Chemical engineering: a root of systems biology and its impacts on biology, biotechnology, and medicine

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VIEWS & COMMENTS

Chemical engineering: a root of systems biology and its impacts on biology, biotechnology, and medicine

Jens Nielsen (✉)[1,2]

1 BioInnovation Institute, DK2200 Copenhagen N, Denmark
2 Department of Life Sciences, Chalmers University of Technology, SE41296 Gothenburg, Sweden

Chemical Engineering has played an important role in developing our modern society. Here, it is discussed how this discipline also has been a cornerstone for development of the field of systems biology, that has significantly impacted basic biological research, development of new biotechnological processes, and advancing human health in the last 10–15 years.

Engineering involves the application of the principles of science and mathematics to solve real world problems and to innovate new products and processes across a wide range of industries and applications. The basics of engineering involve three steps: (1) analysis with the objective of getting new insight and knowledge; (2) design of a new product or service or re-design of an existing industrial process with the objective of improving its performance; and (3) synthesis where the new product or process defined in the design phase is produced or implemented and thereafter evaluated.

Chemical Engineering developed as a separate discipline in the early 20th century in connection with the implementation of the Haber-Bosch process for production of ammonia and the Fischer-Thropsch process for conversion of syngas into hydrocarbons. In 1909 Fritz Haber demonstrated production of ammonia from air using a high-pressurized device and a catalyst, and when the invention was licensed to the chemical company BASF, Carl Bosch was assigned to develop an industrial process. He succeeded with this already in 1910, resulting in commercial scale production in 1913. The Haber-Bosch process has been essential for development of our modern society, as it is only through the large-scale production of ammonia to be used as fertilizer it has been possible to scale agricultural production with the increasing demand over the past 100 years. Fritz Haber received the Nobel Prize in Chemistry in 1918 and Carl Bosch received the same award in 1931. The Fischer-Tropsch process was developed in 1926 by Franz Fischer and Hans Tropsch, both working at the Kaiser-Wilhelm Institute for Chemistry, now a Max Planck Institute. They filed several patents based on their work and licensed these to the German company Brabag that developed a commercial process. This was important for Germany during World War 2 as the country was petroleum-poor but coal-rich, and with the Fischer-Tropsch process syngas, a mixture of carbon monoxide and hydrogen formed from coal through liquefaction, can be converted to hydrocarbons that can be used as liquid transportation fuels. Processes were also established in many other countries, and the Fischer-Tropsch process is still applied in some countries, even though it has become less popular due to its heavy CO_2 footprint. The Fischer-Tropsch process is based on heterogeneous catalysis, and it is therefore more complex than the Haber-Bosch process, and there has been many refinements and improvements of the process since the first plants were established.

The Haber-Bosch and Fischer-Tropsch processes represent cornerstones in development of the chemical industry, and imposed requirements for development of complex catalysts as well as efficient separation processes. This imposed a requirement for a more analytical approach to process design, and in the 1960s this resulted in introduction of mathematical frameworks for describing chemical processes. Hereby chemical engineering education moved from having focus on learning about unit operations to a much more rigorous focus on quantitative description of the individual processes. Rutherford Aris at the university of Minnesota was an important driver of this development as he developed a rigorous modeling framework for describing chemical reactors, whereas Edwin Lightfoot at the university of Wisconsin was an important driver for development of a mathematical framework for transport processes playing key roles in separation. Many others contributed to this development, and it hereby became

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E-mail: JNI@bii.dk

possible to quantitatively analyze and design complex catalytical processes and different separation processes, and chemical engineering hereby developed into a science deeply rooted in mathematical modeling of chemical processes. This resulted in several new textbooks that became to define the essentials of modern chemical engineering, e.g., Transport Phenomena [1] and several different books by Aris (e.g., Aris [2,3]), as well as key journals like Chemical Engineering Science and AIChE Journal. These developments have enabled building the chemical industry as a very important pillar of modern society as it is responsible for efficient production of materials, agrochemicals, feed, and food ingredients, and fine chemicals used as ingredients in cosmetics and household products.

Aris and Lightfoot also embarked, together with others, e.g., Tsuchiya et al. [4], on developing mathematical frameworks for modeling biological systems, and this laid the root for advanced modeling of microbial fermentations [5]. These mathematical frameworks were to some extent ahead of their time, as experimental techniques for model validation were less developed.

With the development of techniques for whole genome sequencing as well as other high-throughput experimental techniques, often referred to as omics analysis, that has enabled parallel measurements of all (or most) mRNAs, proteins, and metabolites, it has become possible to obtain much deeper insight into cellular physiology and this has resulted in a revival of mathematical modeling of cellular systems. This has resulted in detailed mathematical models for dedicated biological processes, e.g., osmotic regulation in yeast [6] and single cell growth of the bacterium *Mycoplasma genitalium* [7]. Today the use of mathematical models for quantitative analysis of cells and cellular processes is referred to as Systems Biology.

Systems Biology has two historical roots: (1) from theoretical biology where mathematical models are used for analysis and simulation of biological processes, e.g., for description of cellular sub-systems; and (2) from genomics where mathematical models are used for analysis or integration of omics data. The first approach is often referred to as bottom-up systems biology as models are built from first principle of knowledge about a specific biological process, whereas the second approach is often referred to as top-down systems biology as it is aimed to integrate omics data with the objective of obtaining new insight into cellular function. Metabolic models evolved early as bottom-up models to describe metabolic sub-systems [8], but with the availability of genome sequences it became possible to reconstruct comprehensive metabolic network for cells, generally referred to as genome-scale metabolic models (GEMs). GEMs are truly rooted in chemical engineering principles as they rely on mass balancing around intracellular metabolites, and they represent a link between traditional chemical engineering disciplines and modern genome research. As discussed recently GEMs have demonstrated wide application for analysis and design of metabolism in basic biology, engineering biology, drug discovery, and biomarker identification [8].

GEMs have enabled much new insight into how the +1000 individual reactions operating in a typical cell interact and coordinate their function to ensure growth and proliferation of living cells. Furthermore, as GEMs are built in a bottom-up fashion from genomic information there is a link between each metabolic reaction, the enzyme that catalyze this reaction, the protein(s) that make up the enzyme, and the genes that encode these proteins. This means that it is easy to integrate omics data into GEMs and, e.g., identify how different parts of the metabolic network are activated at different environmental conditions. Using GEMs reconstructed for different yeast species it has also been possible to identify differences in metabolic features among different species and how these differences associate with environmental habitats of the species [9]. Similarly, reconstruction of GEMs for different experimental model systems, i.e., mice, rats, zebrafish, fruit flies, and nematode made it possible to identify commonalities and differences in metabolic functions between the model systems, which can be used for selection of the right model organism for a specific research project [10].

One area where GEMs have found wide application is in analysis and design of cell factories, e.g., microbial cells used for production of proteins and various other chemicals used as biofuels, materials, feed and food ingredients, and active biopharmaceutical ingredients (Fig. 1). Biobased production of chemicals has in the past 25 years grown to become a very large business [11], and GEMs has demonstrated use for improving existing bioprocesses such as ethanol production, design, and development of novel bioprocesses, e.g., production of 1,4-butanediol and various sesquiterpenes, and development of improved cell factories for production of enzymes and pharmaceuticals [8].

GEMs have also found wide application of studying human metabolism and hereby enable identification of novel biomarkers and drug targets (Fig. 1). Through analysis of transcriptome data, i.e., measurements of all mRNA present in a cell, in different kinds of cancer tissues and comparing expression in corresponding healthy tissues it was found that clear-cell renal cell carcinoma has a unique expression pattern compared with other cancers [12]. Based on further analysis it was identified that this was associated with altered expression of enzymes involved in glycosaminoglycans, and this led to identification of a novel systems biomarker based on measurement of 19 metabolites in blood and urine for detection of ccRCC [13]. Through further studies it was identified that a similar approach could be taken to identify a systems biomarker for multi-cancer detection

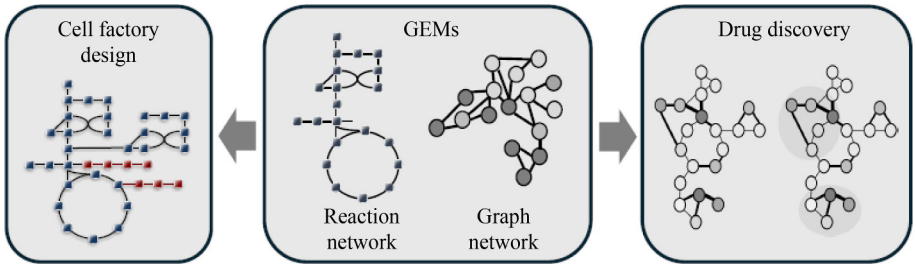

Fig. 1 GEMs are assembled from collection of all metabolic reactions occurring inside a cell. These form a metabolic network describing all the different reactions occurring within the cell, but they also represent a connection between metabolites, enzymes, and genes, and hereby also represent a graphical representation of the metabolic network. GEMs can hereby find two applications: (1) design of cell factories, where the metabolic model is used to simulate how flux through a new pathway can be improved or how the central carbon metabolism can be engineered to over-produce a specific metabolite in the network; (2) drug discovery or biomarker identification, where the graphical representation of the model is combined with omics data to identify co-regulated parts of the network (marked by gray circles on the graph to the right). This can be used to identify parts of the metabolism that is essential for function of, e.g., a cancer cell, and if the activity in this part of the pathway is inhibited by specific metabolites, then cell growth can be inhibited. This approach can also be used to identify biomarkers, as metabolites in the co-regulated parts of the network can be used as biomarkers for the disease.

[14]. GEMs can also be used for identification of novel drug targets, and in several cases, this has resulted in identification of new drugs that have been taken forward for clinical trials [8].

In conclusion, the fundamentals of chemical engineering have been essential for advancing the field of systems biology, and this field has significantly impacted basic biological research, biotechnology, and medicine. It is therefore important to maintain the solid chemical engineering education as this is the fundament not only for the chemical industry but also the rapidly expanding bioindustry, both in the area of engineering biology for solving societal challenges and in the development of novel medicines and health care solutions. Thus, chemical engineering will as it has played a central role in society over the past 100 years, continue to play an important role for improving human and planetary health in the future.

Competing interests The author declare that they have no competing interests.

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References

1. Bird R B, Stewart W E, Lightfoot E N. Transport Phenomena. Hoboken: John Wiley & Sons, 1960
2. Aris R. Vectors, Tensors, and the Basic Equations of Fluid Mechanics. Sudbury: Prentice-Hall, 1962
3. Aris R. Elementary Chemical Reactor Analysis. Sudbury: Prentice-Hall, 1965
4. Tsuchiya H M, Fredrickson A G, Aris R. Dynamics of microbial cell populations. Advances in Chemical Engineering, 1966, 6: 125–206
5. Nielsen J, Villadsen J. Bioreaction Engineering Principles. Cambridge: Academic Press, 1994
6. Klipp E, Nordlander B, Krüger R, Gennemark P, Hohmann S. Integrative model of the response of yeast to osmotic shock. Nature Biotechnology, 2005, 23(8): 975–982
7. Karr J R, Sanghvi J C, Macklin D N, Gutschow M V, Jacobs J M, Bolival B Jr, Assad-Garcia N, Glass J I, Covert M W. A whole-cell computational model predicts phenotype from genotype. Cell, 2012, 150(2): 389–401
8. Nielsen J, Petranovic D. Modeling for understanding and engineering metabolism. QRB Discovery, 2025, 6: e11
9. Lu H, Li F, Yuan L, Domenzain I, Yu R, Wang H, Li G, Chen Y, Ji B, Kerkhoven E J, et al. Yeast metabolic innovations emerged via expanded metabolic network and gene positive selection. Molecular Systems Biology, 2021, 17(10): e10427
10. Wang H, Robinson J L, Kocabas P, Gustafsson J, Anton M, Cholley P E, Huang S, Gobom J, Svensson T, Uhlen M, et al. Genome-scale metabolic network reconstruction of model animals as a platform for translational research. Proceedings of the National Academy of Sciences of the United States of America, 2021, 118(30): e2102344118
11. Nielsen J, Tillegreen C B, Petranovic D. Innovation trends in industrial biotechnology. Trends in Biotechnology, 2022, 40(10): 1160–1172
12. Gatto F, Nookaew I, Nielsen J. Chromosome 3p loss of heterozygosity is associated with a unique metabolic network in clear cell renal carcinoma. Proceedings of the National Academy of Sciences of the United States of America, 2014, 111(9): E866–E875
13. Gatto F, Nookaew I, Nilsson H, Maruzzo M, Roma A, Johansson

M E, Steiner U, Lundstam S, Volpi N, Basso U, et al. Measurements of glycosaminoglycans in plasma and urine for diagnosis of clear cell renal cell carcinoma. Cell Reports, 2016, 15: 1–15

14. Bratulic S, Limeta A, Dabestani S, Birgisson H, Enblad G, Stålberg K, Hesselager G, Häggman M, Höglund M, Simonson O E, et al. Noninvasive detection of any-stage cancer using free glycosaminoglycans. Proceedings of the National Academy of Sciences of the United States of America, 2022, 119(50): e2115328119