Bridging the gap between gene and product

Biochemical engineering

Editorial overview

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The beginning of the 21st century has witnessed an explosion of activity in the field of genomics. This development will have a direct impact on biochemical engineering, which has been undergoing an evolution since the last decade of the 20th century. Biochemical engineers have always served as a bridge between discoveries involving enzymes, cells and biomass at the lab scale to implementation of valuable bioproducts on the commercial scale. In the past 15 years, a plethora of commercial products based upon recombinant DNA technology has emerged, many of which are therapeutic proteins. Improvements in bioprocess design by the biochemical engineer required more intimate knowledge of the driving forces of the technology: genes, enzymes, and cells. In the same time frame, the training of biochemical engineers, which historically provided a holistic view of biochemical systems through quantitative experimental and mathematical descriptions, expanded to also include basic understanding of the tenets of molecular biology. Biochemical engineers have the skills to not only develop processes for chemical and materials based upon molecular biology, but to influence the conception and development of new technologies through organization and synthesis of complex biological phenomena.

The profusion of genome-sequencing projects in progress will lead to the discovery of genes for new enzymes. As acknowledged by many in the research community, the emerging challenge will be to connect gene to function, genotype to phenotype. This review naturally leads to the second gap between mRNA levels and those of their corresponding proteins. In groundbreaking work, Hatzimanikatis and Lee [1] have shown mathematically that expression patterns from both mRNA and proteins are required to understand a gene network. In a parallel set of reviews, Lee and co-workers have provided details of genomic analysis and proteomic analysis. In the first article, Lee and Lee (pp 171–175) review the latest technologies for genome sequencing and for high-throughput techniques for investigation of gene expression. With an eye for quantification, they comment on computational approaches to supplement experimental approaches in relating genotype to phenotype. This review naturally leads to the second review on proteomics by Dutt and Lee (pp 176–179). A key bottleneck in proteomics is the development of technology to quantify synthesis rates, expression levels, and post-translational modification of proteins accurately in a high-throughput manner.

The complexity and enormous volume of data resulting from the genomic era points to the need for mathematical approaches to establish links between genes and their function. Major advances have been made in the ‘downstream’ part of the chain, that is, the mathematical modeling of metabolism from a defined metabolic grid. The group of Nielsen has made significant progress in the area of modeling of steady-state metabolism through the development of metabolic network analysis (MNA) [2]. MNA combines the widely used metabolic flux analysis with isotopic labeling experiments for a more reliable estimation of intracellular fluxes, as well as analysis of the metabolic pathway structure and compartmentation of enzymes and metabolites. In their review, Gombert and Nielsen (pp 180–186) assess critically the steady-state stoichiometric mathematical models and the more powerful dynamic kinetic models. In particular, they highlight the difficulties in dynamic modeling of regulatory and control aspects of metabolism, which are currently limited by incomplete characterization. They suggest that these issues will be resolved with further development of functional modeling of genetic networks (e.g. [1]).

The heart of biochemical engineering in practice is to enable the commercial production of chemicals, materials, and biomolecules. The National Research Council Report on Biobased Industrial Products [3], released in late 1999, emphasizes increasing the use of biological raw materials to make ‘biobased industrial products’, thus helping to achieve long-term sustainability for global economic systems. New technologies and products shaped by the
Biological sciences in close concert with engineering are cited as being necessary for bringing this objective into reality. The remaining four reviews in this section cover applications where genetic manipulation has been used to produce novel products.

Lignocellulosic materials are one of the most abundant renewable resources. Although a significant portion of lignocellulosic materials can be converted into glucose and pentose sugars such as xylose, only glucose can be efficiently fermented by microorganisms. The development of bacteria or yeast that can efficiently ferment both hexose and pentose sugars is needed before the use of lignocelluloses as carbon sources becomes commercially useful. In pioneering work, Aristidou et al. [P1] have applied metabolic engineering tools to construct yeast strains that have improved capabilities in fermentation of the pentose sugar xylose. In the review by Aristidou and Penttilä (pp 187–198), the challenges in the construction of bacteria and yeast strains that can efficiently convert both glucose and pentose sugars to valuable compounds are described, as well as novel approaches to using microorganisms to depolymerize lignocellulose. The importance of the genomic data as a potential source of new biocatalysts is highlighted.

The use of transgenic plants for the production of foreign proteins is an area of intense commercial interest. Post-translational processing, product recovery, and purification are key components in addressing the economic viability of plants as a source of therapeutic proteins. The majority of the cost of production is in separation of the protein from the plant biomass. Plant tissue cultures in bioreactors is an potential alternative technology to plants for the production of therapeutic proteins, offering less expensive product recovery costs as the proteins are secreted into the medium of the bioreactors. One of the first successful demonstrations of this concept [4] was accomplished by Doran (pp 199–204), who has contributed a careful review of the limitations and advantages of this potential technology compared to the intact plant for foreign protein production.

A major investment by pharmaceutical companies in the past decade has been to assess the potential of gene therapy. Viral vector-mediated systems are currently the most effective means of gene delivery and expression. As highlighted by recent clinical trials, however, toxicity and immunogenicity are weaknesses of the current viral vector methodology. A primary driving force for this potential technology is the design of safer and more site-specific vectors. In the design criteria for the construction of these improved vectors, ‘downstream’ bioprocessing considerations are often not considered, thus potentially limiting the production of high quality vectors and subsequently hindering the commercial impact. Progress in the design of vectors, packaging cell lines, and bioprocess operation is presented by Wu and Ataai (pp 205–208), leader of one of the pioneering groups in production of viral vectors [5].

Secondary metabolites are a major source of therapeutic molecules in the pharmaceutical industry. Metabolic engineering of secondary metabolism in microorganisms and directed evolution of enzymes that catalyze reactions in secondary metabolism have the potential to have a dramatic impact on the production of pharmaceutical products and intermediates. In a significant team effort, Buckland et al. [6], in collaboration with academic researchers, are metabolically engineering a new bacterial strain that can produce intermediates for the synthesis of a leading HIV protease inhibitor. Chartrain et al. (pp 209–214) provide a summarizing study of the challenges of metabolic engineering and directed evolution for the production of pharmaceuticals and intermediates. Particularly noteworthy in the review are the contrasting goals of drug discovery research, where a diversity of compounds need to be synthesized, versus bioprocess development, where a specific compound is desired. Also significant is the success of directed evolution in contrast to that of rational design in the optimization of enzyme characteristics.

The future holds tremendous promise as the genomic era progresses in the discovery of new products or improved methods of producing existing ones. The challenge in biochemical engineering will be to bridge the gap between the intellectual potential of the gene to the manufacturing of industrial products.

References


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