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Historical Perspective of Synthetic Biology in Food Production

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Abstract

Due to projections of population increase, which suggest that the world population will reach 8.6 billion people by 2030, as well as the reduction of existing natural resources, studies on food production technologies that minimize the impacts on the environment become relevant. In this context, with the creation of the first living organism controlled by a synthetic genome, since 2010, scientists from several countries study alternatives to produce energetic material and food through synthetic biology. Therefore, the present study sought to identify which the contributions, reflexes, trends and/or challenges of synthetic biology are in food production through a review of the literature. As results, it was noticed that there were significant advances in studies that seek forms of food production with the use of synthetic biology, as well as with technologies that reduce the use of natural resources and the impact of agricultural production on the environment. The topics of food safety, ethics and consumer perception, regarding the use of such technologies, are also emphasized. However, there is much to be studied on the subject, in particular, the need for experimental testing in different crops and processes due to food safety, and feasibility of the industrialization of such technologies.

Keywords

Food Security, Sustainability, Ethics, Consumer Perception, Bioeconomy

1. Introduction

In 1995, the scientist J. Craig Venter and his team began analyzing the sequence of *Mycoplasma genitalium*, an isolated pathogen from the genital and respiratory epithelia of primates, which has one of the smallest genomes of any free living organism and, as such, represented the perfect target genome to recreate. To confirm that this was in fact the minimum requirement for life, Venter and his colleagues initially synthesized the minimal genome, from which the next step would be to transplant it to a receptor cell to initiate the process that had never before been achieved in a laboratory [1].

The first advancement in the researches occurred in 2007, when the team deciphered the chromosome transplant stage, in which Venter and his team transformed one species of bacteria into another, and the confirmation of the success of the transplant was only achieved when the receptor cell began to adopt the physical characteristics of its chromosome donor [2].

However, only in 2010, the creation of the first living organism controlled by a synthetic genome, the *Mycoplasma mycoides JCVI-syn*1.0 bacteria were published [3]. To perform the conversion of a digitized DNA sequence, stored in a computer file, in a living entity capable of growth and self-replication, that is, to recreate life from scratch, an investment of US$ 40 million countless man hours was necessary [2].

In this way, from the discoveries made by Venter and his team, systems have been designed over the last few years, and have been used to manipulate information, build materials, process chemicals, produce energy, provide food, and help maintain or improve human health and the environment [4]. It means that the findings were presented as a promising preparation for the larger goal of transforming natural microorganisms, like bacteria, yeast, algae and viruses in synthetic, to perform predefined and specific functions.

However, the infinite possibilities that arise in detriment of the discovery, also point to relevant considerations about the development of techniques that are still poorly understood, which means weighing whether they would have more positive or negative results [5]. Our ability to project quickly and reliably biological systems which behave as expected remains limited [4].

With the understanding of this problem, this research aimed to identify the reflexes, contributions, challenges and/or trends of synthetic biology, focused on food production. Therefore, a systematic review of the literature was done, considering the scientific publications on this subject. In this way, besides the introduction, this article is composed by the session that deals about the method used to perform the research, which describes the data collection and analysis procedures and, consequently, exposes the results and discussions. Finally, the final considerations are presented, contemplating the limitations of the study and suggestions for future investigations.

2. Method

The research performed is a systematic review of the literature which aims to provide insights on the accumulated knowledge analysis in a set of studies [6], allowing the evaluation through the use of an explicit algorithm instead of the heuristic of systematization [7].

In this way, the structure proposed by Galvão and Pereira [8] was used, which provides: elaboration of the research question; search of the literature; articles selection; data extraction; evaluation of methodological quality; data synthesis (meta-analysis); evaluation of the quality of evidence; and writing followed by publication of the results.

The search for the studies that compose the analyzed portfolio was guided by the Zipf Law, Bibliometrics Law, which is based on the occurrence, incidence or frequency of words in the texts. As a database, the Web of Science was used, and the terms "synthetic biology", "food", and variations in agriculture, represented by "agric*", of which simultaneities are guaranteed by the term "and".

The search filter also included the document type, defining only articles, and, therefore, considered only empirical investigations, and so, the literature review documents were excluded. As a temporal limitation, the publications until the date of September 24, 2018 were considered. Thus, the portfolio of articles analyzed was composed of 13 (thirteen) documents.

Regarding the relevance of the studies, it was observed that, together, they have 413 (four hundred and thirteen) citations, of which the H index corresponds to 5 (five), and the average citations per item is of 31.77. It is noted that, even though the volume of studies published in 2017 has decreased, the citations of such studies have increased year by year since 2010, especially in the years 2016 and 2017.

After verifying the relevance of this theme, it was observed the way in which the scientific publications contemplated it, and the following interrogative question was defined as the guiding question of this research: what are the contributions, reflexes, trends and/or challenges of synthetic biology in food production? Therefore, a thorough reading of the studies, data synthesis, and the evaluation of evidence and results were done, seeking similarities between the analyzed studies. Finally, the findings were contrasted with the literature, aiming to explain the behavior of the phenomenon studied.

3. Results and Discussions

Endy [4] transcribes in his study the words of Szybalksi and Skalka that, in 1978, wrote about the relevance of the work in nucleases restriction, which led us to the new synthetic biology, allowing the description and analysis of not only existing genes, but also new genetic arrangements. However, the author claims that, twenty-seven years later, the engineering of synthetic biological systems is still an expensive, unreliable research process.

The author also proposes possible causes for the problem: the lack of sufficient knowledge about biological systems; that biological systems are too complex to be reliably designed; or both possibilities. The second possibility is the lack of fundamental technologies that could make the engineering of biology an engineering problem, that is, the engineering of biology remains complex because we have never simplified it. Success would help "create the discipline of synthetic biology: an engineering technology based on living systems".

Still according to Endy [4], our ability to quickly and reliably design biological systems that behave as expected remains limited. However, technologies that make biology engineering routine are necessary, as well as field research, and strategic leadership to ensure the development and application of biological technologies.

Thus, in 2010 Bar-Even end team, carried out a study that analyzed the carbon fixation, process by which Carbon Dioxide (CO_2) is incorporated in organic compounds, relevant for sustainability in the production of food and energy.

Through trials of 5000 metabolic enzymes, the authors have identified computationally alternate carbon-fixing pathways that combine existing metabolic building blocks from various organisms, suggesting that some of the proposed synthetic pathways could have significant quantitative advantages over their natural counterparts, such as general kinetic rate, making the process faster and more effective through the use of evolved organisms.

However, according to the authors, the implementation of such alternative cycles presents challenges related to levels of expression, activity, stability, localization and regulation and, therefore, should be explored so that they can be used as a way to improve the production of renewable food and fuels through metabolic engineering and synthetic biology.

Then, in 2013, You *et al.* [9] analyzed the enzymatic conversion of a single biomass vessel pretreated with starch by means of an unnatural synthetic enzymatic pathway from a compound from which the sources are originated from bacteria, fungi, and plants. The study aimed to increase the production of starch-rich cereals and cellulose-rich bioenergy plants with substantial growth potential, minimizing the environmental footprint of agriculture, conserving biodiversity, as well as meeting future world food needs, and sustainability for biofuels and renewable materials. As a result, the study presents an approach to next generation biorefineries, presenting a production model based on a trilemma: food, biofuel and environment.

As early as 2015, two (2) studies were carried out on the subject, being them the studies of Ort *et al.* [10] and Yang *et al.* [11]. Ort *et al.* [10] explores a series of prospective redesigns of plant systems at various scales aimed to increase crop productivity by improving photosynthetic efficiency and performance. However, the study points out the relevant tools and technologies for engineering photosynthesis, its possible applications and current limitations, only suggesting the realization of future projects, by which efforts must lead to new discoveries and technical advances with important impacts on the global productivity problem of crops and bioenergy production.

Likewise, Yang *et al.* [11] also apply efforts in photosynthesis research, but in crassulaceous (CAM), which presents nocturnal CO_2 uptake, facilitates increased water use efficiency, and allows CAM plants to inhabit environments with limited water, such as semi-arid or seasonally dry forests. The proposal suggests increasing dependence on CAM crops, such as Agave and Opuntia, for the production of biomass on semi-arid, abandoned, marginal or degraded agricultural land. Besides the use of the species to produce bioenergy, the study suggests the application in food and feed. However, in the same way as the study by Ort *et al.* [10], the authors state that there is still a long way to explore the potential of CAM crops and bioengineering, requiring the application of field tests and predictive models to evaluate crop productivity, mutant collection analysis, and data management.

In contrast to those findings, in 2016, with the exception of the study by Hoffman [12], which also deals with the engineering of C4 photosynthesis of rice as well as the engineering of wheat and nitrogen fixation of rice, wheat and corn as ways of improving crop productivity, remediation environmental and soil conservation, soil and water, the other studies carried out that year present an emphasis on studies related to the metabolism of fungi and microbial organisms in synthetic biology.

According to Bills and Gloer [13], who analyze fungal species diversity and the diversification of biosynthetic gene clusters, there is an almost unlimited potential for metabolic variation and an untapped resource for the discovery of drugs and agrochemicals. They also point out that the analysis of genome sequencing, using computational tools and analytical chemistry, allows the rapid connection of groups of genes with their metabolic products. However, the study is a review that summarizes the general aspects of secondary metabolism of fungi, and, therefore, does not indicate results by means of applied experimental tests that allow to demonstrate new methodologies that can be replicated. Nevertheless, it suggests that in the same way that secondary metabolites exhibit a variation in chemical structures and biological activities that may benefit humans, animals and plants, they can also lead to contamination. Therefore, highlighting important metabolites derived from fungi that contributed for human health and agriculture could negatively impact crops, food distribution and human environments.

Likewise, Sivasubramaniam and Franks [14] approach the subject of synthetic biology through microbial communities under a theoretical bias, focusing on public perceptions and expectations of individuals with respect to such technology, their potential to help, disrupt and disgust. As results, the authors have identified that public perceptions and expectations of “naturalness” as well as notions of disgust and dread can delay the development of such technologies to their full benefit.

In contrast, fearing the possible negative consequences of the use of synthetic biology technologies, Li *et al.* [15], carry out an experimental study, by which they analyze the 4-hydroxymandelic acid (4-HMA), an aromatic and widely used chemical in the production of pharmaceuticals and food additives by which the production process is environmentally hostile. The authors provide a promising route of biomanufacturing to produce 4-HMA from lignocellulosic biomass as a 4-HMA production approach from renewable and sustainable resources, making the process less aggressive to the environment.

In addition, as a response to concerns about food safety and the environment, in 2017, the studies carried out focus on the analysis of threats to human, animal and ecosystem health, as well as analyzing the acceptance or rejection of the technologies and their application to the consumer. In this context, Heavey [16] analyzes the ethics of synthetic biology from a consequentialist perspective, examining the potential effects on food, agriculture, medicine, fuel, and the advancement of science.

In opposition to the previous study, Bereza-Malcolm *et al.* [17] examined the widespread presence of cadmium in soil and water systems as consequence of industrial and agricultural processes causing environmental contamination and posing a significant threat to human health. Thus, based on this research problem, the authors developed a microbial biosensor, used for in situ detection of cadmium, which allows to reduce human exposure, complementing traditional analytical methods. Then, the biosensor construction was tested on several bacteria, responding satisfactorily. However, the authors highlight the importance of biosensor testing using synthetic biology principles in different bacterial genera.

Finally, in the context of food insecurity, Frewer [18] also analyzes the acceptance or rejection of the consumer of emerging agro-food technologies and their applications, analyzing case studies (pesticides, genetic modification of plants and animals, nanotechnology in agriculture, nutrigenomics in nutritional safety and synthetic biology) considered along a time axis (from the 1950s to 2017). As a result, the author identified that experts and regulators have increasingly recognized the importance of the role of perceptions of risk and benefit, and the normative assumption that consumers are "anti-food technology" is rejected.

Thus, it is clear that the contributions, reflexes, trends and/or challenges of synthetic biology follow a temporal sequence. In 2018, the resumption of experimental studies of new technologies can be observed, as well as the emergence of the bioeconomics approach, bringing the synthetic biology into the sustainable industrial area.

In this context, one of the studies analyzed was that of Grewal *et al.* [19] dealing with the bioproduction of a betalain color palette in Saccharomyces cerevisiae in a synthetic way. Betalains are a family of natural pigments found exclusively in the order of Caryophyllales plants, used as a natural food dye. The study presents the first complete microbial production of betanin in Saccharomyces cerevisiae with a fermentation process that allows faster production of this natural dye. Thus, the work establishes a platform for the microbial production of betalines of various colors as a potential alternative to resource-intensive agricultural production and land.

The second study analyzed was that of Lokko *et al.* [20] linking biotechnology and the bioeconomy to inclusive and sustainable industrial development. It addresses the contribution to the development of agribusiness through the use of biotechnology and the bioeconomy, suggesting interventions through: inputs and agricultural mechanization; modern processing technologies; packaging of perishable products; promotion of food safety in the processing and regulatory environment; and interventions to improve the competitiveness and productivity of production chains. Thus, the authors move from purely biology/engineering studies and process execution to an analysis of the economic and financial viability of these technologies to fit the industrial context.

Thus, as a way of synthesizing the results of the studies, making it easier to visualize a general perspective about the theme and its evolution over the last years, **Table 1** is presented, which allows an understanding of the context of the theme from 1978 to 2018.

Therefore, from the perspective of Endy in 2005 [4], it can be seen from the present analysis, displayed in the format of a time evolution, that thirteen years later, advances are presented in studies that seek ways of producing food using biology supply of food, in the face of a growing trend of such needs in the coming decades. In the same way, the studies presented point to the growing concern about the efficient use of natural resources, which, with increasing population and increased food needs, tend to become increasingly scarce, which evidences the growing need for the sustainability analysis of these new processes. However, there is much to be done on the subject, especially with regard to innovations, new products, new methods of applying synthetic biology for food production, as well as the analysis of the impacts of this production, food safety, disease control, or effects that they may cause to ecosystems, or in relation to consumer perception of such technologies.

Finally, through the results obtained in the present study, it was also possible to create a framework, as shown in **Figure 1**, which presents the themes already related to synthetic biology and its use in food production in the literature. **Figure 1** also presents the themes that are disconnected from synthetic biology, however, there is a lack in the scientific environment of deepening them in the context of synthetic biology in food production.

4. Final Considerations

The guiding research question of the present study sought to identify the contributions, reflexes, tendencies and/or challenges of synthetic biology in food production.

In this context, when analyzing the studies that compose the portfolio of the present review, it can be verified that the studies carried out between 2010 and 2018 involve the testing and analysis of processes, techniques and methodologies for the development of synthetic organisms and their applications in various objects, with a view to sustainable production, be it food, energy, medicines, agrochemicals or others. Although the studies present advances in the area, they suggest the deepening of the theme by researchers from different areas, with a view to filling gaps or improving the findings, thus suggesting the possibility of significant future discoveries.

It is also evidenced that the studies, although filtering the theme of food production, whether for human or animal consumption, also address the use of

Table 1. Time evolution of the theme.

Year	Authors	Authors' contributions
1978	Arber, Nathans and Smith	Discovery of restriction enzymes and their application to problems of molecular genetics. Nobel Prize in Physiology or Medicine 1978
1978	Szybalski and Skalka	Work on restriction nucleases, which led us to new synthetic biology, allowing the description and analysis not only of existing genes, but also of new genetic arrangements.
1995	J. Craig Venter *et al.*	Beginning of sequence analysis of *Mycoplasma genitalium*
2005	Endy	Ability to quickly and reliably design biological systems that behave as expected remains limited.
2007	J. Craig Venter *et al.*	Deciphering of the chromosome transplant stage. The turning of one species of bacteria into another.
2010	J. Craig Venter *et al.*	Creation of the first living organism controlled by a synthetic genome, that is, the bacterium *Mycoplasma mycoides* JCVI-syn1.0.
2010	Bar-Even, *et al.* [1]	Use of synthetic organisms for improvements in the carbon sequestration process. Higher speed and effectiveness in the process compared to the process performed with natural organisms.
2013	You *et al.* [9]	Creation of a production model based on a trilema: food, biofuel and environment, through the enzymatic conversion of unnatural synthetic biomass. It aims to increase production, minimizing the environmental footprint of agriculture, conserving biodiversity.
2015-2016	Ort *et al.* [10] Yang *et al.* [11] Hoffman [12]	Use of synthetic organisms for engineering of photosynthesis aimed to: increase crop productivity; increase efficiency in water use; biomass on semi-arid, abandoned, marginal or degraded agricultural land; application in bioenergy, food and feed; environmental remediation; and conservation of land, soil and water.
2016	Li *et al.* [15]	Experimental study analyzing 4-hydroxymandelic acid (4-HMA), presenting a production approach from renewable and sustainable resources, reducing the impact caused in the environment.
2016	Bills and Gloer [13]; Sivasubramaniam and Franks [14]	Analysis of the metabolism of fungi and microbial organisms. They emphasize the potential of the technologies, yet point out the need for studies on food safety, public perceptions and expectations of individuals regarding such technology.
2017	Heavey [16] Frewer [18]	Analysis of the consequences of such technologies: ethics; food safety; perceptions of risk and consumer benefits; acceptance or rejection of emerging agro-food technologies.
2018	Grewal *et al.* [19] Lokko *et al.* [20]	Resumption of experimental studies of new technologies, as well as the approach of the bioeconomics theme, bringing the topic of synthetic biology into the sustainable industrial area.

synthetic biology and engineering for the production of bioenergy materials, including ways of using waste food and feed as an alternative to sustainable production.

As a similarity between the studies analyzed, the objective was to identify methods of producing food and sustainable energy, with a view to minimize the impact of human population growth, which brings with it challenges related to

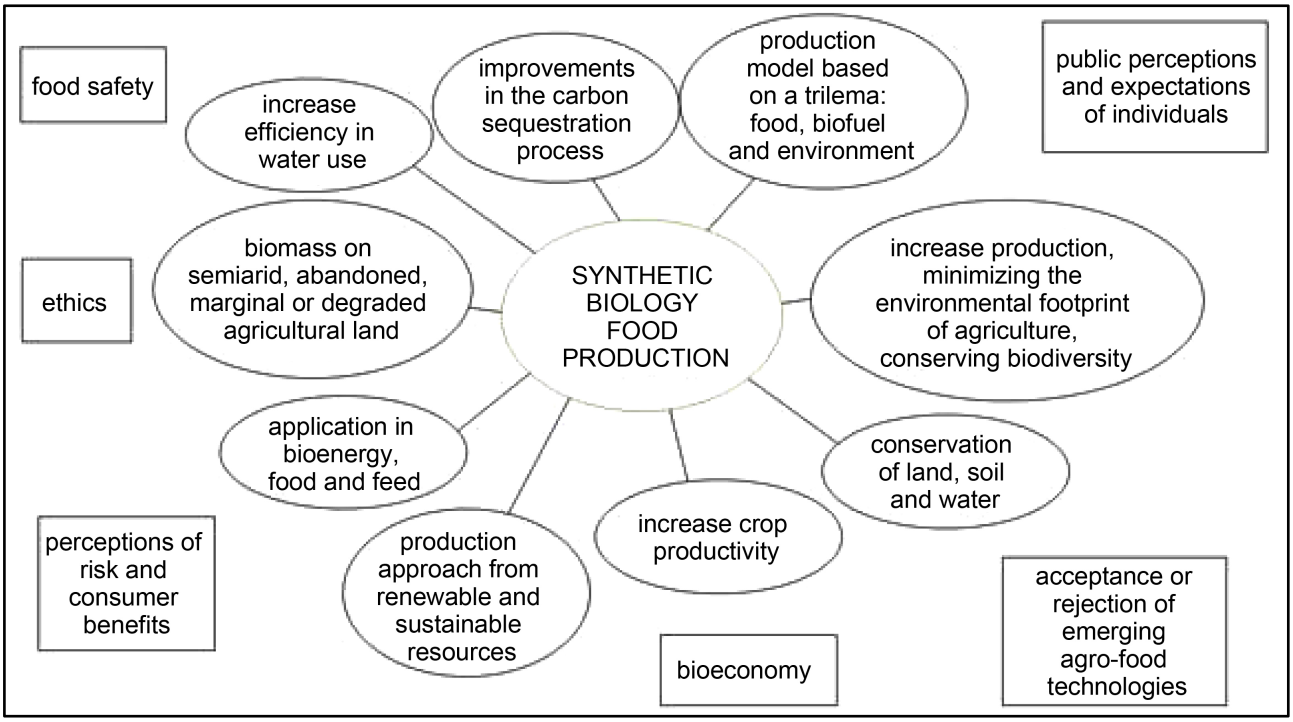

Figure 1. Related themes and disconnected themes to synthetic biology.

the increase of food production, fodder, fiber and fuel.

In addition, there is also a concern for world food security, in view of the use of fungi, bacteria and microbial organisms, which, in the same way can bring benefits to humans, animals and ecosystems, can also trigger serious reactions when analyzed in a substantial way.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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