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Dr. Papoutsakis received his Diploma in Chemical Engineering from the Nat. Technical Univ. of Athens, Greece, and his MS and PhD from Purdue University, IN (USA). Following the completion of his PhD, he started his academic career at Rice University in Houston, Texas as an Assistant Professor, and in 1987 moved to Northwstern University, Evanston, IL, USA, where he was promoted to full professor and eventually appointed to a Walter P. Murphy Chair Professorship. In 2007, he moved to the University of Delaware as Eugene DuPont Chair Professor. Papoutsakis' group is active and has made important contributions in the areas of clostridia genetics and metabolic engineering; animal-cell biotechnology & stem-cell bioengineering with emphasis in hematopoietic stem-cell engineering. He is widely recognized as a leader in metabolic engineering of the industrial anaerobes clostridia as well as in genome engineering. His lab is interested in developing strains of industrial importance in the biorenewable arena, with emphasis on complex, non-pathway dependent traits.

Biofuels research in the 2015 economic environment: when the going gets tough

The importance of metabolic engineering, synthetic biology, and the molecular and biophysical dissection of cell physiology for the development of technologies to produce fuel molecules by biological routes is firmly established. This collection of reviews captures some of the most active areas of research on microbial biofuel production, including promising, emerging concepts. Biofuel production from renewable biomass has attracted an enormous attention worldwide for its promise to pave the way towards energy sustainability. Despite the large and intense efforts and investments of the last 10+ years, it has proven to be difficult to achieve industrial-biofuels production beyond biogas, ethanol and plant-seed derived biodiesel. Production of biofuels from cellulosics is recently facing additional headwinds from two sources. One is the increasing abundance of natural gas worldwide and especially in the US, which has resulted in dramatically reduced methane prices. A more recent one is the dramatic drop in prices of petroleum oil, by more than 50% in the last few months. These developments accentuate the need to relentlessly improve the economics of biofuel production from renewables by addressing high substrate costs, low yields, low titers, and high separation costs. Business as usual clearly is not an option in this competitive environment. Instead, there is a clear need to re-assess the successes and re-direct the priorities to solve the essential issues that prevent bioenergy technologies from reaching the marketplace. We are optimistic that these issues can be resolved, and that intensive innovation of bioenergy technologies will contribute to a sustainable energy generation model for the world.

Virtually all issues that limit industrial-scale production of biofuels are explored in this collection: what is the basis of cell toxicity that limits titers of biofuel molecules in microbial cultures; how can we reduce substrate costs (which account for more than 65% of the total production costs); how can we explore new abundant substrates, such as sunlight, organic waste streams, biogas and natural gas, and how can we simplify process configurations by integration of feedstock pretreatment, fermentation and product recovery. At the same time, pathway engineering, including the modification of existing pathways, the development of totally synthetic pathways, and the optimization of new and old pathways for *in vivo* product fluxes, remains an active area of R&D, and several papers of this collection address critical issues in this field of bioenergy production.

Optimizing the capabilities of native producers based on physiological, energetic and ecological analyses

In terms of product volume, 'first-generation', yeast-based bioethanol production is currently the largest pure-culture industrial biotechnology

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Jack Pronk (1963) holds an MSc from Leiden (Plant Molecular Biology) and a PhD from Delft (Microbiology). In 1991, he joined the Delft Industrial Microbiology group as assistant professor. In 1999, the TU Delft appointed him Antoni van Leeuwenhoek Full Professor. Jack was co-founder and, from 2002 to 2013, scientific director of the Kluyver Centre, a public–private partnership focused on Genomics research on key industrial microorganisms. Jack's research integrates quantitative analysis of metabolism and its regulation in industrial microorganisms with improvement of their performance via advanced metabolic engineering and laboratory evolution. Research in his group on understanding and engineering of central carbon, redox and energy metabolism in *Saccharomyces cerevisiase* has contributed to the development of this yeast into a multipurpose cell factory for production of a wide range of compounds.

process. Ethanol production, in which the ethanol yield on the carbohydrate feedstock (e.g., corn starch or cane sugar) is a key cost-determining parameter, has already been intensively optimized over the past decades. The contribution by Gombert and Van Maris ''Improving conversion yield of fermentable sugars into fuel ethanol in 1st generation yeast-based production processes'' [1] demonstrates that, even in this highly optimized process, engineering of central metabolism has recently led to new strategies for further improvement of conversion efficiencies. In particular, metabolic engineering of redox and energy metabolism in yeast has recently led to significant improvements of the ethanol yield, based on reduction of glycerol and biomass production, respectively.

In their exceptional review ''Ethanol production by engineered thermophiles'' Olson *et al.* [2] analyze the current state of the art in the development of strains to enable ethanol production at high temperature. Thermophilic ethanol production has been viewed for many years as an important technological goal that could lead to substantially reduced production costs largely deriving from the reduced ethanol separation at higher temperatures. Their analysis shows that while cell engineering has improved the productivities of thermophilic ethanol producers, engineering non-ethanol producing thermophiles remains a major challenge.

Fast *et al.* [3] ''Mixed substrate fermentation: novel options for yield improvement in biofuels production'' engage detailed yield calculations and analysis of the literature to argue for the concept of *mixotrophy* as essential for the successful engage acetogens in biofuel production. Acetogens are anaerobic prokaryotes that utilize the celebrated Wood-Ljungdhal pathway to grow on mixtures of CO_2, CO and H_2 (all are syngas components) while producing small amounts of acetate and ethanol and traces a few more metabolites. The ability to fix CO_2 and use these syngas components has the potential to not only use waste gases and reduce CO_2 emissions from fermentation processes, but, significantly, it can dramatically increase the yields of metabolites from carbohydrates when gases are used as co-substrates.

Most currently investigated processes for biofuels production are based on aseptic, pure-culture processes, often involving genetically engineered microorganisms. Mooij *et al.* ''Ecology-based selective environments as solution to contamination in microalgal cultivation'' [4] outline a new, radically different approach. Rather than engineering natural producers for improved production, these authors advocate the use of open cultivation systems, in which carefully designed process conditions and feeding regimes favor the selection of high-producing microbial communities. They illustrate this concept by discussing the selection of lipid-high-producing algae ('survival of the fattest') via dynamic feeding regimes and conclude that use of simple, open cultivation systems and low cost feedstocks offers attractive possibilities to dramatically reduce the costs for biofuels production.

Synthetic product-formation pathways: chemistries, bottlenecks and implementation challenges

Metabolic engineering offers unique possibilities to express pathways for efficient production of naturally occurring compounds in hosts with attractive properties for large-scale industrial production. An industrially relevant and deceptively simple example of this approach is the expression of pathways for the production butanol isomers in bakers' yeast. In ''Metabolic engineering of Saccharomyces cerevisiae for production of butanol isomers'' Generoso *et al.* [5] present an excellent overview of recent progress in research on this intensively studied subject. Their contribution identifies