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OECD OUTLOOK ON INDUSTRIAL BIOTECHNOLOGY

TRENDS IN TECHNOLOGY APPLICATIONS

Abstract

This paper is about the state of the art and current trends of industrial biotechnology. It addresses biotechnological products and technologies in the chemical industry as well as the need for ecologically friendly and economical feedstocks. The potential of emerging synthetic biology and the options of combining biotechnological processes and chemical synthesis in producing new special and bulk products are discussed. Different partnering models supporting the realisation of industrial biotechnology and accelerating the transformation of the industry are presented including governmental initiatives. The status in different regions and the crucial topic of public acceptance is addressed as well.

1. Current Trends

1.1. Established Products of Industrial Biotechnology

Industrial Biotechnology provides biochemicals, biofuels and biomaterials. It is established since decades in the production of **biochemicals** for the pharmaceutical markets, food & feed, fine chemicals, detergents and hygienic products (Tab. 1). Ethanol is booming as **biofuel** since about 10 years[1] and **biomaterials** (*e.g.* poly-lactic acid, PLA) are an emerging field. The global annual sales volume of products produced by industrial biotechnology is about US$ 87 billion - equivalent to 6% of the worldwide chemical sales (2008; EUR[2] 2.535 billion).

Table 1: Examples of established biochemicals

Amino acids	**Lipids**	**Organic acids**	**Alcohols**	**Vitamins**	**Proteins**
L-glutamic acid L-lysine L-threonine	Phytosphingosin	Citric acid Lactic acid Itaconic acid	Ethanol	Riboflavin Cyanocobalamine	Amylase Phytase Antibodies

Most of these established products are available only by biotechnological processes because chemical synthesis offers no alternative. For proteins like enzymes or monoclonal antibodies as well as enantiomerically pure substances like L-amino acids biotechnological processes are the only choice.

1.2.1. Whole cell catalyst

The development of microbial cells as whole cell catalyst in an industrial process for a specific product aims on optimising productivity, yield and final concentration. In the early days of biotechnology accidental mutants were selected according to the process's demand. Today systems biology offers sophisticated tools to understand and engineer the production cell's metabolism.

An economical relevant example is L-lysine. It demonstrates how progress in academic and industrial R&D contributes to commercially successful bioprocesses. This amino acid is produced globally in a

volume of 1 million tons per year[3] primarily as feed additive[4]. The first amino acid (glutamic acid) excreting microorganism has been isolated in 1956[5]. Only a few years later the first fermentation process for L-lysine based on *Corynebacterium glutamicum* has been patented in 1961[6]. In the following years the lysine excretion has been enhanced stepwise by screening of mutants[7 8]. It took 20 years to understand at first the specific biosynthesis pathway[9 10] and later the active excretion of L-lysine[11 12 13]. The total metabolic flux is still a topic of investigation[14 15 16]. Tools for genetic engineering have been developed since the 1980s and in 1996 the genome of *Corynebacterium glutamicum* has been sequenced[17 18 19]. Today systems biology is a tool to analyse the coaction of transcriptome, proteome, fluxome and metabolome[20 21 22 23] not only in amino acid biosynthesis. Based on this knowledge and taking into consideration the whole complex physiological network a theoretical maximum molar yield of *Corynebacterium glutamicum* for lysine production of 82% has been calculated[24]. In fact, the yield achieved in practice is in the range of 55%[25] demonstrating that there is still room to improve the cell's metabolism.

1.2.2. Enzymes

A major hurdle in applying enzymes in industrial processes is still their stability[26 27]. Temperature- and pH-optimum as well as resistance of enzymes can be modulated by functionally neutral mutations that enhance a protein's stability[28].

Directed evolution is the state-of-the-art tool for optimising an enzyme's substrate specificity and reaction selectivity today. Enzymatic activities on new substrates can be obtained by improving variants with broadened specificities or by step-wise evolution by applying increasingly challenging (for the enzyme) substrates[29]. Site-directed mutagenesis is another tool to modify an enzyme's functionality[30] which is based on a careful structure-function analysis[31].

Out of the 6 families of enzymes[32] (oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases), hydrolases represent a special commercial interest because they are robust extracellular proteins; do not require coenzymes and production costs are low[33].

The Process

1.3.1. Fermentation

The fermentation process itself includes three steps: Upstream processing, fermentation and downstream processing. Upstream processing comprises raw material testing and preparation as well as preparation of a contaminant-free and genetically homogenous inoculum, fermentation is the biotransformation itself and downstream processing purification out of the fermentation broth. Concerning raw materials the carbon source is the major cost factor in industrial production of lysine[34]. The cost of purification depends on the endproduct of the process: Lys*HCL needs ion exchange chromatography with prior separation of the biomass, addition of HCl, evaporation and drying[35]. A much simpler process to L-lysine sulphate (feed grade) avoiding the use of HCL and saving ion exchange chromatography as well as biomass separation is also established[36]. Such alternatives demonstrate the impact of process design not only on investment and running cost but also on the environmental burden[37].

The state of the art of lysine and most other whole cell catalytic processes is batch-fermentation. Continuous culture[38] is still restrained because of insufficient genetical stability of microbial high-performance strains[39]. Reducing the genetic variability of the production cell population is an urgent task to be solved.

1.3.2. Enzymatic Catalysis

Most industrial processes use hydrolases in aqueous media for the degradation of complex substrates into products of limited value[40] such as high-fructose syrup. More costly enzymes are used under immobilization as it is demonstrated by the production of acrylamide from acrylonitile by nitrile hydratase[41].

The current trend are processes of organic synthesis to products of higher value like pharmaceuticals and special chemical precursors such as long- chain fatty acids[42]. Modern high-through-put screening technologies and protein engineering help to overcome hurdles of substrate specificity, activity and stability to name just a few[43]. Of special interest are lipases because they perform well in non-aqueous media[44] [45].

1.4 Bioreactor

1.4.1. Fermentors

The state of the art fermentor is the stirred tank reactor (STR) which is relatively easy to operate, to scale up beyond 10 000 litres and to adapt to various processes[46]. Non-conventional bioreactors like bio-film[47], fibrous bed[48] [49] and solid state fermentation[50] reactors might gain relevance in combination with immobilising cells in continuous culture and for special feedstocks and products.

1.4.2. Enzymatic Catalysis

Enzymes are generally poorly stable and hard to recover. Therefore enzyme stabilization and immobilisation is the most relevant strategy in developing commercial processes[51]. State of the art reactors are recirculation batch reactors[52], packed-bed column reactors[53] [54] and expanded or fluidized bed reactors[55] [56]. If the enzyme is of little significance in the total operation cost it is used like a consumable. An example is one of the largest industrial enzymatic processes: In starch liquefication with bacterial alpha-amylase to high-fructose syrup the enzyme is continuously dosed to a tubular reactor where hydrolysis and starch gelatinization occur simultaneously[57].

1.5. Downstream processing

As it has been previously mentioned, biotechnology generally is limited to products which are either i) not available through petrochemical synthesis or ii) available by cost-effective processes (*e.g.* citric acid, gluconic acid) or iii) earn a relatively high market price (itaconic acid, US$ 4 per kg; pyruvic acid, US$ 8 per kg). Carboxylic acids which could be available by aerobic fermentation (e.g. acetic acid, malic acid) or anaerobic processes (e.g. butyric acid, propionic acid) are still produced by petrochemistry because their biotechnological production cost cannot compete with the market price of US$ ~1 per kg[34]. Especially product recovery and purification are too costly[58] and need to be optimised in order to reduce the investment and running cost.

Volatile products are usually recovered by distillation, non-volatile - by precipitation or solvent extraction. Adsorption with ion-exchange resins[59] and electrodialysis with bipolar membranes[60] are state of the art as well. In order to reduce the costs of downstream processing and recovery the integration of these and new technologies in *in-situ* product removal (ISPR) is a real need[61]. Removing carboxylic acids from the fermentation broth by organic solvent extraction has been studied extensively[62] [63] [64]. In addition, continuous removal of the product out of the broth is an essential precondition in developing continuous fermentation processes. Otherwise the final product concentration is limited by end-product inhibition (negative feedback) and the production of by-products is induced. ISPR-processes are successfully established in the production of ethanol, lactic acid and L-phenylalanin[65]. Biological and economical

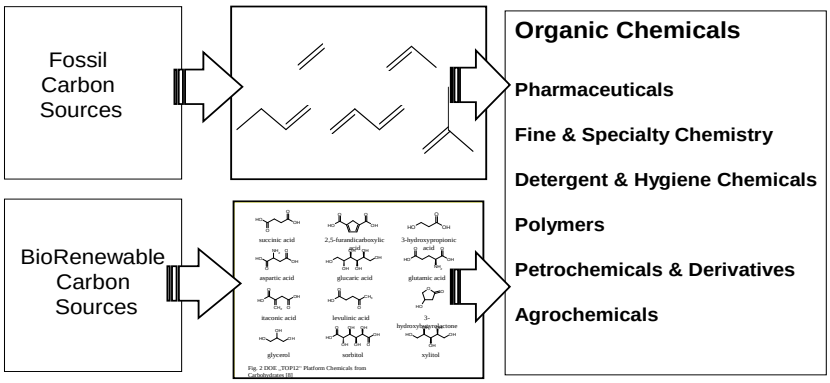
hurdles hinder so far the more general application of ISPR because *i*) the mode of contact between the microorganism and the separation phase is still a limiting factor, and *ii*) ISPR process components are still too complex[66].

2. Emerging Trends

2.1. Platform Chemicals

In order to win the competition with petrochemistry and expand the share of (bio-) chemical products through biotechnological processes, yield and final product concentration must be improved. A real step toward this goal is the creation of biotechnological platform intermediates based on the use of renewable carbon sources. The carbon sources can be transformed then into the very same broad portfolio of end-products produced today from naphta-derived building blocks. 12 such biological intermediates have been identified[67] (Fig. 1).

Fig. 1 Biological intermediates can substitute petrochemical building blocks



Fumaric, malic, succinic and itaconic acid are multifunctional carboxylic acids which might be produced biotechnologically based on renewable carbon sources[68]. Currently these acids are used as food acidulants and in manufacturing polyesters but they might find a future bulk application as building blocks in the synthesis of polyesters and biodegradable polymers[69].

2.2. Processes Combining Biotechnology and Chemical Synthesis

Ethylene stands almost synonymous for petrochemical products. However, it can also be derived by catalytic dehydration from (bio-)ethanol – thus combining the biotechnological production of ethanol with chemical catalysis. Large-scale production of ethylene based on bio-ethanol is announced by Braskem. It will be transformed to HDPE (high density polyethylen) and LDPE (low density polyethylene) from 2010 with a capacity of 200.000 tonnes annually[70]. Dow and Cristalsev announced a joint venture for production of bio-ethylene as well with a planned annual production of 350.000 tonnes per year by 2011[70].

Another relevant biological intermediate is the dicarboxylic acid succinic acid[71]. Roquette and DSM have announced to produce 100 tonnes bio-succinate per year from 2010. It may be transformed into

- 1,4 butandiole (precursor to polyesters, polyurethanes, polycarbonates[72])
- Gamma-butyrolacton (solvent for polyacrylnitil, cellulose acetate, polystyrol; softener, resins[73])
- Tetrahydrofuran (solvent for polystyrole, polyurethane, cellulosenitrate[74])
- N-methyl-2-pyrrolidon (solvent for polyamides, polystyrenes; extractive distillation of carbohydrates; desulfurization of gases[75]

Due to its high cost[76] today the global market of succinate is only 25.000 tonnes annually[77] but the demand in case of a competitive production process could grow to 275.000 tonnes per year[78].

Ethanol and succinate present examples of precursors which are fermented, isolated, purified and subsequently enter synthetic process steps. According to the state of the art there is a clear cut between the biotechnological process and the chemical synthesis. Obviously, compared to a pure petrochemical plant the biotechnological production adds investment and running cost to the conventional chemical synthesis. Integrating biotechnological and chemical technologies is a topic which will be decisive in developing competitive biotech-/chemo combiprocesses. Early developments have already been published[79] [80] [81].

2.3. Biopolymers

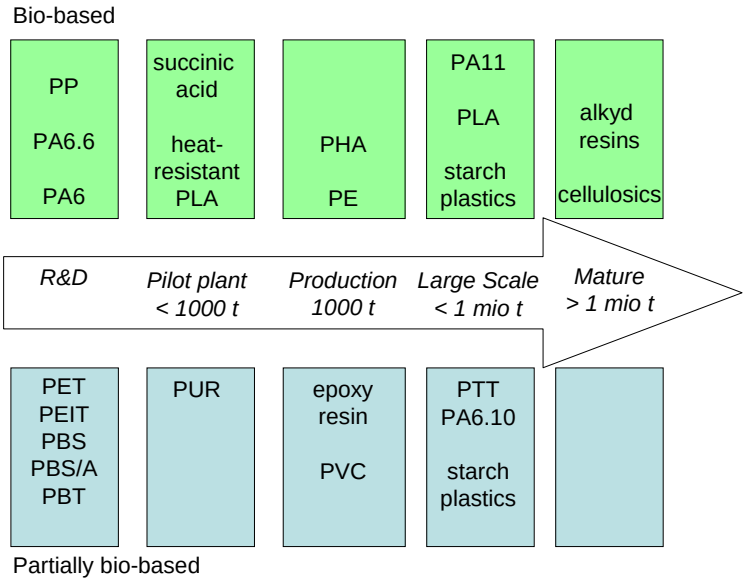
If successful such new applications of biotechnological intermediates as precursors in chemical production will change the industrial relevance of biotechnology significantly. This development opens biotechnology on the one hand an extremely broad field of new applications and asks on the other hand for integration of bio- and chemical processes. One outlet are biopolymers[82] [83] [84]:

- Biomass-based polymers produced from polysaccharides
- Polyesters based on biomass based monomers; e.g. PLA
- Polyesters from biomass-based intermediates: Poly(trimethylene terephtalate) (PTT) from propandiole (PDO)
- Polyesters produced by fermentation or GM plants (Polyhydroxyalcanoate (PHAs[85])
- Polyurethanes based on bio-polyols
- Polyamides (Nylon -6, -66, 69)
- Polyacrylamide based on bio-acrylamide
- Rubber based on bio-isoprene[86]

In 2006[87] 250 million tonnes of plastics have been produced globally whereas the global capacity of bio-based polymers has been estimated at 0,36 million tonnes in 2007. However, this segment is growing since 2003 with an annual rate of 48% in Europe and 38% globally. Its market is seen at 10 - 20% by 2020[88]. The maximum technical substitution potential of bio-based polymers replacing petrochemical plastics is seen at 90% of polymers including fibers. Only 5 different petro-polymers (LDPE/LLDPE (linear low density PE), HDPE, PP (polypropylene), PVC (polyvinyl chloride), PET (PE terephtalate)) cover approximately two thirds of the total plastics market. A substitution potential of up to 100% is seen

esp. for PBT (polybutylene terephtalate), PBS (polybutylene succinate), PET and PE[89]. As shown in Fig. 2 the pipeline of bio-polymers is filled and waits for realisation.

Fig. 2 Development stage of bio-based polymers[90]

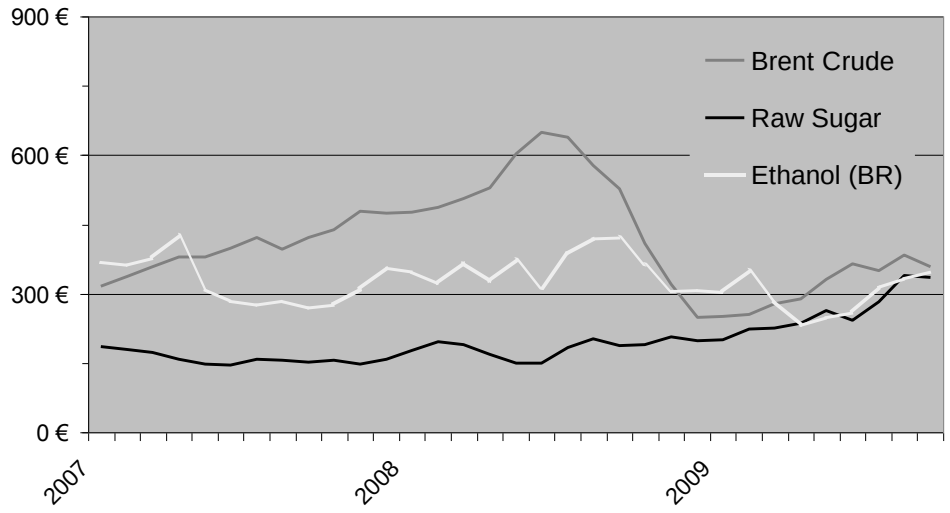


2.4. Renewable Feedstocks

2.4.1. Sugar and Fatty Acids

Ethanol and succinate as well as most other products of biotechnology are based on C_6-sugar. Less processes use fatty acids[91 92]; examples are long-chain dicarboxylic acids like undecandioic acid (DC11) up to hexadecanedioic acid (DC16)[93]. Nevertheless C_6-sugar is the dominant carbon source. The prospective growing sugar consumption for the production of (bio-)chemicals will compete with the food and increasingly the biofuel industry. As biofuel production grows the (bio-)chemical industry will be trapped between the economical factor of rising cost of sugar (Fig. 3[94]) and the societal discussion about land-use for food or fuel[95 96 97].

Fig. 3. Coupling of prices for fossile oil, bio-ethanol and sugar



2.4.2. Lignocellulose

The potential limitation of sugar is already a driver for the use of lignocellulosic carbon sources such as waste biomass from agriculture (straw, corn husk), biomass from grass land[98], or forestry (wood). The capacity of 24 US-companies for so called advanced biofuel – which is predominantly based on lignocellulose - is announced to grow from 7 million gallon per year in 2009 to 640 million gallon per year in 2012[99]. To use so far rotting agricultural biomass the BioCentury Farm has been founded in Ames (Iowa; USA) in October 2009 in order to develop and test integrated harvesting, transport, storage and transformation procedures of such low density organic materials[100].

2.4.3. Plant Breeding for Industrial Purposes

The current agricultural organic waste material could in principle be commercialised as industrial feedstock tomorrow. Therefore optimising biomass becomes a target for plant breeders. The US Department of Energy and the Department of Agriculture spend more than US $ 100 million annually in this field[101]. Minimising waste biomass has been a target for corn breeding since decades; now KWS in Germany reports to double corn biomass from 15 to 30 tonnes per hectare[102]. An alternative to escape the competition with land use for food production is switching to meagre land and growing non-food plants like undemanding switchgrass or miscanthus[103] for energy production[104]. Another breeding target is the integration of the very first step of feedstock processing into the plant itself: Syngenta works on a corn variety which has inserted an amylase gene for degradation of its own starch in sugar[105]. In addition to using agricultural biomass, sugars and fatty acids as renewable carbon sources, plants may be suitable bio-factories to produce end-products directly. Polyhydroxyalcanoate (PHA)[106] or polyhydroxybutyrate (PHB) [107] might be produced by genetically modified plants.

2.4.4. Aquaculture (Algae)

Today algae are used for production of high value niche products (carotenoids, bio-oil (DHA), nutraceuticals). Such products reach a sales volume of $ 6 bio out of an algae-biomass volume of 10.000 t (USA, 2008)[108]. This volume is about 10% of what a bulk chemical plant would need and about 0,1% of a single oil refinery size[109]. Due to their high lipid content – algae biomass consists of 40% lipids, 50% protein and 10% polysaccharides[88] – algae are also in discussion as feedstock for the production of bio-diesel, the more so as their productivity per hectare is up to 30 times higher than agricultural plants like jatropha, palm or rape[110] and reaches up to 33.000 gallons of lipid oil per acre a year[111]. Therefore various companies announced to build algae production facilities. In 2008 Royal Dutch Shell and HR Biopetroleum (CA; USA) formed the joint venture Cellana to build a 20.000 hectare open ponds park in Hawaii till 2012[112] using atmospheric CO_2. CO_2 from coal power plant flue gas is used by Israel's Seambiotic[113] who announced in 2009 to build a US$ 10 million plant in China. Their 1000 m² pilot plant went online in 2005 and will be expanded to 5 hectare. However, at production cost of $ 8 per gallon algae-based biofuel is not yet competitive[114]. The prominent cost factor is energy consumption for pumping the algae broth, harvesting and post-processing because the algae-density in the broth is low (0,5-3 g/l)[115].

To reach competitiveness it needs i) strains of highly productive algae[116], ii) high density cultivation processes reactors[117], iii) transparent reactors distributing light efficiently and iv) efficient aeration systems to solubilise CO_2 in the broth.

2.4.5. Synthesis Gas

Using starch, sugars and fatty acids from fruits or lignocellulose from biomass always requires costly processing and fractionation. In addition a significant share of biomass carbon cannot be used for production of materials as long as there is no significant use of lignin besides burning it. Breaking the whole biomass down to synthesis gas (CO, CO_2, H_2) by fluidized bed gasification (900°C) or entrained gasification (1300°C)[118] and building it up again to the products of desire might be an alternative. *Clostridia* are well known for their ability to grow on syngas[119] [120]. The integration of syngas transformation in a multi-product biorefinery concept has also been discussed[121]. BRI-Energy[122], Ineos-Bio[123] and Coscata work on syngas-based ethanol. Coscata even announced a 100 mio gallon ethanol plant in 2011 using syngas as carbon source[124].

In comparison with heterogeneous catalytic transformation of syngas fermentation is advantageous regarding to high specificity of the biocatalyst, saving of energy, higher resistance against by-products in the gas and robustness against variation in the gas composition[125]. The impact of process parameters like gas flow and pH on cell culture and productivity have been analysed[126] [127]. A question to be solved by process engineering is the low solubility of the gaseous carbon source. By controlling the size of the syngas bubbles[128] [129] [130] or enhancing the pressure in the fermentor[131] the solubility can be improved.

2.5. Biorefineries

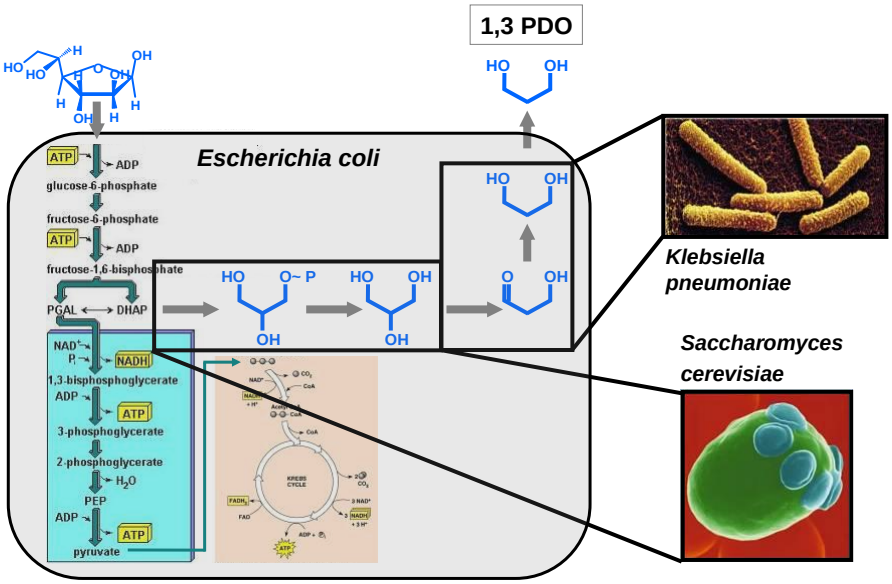
The concept of biorefineries is a combination of integrated plants addressing *i*) processing and fractionation of renewable raw materials; *ii*) transforming feedstocks to various products from food, feed, fibers, bulk and fine chemicals up to biofuel; and *iii*) recycling the products after use where possible[132] [133]. Many concepts deal with plant biomass including lignocellulosic carbon sources[134] but also synthesis gas as the principal carbon source[135]. Handicaps to overcome are: *i*) the early development stage of core technologies (biomass fractionation and transformation); *ii*) high investment volume required [136] (biorefineries compete with amortised petrochemical plants); and *iii*) the lack of economy of scale compared to large petro-refineries[137] [138]. Therefore it is a promising strategy to integrate a biorefinery into an existing chemical production in a stepwise manner as it has been realised in Leuna, Germany[139]. All

technologies discussed in this paper contribute to individual elements of biorefineries (processing feedstocks, developing biocatalysts, processes and downstream processing). As emphasised repeatedly, the integration of subsequent and parallel process steps is important in improving the economy of stand-alone processes. In realising biorefinery concepts it is even the key to success.

2.6. Synthetic Biology

As discussed in the previous sections the transformation of renewable carbon sources to a variety of biotechnological end-products and precursors for chemical processes is state of the art. However, beside the development of highly sophisticated biocatalysts, the range of products is generally limited to products of natural metabolic pathways. An early example of fermentative production of a non-naturally occurring chemical is 1,3-propandiol (Fig. 4).

Fig. 4 The metabolic pathway to 1,3-propandiole



To do so, an *E.coli* host has been equipped with metabolic modules from eukaryotic yeast and prokaryotic *Klebsiella* to produce the unnatural product 1,3-propandiole[140]. Reassembling existing biological pathways and even introducing synthetic metabolic pathway modules into living systems is the topic of synthetic biology. It is the vision of synthetic biology to develop a bank of natural and synthetic metabolic modules and to arrange them according to an engineering plan in a chassis [141]. To ensure that the engineered pathway functions as intended the complex background of the living chassis should be well understood. However, even biotechnology's workhorse *Escherichia coli* is still not fully understood[142] – 24 % of its genes wait for proper characterisation[143]. To reduce the metabolic and genetic complexity the genome of microbial host genomes is stripped off all genetic elements not necessary to live under laboratory and production conditions. Minimising the genome of *E. coli* in that way resulted in improved stability of the genome and transgenic elements as well as more easy genetic manipulation[144]. Especially the last two criteria are extremely relevant to establish a microbial chassis. The methodology to optimise microbial genomes is already in development also for *Corynebacterium*[145] [146]. Beside the availability of host systems two factors currently limit the development of synthetic biology: i) the capacity to synthesize *de novo* non-template driven and error-free large (>5 kbp) segments of DNA and ii) the miniaturisation and

automation of current laboratory protocols for the manipulation and analysis of biological systems[121]. Other topics to be improved are standardisation of parts and devices, clarification of patent issues and educational aspects[147].

2.6.1. Ethical Questions

It should be mentioned that in the public synthesizing and rearranging entire genomes is sometimes perceived as working on "artificial life"[148]. Ethical questions will be debated and need to be answered[149].

3. Co-operation between Relevant Actors

The co-operation between academia and industry for different steps of the industrial biotechnology innovation cycle is shown in Fig 5[150]. It also shows the demand for time and capital in R&D for developing a biotechnological process and product. The stage to which all actors contribute the most is the development of a prototype process while the most fund demanding step is scale-up and investing into the production plant.

Fig. 5 Academia and industry cooperate in developing process

3.1. Coordinating the Development of Industrial Biotechnology

3.1.1. Coordination between the Academia and Industry

Figure 5 showed how academia, SME and industry often cooperate in R&D projects initiated and financed by an individual company. However, changing the whole industry's very basic technology platform(s) and feedstock base is a task too complex for single companies. It needs coordinated technology development and a realization spanning various technologies and markets (feedstocks, plant engineering, process technology, application research in different end consumer industries). Therefore coordination of that transformation should begin with learning about the options and demands of all stakeholders in the transformation process.

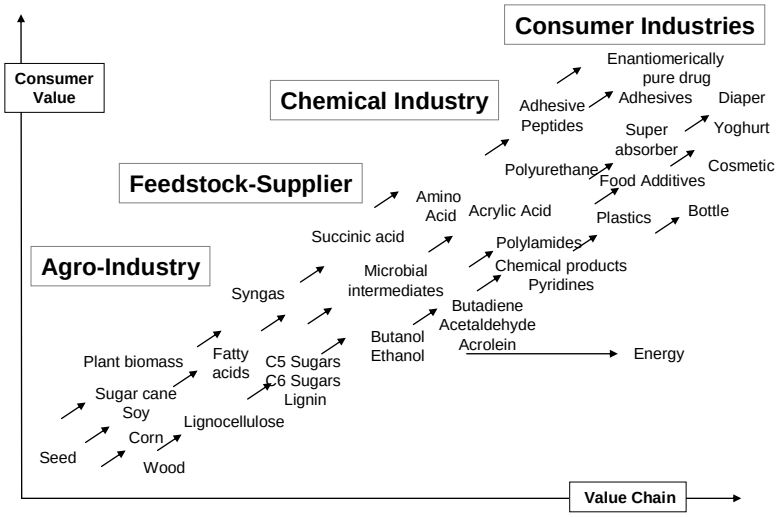
Industry should understand early the application potential of new technologies provided by academia (and often SME as well) and academia and SME should know about future industrial needs and

specifications. Such exchange should include all players of the i) **development**-oriented as well as ii) **production**-oriented value chain.

i) The **development**-oriented value chain starts at academic science and its industrial translation into product ideas and goes through product concept, development, demonstration, pilot, scale-up and production. Its know-how is developed in academia, SME and industry.

ii) Looking on **production** SME and MNE form a complex value chain of providers and processors of feedstocks, platform chemicals, intermediates, and components up to the end products (Fig. 6).

Fig. 6. Production-oriented value chain[151]

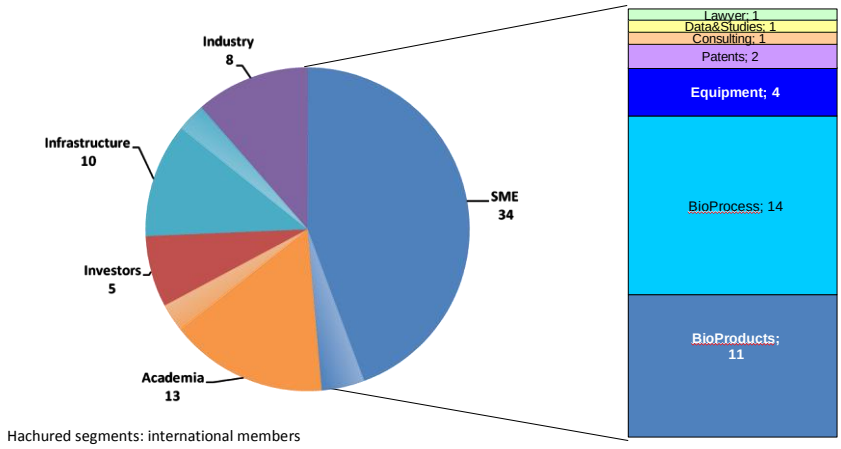


All these parties should be involved in the discussion about the future options and challenges of industrial biotechnology in order to consider early its opportunities and its impact on their very own field. The coordination approach of academia, SME and industry along the whole value chain results in a decisive competitive advantage and accelerates the development significantly.

How such a coordination works is different from region to region and depends on the local business culture. Silicon Valley is a prototype example of self-organized coordination. Scientists, industry people, investors, entrepreneurs, start-ups, law firms and politics are used to network intensively. This culture represents an extremely efficient regional cluster of unique size and complexity. It produced since the 1930ies innovation cycles in electronics, information technology, (pharma-) biotechnology and is today one of the leading regions in clean technologies. The European (!) oil-multi Shell invested 500 million $ in a long-term cooperation with UC Berkely.

A different model is represented by CLIB2021 (Cluster industrielle Biotechnologie 2021[152]) in Germany. This cluster has been initiated by the German Federal Ministry of Education and Research. It started in 2007 with 32 founding members – among them chemical industries like Bayer Technology Services, Cognis, Evonik Industries, Henkel and Lanxess. Since then the cluster grew to 70 academic institutes, SME, industries and investors (Fig. 6), launched R&D projects with a total volume of 50 million EUR, founded 5 start-ups and attracted 10% international members in Europe, North-America and Russia. CLIB's main task is initiating and coordinating academic and industrial R&D in industrial biotechnology for the chemical industry. Like in the Silicon Valley CLIB's success is based on networking and linking the different players along the value chain. But different to California it needed a governmental initiative to organize the cluster.

Fig. 7. Members of CLIB2021



Provided that the cluster members develop a culture of trustful and open exchange of ideas options are identified and realized earlier in a coordinated way than without the coordinating platform of a cluster. Such coordinated development will get an additional push by targeted public promotion. Public funding agencies should be part of the discussion as well. In consultation with all stakeholders they should set priorities based on academic options, industrial needs and public interest. Programs targeting the academia should always include teaching and training of the rising generation.

3.1.2. Examples of Successful Cooperation between Industrial and Public Research Institutions

Successful examples are CBP (Germany)[153] [154], BioHub (France)[155] and BioCar Canada)[156]. They also go back to governmental public funded programs but are focused on specific product segments (BioHub: succinate; BioCar: automotive materials). CBiRC (Iowa; USA)[157] originates from the abundance of agricultural carbon sources in this US-state and targets on transformation of sugars into chemical products.

CBP (Chemisch-Biologisches Prozesszentrum) Leuna (Germany): Since 04/2009 a biorefinery is build on the chemical production site Leuna which will be integrated into the chemical production chains

on site. One of the target products is bio-ethylen. Partners are chemical industries in Leuna, Fraunhofer IGB and the university Stuttgart. The project is funded by the German Federal Ministry of Education and Research (BMBF). The centre will start in 2010.

BioHub (France) is a cereal-based biorefinery in Lestrem (France). It targets on platform-chemicals like succinate and isosorbide. Partners are among others Roquette, DSM and the university of Georgia. The project is funded by the French Industrial Innovation Agency. The isosorbide demonstration plant has been launched in 07/2009.

Ontario **BioCar** Initiative (Canada) represents a partnership between the automotive industry and academic institutes to develop automotive materials from biorenewable carbon sources at the university of Guelph (Ontario). The project is funded by the Ontario Ministry of Research and Innovation. It runs since 2007.

CBiRC (Center for BioRenowable Chemicals; Iowa, USA) focuses on production of chemicals from corn-based sugar. The center is located at the Iowa state university in Ames and offers a network of companies and more academic US-institutes. It is financed by the Iowa Ministry of Research and Innovation and started in 2009. It is complemented by the BioCentury Farm (harvest, transport, storage and transformation of agricultural biomass) and the BioIndustry Center (ecological and economical studies of biomass-based chemical processes).

3.1.3. Barriers Impeding the Translation of R&D to the Markets

A significant part of the coordination efforts should help to overcome the 5 barriers impeding the translation of R&D to the markets.

i. **Understanding** the technological and business potential of academic R&D results needs adequate competence in the targeted industries at least in the lower and middle management and support from the top. The same is true *vice versa* for academics who often do not have sufficient understanding for industrial process and market demands. Therefore competence networks addressing industry as well as academia help to overcome the competence hurdle.

ii. Strong **competitiveness** must be given for the foreseeable future. When competing against a running process based on fossil carbon sources, the alternative process must ensure competitiveness also in scenarios of high energy- and feedstock-cost volatility. Part of this criterion is the investment into the plant – especially if the new one competes against a depreciated this might be a strong barrier. For SME such an investment is an even stronger hurdle. Because new technologies and products often start in niche-markets served by SME before they win more customers SME should get special support.

iii. Multiple product **bio-refinery** models include a complex network of individual process chains starting from biorenewable feedstocks to different intermediates and ending in diverse bio- and chemical endproducts. If the biorefinery is seen at first as a provider of feedstocks like lignocellular carbon sources and platform chemicals the business model is quite clear: Lignocellular sugars and platform chemicals serve the similar and transparent markets of carbon sources and precursors. However, the more transformation steps and products are added the more complex the business model becomes because its various products target different markets – all with their own dynamics. Therefore a multiple product biorefinery needs an effective mass flux flexibility to be able to adapt to different market situations. Such flexible processes are not available yet.

iv. Academia and SME often contribute **intellectual property** (IP) early into the development of a complex process giving them only a reduced time of IP-revenues after launching the final process. Both parties should receive a fair share of the produced value. As late income from IP might be especially a problem for SME the promotion of early IP fees might be discussed.

v. As stated before at least some of the biorefinery products will need further chemical processing. As long as such chemical processes are not available these precursors will find no market. Therefore R&D on the **bio/chemo process** interface should get special attention.

vi. A more general barrier is the availability of well educated scientists (biology, chemistry, botany) and engineers (plant- and process engineering). **Training** the rising generation is a never ending task.

4. Future Priorities

4.1. Future R&D Priorities in Academic and Industrial Research Activities (5 years)

Industrial R&D priorities are i) the **technology push** concerning feedstocks and biocatalysts, ii) improvement of **economics** of established processes, iii) industry's need of **feedstock** flexibility, iv) industry's need of a continuous product **pipeline** and v) the **consumer's demand** for products based on biorenewable feedstocks.

Concerning the **technology push** priorities should be set on advances in academic **scientific research** (systems biology, metabolic engineering, enzyme evolution etc.) and industrial **technology and development** mentioned earlier (ISPR, process integration). Concerning science **synthetic biology** is just emerging. It will give access to biocatalysts and products which have not been in reach through biocatalysis so far. Synthetic biology will increase the diversity of biotechnological processes and products as well as intermediates for biotech/chemical combi-processes significantly. This will give another push to the biorefinery concept.

To reach **economical viability** industrial biotechnology will need reduced investment and running cost. Therefore **reducing the number of process steps** – e.g. by integrating down-streaming and purification in continuous processes - is a crucial question which should be prioritized in R&D. Continuous processes will increase the production capacity significantly, resp. reduce investment and running cost.

Consumers ask increasingly for the ecological – esp. CO_2 – footprint of products. So far there is no standard procedure available how to measure this criterion as part of the Life Cycle Analysis. A model are the the JRC guidelines[158].

4.2. What should be Done by Governments and Industry?

Governments should encourage and promote industrial biotechnology by supporting i) **cooperation** of academia and industry, ii) **graduate students exchange**, iii) **R&D** in relevant sciences and technologies and iv) **financing** the entrance into industrial biotechnology.

i. As shown before, **cooperation** in clusters rather than in single-company partnerships accelerates the development of processes and their penetration into the industry significantly. Public funding programs should promote cluster-building project-management.

ii. R&D clusters depend on personal contacts between scientists in academia and industry. Building of border-crossing clusters should be supported by promoting international **graduate exchange.** This is the first and most cost-efficient step in building a human network.

iii. R&D promotion should focus on i) **feedstocks**, ii) **bio/chemo combiprocesses** and iii) **synthetic biology**.

iv. **Financing** industrial R&D is the entrance into industrial biotechnology. It should be made easier by a) setting off R&D expenses against tax liability and b) public promotion of demonstration plants.

5. Consumer's Acceptance of Industrial Biotechnology

Is industrial biotechnology accepted by the public? There is no clear answer because many people *i*) are just not aware of industrial biotechnology; *ii*) answer with yes, but…., or *iii*) people welcome industrial biotechnology as a source of ecological advantageous processes and economic growth.

Most processes and products are not visible to the public because they are commercialised in a business-to-business relationship. Therefore consumers are not aware of the benefits of Industrial Biotechnology. Confronting them with the technology only may lead to counter-productive misunderstandings like the "industrial use of microorganisms means propagation of (pathogenic) bacteria".

Others are aware of industrial biotechnology and generally welcome its benefits but at the same time criticise *e.g.* the use of GMOs, feedstocks based on transgenic plants and land use competing with food production.

Full acceptance of industrial biotechnology as part of a comprehensive strategy towards a bio-based economy is currently limited to a minority engaged in industrial biotechnology such as academia, business and politics.

Improving acceptance is not only a question of explaining and teaching the technology. It depends on a *i*) perceived benefit to consumers under acceptable risks; *ii*) adherence to key moral values regarding human and non-human life; and *iii*) trust in the governance of the technology[159]. Therefore pure education campaigns about the technology seem not adequate or are even counter-productive[160]. Technological, economical, ecological and social concerns need to be addressed in a respectful dialogue with the different stakeholders. Academia and industry should show in their actions that they intend not only to switch to a bio-based **technology**, but also to change from a petrochemical to a bio-based **economy** as a tool that will contribute to a more sustainable **society** as a whole.

6. Countries' SWOT Analysis

The options and challenges of industrial biotechnology in the OECD-regions EU, USA and Japan as well as the BRIC countries are summarised in the following SWOT-analysis (Tab. 2).

Generally OECD countries are characterized by strong competence in industry as well as science and technology. The US are well appointed with renewable feedstocks esp. if waste biomass is used, whereas the resources in the EU and Japan are limited. Lacking public acceptance of GMOs might turn out as a special handicap of the EU.

The BRIC states may develop to the world's producer of biorenewable feedstocks. On the long range a renewable-based industry might evolve. It needs developing competence in science and technology in these countries to accelerate this process.

Table 2a: SWOT-Analysis: Strengths

	EU	USA	Japan	BRIC
Drivers of industrial biotechnology	chemical industry, ecology, added value products	energy and chemical industry; start ups, venture capital	chemical industry, ecology, added value products	commercialisation of biorenewable carbon sources
Compentence in R&D	strong in biotechnology and chemistry in academia, industry, highest regional R&D density	strong in biotechnology and chemistry in academia, start-ups, industry	strong in biotechnology and chemistry in academia, industry, high regional R&D density	
Public acceptance		GMOs and transgenic plants well accepted	society willing to accept new products	GMOs and transgenic plants well accepted
Availability of biorenewable carbon sources	production of sugar beet, potatoe starch, cereal starch	large production of corn and soy; leading in lignocellulosic ethanol	tradition in marine culture	large production of corn, sugar cane and soy

Table 2b: SWOT-Analysis: Weaknesses

	EU	USA	Japan	BRIC
Drivers of industrial biotechnology	no relevant technology provider in bioenergy	bioenergy dominates too much	no relevant technology provider in bioenergy	industry early in value chain
Compentence in R&D	technology transfer, not enough start-ups		technology transfer, not enough start-ups	only few centers of compentence
Public acceptance	GMOs and transgenic plants not accepted			
Availability of biorenewable carbon sources	limited due to lack of land, importer	limited due to lack of water	insufficient due to lack of land, importer	

Table 2c: SWOT-Analysis: Options

	EU	USA	Japan	BRIC
Drivers of industrial biotechnology	chemical industry seeks feedstock flexibility	chemical industry may add another driver	export bioenergy technologies	development of biorefineries
Compentence in R&D	accelerate partnering and technology transfer, build entrepreneurial culture	licencing technologies	intensify cooperation with more global regions	improvement of academic compentence
Public acceptance	improve acceptance of GMO and transgenic plants as industrial carbon sources			
Availability of biorenewable carbon sources	special plant-based precursors for niche markets	algae cultivation, large scale production of lignocellulosic carbon sources	develop marine biotechnology	become the world's producer of biorenewable carbon

Table 2d: SWOT-Analysis: Challenges

	EU	USA	Japan	BRIC
Drivers of industrial biotechnology	investments in early technologies	establishing ecology as a driver in politics	investments in early technologies	infrastructure
Compentence in R&D				technology transfer into BRIC countries
Public acceptance	resistance against GMO and transgenic plants			
Availability of biorenewable carbon sources	land use for industrial plant cultivation	focus on chemical usage beside bio-ethanol	domestic availability of renewable carbon sources	free trade conditions in all regions

7. Conclusion

Industrial biotechnology evolves as an essential production technology in the chemical industry. It is driven by the technological push of modern process and biocatalyst development.

Esp. the emerging synthetic biology will overcome the current limitation to products living systems provide by nature. Synthetic biology pursues the vision to provide metabolic modules specifically engineered towards man-made chemical compounds. They may serve as precursors for fine and bulk chemicals, thus combining biotechnological processes and chemical synthesis. Commercial success will depend on process-integration reducing investment and running cost. More cost-effective down-streaming in aqueous biotechnological systems will be part of the solution.

A further driver is the market pull of ecologically friendly and competitive feedstocks. Because fossil carbon sources are limited and characterized by high price volatility the industry explores the total spectrum of alternative bio-renewable carbon sources.

The transformation process from a petro-based chemical industry to a bio-renewable-based bio-chemical industry is complex. Partnering in cluster structures will accelerate the transformation. Governmental initiatives including public funding should promote clusters and ease the transformation.

This transformation process is not only an industrial and technical issue. It affects the whole society and needs therefore continuous information of the public and a respectful dialogue with all stakeholders.

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