Review Article

Microbial Cell Factories in Bioprocessing Engineering: Metabolic Engineering for Sustainable Biomanufacturing

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Abstract: Microbial cell factories—microorganisms reprogrammed to convert renewable feedstocks into value-added molecules—have become central to modern bioprocessing engineering. Advances in systems and synthetic biology, genome editing and high-throughput screening now permit the rational design of strains that manufacture fuels, bulk and fine chemicals, pharmaceuticals and materials that were previously accessible only through petrochemical routes. This review outlines the conceptual framework and enabling technologies of microbial cell factory development, including host (chassis) selection, pathway construction and balancing, flux optimisation through metabolic and regulatory engineering, and the iterative design–build–test–learn cycle. Landmark achievements are highlighted, among them the semi-synthetic production of the antimalarial precursor artemisinic acid in Saccharomyces cerevisiae, the commercial fermentative manufacture of 1,3-propanediol and 1,4-butanediol, and gas fermentation of carbon-monoxide- and carbon-dioxide-rich streams by acetogenic bacteria. The expanding toolbox of CRISPR-based genome editing, dynamic biosensor-driven control, genome-scale metabolic modelling and machine learning is discussed as a driver of predictable strain engineering. Attention is also given to non-conventional hosts such as Yarrowia lipolytica and Pichia pastoris, and to the bioprocess considerations—medium design, fermentation mode, oxygen transfer, scale-up and downstream recovery—that decide whether a promising strain becomes an economically viable process. Persistent challenges, including metabolic burden, redox and cofactor imbalance, modest product titres, and the gap between laboratory and industrial performance, are examined alongside emerging solutions. Microbial cell factories are positioned as a cornerstone technology for a sustainable, circular bioeconomy.

Keywords: Bioprocessing engineering; CRISPR; Fermentation; Metabolic engineering; Microbial cell factory; Saccharomyces cerevisiae; Synthetic biology; Yarrowia lipolytica.

Citation: Subiksha Periyasamy and Berciyal Golda Peter. Microbial Cell Factories in Bioprocessing Engineering: Metabolic Engineering for Sustainable Biomanufacturing. *Int J Adv Interdis Res*. 2026, 06, e004.

Received : 22 Jul 2026
Revised : 28 Aug 2026
Accepted : 21 Aug 2026
Published : 11 Sep 2026

INTRODUCTION

The dependence of modern society on petroleum-derived fuels and chemicals, together with mounting concern over greenhouse-gas emissions and resource depletion, has driven an urgent search for renewable, low-carbon routes to manufacturing [1]. Biological production—the use of living cells as catalysts that convert inexpensive substrates into desired products—offers one of the most promising alternatives and lies at the heart of bioprocessing engineering. Within this field, the concept of the microbial cell factory has emerged as a unifying idea: a microorganism deliberately

engineered so that its metabolism is redirected toward the efficient synthesis of a target molecule [2]. Rather than treating the cell as a black box, the contemporary bioprocess engineer reprograms its genetic and regulatory circuitry so that carbon, energy and reducing power flow preferentially toward the product of interest.

The range of molecules that microbial cell factories can produce is remarkably broad, spanning bulk commodity chemicals, liquid transport fuels, industrial enzymes, food and feed additives, nutraceuticals, cosmetic ingredients and high-value pharmaceuticals [2, 3]. What unites these diverse targets is a common engineering logic. A suitable host is selected, one or more biosynthetic pathways are introduced or amplified, competing reactions are attenuated, and the resulting strain is cultivated under controlled conditions that maximise titre, rate and yield. The maturation of systems metabolic engineering—which integrates genome-scale analysis, synthetic biology and evolutionary approaches—has transformed this logic from a largely empirical craft into an increasingly predictive engineering discipline [3, 4].

This review provides a concise overview of microbial cell factories from the perspective of bioprocessing engineering. It describes the selection of microbial chassis, the enabling technologies that make rational strain design possible, and representative flagship products that have reached commercial or near-commercial status. It then considers the bioprocess and scale-up factors that determine industrial viability, and closes with the principal challenges and future directions for the field.

THE MICROBIAL CHASSIS: HOST SELECTION

The choice of host organism, or chassis, is the first and often decisive step in cell factory development. An ideal chassis grows rapidly on inexpensive media, tolerates industrial process conditions, is genetically tractable, and is recognised as safe for its intended application. In practice, no single organism satisfies every requirement, and host selection therefore reflects a compromise between physiological capability and engineering convenience [4].

The bacterium Escherichia coli remains the workhorse of the field owing to its fast growth, well-characterised genetics and an unrivalled molecular toolkit; it has been engineered to produce amino acids, organic acids, biofuels and pharmaceutical intermediates. The yeast Saccharomyces cerevisiae is equally prominent, particularly for products that require eukaryotic folding, compartmentalisation or cytochrome-P450 chemistry, and it withstands the low pH and high osmolarity typical of industrial fermentation. Beyond these two model organisms, so-called non-conventional hosts are gaining ground: the oleaginous yeast Yarrowia lipolytica offers abundant acetyl-CoA and lipid precursors for the synthesis of fatty acids, terpenoids and polyketides [19], while the methylotroph Pichia pastoris (Komagataella phaffii) is a leading

platform for high-titre secretion of recombinant proteins. Filamentous fungi such as Aspergillus species dominate industrial enzyme and organic-acid manufacture, and acetogenic and cyanobacterial hosts extend the substrate range to gaseous and photosynthetic feedstocks. Matching the metabolic and tolerance profile of the chassis to the target product and feedstock is a foundational engineering decision that constrains everything that follows (Table 1).

Table 1: Principal microbial chassis used as cell factories and their engineering characteristics

Host organism	Type	Key advantages	Representative products	Main limitations
Escherichia coli	Bacterium	Fast growth; unrivalled genetic toolkit; well-characterised metabolism	Amino acids, organic acids, biofuels, drug intermediates	Endotoxin; limited protein folding; phage sensitivity
Saccharomyces cerevisiae	Yeast	Eukaryotic folding; P450 chemistry; acid and osmotic tolerance; GRAS status	Terpenoids, alkaloids, isoprenoids, ethanol	Slower growth; Crabtree effect (ethanol overflow)
Yarrowia lipolytica	Oleaginous yeast	Abundant acetyl-CoA and lipid precursors; grows on hydrophobic substrates	Fatty acids, terpenoids, polyketides, lipids	Fewer genetic tools than model hosts
Pichia pastoris	Methylotrophic yeast	High-density growth; strong regulated promoters; efficient secretion	Recombinant and therapeutic proteins	Methanol handling; hyper-glycosylation
Aspergillus spp.	Filamentous fungus	High secretion capacity; industrial robustness	Industrial enzymes, citric and other organic acids	Complex morphology; viscous broths
Clostridium autoethanogenum	Acetogenic bacterium	Fixes CO/CO_2 gases via Wood–Ljungdahl pathway	Ethanol and chemicals from waste gases	Strict anaerobe; low energy yield

ENABLING TECHNOLOGIES FOR STRAIN ENGINEERING

The transformation of a wild-type microbe into an efficient cell factory rests on a layered toolbox of molecular and computational techniques. Classical metabolic engineering focused on the overexpression of rate-limiting enzymes and the deletion of competing pathways to redirect flux toward a product. While powerful, this targeted approach is limited by the highly interconnected and tightly regulated nature of cellular metabolism, in which a single genetic change can trigger unforeseen compensatory responses [3].

Synthetic biology has supplied a growing library of standardised, characterised genetic parts—promoters, ribosome-binding sites, terminators, and regulatory circuits—that allow biosynthetic pathways to be assembled and tuned with predictable behaviour [5]. Balancing the expression of successive pathway enzymes is critical, because the accumulation of a toxic or inhibitory intermediate can negate the benefit of a high-flux pathway. Fine control of relative enzyme levels, achieved through promoter engineering, codon

optimisation and modular pathway design, is therefore a central task of the discipline.

Genome editing has been revolutionised by CRISPR–Cas systems, which enable rapid, precise and multiplexed modification of microbial genomes in hosts ranging from E. coli to S. cerevisiae [6, 7]. Catalytically inactive Cas variants (dCas9) further permit CRISPR interference and activation, so that gene expression can be tuned up or down without altering the underlying DNA sequence. Dynamic regulation represents a further advance: metabolite-responsive biosensors can be coupled to pathway genes so that the cell autonomously adjusts flux in real time, relieving the trade-off between growth and production and preventing the build-up of toxic intermediates [8].

Underpinning these experimental tools is a computational layer. Genome-scale metabolic models allow the in-silico prediction of gene-knockout and overexpression targets before any strain is built [9], while the accumulation of large multi-omics datasets has made machine learning an increasingly valuable guide to strain and process optimisation. Together these capabilities are organised into the iterative design–build–test–learn cycle, in which each round of engineering informs the next, progressively shrinking the vast search space of possible genetic designs and accelerating the path to a high-performing strain (Figure 1) [3, 4].

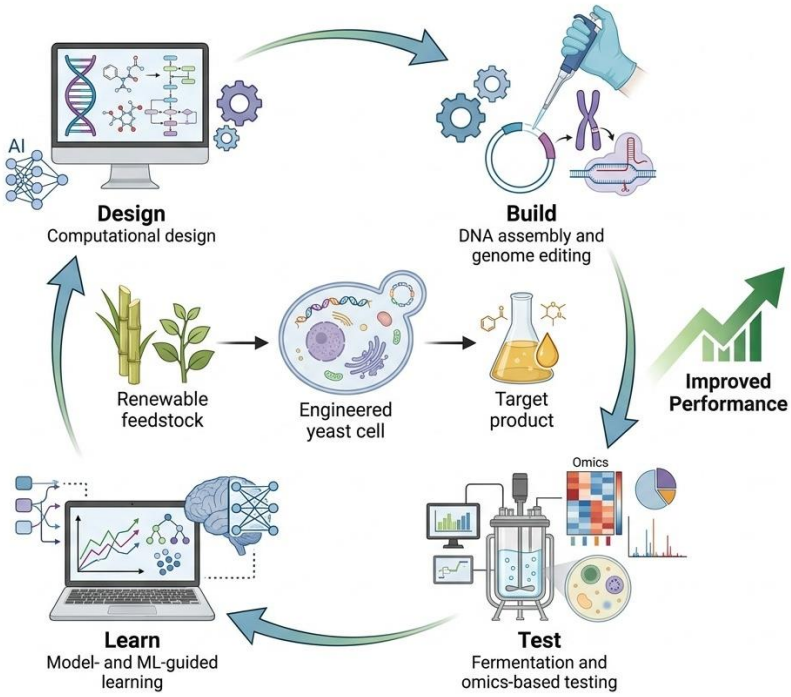

Figure 1. The iterative design–build–test–learn (DBTL) cycle of microbial cell factory development. A renewable feedstock is converted by an engineered microbial chassis into a target product; successive rounds of computational design, DNA assembly and genome editing, fermentation and omics-based testing, and model- and machine-learning-guided learning progressively improve strain performance

FLAGSHIP PRODUCTS AND PROCESSES

The practical value of microbial cell factories is best appreciated through the products that have reached industrial or clinical significance. In the pharmaceutical arena, the microbial synthesis of the antimalarial precursor artemisinic acid in engineered S. cerevisiae is a defining achievement. By importing and optimising a plant-derived terpenoid pathway, yeast was engineered to accumulate artemisinic acid at high titre [10]; subsequent strain and process improvements enabled semi-synthetic artemisinin to be manufactured at commercial scale, providing a stable supplementary supply of a drug otherwise dependent on variable plant harvests [11]. The same isoprenoid logic has since been extended to the yeast-based synthesis of complex plant alkaloids, including the complete biosynthesis of opioids from simple sugars [12], and to the production of the anticancer precursor taxadiene in E. coli [13].

Among commodity chemicals, the fermentative production of 1,3-propanediol represents a landmark in industrial biotechnology. An engineered E. coli strain converting glucose to this polyester monomer displaced a petrochemical route and demonstrated that a bio-based process could compete on cost and performance [14]. The subsequent design of an E. coli strain for the direct fermentation of 1,4-butanediol—a molecule with no natural biosynthetic pathway—showed that entirely non-natural routes could be conceived, modelled and realised, and the process was commercialised [15]. These successes established microbial cell factories as credible competitors to established chemical manufacturing.

The field has also targeted advanced biofuels that surpass the fuel properties of ethanol. Non-fermentative pathways were engineered to divert amino-acid precursors toward branched-chain higher alcohols such as isobutanol [16], while fatty-acid metabolism has been redirected in both E. coli and S. cerevisiae to yield fatty-acid esters, alkanes and other diesel-like molecules directly from renewable biomass [17, 20]. A particularly promising frontier is the use of one-carbon and gaseous substrates. Acetogenic bacteria such as Clostridium autoethanogenum ferment carbon-monoxide- and carbon-dioxide-rich industrial off-gases into ethanol and other chemicals through the Wood–Ljungdahl pathway, a gas-fermentation platform now operating at commercial scale that couples chemical production with carbon capture [18]. Collectively these examples, summarised in Table 2, map the trajectory of the field from high-value, low-volume pharmaceuticals to low-value, high-volume fuels and commodities [21]..

BIOPROCESS INTEGRATION AND SCALE-UP

A high-performing strain is a necessary but not a sufficient condition for a successful bioprocess. The performance observed in a shake flask frequently deteriorates on scale-up, because large bioreactors impose gradients of dissolved oxygen, pH, temperature and substrate concentration that cells do

not experience in small vessels. Bridging this gap is a core responsibility of bioprocessing engineering and requires the strain and the process to be developed together rather than in sequence [22].

Table 2: Representative products manufactured by engineered microbial cell factories

Product	Category	Host	Feedstock	Status	Ref.
Artemisinic acid	Pharmaceutical precursor	*S. cerevisiae*	Sugars	Commercial	[10, 11]
Opioids	Pharmaceutical	*S. cerevisiae*	Sugars	Proof of concept	[12]
Taxadiene	Anticancer precursor	*E. coli*	Glucose	Pilot	[13]
1,3-Propanediol	Polymer monomer	*E. coli*	Glucose	Commercial	[14]
1,4-Butanediol	Commodity chemical	*E. coli*	Sugars	Commercial	[15]
Isobutanol	Advanced biofuel	*E. coli*	Glucose	Pilot / scale-up	[16]
Fatty-acid biofuels	Biofuel	*E. coli* / *S. cerevisiae*	Plant biomass	Demonstration	[17, 20]
Ethanol	Fuel / chemical	*C. autoethanogenum*	CO / CO_2 gases	Commercial	[18]

Key process variables include the composition of the culture medium, the mode of operation—batch, fed-batch or continuous—and the control of oxygen transfer, which is often the limiting factor in aerobic fermentation. Fed-batch operation, in which substrate is supplied gradually, is widely used to avoid substrate inhibition and overflow metabolism while sustaining high cell densities. Precise on-line monitoring and feedback control of these parameters, increasingly informed by process models and soft sensors, keep the population within the physiological window in which the engineered pathway performs best. Reactor geometry, mixing and mass-transfer characteristics must in turn be chosen to preserve laboratory performance at cubic-metre scale.

Downstream processing—the recovery and purification of the product from the fermentation broth—frequently dominates the overall cost of manufacture, particularly for low-value bulk chemicals present at modest concentration in a complex aqueous mixture. The choice of separation technology, whether extraction, precipitation, membrane filtration, adsorption or distillation, is dictated by the physical and chemical properties of the product and by the required purity. Efficient, low-energy recovery is therefore an integral design objective, and product titre, secretion and stability are engineered into the strain from the outset precisely because they govern the feasibility and cost of downstream operations.

CHALLENGES AND FUTURE PERSPECTIVES

Despite substantial progress, several persistent obstacles limit the wider deployment of microbial cell factories. The expression of a heterologous pathway imposes a metabolic burden that diverts resources from growth and can render an engineered strain unstable or prone to loss-of-production mutants over successive generations. Imbalances in redox cofactors and precursor supply constrain flux toward the product, while many laboratory strains achieve titres, rates and yields that fall short of the thresholds required for economic viability. The tolerance of the host to its own product and to inhibitors present in inexpensive, real-world feedstocks is a further frequent bottleneck.

Emerging strategies address these limitations on several fronts. Dynamic and autonomous control circuits balance growth against production and buffer against toxic intermediates [8]; adaptive laboratory evolution improves tolerance and robustness; and cell-free and co-culture systems distribute complex pathways across specialised populations or remove the constraints of cell viability altogether. Machine-learning-guided design, coupled with automated, high-throughput “biofoundry” infrastructure, is accelerating the design–build–test–learn cycle and improving the predictability of strain engineering [3]. The expansion of feedstocks toward carbon dioxide, industrial waste gases, lignocellulosic hydrolysates and other non-food substrates aligns the technology with the goals of a circular, low-carbon economy [18]. Progress in genome-scale modelling and in the engineering of non-conventional and consortium-based systems is expected to widen still further the range of accessible products and substrates.

CONCLUSION

Microbial cell factories have evolved from a promising laboratory concept into a mature technology that already underpins the commercial production of pharmaceuticals, commodity chemicals and fuels. The convergence of systems and synthetic biology, CRISPR-based genome editing, dynamic regulation and computational design has made strain engineering faster and more predictable, while advances in fermentation and downstream processing translate engineered strains into viable industrial processes. Significant challenges remain—metabolic burden, cofactor imbalance, modest titres and the persistent gap between laboratory and industrial performance—but the direction of travel is clear. As feedstocks broaden to include waste gases and non-food biomass, and as design tools grow more powerful, microbial cell factories are set to become a cornerstone of sustainable manufacturing and of the emerging circular bioeconomy.

CONFLICT OF INTEREST

The Authors have no Conflict of Interest.

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