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Research review paper

Production of biofuels and biochemicals by in vitro synthetic biosystems: Opportunities and challenges

Yi-Heng Percival Zhang *

Biological Systems Engineering Department, Virginia Tech, 304 Seitz Hall, Blacksburg, VA 24061, USA
Cell Free Bioinnovations Inc., Suite 1200B, 2200 Kraft Drive, Blacksburg, VA 24060, USA
Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, 32 West 7th Avenue, Tianjin Airport Economic Area, Tianjin 300308, China

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ABSTRACT

The largest obstacle to the cost-competitive production of low-value and high-impact biofuels and biochemicals (called biocommodities) is high production costs catalyzed by microbes due to their inherent weaknesses, such as low product yield, slow reaction rate, high separation cost, intolerance to toxic products, and so on. This predominant whole-cell platform suffers from a mismatch between the primary goal of living microbes – cell proliferation and the desired biomanufacturing goal – desired products (not cell mass most times). In vitro synthetic biosystems consist of numerous enzymes as building bricks, enzyme complexes as building modules, and/or (biomimetic) coenzymes, which are assembled into synthetic enzymatic pathways for implementing complicated bioreactions. They emerge as an alternative solution for accomplishing a desired biotransformation without concerns of cell proliferation, complicated cellular regulation, and side-product formation. In addition to the most important advantage – high product yield, in vitro synthetic biosystems feature several other biomanufacturing advantages, such as fast reaction rate, easy product separation, open process control, broad reaction condition, tolerance to toxic substrates or products, and so on. In this perspective review, the general design rules of in vitro synthetic pathways are presented with eight supporting examples: hydrogen, n-butanol, isobutanol, electricity, starch, lactate,1,3-propanediol, and poly-3-hydroxylbutyrate. Also, a detailed economic analysis for enzymatic hydrogen production from carbohydrates is presented to illustrate some advantages of this system and the remaining challenges. Great market potentials will motivate worldwide efforts from multiple disciplines (i.e., chemistry, biology and engineering) to address the remaining obstacles pertaining to cost and stability of enzymes and coenzymes, standardized building parts and modules, biomimetic coenzymes, biosystem optimization, and scale-up, soon.

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* Corresponding author. Tel.: +1 540 231 7414.
E-mail addresses: ypzhang@vt.edu, profCH2O@outlook.com.

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1.Introduction

The sustainability revolution is taking place in this century mainly due to concerns of depleting fossil fuels and climate changes. At the same time, growing world population and increasing living standards require more natural resource consumption. Biomass produced from terrestrial plants is the most abundant renewable bioresource, approximately five times global energy consumption (Zhang, 2013). Biomass and its carbohydrates are the sole cost-competitive energy and carbon sources that will be converted to produce biofuels and biochemicals instead of fossil fuels (Wyman, 1999). Compared to low energy concentration (i.e., nonpoint) solar energy, biomass is a concentrated chemical energy, which could be harvested, stored, transported, and converted to other chemical energy forms relatively easily (Zhang, 2011c).

Human beings had utilized living whole-cell microorganisms for making numerous fermentative products for thousands of years. Living whole-cell fermentation is the predominant biomanufacturing platform (Fig. 1a). However, the primary goal of microorganisms is their proliferation while bioconversions are the side effects. Recent advances in synthetic biology and systems biology present numerous breakthroughs, such as the production of non-natural products (e.g., 1,4-butanediol (Yim et al., 2011), and isobutanol (Atsumi et al., 2008)). However, some inherent constraints of living microorganisms (e.g., net ATP generation, intact cellular membrane) prevent them from implementing some important chemical reactions, for example, 12 H_2 production from one glucose and water.

Whole cell lysates (Fig. 1b) have been used as an important scientific tool to investigate complicated biological reactions for more than 100 years. For example, Eduard Buchner discovered that the yeast lysate converted glucose to ethanol (Buchner, 1897). Due to his paradigm-shifting discovery, he won the Nobel Chemistry Prize in 1907. Later, numerous scientists applied this tool to discover and study natural metabolic pathways. For example, Harden et al. discovered key enzymes in glycolysis (Nobel Chemistry Prize 1929), Calvin elucidated the CO_2 assimilation in plants (Nobel Chemistry Prize 1961), and Nirenberg and Matthaei interpreted the genetic code and its function in protein synthesis (Nobel Physiology Prize 1968) (Matthaei et al., 1962). Recently, cell-free protein synthesis has been suggested to be the fastest way to make recombinant proteins, even for membrane or complicated proteins (Carlson et al., 2012; Swartz, 2013). Cell-free protein synthesis has been scaled up to 100 l levels recently (Hodgman and Jewett, 2012).

In vitro synthetic biosystems emerge as a manufacturing platform by the assembly of numerous enzymes and enzyme complexes from different sources and/or (biomimetic) coenzymes (Fig. 1c). Such systems could surpass the constraints of whole-cells and cell lysates for implementing some biological reactions that microbe cannot do, for example, high yield production of hydrogen (Martín del Campo et al., 2013), or enzymatic transformation of cellulose to starch (You et al., 2013). Although in vitro synthetic biosystems are on their early stage, they have a great potential to becoming a disruptive biomanufacturing platform, especially for low-cost production of biofuels and biochemicals. Table 1 presents the comparison of biomanufacturing advantages between whole cell-based fermentations and in vitro (cell-free) synthetic systems, from product yield, volumetric productivity, reaction condition, product separation, product titer, product purity to process control and optimization. Among them, three key criteria of biomanufacturing are (i) product yield mainly related to feedstock cost, (ii) volumetric productivity (or reaction rate) mainly related to capital investment, and (iii) product separation (or product titer) mainly related to processing costs.

The history of biomanufacturing platforms accompanied with key milestones is presented in Fig. 2. Before Louis Pasteur clearly proposed the theory of biogenesis (1864), human beings had used microorganisms

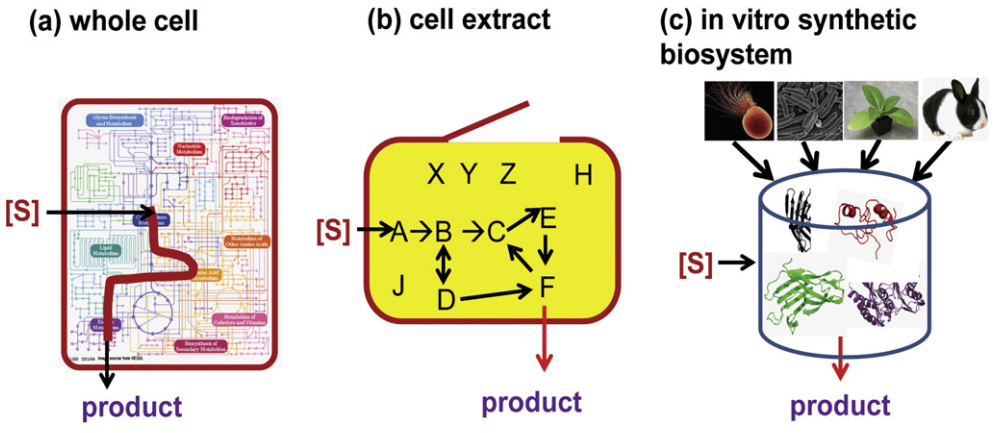

Fig. 1. Schemes of biotransformation catalyzed by whole cell (a), cell extract (b), and in vitro synthetic biosystem (c).

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