BIOTECHINTELLECT, 2027, 4 (1) e1 (1-23)

https://jbiotechintel.com/index.php/biotechintel

Review Article

eISSN: 3115-7920

OPEN ACCESS

Artificial Intelligence as Transformative Tool in Polyhydroxyalkanoate Research and Production over the Coming Decades

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Article history:

Received	17 Sep 2026
Revised	18 Nov 2026
Accepted	23 Nov2026
Published online	25 Nov 2026

Keywords: Polyhydroxyalkanoates (PHA); Artificial intelligence; Machine learning; Bioprocess optimization; Circular bioeconomy

How to cite this article:
Koller M. Artificial intelligence: as transformative tool in polyhydroxyalkanoate research and production over the coming decades. BiotechIntellect, 2027; 4(1): e1, 1-23.
https://doi.org/10.66224/BiotechIntellect.4.1.65

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ABSTRACT

Background and Objective: Polyhydroxyalkanoates (PHAs) are a diverse family of prokaryotic polyesters with considerable potential as bio-based and biodegradable alternatives to conventional petrochemical plastics. However, despite decades of intensive research and development, their broader adoption and ultimate market breakthrough remain constrained by production costs, variable feedstock quality, difficulties in controlling intracellular polymer architecture, energy- and solvent-intensive recovery, regulatory aspects, and uncertainty regarding performance and biodegradation under real-world conditions. Artificial intelligence (AI), particularly machine learning (ML), is increasingly regarded as a tool of choice for addressing these intertwined limitations. AI and ML can advance PHA production by extracting predictive relationships from genomic, process (fermentation and downstream processing), materials, environmental, and techno-economic data. Over the coming decades, AI is likely to play a decisive role in supporting the synthetic-biology-based design of microbial cell factories, accelerating enzyme and pathway engineering, enabling adaptive control of continuous and discontinuous fermentation processes, improving the economics and sustainability of downstream product recovery, and linking molecular architecture to processing behavior, product performance, and end-of-life scenarios.

Results and Conclusion: Importantly, the greatest gains are expected to arise not from replacing mechanistic science, hence, knowledge of the underlying biological, chemical, and physical mechanisms, but from integrating data-driven models with metabolic models, bioreactor engineering, polymer architecture, life-cycle assessment, and application-specific testing. Accordingly, this critical review examines the anticipated impact of AI across the entire PHA value chain, discusses the scientific and infrastructural conditions required for reliable deployment, and presents a vision in which increasingly autonomous research platforms and digitally coordinated and managed biorefineries may emerge. It argues that trustworthy datasets, uncertainty-aware modelling, interoperability, and rigorous experimental validation will determine whether AI delivers genuine advances rather than merely accelerating the optimization of inadequately defined, low-performing systems.

What is "already known":	• PHA is bio-based & biodegradable polyesters with tuneable properties; performance & biodegradation depend on composition, processing, and environmental conditions. • Wider PHA adoption remains constrained by production costs, variable feedstock quality, scale-up challenges, and resource-intensive recovery while preserving polymer quality. • Mechanistic modelling and selected machine-learning applications already support PHA research, including property and biodegradation prediction, but broader AI-enabled optimization requires representative data and process-specific experimental validation.
What this article adds:	• Integrated perspective on how AI could connect strain and enzyme design, feedstock selection, fermentation, recovery, materials performance, and end-of-life assessment across the PHA value chain. • PHA applications and methodological precedents from prospective AI capabilities, outlining a conditional outlook from near-term decision support to autonomous laboratories and digitally coordinated biorefineries. • Identifies data, hybrid modelling, experimental validation, and governance requirements needed to translate predictive advances into reproducible economic and environmental benefits rather than shifting burdens between production stages.

1. INTRODUCTION: SCIENTIFIC AND INDUSTRIAL CONTEXT

Polyhydroxyalkanoates (PHAs) are synthesized as organelles-like intracellular carbonaceous inclusion bodies ("carbonosomes") by numerous prokaryotic microorganisms from the two domains bacteria and archaea. For the microorganisms producing them, PHAs serve as carbon and energy reserves, often under conditions in which carbon is abundant while another nutrient limits cell proliferation [1]. Moreover, they play additional key roles for cells producing them, such as acting as effective stress protectants. In that context, PHA biosynthesis can be understood as a metabolic "SOS response" by serving as an immediate survival strategy when microorganisms encounter environmental stress or nutrient imbalances. Rather than acting as a classic genetic DNA-repair signal, PHA biosynthesis functions as a physiological alarm and protective shield that stabilizes the cell during unfavorable conditions [2]. PHA biosynthesis can also act as an electron sink: during P(3HB) synthesis, NADPH or NADH donates electrons and is converted back to NADP+ or NAD+, helping maintain cellular redox balance [3].

A growing number of microbial genera, including 150 bacterial genera with diverse metabolic lifestyles (autotrophic, phototrophic, chemotrophic, organotrophic, mixotrophic, and others) and 17 haloarchaeal genera, have been reported to accumulate PHAs as intracellular inclusion bodies [4, 5]. Collectively, these genera encompass hundreds of species capable of naturally synthesizing PHAs as carbon and energy reserves, often when carbon is abundant but other nutrients, such as nitrogen or phosphorus, are deprived [6]. A specific archaeal example is the recently reported production of poly(3-hydroxybutyrate) (P(3HB)) by the extremely halophilic archaeon *Halarchaeum acidiphilum* [7].

More than 150 hydroxyalkanoates have been reported as PHA building blocks [8, 9], although some exotic monomers have only been polymerized in vitro [10]. Monomer identity and sequence, molecular mass and polydispersity, crystallinity, and additives yield materials ranging from stiff thermoplastics to elastomers and functional polymers [11]. PHAs are classified as homo- or heteropolyesters (including copolymers, terpolymers, and quarterpolymers) according to monomer diversity, and as short- or medium-chain-length PHAs (scl-PHA, mcl-PHA) according to the number of carbon atoms per monomer; short-chain-length monomers contain up to five carbon atoms, and medium-chain-length monomers between six and 14 carbon atoms [12]. This versatility also complicates PHA research: Poly-mer characteristics depend on strain genetics, substrate composition, cultivation conditions, cellular physiology, recovery, and processing [13].

Current and emerging applications of PHA biopolyesters span commodity products and higher-value functional materials, although their technological maturity differs substantially. Packaging is an established application area; particularly films, where renewable feedstocks—including food waste considered in recent PHA bioprocessing research [14]—and microbial degradability motivate substitution of conventional plastics. Nevertheless, cost, processing stability, and application-specific performance matching the expectations of customers remain important constraints [15]. This connection extends beyond packaging: Koller [16] describes the food chain as a source of carbon feedstocks for PHA biosynthesis and organic fillers for PHA-based materials, as well as an application area for PHA-based food packaging. Beyond packaging, prospective industrial uses include textiles, agricultural products, automotive components, and electronics, but broad utilization and market success still depends on cost-competitive produ-

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ction and reliable scale-up rather than biodegradability alone [17].

Agricultural development of PHA particularly targets materials intended for soil contact, including alternatives to conventional mulch films and cultivation containers. Importantly environmental suitability requires realistic field assessment: Degradation depends on formulation, morphology, soil conditions, and microbial activity, while concentrated PHA inputs can temporarily immobilize nutrients in soil [18]. In this context, Obruca *et al.* emphasize that, at realistic environmental and agricultural loading rates, most reported soil effects of biodegradable polyesters like PHA are transient and comparable to those of natural organic inputs like lingocellulose. Fragmentation and biofilm formation are inherent stages of biodegradation, not necessarily evidence of harm; risk assessment should consider exposure levels, effects over time, and standardized methods [19].

Biomedical research represents another major direction, exploiting tuneable mechanical properties and resorption for wound dressings, implantable devices, tissue-engineering scaffolds, and controlled drug delivery [20-22]. Within regenerative medicine, PHA-based scaffolds and carriers are being investigated for bone, cartilage, tendon, ligament, skin, and other tissue-repair application. However, these opportunities should not be confused with universal clinical readiness, because production costs, biological responses, and formulation control remain unresolved for many systems and therefore constitute main directions for future research [23].

Additive manufacturing further expands the PHA design space by enabling customized geometries: Recent work demonstrated fused-deposition modelling of PHA/seashell-powder biocomposites, illustrating a route that combines renewable fillers with printable polymer matrices, without itself establishing biodegradation under natural receiving conditions [24]. Related advances include melt-extrusion 3D printing (layer-by-layer deposition of molten polymer through a nozzle) of poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (P(3HB-co-3HHx)) scaffolds supporting human chondrocyte function in vitro [25] and 3D-printed barium titanate /P(3HB) nanocomposite scaffolds with piezoelectric properties (i.e., the ability to generate electrical charge under mechanical stress) for potential bone tissue engineering applications [26]. These printing examples frame the challenge explored in section “Materials informatics, processing, and application-specific design”, linking composition and processing to the geometry and performance required for a defined application.

Overall, the application landscape for PHA is shifting from generic plastic replacement toward purpose-driven and purpose-designed materials whose composition, processing history, service performance, and end-of-life behaviour are evaluated together. Advancing PHA development on both a quantitative and qualitative basis therefore requires integration across scientific disciplines, linking microbial and metabolic engineering with process design, materials performance, and sustainability assessment [27, 28]. Microbiologists optimize production strains; metabolic engineers redirect carbon and reducing power (NADH, NADPH) in metabolic fluxes; process engineers control oxygen transfer, temperature, pH-value, redox potential, and substrate feeding; polymer scientists characterize structure and properties; and sustainability researchers evaluate feedstocks, emissions, disposal scenarios, and ecological footprints [29, 30]. Commercial competitiveness of PHA on the plastic market depends on all these factors [31]. A strain with a high intracellular PHA fraction may still be unattractive if it requires a costly refined

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substrate, grows at slow rate, generates a polymer that is difficult to recover from biomass, or yields materials with a too narrow processing window (the range of conditions allowing melt shaping without excessive thermal polymer degradation) or with properties not meeting the expectations of customers and applicants [32, 33].

AI is well suited to this multivariable landscape because it can integrate individual, singular observations and identify nonlinear interactions that conventional one-factor-at-a-time experimentation cannot handle. AI´s role and promise, however, should be framed carefully. Algorithms do not eliminate the need for causal understanding, standardized measurement, or scale-up experiments [34, 35]. Their most valuable function is to prioritize hypotheses, select informative experiments, quantify uncertainty, and coordinate decisions across biological and engineering scales [36]. In this sense, AI may become an organizing tool for PHA science rather than a self-contained solution or even a universal panacea to the current plastic dilemma.

2. DATA FOUNDATIONS AND AI-GUIDED DISCOVERY

An important near-term opportunity for AI is to support the organization and use of existing knowledge through automated extraction of information from the large body of existing scientific literature [37]. PHA data are scattered across publications (several thousand PHA-related articles are found in databases), numerous patents, strain collections, laboratory notebooks, and industrial records. Critical descriptors are often incomplete: Consistent, unambiguous polymer nomenclature is essential for literature searching and data integration [38]. For example, “poly(3-hydroxybutyrate)” (P(3HB)) explicitly specifies the hydroxyl-group position omitted in the less precise but still frequently used designation “polyhydroxybutyrate” (PHB), while molecular mass, polydispersity, monomer composition, cultivation history, specimen geo-metry, conditioning, and (bio)degradation environment may not all be documented for a given PHA sample. Natural-language processing and knowledge graphs can extract entities and relationships from this literature [39-41], but machine-readable reporting standards will be essential, according to the well-known FAIR (Findable, Accessible, Interoperable, Reusable) data principles [42]. Shared ontologies should connect organism, genotype, enzyme, substrate, reactor conditions, polymer microstructure, processing history, test method, product function, and end-of-life scenarios.

Once curated, these datasets can support supervised models that predict volumetric and specific productivity, PHA content (mass fraction) in biomass, monomer composition, molecular properties, and (bio)degradation kinetics. Unsupervised learning can reveal clusters of strains, feedstocks, or process states that are not obvious from taxonomic or operational labels. Bayesian approaches (i.e., statistical methods that update prior knowledge with observed data to estimate probabilities and uncertainty) are especially relevant because laboratory datasets are often small and uneven; they can combine prior mechanistic knowledge with observations and return uncertainty estimates rather than deceptively precise point predictions. Active learning can then select and propose the next experiment expected to potentially reduce uncertainty or improve a target response most efficiently [43, 44].

In the coming decade, researchers are likely to adopt closed experimental cycles in which models propose conditions, robotic or semi-automated platforms execute cultivations and analyses, and results update and steadily improve the models [45]. Such cycles can screen combinations of carbon sources, nutrient limitations, tempera-

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ture, pH-value, dissolved oxygen concentration, and feeding profiles far more efficiently than exhaustive multifactorial designs or even trial-and-error experiments. Nevertheless, data quality will remain the limiting factor. Negative results, failed fermentation batches, batch-to-batch variation, and complete metadata are scientifically valuable as they still provide "lessons learnt", and therefore must be retained. Without them, AI systems will inherit publication bias and may overestimate the robustness of promising routes [46]. These links between curated data, predictive modelling, and iterative experimentation are summarized in Figure 1 "Data foundations for AI-guided PHA discovery."

3. STRAIN DESIGN; ENZYMES; AND METABOLIC PATHWAYS

AI-assisted strain engineering could substantially shorten the path from genomic information to efficient PHA-producing cell factories [47]. Genome-scale metabolic models already describe feasible flux distributions under physicochemical constraints.

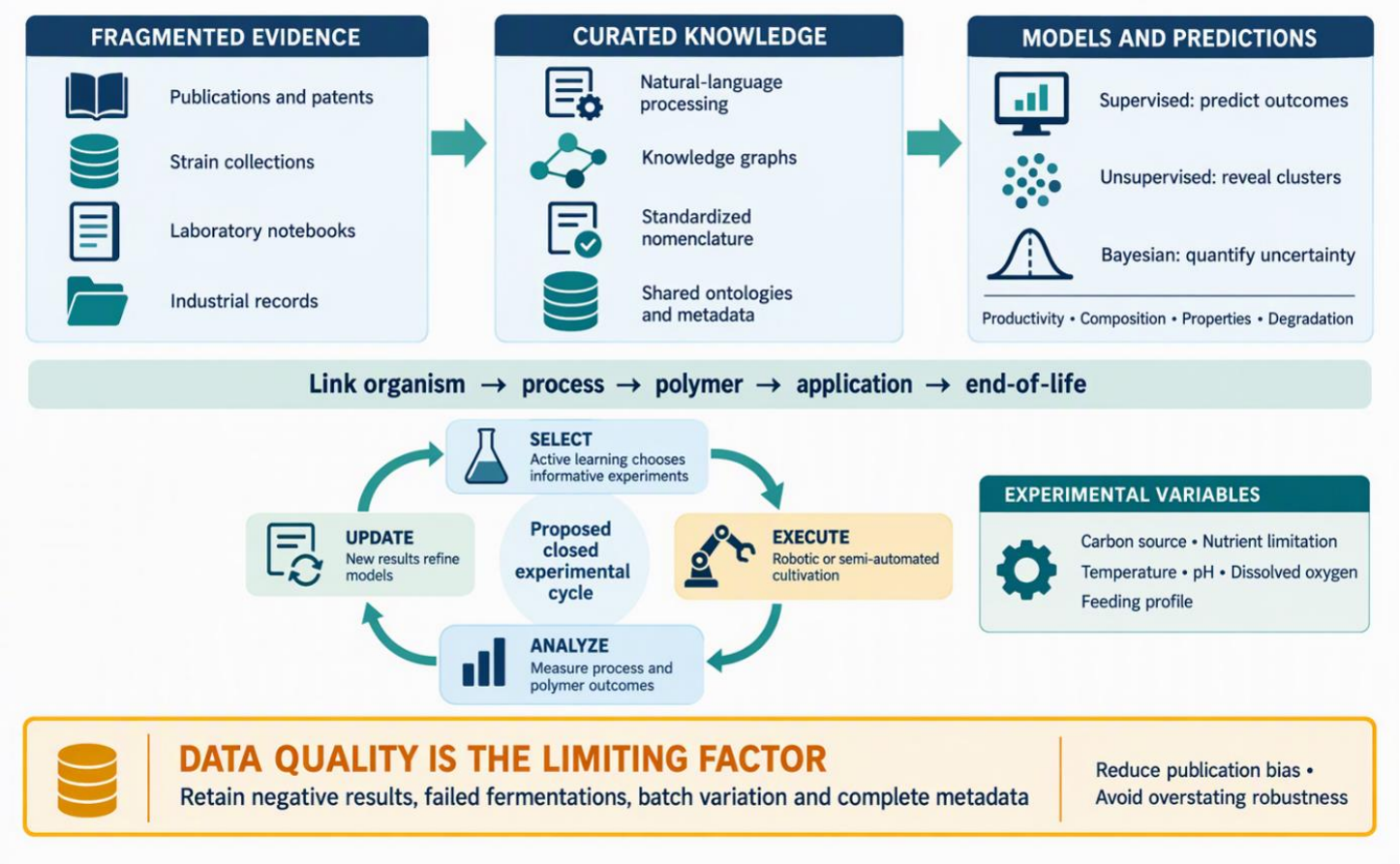

Figure 1 Data foundations for AI-guided polyhydroxyalkanoate (PHA) discovery.

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Enuh *et al.* [48] constructed and validated a genome-scale metabolic model of the Gram-Halomonas elongata 153B and used computational optimization to identify candidate engineering targets for increased PHA production; importantly, these predictions do not themselves establish experimentally improved PHA-producing strains. Machine learning (ML) can complement these models by learning regulatory effects, enzyme limitations, stress responses, and genotype–phenotype relationships that are difficult to encode mechanistically [49]. Hybrid systems may rank gene knockouts, promoter changes, cofactor-balancing strategies, transport functions, and pathway insertions according to predicted effects on yield, rate, polymer composition, and cellular fitness [47]. Protein language models and structure-prediction methods are established computational tools for guiding protein engineering, while generative models provide approaches for proposing enzyme sequences and exploring sequence–function relationships [50, 51]. These general methodological advances should be distinguished from their prospective application to PHA-related enzymes: The cited review articles by [50, 51] do not establish their effectiveness for PHA synthases, depolymerases, precursor-generating enzymes, or enzymes involved in substrate utilization. In PHA research, however, such tools could help prioritize enzyme variants with altered substrate specificity, improved thermostability, reduced susceptibility to inhibition, controlled incor-poration of unusual monomers, or compatibility with non-model hosts. Coupling model-generated candidates with active-learning campaigns could focus testing on a small, informative subset, but the benefits would need to be demonstrated for each enzyme and production host. Experimental confirmation would remain indispensable because excellent catalytic performance in vitro does not guarantee adequate expression, localization, cofactor supply, or metabolic integration in vivo.

Mixed microbial communities (MMCs) offer a route to PHA production from variable waste streams, while meta-omics can help characterize their dynamics. Combining metagenomics (i.e., analysis of the collective DNA of a microbial community) and metatranscriptomics (i.e., analysis of community RNA to identify which genes are definitely expressed), Yao *et al.* [52] documented phage–bacterial interactions and transcription of phage-associated genes potentially involved in PHA synthesis in enriched PHA-producing communities. These data contribute to a deeper understanding of the succession of bio-logical communities; still, they do not demonstrate AI-guided control or establish that manipulating the identified interactions would stabilize PHA accumulation. Prospectively, models integrating community profiles with operational data could help identify candidate adjustments to feast–famine regimes with MMCs, retention times, or nutrient ratios, but their effects on enrichment of PHA-accumulating cell, productivity, and culture stability would require experimental validation. For pure cultures, microbial engineering strategy can broaden substrate use and address production and recovery constraints [53]; AI-assisted prioritization of such stra-tegies remains a further opportunity. Future PHA optimization should balance productivity and pol-ymer composition with microbial growth, genetic stability, molecular mass, and recoverability, seeking Pareto optimal designs (objective can be improved without adversely affecting at least one other) rather than maximizing titer alone. Also, Wang *et al.* [54], which examines production–burden trade-offs in glucaric acid production by *Escherichia coli*, provides non-PHA methodological context rather than validation of these PHA-specific objectives. These design trade-offs are summarized in Figure 2 “AI-assisted design of PHA cell factories.”

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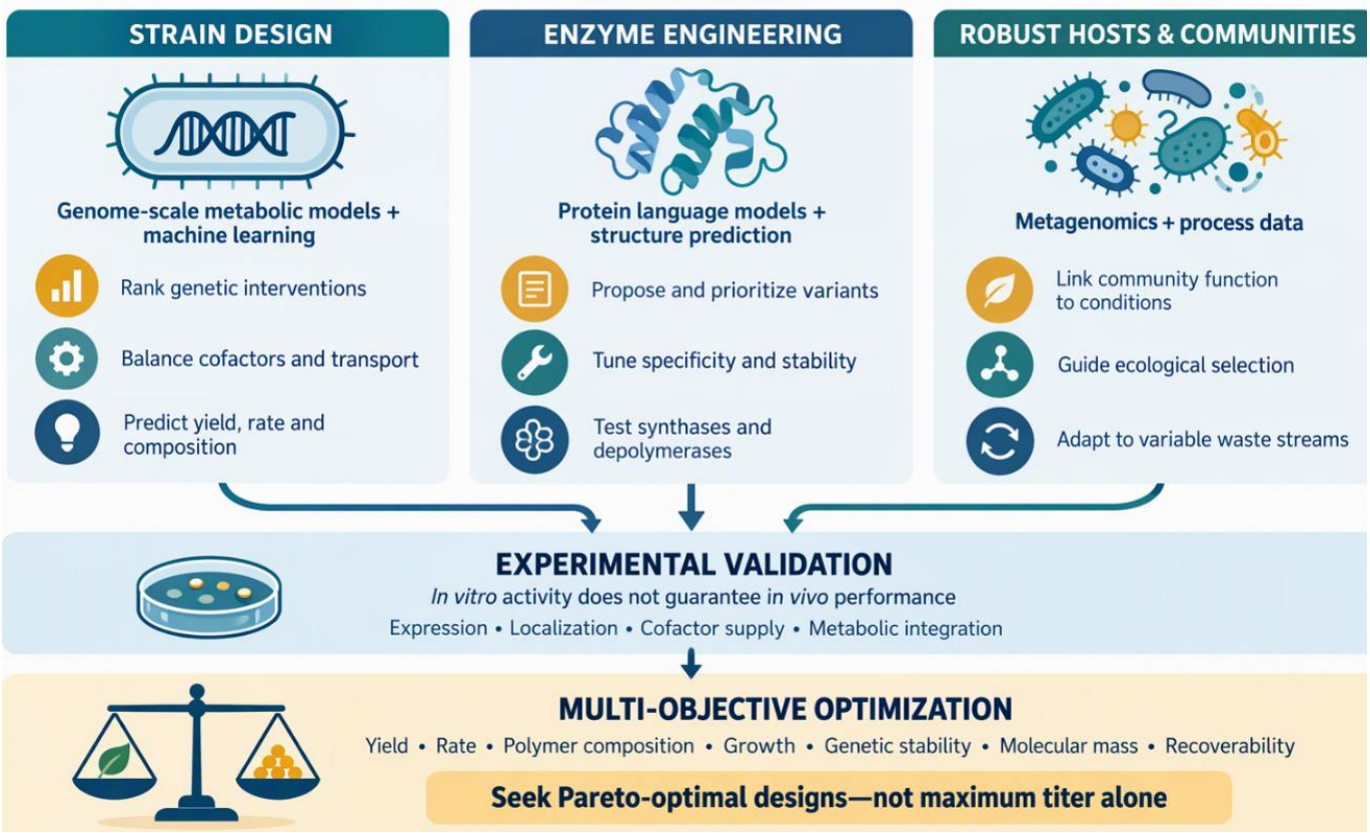

Figure **2** AI-assisted design of polyhydroxyalkanoate (PHA) cell factories

4. INTELLIGENT FEEDSTOCK SELECTION AND INTEGRATION INTO CIRCULAR BIOREFINERY CONCEPTS

Feedstock selection is an important handle for reducing PHA production costs. Khosravi-Darani *et al.* [55] review inexpensive carbon sources, particularly C1-compounds like methane, methanol, syngas, and CO2, as alternative inexpensive substrates for P(3HB) production. For methane-based P(3HB) production, Safaeian *et al.* [56] review methanotrophic cultivation and compare reactor configurations in terms of methane conversion, gas–liquid mass transfer, and productivity, providing process-engineering context rather than evidence of AI-enabled control. Montazer and Khosravi-Darani [14] examine food waste as a low-cost, carbon-rich feedstock for microbial lipid and PHA production, highlighting opportunities for resource valorization and improved economic and environmental performance. Tripathi *et al.* [57] complement this feedstock perspective by reviewing hydrothermal pretreatment of lignocellulosic waste for PHA copolymer production and potential food-packaging applications. These opportunities form part of the broader effort to establish commercially viable PHA production routes reviewed by Koller and Mukherjee [31], rather than demonstrating that any particular feedstock is inherently sustainable. Prospectively, AI-enabled spectroscopy, sensor fusion, and rapid compositional analysis could help characterize incoming complex feedstock streams. Models linking these measurements to cultivation data could then be evaluated for predicting fermentability, inhibitor burden, nutrient demand, and polymer composition. If validated for the relevant feed-stocks and production organisms, such tools could support lot-specific adjustments to pre-treatment, blending, supplementation, and inoculation instead of reliance on a fixed cultivation recipe.

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Modelling and optimization approaches developed for biomass-to-biorefinery supply chains provide a methodological basis for considering networks rather than isolated reactors [58]. Applied prospectively to PHA production, such models could support regional and local feedstock allocation. They could match regional supplies of agricultural residues, food-processing side streams, spent lipids, wastewater-derived volatile fatty acids, CO2-rich industrial off-gases or methane from wastewater treatment plants or biogas plants with suitable organisms and plant capacities. Such systems would consider transport distance, storage losses (e.g., spoilage, frass), competing uses (once, a "waste stream" gets an application, it´s typically no longer a "waste"!), land and water implications, energy prices, and seasonal availability. Coupling process simulation with life-cycle assessment (LCA) and techno-economic analysis (TEA) provides a framework for evaluating integrated PHA biorefinery routes [30]. Importantly, optimization criteria should include absolute resource use and verified displacement of fossil-based products, not merely the use of a nominally renewable carbon source, consistent with a full-life-cycle perspective on PHA development [59]. By the 2030s, digital twins (i.e., virtual process models linked to operating data from the physical plant) of integrated biorefineries may coordinate substrate conversion, PHA accumulation, coproduct recovery, utilities, and waste treatment and recycling. Real-time data could be used to select the most valuable product candidate under changing feedstock and market conditions. However, circularity claims require transparent system boundaries. Valorizing a residue does not eliminate process-related environmental burdens: An LCA of PHA production from palm oil mill effluent by Lim *et al.* recently identified cultivation, electricity consumption, and solvent (chloroform) use during extraction as major contributors to the impact categories assessed [60]. AI can expose these trade-offs, but only when environmental and social constraints are both explicitly represented in the objective function. These links between feedstock characterization, adaptive operations, and circularity assessment are summarized in Figure 3 "AI-guided feedstock selection and integration into circular PHA biorefineries."

5. FERMENTATION; SCALE-IP; AND AUTONOMOUS CONTROL

5.1 Mathematical Modelling

Mathematical modelling provides a quantitative framework for linking microbial growth, substrate consumption, and intracellular PHA accumulation during the fermentation process, thus helping researchers compare cultivation strategies, identify opportunities to improve productivity, and reduce the number of needed experiments in the laboratory [61]. In a PHA-specific example, Lhamo and Mahanty [62] combined growth and product-formation kinetics with model selection, cross-validation, and parameter sensitivity analysis to design batch-startup conditions for *Cupriavidus necator*. Such models also provide a mechanistic foundation for hybrid AI approaches, but their usefulness depends on reliable parameter estimation and validation for the organism, substrate, and operating conditions considered [61, 62]. Published approaches include formal kinetic, low-structured, dynamic, metabolic (highly structured), cybernetic, artificial neural-network, and hybrid models for describing PHA production [61].

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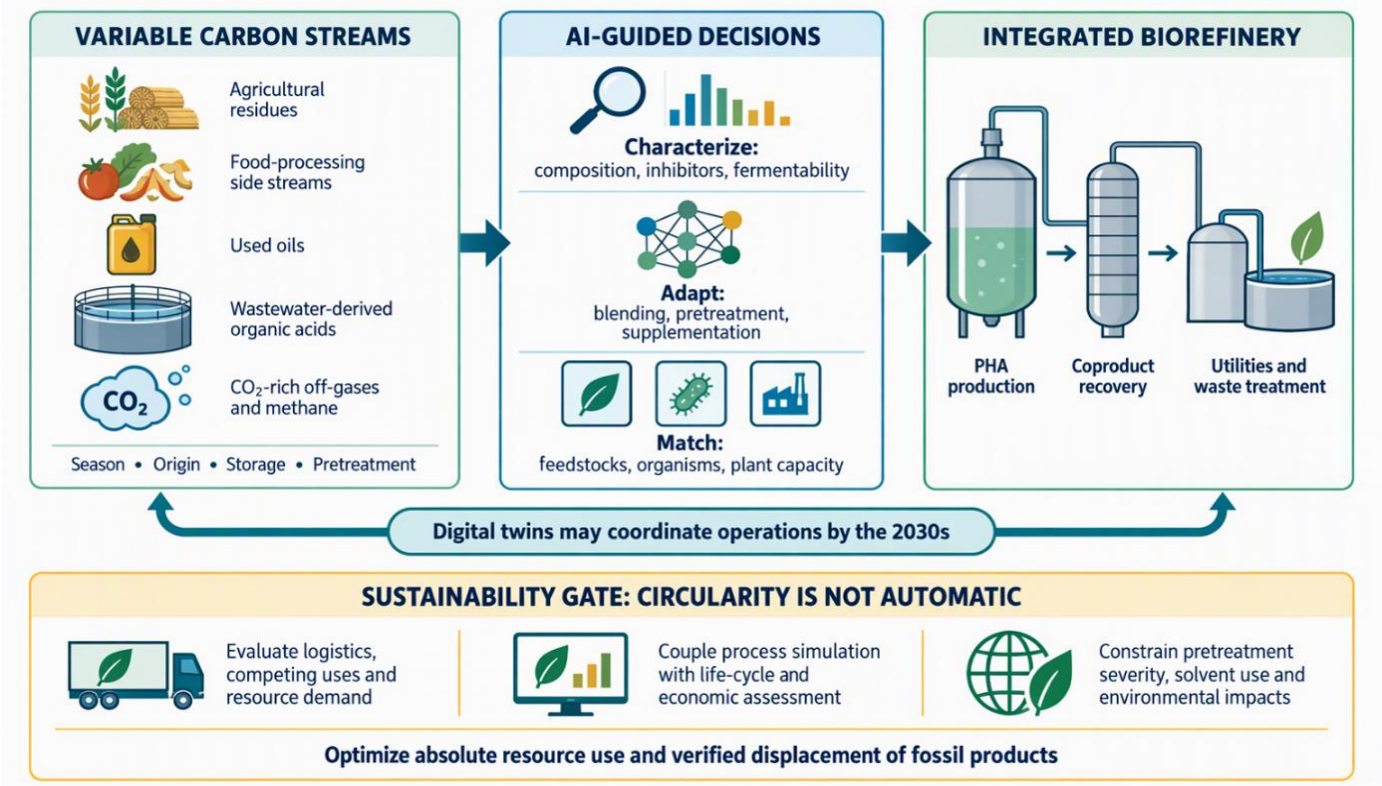

Figure **3** Optimized fermentation process for probiotic production.

5.2 Process Monitoring and Soft Sensor

Complementing this modelling framework, process monitoring must account for the dynamic and partially observed nature of PHA fermentation [17]. Biomass concentration, intracellular polymer fraction, nutrient status, and substrate consumption evolve during cultivation [17]. Culture broth rheology can also change: Time-dependent viscosity and oxygen-transfer effects were demonstrated experimentally in high-cell-density Pseudomonas putida LS46 cultures producing PHA [63]. Conventional monitoring combines online process measurements with offline analyses; bioprocess models can integrate these data for monitoring and control [17, 35, 64, 65]. Machine-learning (ML) soft sensors (i.e., software-based models that estimate difficult-to-measure process variables from available measurements) can infer otherwise unavailable states from these signals and from spectroscopic measurements. Their predictions could support timely transitions between growth and accumulation phases, adaptive feeding, and early detection of contamination or metabolic drift.

5.3 Adaptive control and safeguards

Building on these monitoring capabilities, adaptive control represents a further opportunity. Recent non-PHA studies provide methodological precedents: Bolmanis *et al.* [64] experimentally validated hybrid model-predictive substrate-feed control in recombinant Pichia pastoris fermentations, whereas Uthravalli *et al.* [66] investigated reinforcement-learning feed optimization in a simulated Aspergillus niger enzyme-production process. Applied prospectively to PHA fermentation, these approaches could guide feeding and potentially aeration, but productivity gains and compliance with constraints on oxygen transfer, foaming, heat removal, and by-product formation would require process-specific validation. Safe deployment will require controllers trained in simulation and bounded by mechanistic and operational rules. Exploration that is acceptable

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in a laboratory-scale bioreactor is not acceptable in a large vessel containing a valuable production batch [67]. Human oversight, fail-safe modes, and interpretable alarms will still remain necessary.

5.4 Continuous cultivation

Alongside monitoring and control, the choice of cultivation mode is another consideration: continuous cultivation offers an alternative to fed-batch PHA production, with potential benefits in productivity, reduced downtime, and product consistency; multistage systems can separate conditions favoring biomass growth from those promoting intracellular PHA accumulation [68]. Atlić *et al.* demonstrated continuous P(3HB) production by *Cupriavidus necator* in a cascade of five stirred-tank reactors, with balanced growth in the first stage followed by nitrogen-limited polymer accumulation [69]. Continuous PHA cultivation therefore has an experimental foundation independent of AI. Prospectively, hybrid models and soft sensors could support adjustments to dilution rates and nutrient supply, but improved long-term stability and polymer consistency would require validation under sustained operation.

5.5 Scale-up and validation

Across these cultivation and control strategies, scale-up remains a key challenge in translating laboratory-scale PHA production into industrial practice: Pilot-scale development must establish suitable production strains, effective fermentation and process-control strategies, and polymers with application-appropriate properties, while addressing the limited commercial competitiveness of PHA production [17]. Large bioreactors can develop gradients in DO, substrate concentration, temperature, and pH-value that cells experience as fluctuating microenvironments [70]. Hybrid models coupling computational fluid dynamics with cellular reaction kinetics could help predict how fluctuating reactor environments affect cellular performance during scale-up [70]. AI may identify scale-down regimes that reproduce industrial stress histories, enabling strains and control policies to be tested realistically before transfer. Fleet learning across multiple reactors could further distinguish local equipment effects from biological variation. Over time, these tools may reduce failed scale-ups and enable continuous or semi-continuous PHA processes where productivity, consistency, and contamination risk are balanced quantitatively. These prospective links between monitoring, adaptive control, and scale-aware validation are summarized in Figure 4 “AI-Assisted PHA Fermentation and Scale-Up.”

6. DOWNSTREAM PROCESSING AD QUALITY-BY-DESIGN

Intracellular PHA accumulation complicates recovery: Extraction or removal of surrounding cellular material must achieve adequate purity without compromising polymer properties [32, 71, 72]. Harvesting, disruption, extraction, washing, solvent recovery, drying, and purification add substantial costs [32]. Environmental impacts depend on the process; e.g., for PHA derived from palm oil mill effluent, cultivation, electricity use, and chloroform extraction were major contributors to the impact categories assessed [60].

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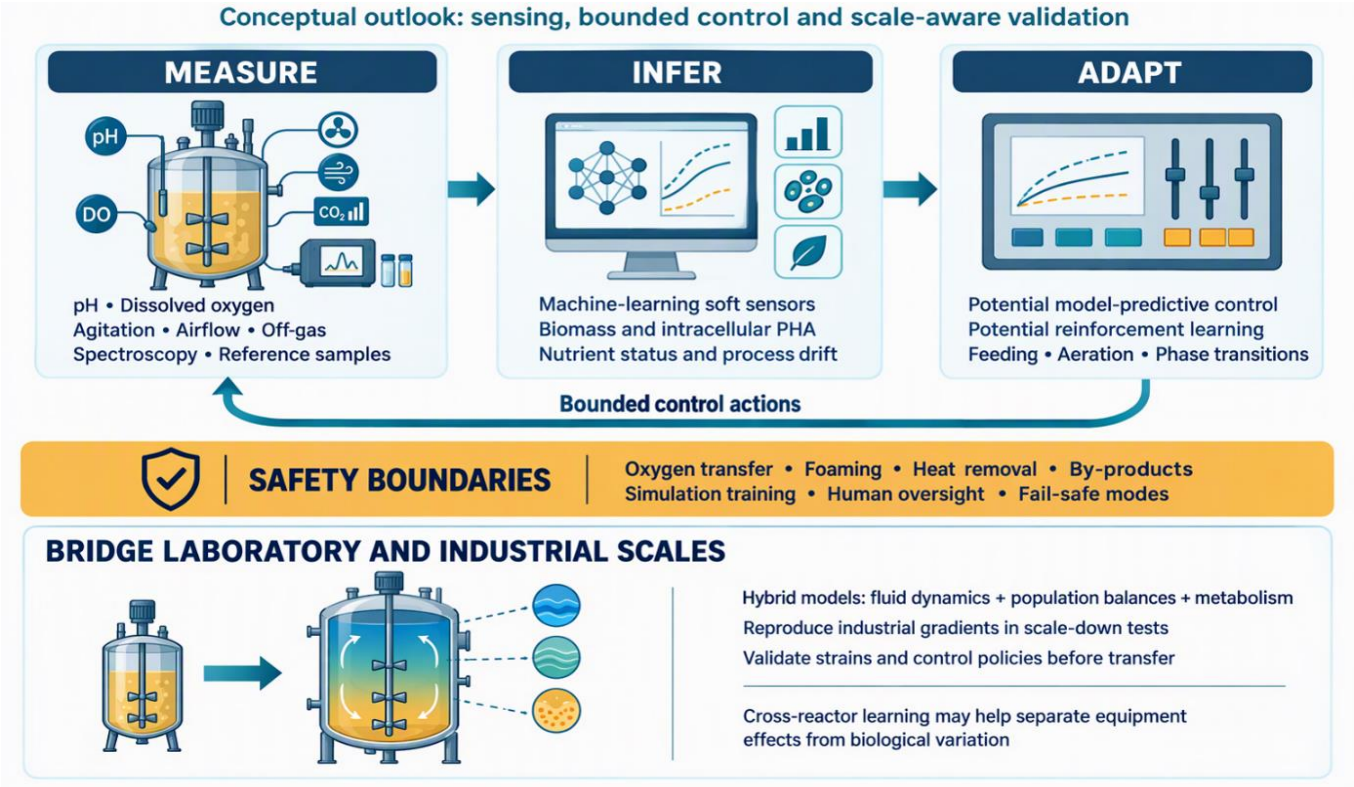

Figure **4** AI-Assisted PHA Fermentation and Scale-Up.

Prospectively, AI could help compare and optimize mechanical, chemical, enzymatic, biological, aqueous, and solvent-based recovery routes against yield, purity, molecular-mass retention, solvent toxicity, energy and water use, cycle time, and recyclability. Soft sensors and predictive chemometrics (i.e., statistical modelling of chemical measurements, such as spectra, to predict concentrations or material properties) provide a methodological basis for downstream monitoring in biopharmaceutical separations [73]. As a PHA-specific analytical precedent, Isak *et al.* [74] combined FTIR spectroscopy with partial least squares (PLS) regression to predict PHA content in mixed- and pure-culture biomass against gas-chromatographic reference measurements; this does not establish an assay for residual biomass or purity in recovered polymer. For PHA recovery, image-based assessment of cell disruption or particle morphology and spectral prediction of residual biomass or polymer quality still remain prospective applications requiring process-specific validation.

Data-driven control could transform recovery from a fixed sequence into an adaptive operation. For example, the severity of disruption and extraction might be adjusted according to cell morphology, PHA mass fraction in biomass, polymer crystallinity, and the intended product application. Models could predict when additional purification produces little functional benefit, avoiding unnecessary resource and time consumption. AI-guided design of recyclable solvent systems or selective enzymes may further reduce downstream impacts, although experimental safety and mass-balance verification must govern selection. For supercritical-fluid routes, Khosravi-Darani *et al.* [75] measured the equilibrium solubility of P(3HB) in supercritical CO2, examined the effects of pressure, temperature, and solvent density, and correlated the data by Chrastil model. Such measurements could inform prospective hybrid models for evaluating

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supercritical-fluid operating conditions; still, the study provides physicochemical data rather than a demonstration of AI-assisted polymer recovery.

A quality-by-design framework would connect upstream and fermentation history to downstream behavior and final specifications. Quality-by-design, process analytical technology, and digital-twin approaches already provide a methodological basis for moving beyond end-point quality testing in biopharmaceutical manufacturing [76]. Applied prospectively to PHA production, models could help investigate links between deviations in color, odor, molecular mass, thermal stability, or residual contaminants and feedstock or process events; these relationships would require process-specific validation. This traceability is particularly important for medical, food-contact, and high-performance applications. In future production plants, each batch may carry a digital record covering substrate origin, bioprocess conditions, purification, compounding, and test results. Such records could support certification, regulatory review, and model updates while protecting confidential manufacturing information. These proposed links between adaptive recovery, resource use, and quality traceability are summarized in Figure 5 "AI-Assisted PHA Recovery and Quality-by-Design."

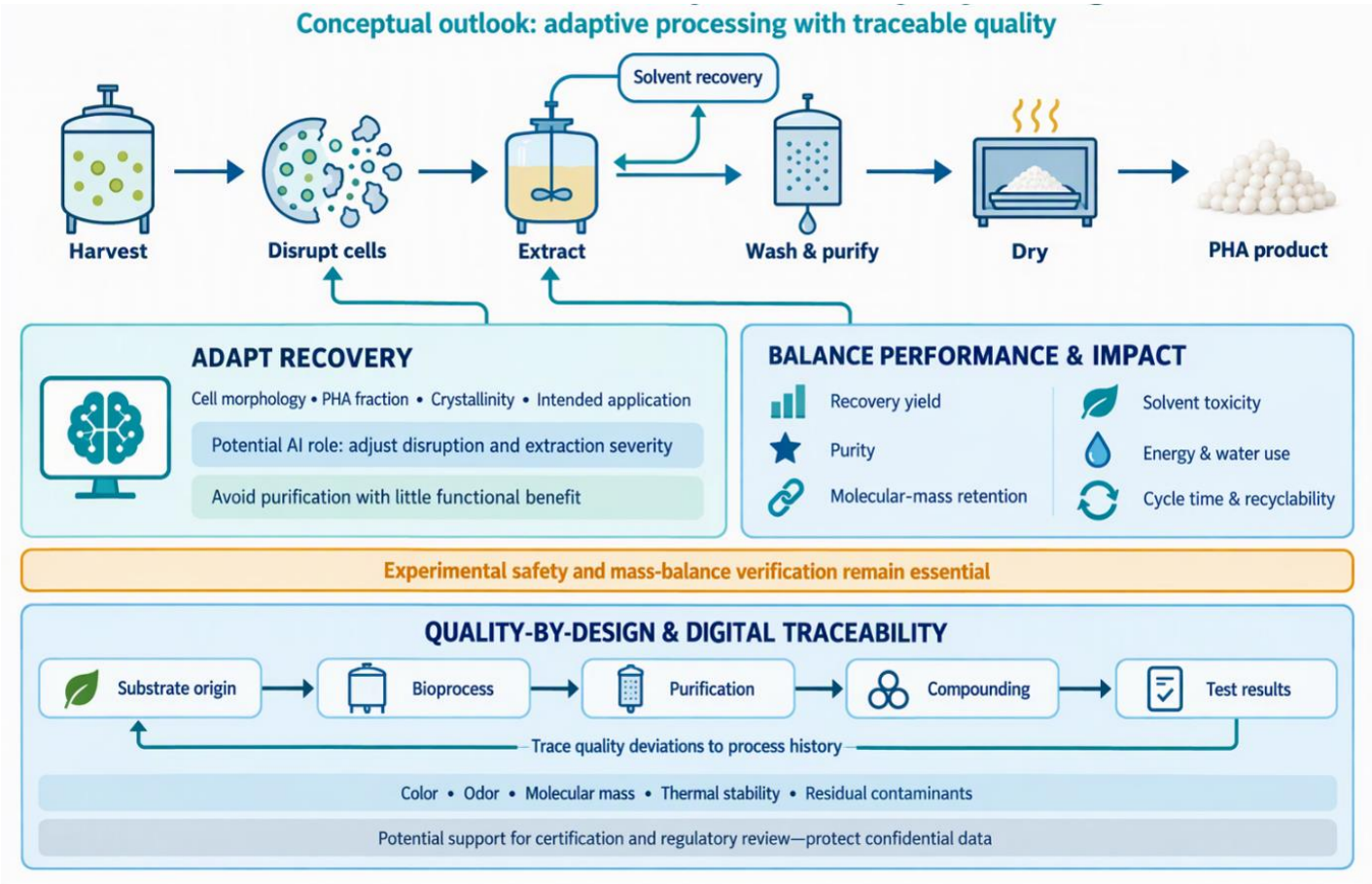

Figure **5** AI-assisted PHA recovery and quality-by-design.

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7. MATERIAL INFORMATIC, PROCESSING, & APPLICATION-SPECIFI DESIGN

The diversity of PHA structures creates an inverse-design problem: Given a desired application, which monomer composition, sequence (random distribution of monomers or blocky structure), molecular mass, morphology, additives, and processing conditions will deliver the required performance? This application-led framing is consistent with the structure–property–processing–performance perspective reviewed by Lalonde *et al.* [77]. Materials informatics can link descriptors of polymer chemistry and microstructure with tensile behavior, barrier properties, thermal transitions, crystallization, melt stability, surface properties, sterilization response, and processability. A specific PHA example is the prediction of mechanical properties of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (P(3HB-co-3HV))/graphene oxide/nanoclay composites using neural-network, decision-tree, and support-vector models [78]; however, this does not validate prediction of the full property range listed above. Models trained on carefully standardized data could identify the most informative experiments and reduce the large search space of copolymers, blends, plasticizers, fillers, and processing windows.

AI may assist in balancing properties that are usually antagonistic. Increasing crystallinity can improve stiffness and barrier performance but may reduce toughness and alter degradation ability. Introducing flexible monomers in the PHA matrix can broaden processing windows yet affect strength and cost. Multi-objective algorithms can map these trade-offs and propose formulations tailored to packaging, agriculture, coatings, adhesives, fibers, additive manufacturing, or biomedical devices. Complementary recyclable-by-design strategies for PHAs, potentially guided by ML tools, have been discussed by Clarke *et al.* [79], who argue that prioritizing efficient mechanical, chemical, or enzymatic recycling over biodegradation or composting can improve the carbon footprint and economics of PHA systems. Physics-informed models could constrain predictions by thermodynamics, crystallization kinetics, and conservation principles, thereby improving extrapolation beyond the measured domain.

Equally important is the connection between product design and end-of-life behavior. Biodegradation is not an intrinsic binary label; it depends on polymer structure, specimen thickness and shape, additives, crystallinity, microbial ecology, temperature, moisture, oxygen, and test duration. Koller *et al.* [80] review how PHA composition, microstructure, and receiving conditions influence biodegradation in freshwater, seawater, soil, home and industrial composting, and anaerobic environments. Complementing this environmental perspective, Lackner *et al.* [81] review PHA copolymers beyond P(3HB), hence, the “PHAmiliy”, their end-of-life pathways, biodegradability standards, and depolymerase-mediated degradation, while highlighting that not all copolymers have been fully evaluated across diverse environmental conditions. A PHA-specific example is the use of random forest (i.e., models that average predictions from many randomized decision trees) and XGBoost models (i.e., Extreme Gradient Boosting models that build decision trees sequentially to correct prediction errors) trained on literature-derived laboratory data to predict mineralization-based biodegradation of P(3HB-co-3HV) formulations [82]. Broader prediction of degradation trajectories and uncertainty would require representative data and validation for each receiving environment. Such tools could help designers avoid overgeneralizing results from one environment to another and could guide materials toward realistic disposal scenarios. By the 2040s, product-development platforms may simul-

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taneously optimize manufacturability, service life, safety, recyclability where appropriate, and biodegradation under defined receiving conditions. These prospective links between application-led design, property trade-offs, and environment-dependent biodegradation are summarized in Figure 6 “AI-Assisted PHA Materials Design.

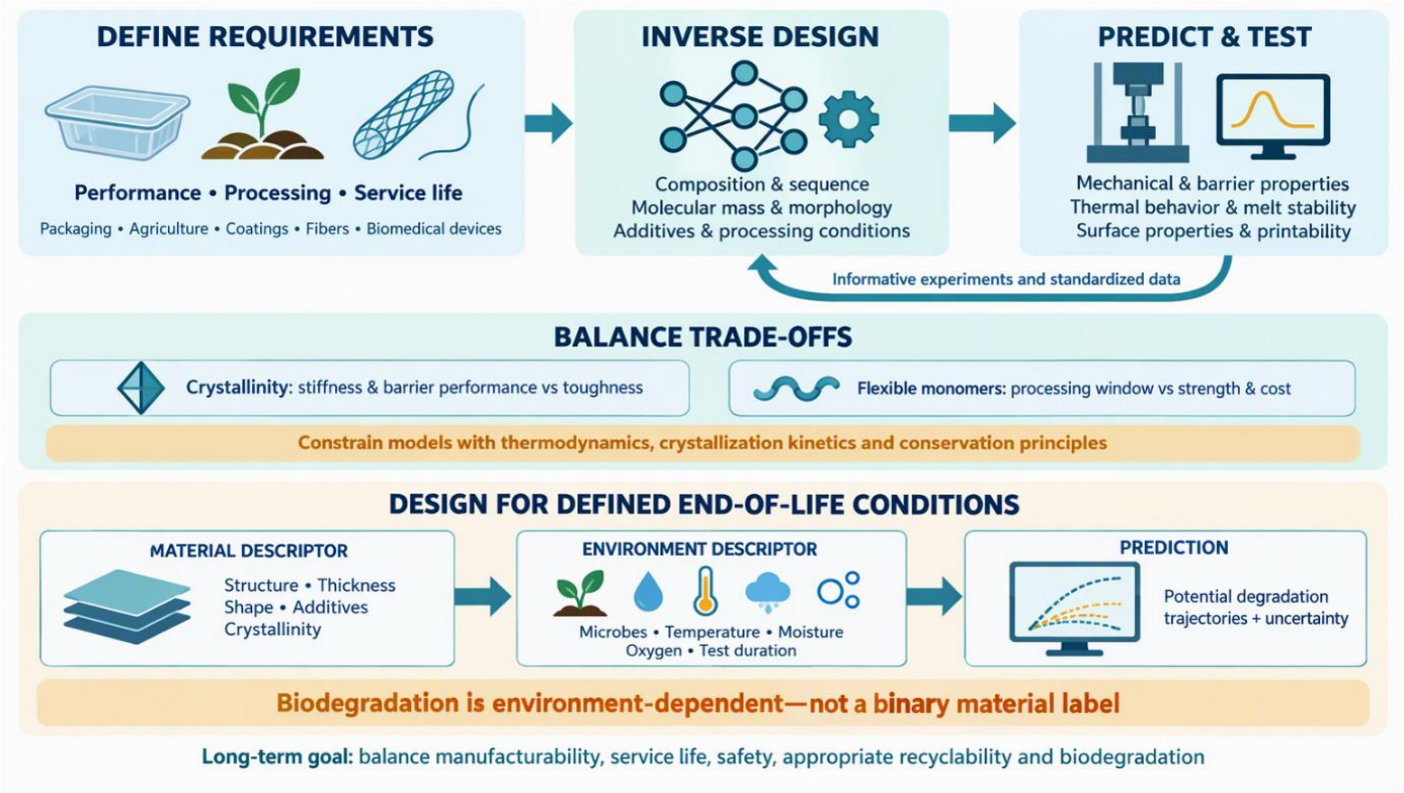

Figure **6** AI-Assisted PHA Materials Design.

8. SUSTAINABILITY ASSESSMENT: GOVERNANCE; AND SCIENTIFIC RISK

ML offers general methodological tools for addressing life-cycle inventory gaps, quantifying uncertainty, and updating environmental assessments [83]; applying these tools to PHA systems would require representative process and pilot data. PHA-specific integration of process, environmental, and economic modeling has been demonstrated computationally by Sadhukhan *et al.* [84], who coupled dynamic simulation with LCA, TEA, and Monte Carlo uncertainty analysis (i.e., repeated model runs with randomly sampled inputs to quantify how input uncertainties affect predicted outcomes) for lignocellulosic PHA biocomposites; however, this is not a demonstration of AI-assisted assessment. Comparisons with fossil-based plastics and other bio-based materials should address a defined function rather than mass alone, accounting for differences in thickness, service life, and waste-management pathways. Prospective scenario analyses assisted by AI could examine renewable electricity, solvent recovery, carbon-source allocation, methane formation during anaerobic degradation, and the availability of composting or wastewater infrastructure.

Several risks accompany greater reliance on AI. Transfer of laboratory-trained models to variable industrial streams requires validation: Changes in raw materials, biological variability, and modified pro-cess strategies can degrade bioprocess soft-sensor predictions [65]. Correlation may be mis-

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taken for causation, and optimization may exploit measurement artifacts. Restricted access to data and code can limit reproducibility [85], while automated systems may amplify errors rapidly. Cybersecurity becomes relevant when digital twins and control systems are connected to produc-tion equipment [86]. Concentration of AI resources and unequal access to data and computation could also disadvantage smaller laboratories and producers, reflecting broader access and private-sector governance concerns in AI-enabled science [87].

Responsible deployment therefore requires data provenance, version control, documented preprocessing, external validation, uncertainty reporting, and clear domains of applicability [85, 88]. Benchmark development should distinguish interlaboratory measurement comparability from model robustness under disturbances. In this context, Hafner *et al.* [89] provide an inter-lab-oratory measurement-reproducibility precedent from biochemical methane potential assays, whereas Uthravalli *et al.* [66] tested fermentation-control robustness under simulated process disturbances. Neither study establishes an interlaboratory PHA-model benchmark; incorporating comparable measurements and realistic perturbations remains a proposed requirement for PHA applications. Explainability should be matched to the decision: A mechanistic rationale is essential for strain design or regulatory safety, whereas a highly accurate soft sensor may be acceptable if it is continuously checked against reference analyses. Public–private consortia could define minimum information standards without forcing disclosure of all commercially sensitive details. Education will also matter; future PHA researchers should be able to evaluate both biological experiments and model assumptions [87]. These requirements for sustainability assessment, uncertainty-aware validation, and transparent data governance are summarized in Figure 7 "Responsible AI for sustainable PHA systems."

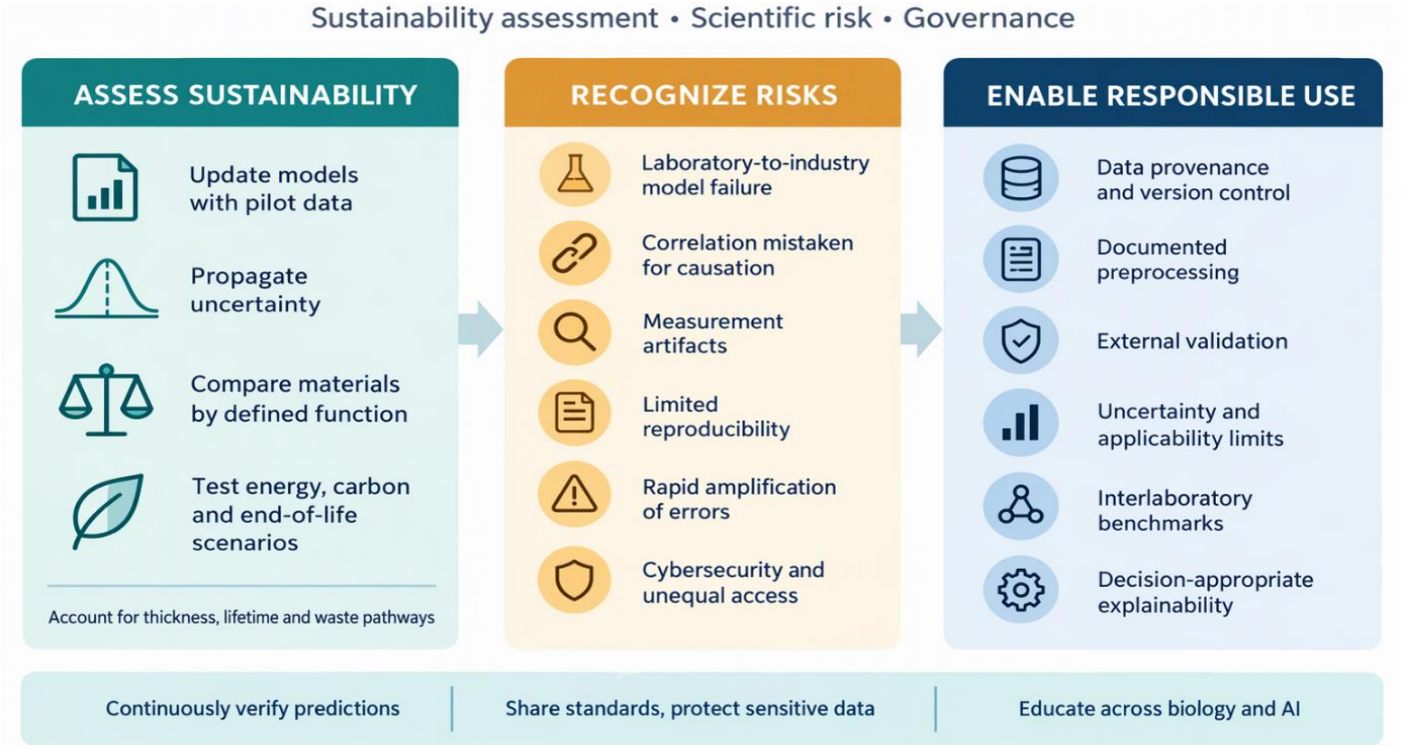

Figure 7 Responsible AI for sustainable polyhydroxyalkanoate (PHA) systems.

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9. AN OUTLOOK FOR THE COMING DECADES

During the late 2020s and early 2030s, the most realistic advances are expected to derive from better data curation, predictive soft sensors, literature mining, Bayesian experimental design, and hybrid models for specific strains and reactors. AI most probably will mainly expand expert-led work. Laboratories that standardize metadata and connect cultivation with detailed polymer characterization most likely will gain a decisive advantage, because their datasets will permit models to learn across the entire production–structure–property chain.

From the 2030s into the 2040s, increasingly automated "self-driving" laboratories may execute iterative strain, fermentation, recovery, and formulation campaigns. Digital twins may become routine in demonstration plants, and transfer learning could adapt models between scales, sites, and feedstocks. Federated learning may allow companies to improve shared models without directly exchanging sensitive raw data. At this stage, the key scientific shift will be from optimizing isolated unit operations to co-designing organisms, processes, materials, and end-of-life pathways.

Beyond the 2040s, mature AI systems could coordinate distributed biomanufacturing networks that use regionally and locally available carbon streams and produce application-specific PHA grades. Generative biological and materials models may propose new monomer combinations and biosynthetic routes, while autonomous platforms test them under constraints derived from safety, economics, and environmental performance. Yet this vision is conditional. It depends on reliable sensors, harmonized analytical methods, robust automation, access to representative data, and regulatory frameworks that can evaluate adaptive systems.

The most credible long-term outcome is not a single universal PHA that replaces all conventional plastics. Rather, AI may enable a portfolio of well-characterized PHA materials deployed where their synthesis route, functional properties, and managed or environmental fate create a demonstrable advantage. Success should be measured by reproducible reductions in resource use and pollution, not by model accuracy or productivity alone. Table 1 compares current PHA challenges with potential AI-enabled improvements and the conditions required to realize them over the coming decades.

10. CONCLUSION

As shown in the individual sections of this article, AI is indeed positioned to become a powerful integrator of PHA research and production. It can connect genome and enzyme design with metabolism, feedstock variability, reactor design and dynamics, product recovery and purification, polymer processing, product performance, biodegradation, and sustainability assessment.

The immediate benefits will be:

i) faster hypothesis generation

ii) more informative experimentation

iii) earlier detection of process deviations and bottle necks

iv) better prioritization of scale-up options.

Longer-term benefits may include:

i) autonomous experimentation

ii) adaptive biorefineries

iii) inverse design of PHA grades for defined applications

iv) tailored design of PHA for different disposal environments.

These advances will not emerge from algorithms alone. PHA systems are biologically variable, physically complex, and strongly context-dependent.

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Table 1. Current status and challenges across the PHA value chain compared with potential AI-enabled improvements over the coming decades.

PHA value-chain area	Current status and key challenges	Potential AI-enabled improvements	Conditions for reliable benefit	References
Data foundations	Knowledge is dispersed across publications and industrial records; metadata and nomenclature are inconsistent, and negative results are underreported.	Literature mining, shared ontologies, and curated datasets could connect production conditions, polymer structure, performance, and end-of-life data.	Standardized reporting, provenance, and retention of failed experiments.	[37, 88]
Strain and enzyme engineering	Genotype–phenotype relationships and metabolic trade-offs complicate selection of productive, robust hosts and enzyme variants.	Hybrid metabolic models, protein models, and active learning could prioritize engineering targets and informative experiments.	Confirm predicted gains experimentally; assess fitness, stability, composition, and recoverability.	[47, 48]
Feedstocks and biorefinery integration	Variable waste-stream composition and substrate costs complicate cultivation; renewable origin alone does not establish sustainability.	Sensor-based characterization could guide lot-specific pretreatment, blending, and feeding; network models could support regional feedstock allocation.	Representative feedstock data, validated predictions, and transparent environmental boundaries.	[14, 30]
Fermentation monitoring and control	Biomass, intracellular PHA, nutrient status, and broth rheology change during cultivation; important states are not continuously measured.	Soft sensor and hybrid model could support adaptive feeding & phase transitions; constrained controller coordinate process actions, including dilution-rate and nutrient-supply adjustments in continuous cultivation.	Reference analyses, uncertainty estimates, human oversight, and fail-safe control.	[17, 35, 68, 69]
Materials design and processing	Composition, crystallinity, additives, and processing interact; stiffness, toughness, stability, and cost can conflict.	Property prediction & inverse design could narrow formulation search & identify application-specific trade-offs.	Standardized testing, application-specific validation, and explicit model applicability limits.	[17, 70]
End-of-life performance	Biodegradation depends on formulation, geometry, receiving environment, and test duration; laboratory results are not universally transferable.	Environment-specific models could guide degradation testing and uncertainty analysis, linking product design with realistic disposal routes.	Distinguish mineralization from other degradation measures; validate under relevant receiving conditions.	[71, 72]
Sustainability and economics	Environmental and economic outcomes depend on feedstock, energy, recovery, product function, and waste management; inventories remain uncertain.	ML-assisted inventories and coupled process– life-cycle assessment –economic models could support updated comparisons and scenario screening.	Function-based comparisons, transparent assumptions, uncertainty reporting, and measured pilot inventories.	[77, 78]
Governance and deployment	Limited data access, model drift, poor reproducibility, and connected-control cybersecurity impede reliable adoption.	Shared standards, documented workflows, and monitored models could support reproducible and increasingly coordinated operations.	External validation, secure systems, expert skills, and equitable access to data and computation.	[18, 82]
Materials design and processing	Composition, crystallinity, additives, and processing interact; stiffness, toughness, stability, and cost can conflict.	Property prediction and inverse design could narrow formulation searches and identify application-specific trade-offs.	Standardized testing, application-specific validation, and explicit model applicability limits.	[83, 84]
End-of-life performance	Biodegradation depends on formulation, geometry, receiving environment, and test duration; laboratory results are not universally transferable.	Environment-specific models could guide degradation testing and uncertainty analysis, linking product design with realistic disposal routes.	Distinguish mineralization from other degradation measures; validate under relevant receiving conditions.	[86, 88]

Note: This synthesis is not a quantified forecast. References support current challenges and methodological precedents, not all proposed AI capabilities or deployment dates. Illustrative horizons extend from near-term data integration to automated laboratories and coordinated production networks; benefits depend on representative data, experimental validation, and demonstrated economic and environmental gains.

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Mechanistic knowledge, standardized experiments, representative pilot data, and critical validation must therefore remain central. Models should express uncertainty, address mass and energy balances, and be evaluated outside the conditions used for training. Environmental claims must be tied to specific functions and end-of-life scenarios, while governance must address transparency, cybersecurity, access, and responsibility for automated decisions.

Only if all these requirements are met, AI could act as a transformative hub to move PHA development from fragmented, empirical optimization toward an integrated science of circular materials. The decisive contribution of AI will be its capacity to coordinate choices across scales and disciplines, revealing when a biological improvement strengthens the overall system and when it merely shifts burden and challenges to another stage. Over the next several decades, this systems-level intelligence may be as important as any individual breakthrough in strain productivity, feedstock availability, breakthroughs in downstream processing, or polymer chemistry.

11. DECLARATION

11.1. Acknowledgment

The author declares that no conflict of interest exists that could have appeared to influence the work reported in this paper.

11.1.1. Funding

The author declares that they have not received any financial support for their research.

11.2. Data availability

No data was used for the research described in the article.

11.3. Ethics statement

Not applicable.

11.4. Author Contributions Statement

MK: Acted as sole author

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