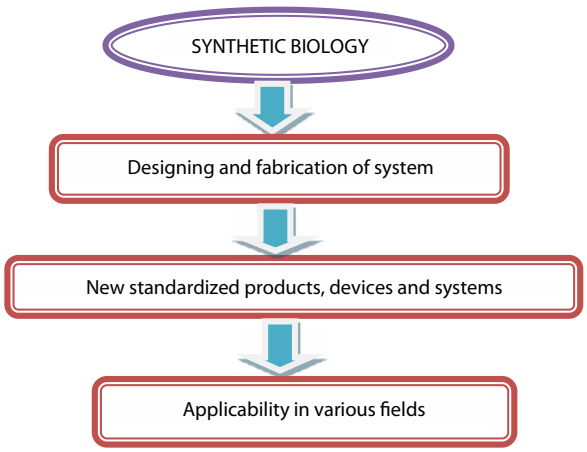

Figure 1: General synthetic biology.

Advantages of computational methodologies and synthetic biology [3,4]

1) Used to construct new genetic molecules [DNA &RNA] with newer biological behavior.
2) Mathematical modeling of biological science is possible through computational methods.
3) Used to build logical and informative architecture which is essential for vitality of life.
4) Applicable for synthetic gene regulatory network.
5) Can be written in algorithm form.
6) Provides detail mechanistic picture and view about dynamic behavior of biological system.
7) Posses strong predictive character.
8) Rational designing and engineering is possible.
9) Molecular kinetic and dynamic parameters can be determined through simulation approach.

Disadvantages of computational methodologies and synthetic biology [5]

1) Time consuming

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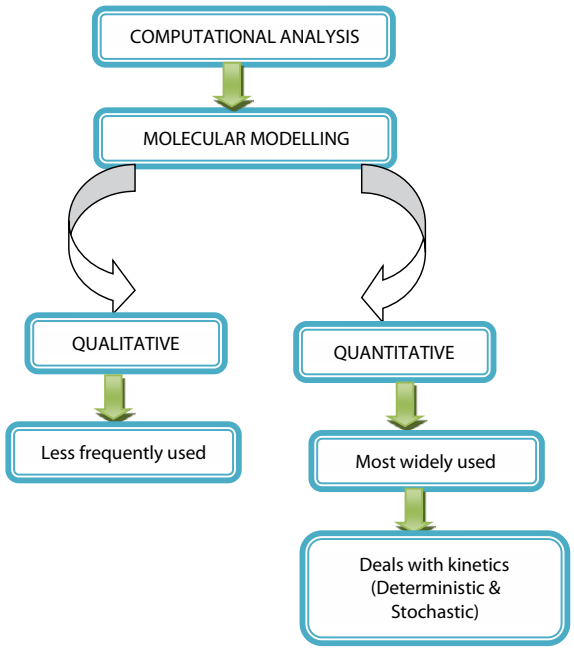

Figure 2: Types of computational analysis.

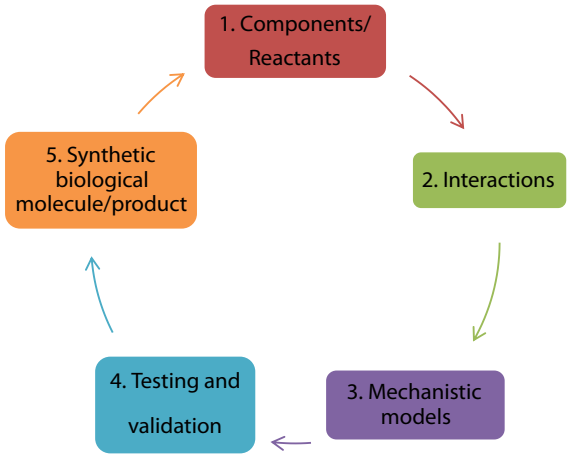

Figure 3: Steps in designing of synthetic biological compound.

2) Expensive

3) Lack of specificity and precision

4) Quantitative information and data is mandatory for synthetic biology; which is difficult to obtain.

Components used in designing of synthetic biological product

Designing of synthetically biological compound through computational approach uses Bottom-Up method and Circuit engineering analogy. The various steps in designing of synthetic biological product is shown in Figure 3. Synthetic biological products can be produced from bacterial species, yeast and mammalian cells. Thus, it is applicable for both simpler and complex organisms [6].

For a well-established synthetic model and construct the building block materials required are oscillator, switches, logical gates (AND) and comparators. Besides these components algorithm is used. In case of genetic product/molecule the required components are promoter sequence, operator sequence, ribosome binding site, termination site, reporter protein, activator protein and repressor protein. One of the most common examples of phenotypic synthetic biological construct is of Tetracycline which explains the transcription and translation process of protein synthesis both in presence and absence of tetracycline i.e. in OFF STATE and in ON-STATE [7-9].

Techniques of Computational Analysis

The multi-scale simulation of synthetic biology can be achieved from following methods:

- Slow Discrete Region [SDR]
- Slow Continuous Region [SCR]
- Fast Discrete Region [FDR]
- Fast Continuous Stochastic Region [FCSR]
- Fast Continuous Deterministic Region [FCDR]
- Hybrid Models [HM] [10]

Some of the methods of producing synthetic genetic circuits through engineering of above techniques is shown in Figure 4. The steps for designing synthetic engineered product through computational approach are explained in Figure 5.

Models used for synthetic biology

Based on the level of resolution and time scale the various models used in designing of synthetic biology are as under:

- ODEs – Ordinary Differential Equations
- PDEs – Partial Differential Equations
- SDEs – Stochastic Differential Equations
- MPS – Markow's Jump Process [11]

These models are used for simple and homogenous synthetic biology. Besides these models; SSAs – Stochastic simulation analysis, CMEs – Chemical Master Equations, LRT – Likelihood Ratio Test, AIC – Akaike Information criterion and BIC – Bayesian Information Criterion are used [12]. The detailed descriptions of these models are discussed in the article of McDonald James in year 2011.

Softwares used in synthetic biology

It is impossible to design a synthetically biological compound without the use of software. The software used for designing, computation and analysis of synthetic biology are known as the Synthetic Biology Software Suite (SynBioSS). This software is used for the generation, storing, retrieval and quantitative simulation of synthetic biological networks. It is open Source software which can run on Windows, Mac OS, and Linux/UNIX [13-15]. The list of tools, softwares and databases used in synthetic biology is discussed in Table 1.

Conclusion

With the advances in technology and high throughput screening, researches are shifting towards computational approaches for designing of genetic materials like DNA, RNA, nucleic acid, proteins etc. This system provides connectivity between kinetics and dynamics

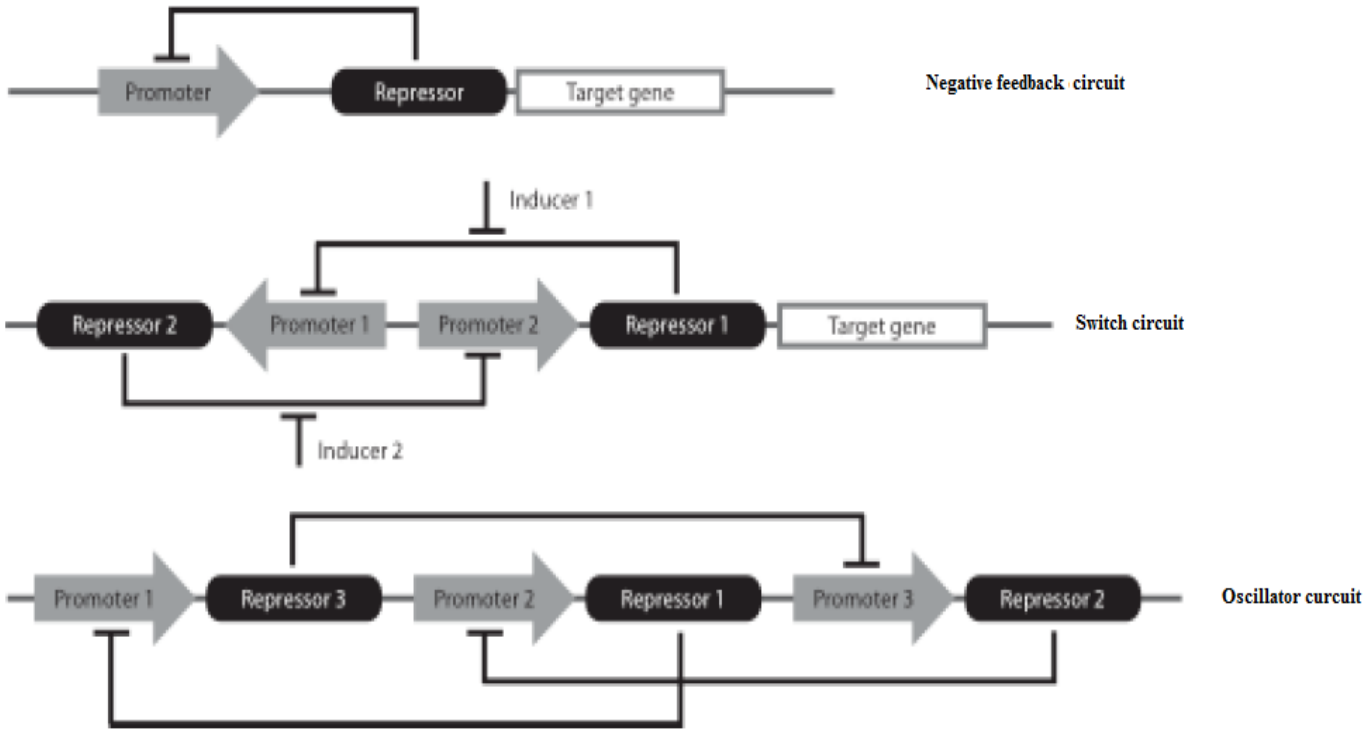

Figure 4: Techniques for producing synthetic engineered genetic circuits (Modified and adapted from Kevin Truong, [1].

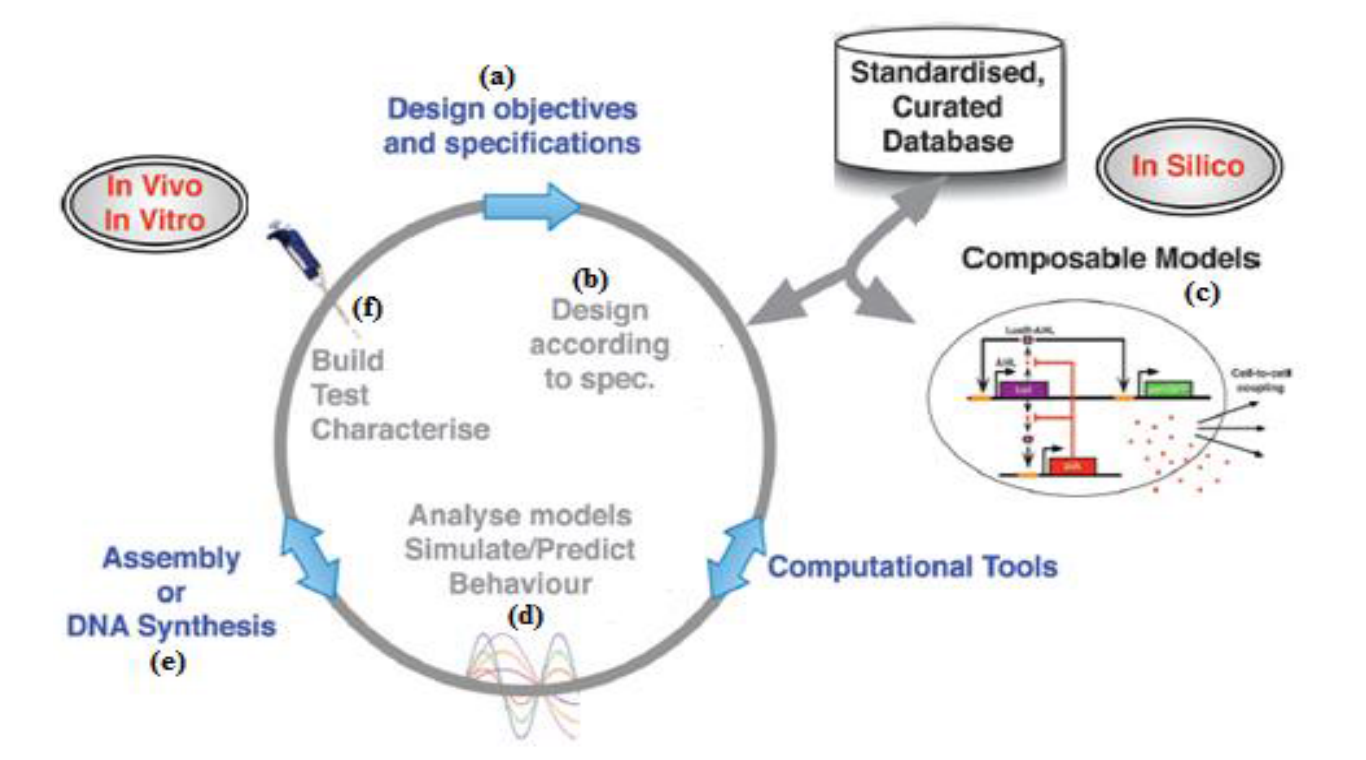

Figure 5: Steps involved in designing synthetic engineered product [Modified and adapted from Paul S. Freemont].

Tools	Application	Software	Application	Databases	Applications
Virtual Cell	For modeling and testing biological networks	BioSPICE	To access computational tools	BioModels	Contains peer-reviewed published quantitative models
STOCKS & stoch-Sim	Stochastic kinetic simulation tool used for biochemical process and chemical reaction	Cell Designer	For diagrammatic editing of biological networks	BRENDA	Contains information about properties and functions of enzymes
BioJake	Visualization tool for manipulating metabolic pathways	Gepasi	For modeling chemical and biochemical reaction networks	KEGG [Kyoto Encyclopedia of Genes and Genomes]	Contains information about gene function
CellWare	For deterministic and stochastic cellular events	Systems Biology Workbench (SBW)	For communication between software applications	ERGO (WIT)	Contains information for comparative analysis
COPASI	For simulation of biochemical events	Genetdes, RoVerGeNe	For automated circuit design	Alliance for Cellular Signaling (AfCS)	Contains information for studying signal process
Dynetica	To study kinetic model of dynamic network	GenoCAD, ProMoT	For GUI circuit designing	MetaCyc	Contains information about metabolic pathway of model organism
Pathway Tools	For creating model organism databases	ORBIT, RBS Calculator, PRODART	For biomolecular designing	BioSilico	Integrated web-based system for studying metabolic process and pathways

Table 1: Applications of tools, Softwares and databases used in synthetic biology.

interactions using mathematical and biological approach. This will be beneficial for betterment in biotechnological and medical fields. In future, it would be possible to study the behavior of higher level biological functions *in silico*. Modeling can generate design principles for rational biological engineering.

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