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REVIEW ARTICLE

Relevance of microbial coculture fermentations in biotechnology

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Summary

The purpose of this article is to review coculture fermentations in industrial biotechnology. Examples for the advantageous utilization of cocultures instead of single cultivations include the production of bulk chemicals, enzymes, food additives, antimicrobial substances and microbial fuel cells. Coculture fermentations may result in increased yield, improved control of product qualities and the possibility of utilizing cheaper substrates. Cocultivation of different micro-organisms may also help to identify and develop new biotechnological substances. The relevance of coculture fermentations and the potential of improving existing processes as well as the production of new chemical compounds in industrial biotechnology are pointed out here by means of more than 35 examples.

Introduction

Chemical substances worth several billion Euros are produced each year by biotechnological processes as fuels, bulk and fine chemicals and pharmaceuticals using renewable resources. Because sterile cultivation enables an easy way of controlling microbial milieu, growth and product formation, most of the products in industrial biotechnology today are formed using processes involving a single microbial strain. On the other hand, there are many instances where the utilization of cocultures appears to be advantageous over a single micro-organism because of the potential for synergistic utilization of the metabolic pathways of all involved strains in a coculture situation. Most biotransformations in nature take place by the combination of metabolic pathways from different micro-organisms. Some examples for the coexistence of different micro-organisms are the forest soils, compost piles, the aerobic and the anaerobic zones of water, spontaneous fermentations of sugar-containing saps and the human skin. Mammalian intestine with involvement of up to 500 strains (Mai and Morris 2004) is another example for a very complex, natural mixed microbial system; the interactions between supply of substrates and the utilization of metabolites have formed the basis of analysing behaviour of the human gut (Belenguer *et al.* 2006).

Definitions as used in this text

Coculture
Anaerobic or aerobic incubation of different specified microbial strains under aseptic conditions.

Mixed culture
Anaerobic or aerobic incubation of different sometimes unspecified micro-organisms; may be conducted under septic conditions.

In cocultures, degradation and metabolization of substrates occur by the combined metabolic activity of the known microbial strains under aseptic conditions. Mixed cultivations are often found in nature under septic conditions with unspecified microbial strains. In a habitat, different micro-organisms may compete for substrates as well as act symbiotically. Micro-organisms have evolved mechanisms to protect their substrates and to defend their habitat against competitors. *Xanthomonas campestris* synthesizes the carbohydrate polymer xanthan as a

storage substance that is degraded by only a few other micro-organisms. Acidogenic bacteria produce organic acids that suppress acid-intolerant organisms by reducing medium pH as well as by causing growth inhibition in micro-organisms (Taniguchi *et al.* 1998). Some strains of the genus *Lactobacillus* defend their habitat against other Gram-positive bacteria by the secretion of growth-inhibiting substances such as nisin or lactain F (Dalmau *et al.* 2002). In other cases, there may be a symbiosis among different micro-organisms caused by synergies of their different enzymatic systems and metabolic pathways (Yara *et al.* 2006). Lichens, including more than 1500 species consisting of cyanobacteria and yeasts, are an example of symbiotic relationship between different micro-organisms (Rikkinen *et al.* 2002). This symbiosis has lasted for over 600 million years (Yuan *et al.* 2005). This long survival can be viewed as evidence of the great benefit for partners in this symbiosis.

The natural cooperation of different micro-organisms is utilized in only a few applications in industrial biotechnology. In most cases, pure cultures are utilized for formation of the desired product(s), and the undesired micro-organisms are eliminated by sterile working conditions. Exceptions where cocultures are industrially applied are wastewater treatment, biogas production, biological soil remediation (Chaudhry and Chapalamadugu 1991) and the production of traditional foods. Examples of the utilization of cocultures in food industry are the production of cheese (Martin *et al.* 2001), yoghurt (Sodini *et al.* 2000), sauerkraut, sourdough (Kariluoto *et al.* 2006), kefir (Lopitz-Otsoa *et al.* 2006), African fermented dairy products (Narvhus and Gadaga 2003), salami (Dicks *et al.* 2004), whisky (Van Beek and Priest 2002), cacao beans (Schwan and Wheals 2004) and Belgian beer such as Lambic (De Cort *et al.* 1994). A mixed culture of different yeasts and several bacteria is also important in wine production wherein the involved micro-organisms grow during fermentation in a special succession influencing the aroma and flavour profile of the wine (Fleet 2003; Clemente-Jimenez *et al.* 2005; Renouf *et al.* 2006). Modification of raw materials during food production by cocultures results in improved texture, taste and flavour, and in microbial stabilization (Schwenninger and Meile 2004; Benkerroum *et al.* 2005; Janssen *et al.* 2006). This protection may be caused by a decreased pH-value or by the formation of growth-inhibiting substances such as lactic acid, acetic acid or ethanol. Further stabilization may be achieved by the reduction of available carbohydrates as well as by the secretion of bacteriostatic or bactericidal substances such as nisin (Dalmau *et al.* 2002; Achemchem *et al.* 2006; Liu *et al.* 2006). Growth and product formation are not effected through external regulation but by modification of internal conditions such as oxygen availability, pH and substrate and product concentrations during the given examples of fermentation processes.

A further advantage of cultivation of cocultures is the possibility of utilizing secondary products (e.g. whey, molasses) cheaper than glucose as substrates for biotechnological production of chemicals. Using substrates other than glucose offers potential to develop biological production processes at competitive costs. Furthermore, cocultivation processes can help find new substances of industrial interest, because a number of secondary metabolites are produced during cocultivation (Oh *et al.* 2007).

Besides having the industrial importance, coculture systems have medical implications as well. Penttinen *et al.* (2005) reported strongly increased induction of apoptosis in mammalian cells by spores produced in a coculture of *Streptomyces californicus* with *Stachybotrys chartarum* in comparison with the spores of *Streptomyces californicus* grown in pure culture.

Interactions between micro-organisms in coculture systems

Cells present in a medium communicate with each other either by direct cell-to-cell-interactions (Meyer and Stahl 2003) or through the signal substances in the fermentation broth. An example of the chemical trigger substances is the acetylated homoserine lactone (AcylHSL). Production of bioluminescence protein, Lux 1, triggered by intracellular binding of AcylHSL to LuxR-proteins that are homologous to the transcription factor (Fuqua *et al.* 2001; Joint *et al.* 2002) is shown in Fig. 1. Low concentrations of AcylHSL do not trigger the bioluminescence response that occurs only when a significant number of

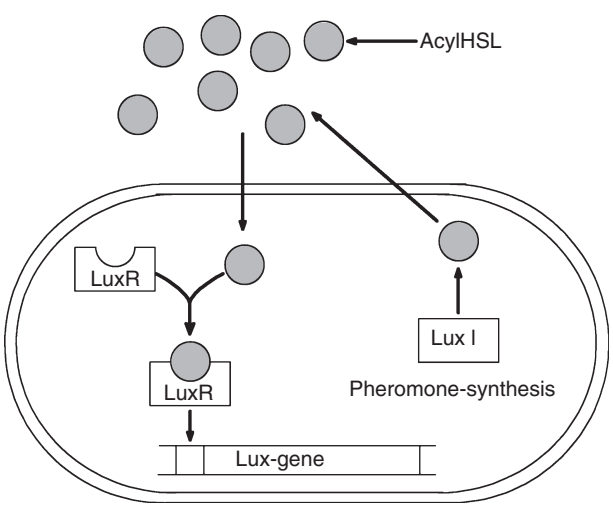

Figure 1 Regulation of bioluminescence in Gram-negative bacteria by Acetylated Homoserine Lactone, AcylHSL [from Fuchs *et al.* (2007)].

cells are present in a colony to cumulatively produce AcylHSL to concentration levels enough to cause expression of Lux-1 protein. An elevated concentration of Lux-1 protein in the cell leads to an increased production of AcylHSL, causing a positive feedback regulation.

The communication by secreted chemical substances such as AcylHSL is an example of quorum sensing (the process in which single-cell organisms, usually bacteria, determine population density by detecting the concentration of small, diffusible signal molecules). Induction of responsible genes may occur dependent on the concentration of micro-organisms with respect to that of the signal substances (Miller and Bassler 2001). The microbial reaction to the presence of other cells can be observed within or between different species (Crespi 2001). One example of the interaction within a microbial strain is the formation of fruiting bodies by Myxobacteria (Sliusarenko *et al.* 2007). The marine bacterium *Pseudoalteromonas tunicata* secretes the antibacterial protein AlpP in biofilms (*Rao et al. 2005*). Moons *et al.* (2006) reported the production of antimicrobial proteins in the Gram-negative bacterium *Serratia plymuthica*, controlled by quorum sensing. Intracell communication by AcylHSLs takes place even between microbes of different species and genera. Joint *et al.* (2002) reported communication between the eukaryotic algae *Enteromorpha zoospores* and the prokaryotic bacteria *Vibrio anguillarum. Aspergillus giganteus* produces increased amounts of the antifungal protein (AFP) in cocultivation with *Fusarium oxysporum* (Meyer and Stahl 2003). Further examples for reactions controlled by quorum sensing include production of antibiotics and the development of virulence factors (Williams *et al.* 2000).

In contrast to a pure culture, interactions between the different micro-organisms play a critical role in a coculture. Growth of cells of one strain may be enhanced or inhibited by the activities of other micro-organisms present in the medium. The same is also true for the formation of primary and secondary metabolites (Keller and Surette 2006) and when triggered by the presence of cocultivating cells, it may be a unique characteristic of the cocultivation processes. Activation of microbial promoters that could not be observed in pure cultures indicates the potential of production of new substances, possibly of industrial interest, in cocultures (Moller *et al.* 1998).

Although examples dealing with negative control of growth of cells in a mixed culture by the production of inhibitory primary and secondary metabolites abound, an interactive promotion of growth also occurs in many instances. Sodini *et al.* (2000) described an increased growth rate of cells during cocultivation of different strains of lactic acid bacteria as a result of interchanging growth factors. Enhanced growth rate can also be observed because of the enzymatic activity of one strain in the coculture supplying another strain its substrate (Qian *et al.* 2006). Reduction of growth-inhibiting substances by one strain in the coculture was reported by Cheirsilp *et al.* (2003), improving growth of the other partner of the coculture. Another positive interaction in cocultures may take place through the reduction of available oxygen by aerobic microbes creating anaerobic conditions that promote the growth of anaerobic or microaerophilic strains especially in biofilms. This kind of microbial mixed culture provides protection from environmental influences. On the other hand, the interactions between microorganisms in mixed culture environments may not always lead to desirable consequences. The resulting strongly decreased sensitivity of micro-organisms in biofilms to disinfectants and antibiotics can cause severe problems because of their incomplete elimination in industry and medicine (Stewart and Costerton 2001).

Utilization of the combined metabolic pathways and the controlled activation of genes by the interactions occurring in cocultivations offer several opportunities for industry and science. These possibilities are discussed in next sections.

Potential utilization of coculture fermentations in industrial biotechnology

Biological production of fine chemicals for the chemical industry using renewable resources has an increasing relevance. A spectrum of potential products formed by mixed or coculture cultivations is presented in Fig. 2. Energy consumption and the use of environmentally hazardous substances can often be reduced by biotechnological production processes. Further advantages may be the production of pure enantiomers, reduced steps required in synthesis of products, and less stringent security needs resulting in reduced production costs. The risk of accidents decreases as a result of lower process temperatures and normally low pressures in biotechnological processes in contrast to many chemical processes. Moderate process conditions result in lower required charge in the field of process security and approval procedures (Rhein *et al.* 2002).

In the examples cited from literature, cocultivation may result in increased yields, a reduction of process costs because of cheaper (sometimes even unsterile) substrates (Kleerebezem and Van Loosdrecht 2007) and control of product quality. In some cases, production of substances normally not formed by pure cultures can be observed through the induction of appropriate genes in cocultivation processes. Coculture and mixed culture fermentation may have a great impact on the development of biofuels, bioenergy and biobased products.

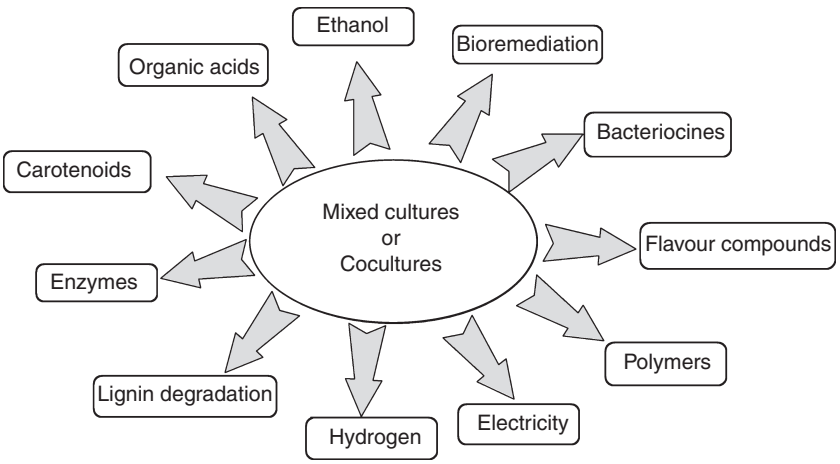

Figure 2 Substances and applications where utilization of coculture or mixed culture fermentation processes is advantageous.

Bulk chemicals, fine chemicals and biofuels

Ethanol

The production of ethanol by fermentation of starches and cellulosic materials is gaining increasing interest because of the increasing economy of bioethanol production caused by the high oil price. Abate *et al.* (1996) described ethanol production by a coculture of *Zymomonas mobilis* and *Saccharomyces sp*. with higher yields and production rates than with either micro-organism in pure culture. The utilization of inulin from artischoke as a substrate for ethanol production by a coculture of *Z. mobilis* and *Kluyveromyces fragilis was described by* Szambelan *et al.* (2004). They achieved a conversion of 94% of the theoretical maximum. In case of sorghum as a substrate for the ethanol production, Mamma *et al.* (1996) suggested a coculture fermentation process with *Saccharomyces cerevisiae* and *Fusarium oxysporum.* Hydrolysis of cellulose and fermentation of the released sugars occurs simultaneously in this example. Another combination of a mould and a yeast for the production of ethanol was reported by Ward *et al.* (1995). *Kluyveromyces marxianus* and *Talaromyces emersonii* were cocultivated at a temperature of 45°C in this example.

Utilization of cellulosic materials for the production of ethanol is hampered by lack of adequate progress in producing monosaccharides from cellulose and in efficient utilization of all the sugars formed. Because products of hydrolysis often cause feedback inhibition of enzymes used for hydrolysis, simultaneous hydrolysis and fermentation has been proposed. An advantage of simultaneous hydrolysis and fermentation of cellulose lies in avoiding the accumulation of glucose and disaccharides. Hence, no product inhibition of the cellulolytic enzymes occurs (Sun and Cheng 2002). Up to now, no single micro-organism (wildtype or recombinant) with a high cellulolytic activity and a simultaneous high yield and production rate of ethanol is known (Demain *et al.* 2005). Considerable improvement in this area has been observed using cocultivation of different micro-organisms for ethanol production from cellulose. Qian *et al.* (2006) reported about a conversion rate of 96·1% within 48 h using softwood hydrolysate as substrate in a coculture fermentation of *Saccharomyces cerevisiae*, *Pachysolen tannophilus* and a recombinant *Escherichia coli* strain. A coculture system of the anaerobic cellulolytic bacterium *Clostridium straminisolvens* and aerobic bacteria resulted in a strong increase in cellulase activity (Kato *et al.* 2004). They explained this improved enzyme production by the consumption of all available oxygen and metabolic degradation of inhibiting substances by aerobic organisms, creating better conditions for *Clostridium straminisolvens*.

Process development for coculture fermentation is crucial for successful application. Farid *et al.* (2002) reported about an increased ethanol production by optimizing the point of inoculation with the second strain of the coculture. Ethanol can also be produced by mixed fermentation instead of coculture fermentation. In this kind of fermentation, unspecified micro-organisms are utilized. Holtzapple *et al.* (1999) developed a stable mixed fermentation system 'MixAlco' for the production of ethanol using unsterile biomass and waste materials as substrates. This offers the opportunity for ethanol production without creating a competition between food and fuel production.

Hydrogen

Hydrogen has lately been in the news as a source of clean energy. It is especially interesting because of its use in fuel cells in space applications where production of any extra waste is highly undesirable. Hydrogen can be produced from renewable resources using obligate anaerobes and

fermentative microbes such as *Clostridium* (Karube *et al.* 1976), *Enterobacter* (Rachman *et al.* 1997) and *Escherichia* (Sode *et al.* 2001). These organisms produce hydrogen from carbon sources such as glucose in pure culture rapidly but with low yields. Requirements of strict anaerobic conditions for the cultivation of obligate anaerobe *Clostridium* have been avoided by coculturing it with facultative *Enterobacter* that acts as scavengers of oxygen in the medium (Yokoi *et al.* 1998). Miyake *et al.* (1984) have reported using a coculture of *Clostridium butyricum* with a photosynthetic bacterium and achieved a net production of 7 moles of hydrogen per mole of glucose. Asada *et al.* (2006) achieved similar molar yields of hydrogen from glucose using a coculture of *Lactobacillus delbrueckii* with a photosynthetic microbe, *Rhodobacter spheroids*. Here, *Lactobacillus* forms lactic acid, which is rapidly converted into hydrogen by the photosynthetic microbe.

Another attempt to produce hydrogen was made by Hsiao *et al.* (2009) using molasses as substrate. A 12–220% increase in hydrogen formation is described by the utilization of a coculture of *Clostridium pasteurianum* F40 or *Clostridium tyrobutyricum* F4 with *Clostridium sporosphaeroides* in comparison with single cultivation. An explanation for this improved hydrogen production might be the utilization of glutamate for the hydrogen production by *C. sporosphaeroides*. Another cheap substrate for hydrogen production is sugarcane distillery effluent. Vatsala *et al.* (2008) used a coculture of *Citrobacter freundii*, *Enterobacter aerogenes* and *Rhodopseudomonas palustris* in a pilot plant with a volume of 100 m^3. The economic evaluation of the production process attests a net gain of $37 000 per year with a yield of 2·7 mol hydrogen per mol glucose. Zeidan and van Niel (2009) were able to increase this yield up to 3·8 mol of hydrogen per mol of C6 sugar (95% of maximal theoretical yield) during a thermophilic cocultivation of *Clostridium kristjanssonii* and *Clostridium saccharolyticus*.

Cui *et al.* (2009) demonstrated the possibility to produce hydrogen by a mixed culture of different bacteria (dominated by *C. pasteurianum*) using beer lees as substrate. In the developed process strategy, an acidic pretreatment drastically increases the hydrogen yield, indicating a low hydrolytic activity of the involved microorganisms. An alternative for the pretreatment of the substrates might be the direct conversion of lignocellulosic material by adapted cocultures. Levin *et al.* (2009) reported about defined cocultivation processes with *Clostridium thermocellum* and *Thermoanaerobacterium sp.* This microbial combination improves the utilization of xylose followed by the hydrogen production.

These authors suggest the development of 'designer consortia' for the production of hydrogen in biorefineries.

Acetic acid

The worldwide annual production of biologically produced acetic acid is more than 190 000 tons (Syldatk 2006). A part of this organic acid is obtained biotechnologically using strains of *Acetobacter* and *Gluconobacter* for the oxidation of ethanol in submerged fermentations. Most of the acetic acid thus produced is utilized in food industry, but some of the acid is used also in the chemical and pharmaceutical industry and in the production of environmentally friendly road salt in the form of Ca and Mg salts. In modern, industrially applied production processes, acetic acid concentrations up to 20% and space-time yields up to 100 g/(l × h) can be achieved. Yields of 94% are obtained in industry (Fregapane *et al.* 1999).

Kondo and Kondo (1996) reported the utilization of a coculture of *Zymomonas mobilis* and *Acetobacter sp*. for the production of acetic acid from glucose with a yield of 95·5% of theoretical maximum. Glucose is fermented to ethanol that is oxidized to acetic acid nearly simultaneously by *Acetobacter sp* in the same bioreactor. This alternative fermentation process reaches comparable yields with industrially applied processes offering the advantage of ethanol formation and acetic acid production simultaneously in one single bioreactor. Talabardon *et al.*(2000) achieved a comparable yield of 96% of theoretical maximum using a coculture of *Clostridium thermolacticum* and *Moorella thermoautotrophica* for the production of acetic acid using lactose as substrate. A threefold increase in the production rate of acetic acid is described by Collet *et al.* (2005) in a coculture of *Clostridium thermolacticum, Moorella thermoautotrophica* and *Methanothermobacter thermoautotrophicus* at a temperature of 58°C in comparison to pure culture of *C. thermolacticum*. The increase in production rate is explained by the conversion of the undesirable lactic acid to acetic acid by *Moorella thermoautotrophica* and by the reduction of hydrogen partial pressure by *Methanobacter thermoautotrophicus*.

Lactic acid

Lactic acid can be used for the synthesis of polylactate (PLA) besides its utilization in the food, pharmaceutical and textile industry. PLA has a wide range of applications. In the form of foils, it can be applied for the production of packages; as a fibre, it is used in the production of clothings (Ingeo® fiber; Natureworks LLC, Minnetonka, MN). It can also be applied in medicine for nontoxic implants (Liu *et al.* 2004) and injectable carriers of tissue cultures (Kang *et al.* 2006). Dow Chemical Inc. and Cargill Inc. have already built a plant with a capacity of 140 000 tons PLA per year (Steinbüchel 2006). Lactic acid is produced in fermentation processes using glucose or glucose-producing

polymers as substrate (Ramakrishna *et al.* 2009). In case of substrates containing cellulose, the addition of cellulases and amylases has been found to be beneficial (Tanaka *et al.* 2006). Simultaneous saccharification and fermentation (SSF) utilizing microbial cocultures saves the addition of these enzymes (Roble *et al.* 2003). Furthermore, substrates in high concentrations can be utilized decreasing production volume and processing costs. Cheaper substrates may be used in lactic acid production when coculture fermentations are utilized as described previously. Utilization of cheaper substrates is critical because carbon source is often the greatest contributor to the cost of microbial products and the price of PLA has to compete with plastics based on mineral oil (John *et al.* 2007).

Cocultivation processes offer the utilization of lignocellulose hydrolysates in the production of lactic acid. Taniguchi *et al.* (2004) reported production of lactic acid from a mixture of xylose and glucose, as a model hydrolysate, to a concentration of 95 g l^{-1} and an optical purity of 96%. In cultivation with a single micro-organism, nearly no degradation of xylose was observed. In cocultures, xylose was metabolized to lactic acid by a two-step conversion involving *Enterococcus casseliflavus* and *Lactobacillus casei*. The simultaneous conversion of a mixture of glucose and xylose to lactic acid by *E. coli* knockout strains is described by Eiteman *et al.* (2009).

Further examples for the industrially relevant bulk chemicals produced by coculture fermentation processes are gallic acid (Banerjee *et al.* 2005), 2-Keto-L-gluconic acid (Yin *et al.* 2001; Bremus *et al.* 2006), polyglutamate (Xu *et al.* 2002), butanol (Bergstrom and Foutch 1985) and hydrogen (Fang and Liu 2002; Khanal *et al.* 2006).

Biopolymers

Non-mineral-oil-based polymers can be produced by micro-organisms using renewable resources. Besides the utilization of renewable substrates, the biodegradability of such polymers is a great advantage of these biopolymers (Patnaik 2005). Use of biodegradable plastics can reduce the landfill requirement of municipal wastes by 16% (EPA 2009). Polyhydroxyalkanoates (PHAs) are of great interest among the biopolymers. This group consists of over 125 different kinds of polymers (Rehm and Steinbuchel 1999), some of which are already produced industrially (Lemos *et al.* 2006). PHAs show lower oxygen permeability than polyethylene and propylene; as a result, they are preferred for packing materials (Salehizadeh and Van Loosdrecht 2004). Improving the fermentative production of PHAs by a coculture of *Azotobacter chroococcum* and *Bacillus megaterium* is suggested by Zhang *et al.* (2003). By the application of neural optimization, the PHB yield of a coculture of *Ralstonia eutropha* and *Lactobacillus delbrueckii* could be increased by 19·4% compared with the single cultivation of *R. eutropha (Patnaik 2009)*.

The price of microbial PHA is strongly dependent on the price of substrates (Khanna and Srivastava 2005). To reduce this cost, Lemos *et al.* (2003) suggest the utilization of propionate-containing wastewaters as a substrate for mixed culture fermentations to produce PHAs. The application of mixed culture fermentation processes, utilizing agricultural and/or industrial wastes, could be very promising in increasing financial attractiveness of PHA production (Dias *et al.* 2006; Verlinden *et al.* 2007).

Lactic acid bacteria can be used not only for the production of lactic acid as substrate for PLA, but also for the production of other biopolymers. *Lactobacillus kefiranofaciens* is able to form the polydextrin, kefiran. This polymer consists of equal amounts of glucose and galactose and has an average molecular mass of 7.6×10^5 g mol^{-1} (Maeda *et al.* 2004b). In animal tests, the intake of kefiran resulted in strongly decreased hypertension and blood fat (Maeda *et al.* 2004a). Hence, the authors suggest the application of kefiran in functional foods. The yield of kefiran can be increased by cocultivation of lactic acid bacteria and the yeast *Saccharomyces cerevisiae* (Cheirsilp *et al.* 2003). Frengova *et al.* (2002) produced kefiran by a cocultivation of *Lactobacillus delbrueckii* ssp. *bulgaricus* and *S. cerevisiae*. In contrast to the pure cultures, the yields could be increased by 70%. A part of this strong increase may have resulted from the consumption of the produced growth-inhibiting lactic acid by the yeast (Tada *et al.* 2007).

The industrial production of polydextrans using whey filtrate as substrate and a coculture of *Rhodotorula rubra*, *Streptococcus thermophilus* and *Lactobacillus bulgaricus* is suggested by Simova *et al.* (2004a). Biotechnological production of another important biopolymer, the cellulose, by a coculture fermentation process consisting of *Gluconacetobacter xylinus* and *Lactobacillus mali* is described by Seto *et al.* (2006). The ecological advantage of fermentative production of cellulose over wood is discussed by Keshk *et al.* (2006). Possible uses of this product could be the medical and pulp and paper industries (Keshk and Sameshima 2005).

Biopolymer succinoglycan production by coculture fermentation process involving *Cellulomonas cellulans* and *Agrobacterium tumefaciens* has been described by Kurata *et al.* (2003). This biopolymer is a potential flocculation additive that does not exhibit noxious or environmentally hazardous effects that are associated with many currently used flocculation additives that contain aluminium. Use of succinoglycan in flocculation additives would enable reduction of subsequent wastewater treatment costs.

Utilization of coculture fermentation processes may improve product quality as well, besides possible reduction

of substrate costs and replacement of environmentally hazardous substances. Kim and Day (1994) reported production of dextrans having lower molecular mass by cocultivation of *Leuconostoc mesenteroides* and *Lipomyces starkeyi* than by *Leuconostoc mesenteroides* alone in pure culture. The low-molecular-mass product is potentially more clinically useful for the application in blood plasma extenders and blood flow improvers.

Enzymes

Cocultures of different micro-organisms may be also advantageous for the production of enzymes. One example is the production of laccases (EC 1.10.3.2). These enzymes are able to hydrolyse the polymer lignin and may allow the utilization of this complex biopolymer for the production of fine chemicals (Eggert *et al.* 1998). Further applications of laccases may be the decolourization of textile dyes (Harazono and Nakamura 2005) or the production of biosensors (Roy *et al.* 2005). Transition elements such as manganese (Faraco *et al.* 2003) or phenolic compounds (Soden and Dobson 2001) are often necessary for the expression of laccases in moulds. Utilization of both compounds results in cost-intensive wastewater treatment. Crowe and Olsson (2001) described the induction of laccase production by cocultivating *Rhizoctonia solani* and *Pseudomonas fluorescens*. The natural induction of laccase production led to a 40-fold increase in the production of laccase during a cocultivation of *Trichoderma harzianum* and *T. versicolor* compared with single cultivation (Baldrian 2004). Also, Verma and Madamwar (2002) and Zhang *et al.* (2006) reported a strong increase in laccase production. The laccase production using *Trametes sp*. AH28-2 in cocultivation with *Trichoderma sp*. ZH1 is comparable to the that using induction with toxic compounds. Additionally, the formation of a laccase only produced with contact to the other microorganism during cocultivation was reported (Zhang *et al.* 2006). These biological approaches may be an environmentally friendly and cost-saving alternative for the production of laccases.

Another industrially important enzyme is tannase (EC 3.1.1.20). It is used in food, feed, pharmaceutical and textile industry (Mahapatra *et al.* 2005). A detailed compilation of yeasts, bacteria and moulds expressing tannase, as well as patented applications and production processes, are published by Aguilar *et al.* (2007). Banerjee *et al.* (2005) described the advantages of tannase production by a coculture of *Rhizopus oryzae* and *Aspergillus foetidus*.

Increased production of cellulases by a coculture of two moulds *Aspergillus ellipticus* and *Aspergillus fumigatus* was described by Gupte and Madamwar (1997). Also, the cocultivation *of Aspergillus niger* and *Trichoderma reesei* increased cellulase production significantly (Ahamed and Vermette 2008).

Production of food additives

Carotenoids

Carotenoids are used in food industry as colouring agents, as nutraceuticals and as antioxidants (Maldonade *et al.* 2007). Carotenoids may be extracted from plants or produced by chemical synthesis or produced from biotechnological processes. Biological production processes offer the opportunities of reducing seasonal dependence on the supply of raw materials and utilization of cheaper substrates (Mapari *et al.* 2005). Buzzini (2001) suggested a coculture of *Rhodotorula glutinis* and *Debaryomyces castellii* for the production of carotenoids from corn – *D. castellii* hydrolyses the polysaccarides in the medium, and the free sugars are then utilized by *Rh. glutinis*, producing the pigments.

Production of carotenoids by a coculture of the lactose-negative yeast *Rhodutorula rubra* and *Lactobacillus casei* ssp. *casei* has also been reported (Simova *et al.* 2003, 2004b). Here, whey filtrate was used as carbon source. Lactose was hydrolysed by *Lactobacillus casei,* enabling the growth of *Rh. rubra* and product formation. Frengova *et al.* (2003) have also reported carotenoid production by cocultures of *Rh. rubra* and *Lactobacillus casei* ssp. *casei*.

Aroma and flavour substances

The demand for aroma and flavour substances is ever increasing. Their extraction from natural resources such as fruits and vegetables is often expensive. Biotechnological production of aroma components may be a good alternative to extraction from natural resources. The flavours thus produced can be declared as 'natural flavour' if the raw materials/precursors for fermentation or enzymatic biotransformation and the product are found in nature or in traditional foods (Vandamme and Soetaert 2002).

Precursors suitable for the production of flavour substances can be carotenoids (Rodriguez-Bustamante and Sanchez 2007). The enzymatic cleavage of carotenoids occurs in plants naturally and contributes to their characteristically aromatic compounds (Simkin *et al.* 2004). Some aromatic compounds can be produced in pure culture. In other cases, a coculture fermentation process may be advantageous or even necessary, for example during the production of components of tobacco aroma. It can be produced by transformation of the carotenoid lutein by a coculture of *Trichosporon asahii* and *Paenibacillus amylolyticus* (Rodriguez-Bustamante

et al. 2005). Cleavage of lutein was metabolized by *T. asahii.* Simultaneously, the antimicrobial substance β-ionone was produced. *P. amylolyticus* is able to reduce this growth-inhibiting substance to the innocuous derivates 7,8-dihydro-β-ionone, 7,8-dihydro-β-ionol and 3.hydroxy-β-ionone (Maldonado-Robledo *et al.* 2003). A toxification of *T. asahii* can thus be avoided by the coculture fermentation. A further coculture fermentation process for the production of tobacco flavour components was described by Sanchez-Contreras *et al.* (2000).

Production of antimicrobial substances

The discovery of antibiotics by Alexander Flemming in 1929 revolutionized the treatment of bacterial diseases such as scarlet fever, gonorrhoea, infected wounds and pneumonia (Demain and Elander 1999). Today, more efforts are being made to the research and development of new antibiotic substances because of the increasing number of pathogenic antibiotic-resistant strains (Appelbaum 2006). A very promising group of substances are the more than 500-member family of antimicrobial peptides (Hancock and Patrzykat 2002; Lai *et al.* 2004), many of them showing a high antibacterial activity (Deslouches *et al.* 2005). Production of these peptides by many micro-organisms has been reported, wherein their expression may be constitutive or induced by the presence of signal substances formed by micro-organisms (Schroder and Harder 2006).

A well-known example of antimicrobial peptides is the antibiotic nisin. It has been approved for microbial stabilization of food in England for over 50 years. Further applications are cosmetics and pharmaceuticals (Delves-Broughton *et al.* 1996). Nisin acts by increasing permeability of membranes of Gram-positive bacteria resulting in growth inhibition or even cell death. It is produced by *Lactococcus lactis*, but its production can be increased by cocultivation of the lactic acid bacterium *with Saccharomyces cerevisiae* or *Kluyveromyces marxianus* (Shimizu *et al.* 1999; Liu *et al.* 2006). Voravuthikunchai *et al.* (2006) reported the production of an antimicrobial peptide by *Lactobacillus reuteri,* effective against methicillin-resistant *S. aureus* (MRSA).

Production of antibacterial peptides may be enhanced by recombination techniques after identification and characterization of the encoding genes by homologous or heterologous expression in micro-organisms (Brede *et al.* 2005). Production of antibacterial peptides by cocultures may be advantageous in areas where no recombinant micro-organisms should be used. The induction of plantaricin production by the cocultivation of *Lactobacillus plantarum NC8* and *Lactococcus lactis* is described by Maldonado *et al.* (2004). These authors hypothesized a quorum-sensing mechanism responsible for the induction.

Besides the production of antimicrobial peptides, coculture fermentation processes may lead to the discovery and characterization of new antimicrobial peptides also attributable to the unique induction phenomenon observed in cocultivation. In this context, Rojo-Bezares *et al.*'s (2007) report of the formation of a bactriocide by *Lactobacillus plantarum J23* in coculture with *Oenococcus oeni*, *Lactobacillus* ssp. or *Pediococcus species* only is noteworthy.

The number of antimicrobially active substances produced by strains of the genus *Streptomyces* is estimated to be as many as 100 000. Today, only 3–5% of these substances are known. Slattery *et al.* (2001) published the cocultivation-dependent formation of antibiotics by a strain of *Streptomyces* with different marine bacteria, indicating the importance of coculture fermentations for the discovery of new antibiotics.

Besides bacteria, various fungi also produce and secrete antimicrobial substances. The antifungal protein (AFP) from *Aspergillus giganteus* inhibits the growth of human and plant pathogen filamentous fungi by permeabilizing their cellular membrane (Theis *et al.* 2003). On the other hand, bacteria, yeasts and endothelian cells are not influenced by AFP (Szappanos *et al.* 2006). The possibility of the application of AFP in medicine and plant protection is discussed by Hagen *et al.* (2007). During the cocultivation of *Aspergillus giganteus* and *Fusarium oxysporum,* an increased production of AFP was observed (Meyer and Stahl 2003). Direct cell–cell interactions between the micro-organisms might be responsible for the enhanced production.

The examples described here show the impact of coculture fermentations on the development and production of antimicrobial substances. During production processes of foods and pharmaceuticals, the possible horizontal gene transfer and its impact on the products have to be considered (Heng *et al.* 2007).

Microbial fuel cell

Microbial fuel cells (MFC) represent a very innovative field of research. Recent review articles dealing with the development of MFCs indicate the great interest and high potential of the microbial power generation (Bullen *et al.* 2006; Stams *et al.* 2006; Du *et al.* 2007; Schroder 2007). The production of electricity in MFCs enables direct conversion of biomass to electricity without the circuitous route of e.g. ethanol or biogas production. Nearly every organically degradable compound may be utilized for the production of electricity (Logan 2007). In the MFCs, the capability of special micro-organisms, the so-called exoelectrogenes, is utilized to transfer electrons to solid substrates (anode) under anaerobic conditions

(Bond and Lovley 2003). The simultaneously produced protons bind to oxygen at the cathode consuming electrons in the aerobic chamber of the MFC.

The utilization of dilute solutions in MFCs is advantageous. Ren *et al.* (2007) reported about the production of electricity from medium containing cellulose, by a coculture of *Clostridium cellulolyticum* and *Geobacter sulfurreducens.* Also, a biofilm-forming coculture of *Acetobacter aceti* and *Gluconobacter roseus* was applied for the current production (Karthikeyan *et al.* 2009). Rismani-Yazdi *et al.* (2007) developed a complex mixed culture for the utilization of cellulose during the electricity production.

The power generation by a mixed culture during wastewater treatment is reported by Kargi and Eker (2007). Some of the strains identified were *Geobacter* sp., *Desulfuromonas* sp., *Alcaligenes faecalis*, *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Clostridium* sp., *Bacteroides* sp., *Aeromonas* sp. and *Brevibacillus* sp. The advantage of utilizing mixed cultures in contrast to cocultures is increased process stability and the metabolic conversion of different substrates (Pham *et al.* 2006).

Bioremediation

Harmful chemical substances as organophosphate esters, alkanes, polycyclic aromatic hydrocarbons (PAH) and polychloride biphenyls (PCB) may be set free during accidents, incautious handling, application in agricultural pesticides or in waste and faeces. If these substances are not eliminated from the atmosphere, they will cause serious damage to ecology and human health. Therefore, processes have to be developed to remove the harmful chemicals. In many cases, the degradation can be achieved at lower costs.

Li *et al.* (2008) present results about the synergistic effect between *Mycobacterium* sp. and *Cladosporium* sp. during the degradation of diesel pollution. Many microorganisms involving strains of *Rhodococcus* sp., *Burkholderia* sp., *Mycobacterium* sp., *Stenotrophomonas* sp., *Alcaligenes* sp., *Sphingomonas* sp., *Phanerochaete* sp., *Pleurotus* sp., *Trametes* sp., *Penicillium* sp. and *Cunninghamella* sp. are known to degrade PAHs containing four benzene rings in single cultivation. However, during the degradation of PAHs containing five benzene rings by single cultivations only particular steps of the mineralization are observed (Boonchan *et al.* 2000). The utilization of a coculture of the fungus *Penicillium janthinellum* and the bacterium *Stenotrophomonas maltophilia* offers the possibility for the degradation of these mutagenic and carcinogenic PAHs (Boonchan *et al.* 2000).

Kim and Lee (2007) described the degradation of PAHs by a coculture of *Penicillium* sp. and *Rhodococcus* sp. They assumed a first oxidizing step catalysed by fungal enzymes resulting in an improved solubility of the PAHs. Afterwards, the bacterium is able to catalyse further oxidizing steps. An actual overview of more than 20 microorganisms degrading aromatic compounds is given by Seo *et al.* (2009). Another large group of hazardous pollutants are the organophosphate esters including tris (2-chloroethyl) phosphate (TCEP) and tris(1,3-dichloro-2-propyl) phosphate (TDCPP). These chemicals are used worldwide in pesticides, flame retardants and plasticizers in large amounts (WHO: Environmental Health 1997). Increasing amounts of these toxic and mutagenic substances are detected in soil (Fukushima *et al.* 1992), sediments (Kawagoshi *et al.* 1999) and even in drinking water (LeBel *et al.* 1981). To avoid further accumulation in environment, microbial degradation processes of TCEP and TDCPP using mixed cultures of *Acidovorax* sp., *Sphingomonas* sp. and *Aquabacterium* sp. were developed by Takahashi *et al.* 2008. This coculture was also able to degrade the toxic metabolites by dechlorification.

The given examples indicate the great chances of utilization of combined enzymatic activities of different micro-organisms in the degradation of pollutants in water and soil.

Utilization of Lignocellulose in bioconversion

Lignocellulose is the major structural component of all plants and consists mainly of cellulose, hemicellulose and lignin. To utilize the lignocellulose for the production of biofuels or biobased chemicals, discussed in previous sections, an efficient hydrolysis of the different branched polysaccharides followed by the conversion of glucose and xylose is required. Coculture fermentation processes offer the possibility to implement all necessary enzymatic conversions in one bioreactor. In some cases, a stepwise fermentation process is suggested.

The simultaneous conversion of glucose and xylose to ethanol by the coculture of *Z. mobilis* and *P. stipidis* was reported by Fu *et al.* (2009). Maki *et al.* (2009) reported about several applications of *Clostridium thermocellum* together with other strains of *Clostridium* sp. or *Thermoanaerobacterium saccharolyticum*. The cellulase- and hemicellulase-producing *C. thermocellum* can only metabolize glucose, whereas the other micro-organisms can utilize the hemicellulose-derived pentoses. This cocultivation process improves product formation because of avoiding substrate competition between species.

Table 1 presents an overview of the mixed culture and coculture fermentation processes described in this article.

Table 1 Overview of cocultures applied in biotechnology

Product/process	Applied micro-organisms	Reference
Food industry		
Cheese	Yeast, bacteria, moulds	Martin *et al.* 2001
Yoghurt	*Lactobacillus* sp., *Streptococcus* sp.	Sodini *et al.* 2000
Kefir	*Candida kefyr, Lactobacillus* sp., *Kluyveromyces* sp., *Saccharomyces* sp.	Lopitz-Otsoa *et al.* 2006
African fermented dairy products	*Candida* sp., *Saccharomyces* sp., *lactic acid bacteria,*	Narvhus and Gadaga 2003
Sourdough	*Lactobacillus* sp., *Saccharomyces* sp.	Kariluoto *et al.* 2006
Salami	*Lactobacillus* sp., *Pediococcus* sp., *Micrococcus* sp., *Staphylococcus* sp.	Dicks *et al.* 2004
Whisky	*Streptococcus* sp., *Lactobacillus* sp., *Saccharomyces* sp.	Van Beek and Priest 2002
Lambic	*Lactobacillus* sp., *Brettanomyces* sp.	De Cort *et al.* 1994
Wine	*Saccharomyces* sp. *Brettanomyces* sp., *Pichia* sp., *Gluconobacter* sp., *Acetobacter* sp.	Clemente-Jimenez *et al.* 2005; Fleet 2003; Renouf *et al.* 2006
Cacao beans	Yeasts, lactic acid bacteria, acetic acid bacteria	Schwan and Wheals 2004
Bulk chemicals, fine chemicals and biofuels		
Ethanol	*Zymomonas mobilis, Saccharomyces* sp.	Abate *et al.* 1996
	Zymomonas mobilis, Kluyveromyces fragilis	Szambelan *et al.* 2004
	Saccharomyces cerevisiae, Fusarium oxysporum	Mamma *et al.* 1996
	Kluyveromyces marxianus, Talaromyces emersonii	Ward *et al.* 1995
Butanol	Different Clostridium strains	Bergstrom and Foutch 1985
Hydrogen	*Clostridium* sp., *Enterobacter* sp.	Yokoi *et al.* 1998
	Clostridium butyricum, Rhodopseudomonas sp.	Miyake *et al.* 1984
	Lactobacillus delbrueckii; Rhodobacter spheroids	Asada *et al.* 2006
	Clostridium pasteurianum, Clostridium tyrobutyricum, Clostridium sporosphaeroides	Hsiao *et al.* 2009
	Citrobacter freundii, Enterobacter aerogenes, Rhodopseudomonas palustris	Vatsala *et al.* 2008
	Clostridium kristjanssonii, Clostridium saccharolyticus	Zeidan and van Niel 2009
	Clostridium pasteurianum, Different bacteria	Cui *et al.* 2009
	Clostridium thermocellum, Thermoanaerobacterium sp.	Levin *et al.* 2009
Acetic acid	*Zymomonas mobilis/Acetobacter* sp.	Kondo and Kondo 1996
	Clostridium thermolacticum/Moorella thermoautotrophica	Talabardon *et al.* 2000
	Clostridium thermolacticum, Moorella thermoautotrophica, Methanothermobacter thermoautotropicus	Collet *et al.* 2005
Lactic acid	*Enterococcus casseliflavus, Lactobacillus casei*	Taniguchi *et al.* 2004
	Different rec. *Escherichia coli* strains	Eiteman *et al.* 2008
Gallic acid	*Aspergillus foetidus, Rhizopus oryzae*	Banerjee *et al.* 2005
2-Keto-L-gluconic acid	*Gluconobacter oxydans, Bacillus megaterium*	Bremus *et al.* 2006
Polyglutamate	*Bacillus subtilis, Corynebacterium glutamicum*	Xu *et al.* 2002
Polyhydroxyalkanoate	*Azotobacter chroococcum, Bacillus megaterium*	Zhang *et al.* 2003
	Ralstonia eutropha, *Lactobacillus delbrueckii*	Patnaik 2009
Kefiran	*Saccharomyces cerevisiae, Lactobacillus* sp.	Cheirsilp *et al.* 2003; Frengova *et al.* 2002
Polydextrans	*Rhodutorula rubra, Streptococcus thermophilus, Lactobacillus bulgaricus*	Simova *et al.* 2004a
Cellulose	*Gluconacetobacter xylinus, Lactobacillus mali*	Seto *et al.* 2006
Biopolymer	*Cellulomonas cellulans, Agrobacterium tumefaciens*	Kurata *et al.* 2003
Dextrans	*Leuconostoc mesenteroides, Lipomyces starkeyi*	Kim and Day 1994
Laccase	*Rhizoctonia solani, Pseudomonas fluoreszenz*	Crowe and Olsson 2001
	Trichoderma harzianum, *T. versicolor*	Baldrian 2004
	Pleurotus ostreatus, Phanerochaete chrysosporium	Verma and Madamwar 2002
	Trametes sp., *Trichoderma* sp.	Zhang *et al.* 2006

Table 1 (*Continued*)

Product/process	Applied micro-organisms	Reference
Tannase	*Penicillium glaucum, Aspergillus niger*	Aguilar *et al.* 2007
	Rhizopus oryzae, Aspergillus foetidus	Banerjee *et al.* 2005
Cellulase	*Aspergillus ellipticus, Aspergillus fumigates*	Gupte and Madamwar 1997
	Aspergillus niger, *Trichoderma reesei*	Ahamed and Vermette 2008
Food additives		
Carotenoid	*Rhodutorula glutinis, Debaromyces castellii*	Buzzini 2001
	Rhodutorula rubra, Lactobacillus casei	Frengova *et al.* 2003; Simova *et al.* 2004b
Tobacco aroma	*Trichosporon asahii, Paenibacillus amylolyticus*	Rodriguez-Bustamante *et al.* 2005
	Geotrichum sp., *Bacillus* sp.	Sanchez-Contreras *et al.* 2000
Antimicrobial substances		
Nisin	*Lactobacillus* sp., *Saccharomyces cerevisiae, Kluyveromyces cerevisiae*	Liu *et al.* 2006
Antifungal Protein (AFP)	*Aspergillus giganteus; Fusarium oxysporum*	Meyer and Stahl 2003
Antibacterial Protein (AlpP)	*Pseudoalteromonas tunicate; Alteromonas* sp.	Rao *et al.* 2005
Antimicrobial Proteins	*Serratia plymuthica; Escherichia coli*	Moons *et al.* 2006
Plantaricin	*Lactobacillus plantarum, Lactococcus lactis*	Maldonado *et al.* 2004
Antibiotics	*Streptomyces* sp.; different marine bacteria	Slattery *et al.* 2001
Microbial fuel cell (MCF)		
Electricity	*Clostridium cellolyticum, Geobacter sulfurreducens*	Ren *et al.* 2007
	Geobacter sp., *Desulfuromonas* sp., *Alcaligenes faecalis*	Kargi and Eker 2007
	Acetobacter aceti, *Gluconobacter roseus*	Karthikeyan *et al.* 2009
Bioremediation		
Pollutant degradation	*Penicillium janthinellum*, *Stenotrophomonas maltophilia;*	Boonchan *et al.* 2000
	Sphingomonas sp. and *Aquabacterium* sp.	Takahashi *et al.* 2008
	Cladosporium sp., *Mycobacterium*	Li *et al.* 2008
Lignocellulose for bioconversion		
Lignocellulose degradation	*Zymomonas mobilis*, *Pichia stipidis*	Fu *et al.* 2009
	Clostridium thermocellum, Thermoanaerobacterium saccharolyticum	Maki *et al.* 2009

Conclusions

The given examples of possible applications of coculture fermentation processes illustrate the increasing importance of this kind of fermentation in industrial biotechnology. Coculture fermentations can be utilized in the production of foods, food additives, pharmaceuticals, enzymes, bulk and fine chemicals, bioremediation and degradation of lignocelluloses. They offer the opportunity to use cheap substrates, increase yields and product quality. Further potential of cocultures rests in the discovery of new substances with industrial or pharmaceutical interest such as fine chemicals or antibacterial active substances and other secondary metabolites that are produced in cocultivation only.

The controlled cultivation of cocultures enables the synergistic utilization of the metabolic pathways of the participating micro-organisms under industrial, reproducible and controlled conditions. The optimal values of process parameters (pH, temperature and oxygen demand) and the acceptable ranges of substrate and product concentrations have to be known and considered to achieve the controlled fermentation, as in pure culture cultivation. In coculture fermentation processes, the complexity of possible interactions (positive or negative) has to be taken into account. All aspects, the process parameters, the produced and secreted substances and possibly the occurring biotransformations, may provide an opportunity to control growth and product formation during coculture fermentation processes. Parameters have to be found enabling the utilization of the desired part of the metabolic pathway of every single strain in coculture to achieve the development of a controlled coculture fermentation process and to form the favoured product.

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