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Programmable Biomanufacturing Cells with Evidence-Bounded Control over Metabolic State, Product Quality, Yield, and Process Robustness across Manufacturing Scales

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ABSTRACT

Biomanufacturing cells are increasingly engineered with synthetic regulatory circuits, dynamic metabolic controls, automated design workflows, and process-aware sensing. Nevertheless, individual engineering improvements do not by themselves create manufacturing systems capable of coordinating metabolic state, recombinant-protein processing, product quality, productivity, and robustness across scales. This article proposes an evidence-bounded programmable biomanufacturing-cell architecture as an original non-empirical synthesis. The architecture separates manufacturing objectives, state sensing, limited state estimation, evidence qualification, constraint-aware policy selection, biological and process actuation, outcome monitoring, and fail-safe execution. Metabolic-state control is treated as an observability and controllability problem rather than as a single-biosensor task. Expression, folding, secretion, modification, and cellular stress are incorporated as interdependent control domains whose manipulation must remain subordinate to product-quality and biosafety constraints. Scale robustness is defined as the preservation of acceptable state estimation and intervention behavior under bioreactor gradients, process fluctuations, host adaptation, and manufacturing-domain change. Evidence thresholds determine whether an intervention may proceed, requires additional testing, should revert to a previously supported operating condition, or must be escalated for human review. The proposed architecture further distinguishes optimization evidence from validation, technical capability from manufacturing readiness, and model confidence from justified decision authority. Validation would require staged component testing, integrated perturbation studies, scale-down and scale-transfer evaluation, longitudinal genetic and phenotypic stability assessment, product-specific analytical verification, containment testing, and governance oversight. The contribution is therefore an organizing architecture and set of testable relationships rather than a validated controller, regulatory framework, or deployment-ready manufacturing system.

Key words: *Pharmaceutical biotechnology, Biomanufacturing, Cell factory, Bioprocess, Biologic developability, Synthetic biology*

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INTRODUCTION

Synthetic biology has produced commercially relevant organisms and biologically derived products, demonstrating that engineered cellular functions can move beyond laboratory proof of concept. These examples

also show that commercial translation depends on coordinated biological design, production conditions, measurement systems, and operational constraints rather than on an isolated genetic modification [1].

The design of a productive cell factory is intrinsically coupled. Carbon allocation, precursor availability, cofactor balance, energy demand, pathway toxicity, transport, host physiology, and competing cellular functions jointly influence the attainable production phenotype. Consequently, increasing pathway expression or introducing an additional biosynthetic reaction does not establish that yield, productivity, stability, and product quality will improve together [2].

Productive capacity is also conditional on the relationship among host, product, pathway, and cultivation environment. Comparative evaluation of microbial production hosts indicates that performance cannot be represented by a universal host ranking because the relevant metabolic and physiological advantages change with the target molecule and production context [3]. A similar dependency applies to recombinant proteins, for which secretion, folding, modification, degradation, and host-cell characteristics may become dominant constraints.

This Original Biomanufacturing Architecture Article proposes an evidence-bounded programmable biomanufacturing-cell architecture for integrating these coupled domains. The objective is not to describe an empirically validated controller or prescribe a manufacturing strategy. Instead, the article defines the proposed system components, their permissible relationships, the evidence conditions governing intervention, the trade-offs among yield, product quality, and robustness, and the boundaries separating conceptual plausibility from manufacturing decision readiness.

From engineered production cells to programmable manufacturing systems

An engineered production cell generally contains one or more designed functions intended to increase formation, processing, or recovery of a target product. Such cells remain vulnerable to metabolic burden, stress responses, resource competition, genetic instability, toxicity, and incomplete control over phenotype. These limitations can shift during cultivation, meaning that a design optimized at one time point or operating condition may not remain optimal throughout production [4].

Programmability adds conditional behavior. Growth-coupled selection, for example, can link synthetic-module performance to cellular fitness and thereby enrich productive phenotypes [5]. This represents a meaningful transition from static pathway installation toward rule-governed cellular behavior. However, growth coupling is not equivalent to real-time process control, and the selected relationship may fail when the product, medium, host background, or selective environment changes.

Operation outside tightly controlled laboratory conditions introduces additional requirements. Engineered systems must preserve function despite environmental variation, evolutionary pressure, incomplete sensing, operational disturbances, and containment obligations [6]. In pharmaceutical biotechnology, these requirements are joined by critical quality attributes, impurity control, process reproducibility, biologic developability, and the need to distinguish a high-producing phenotype from a manufacturing-acceptable phenotype.

A programmable manufacturing system is therefore defined here as a cell-based or biologically driven production arrangement in which measured state information can condition a bounded set of interventions. Programmability alone is insufficient. The system must also specify what may be sensed, which states may be inferred, which interventions are permitted, what evidence justifies an intervention, which quality or biosafety constraints can veto optimization, and when control must revert to non-action or human oversight. This expanded definition forms the basis of the proposed architecture.

Proposed evidence-bounded cell-control architecture

Automated design–build–test–learn workflows demonstrate the value of separating biological design, construction, measurement, and learning functions [7]. The proposed architecture extends this functional separation into manufacturing control. It distinguishes the generation of evidence from the authority to act on that evidence, preventing an optimizer, prediction model, or biosensor output from being treated automatically as a justified intervention.

Algorithm-driven biosystem platforms can iteratively select designs and use experimental measurements to update subsequent choices [8]. Their decisions nevertheless remain bounded by the variables measured, the interventions available, the objective encoded, and the design space explored. The proposed architecture consequently places an evidence-qualification layer between state estimation and policy selection.

Figure 1 presents the original conceptual synthesis for programmable biomanufacturing-cell control architecture, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

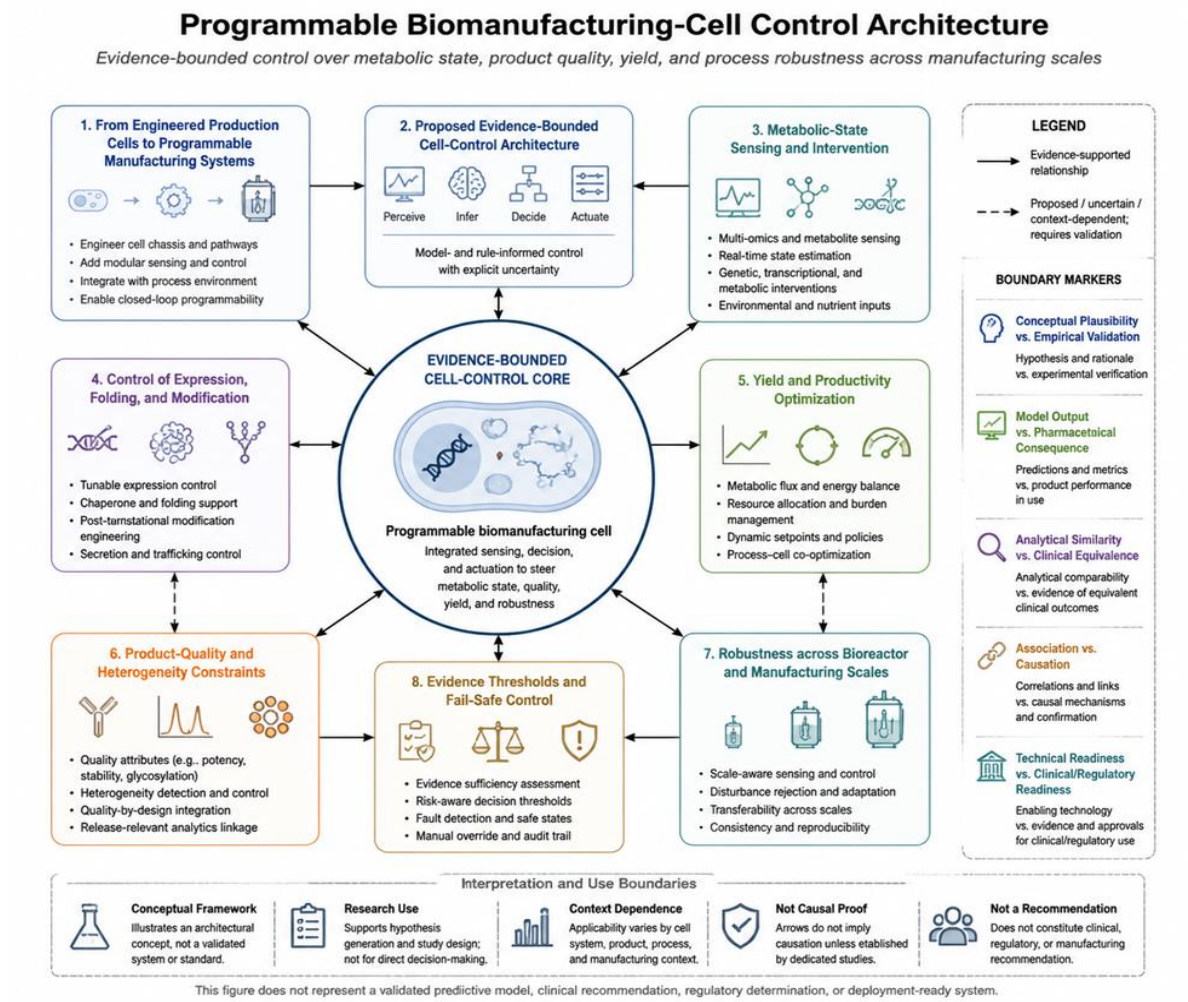

Figure 1. Programmable Biomanufacturing-Cell Control Architecture

The figure is an original conceptual synthesis developed for "Programmable Biomanufacturing Cells with Evidence-Bounded Control over Metabolic State, Product Quality, Yield, and Process Robustness across Manufacturing Scales." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

A limited world model or state estimator is proposed to combine intracellular signals, extracellular measurements, process analytical data, equipment conditions, and scale-relevant information. Digital-twin concepts provide a useful direction for connecting biological state, process behavior, and scale-up reasoning, but they do not establish that a sufficiently accurate or decision-ready representation currently exists for the proposed architecture [9]. The estimator must therefore expose uncertainty, missing variables, calibration limits, and the manufacturing domain in which its outputs have been evaluated.

Automated experimentation, algorithmic biosystem design, and digital-twin development collectively motivate the separation of state estimation, evidence qualification, and policy selection, but they do not validate the integrated architecture proposed here [7-9]. The policy layer is organized hierarchically: biosafety and predefined product-quality constraints take precedence over process robustness, which in turn constrains yield and productivity optimization. These priorities are proposed governance rules rather than empirically established universal weightings.

The control cycle begins with a declared manufacturing context comprising the host or cell line, product, critical quality attributes, medium, feed strategy, bioreactor configuration, and scale. Sensors generate observations; the

estimator proposes a bounded representation of cellular and process state; and an evidence register records provenance, calibration, domain relevance, reproducibility, and uncertainty. Only interventions satisfying the applicable evidence and constraint conditions may proceed. Otherwise, the system should request additional evidence, maintain the current condition, return to a previously supported operating envelope, or escalate the decision to qualified human oversight.

Metabolic-state sensing and intervention

Metabolic state is defined here as the context-dependent configuration of fluxes, metabolite availability, redox and energy balance, growth commitment, stress, and resource allocation that is relevant to a specified manufacturing decision. It cannot normally be observed directly through a single signal. Population-density-responsive circuits demonstrate that an accessible proxy can trigger dynamic regulation of production flux, but density remains only one partial representation of cellular state [10].

Intracellular metabolites can provide more mechanistically proximal control signals. Pyruvate-responsive circuits have been used to redirect central metabolism dynamically, showing that metabolite sensing can connect an endogenous state variable to a defined intervention [11]. Such evidence supports sensor–actuator coupling, but not the assumption that one metabolite captures pathway capacity, cellular health, product quality, or future process behavior.

External actuation provides a complementary strategy. Optogenetic regulation can temporally separate growth and production and can adjust engineered metabolic activity through controlled light inputs [12]. Its usefulness at manufacturing scale remains conditional on light delivery, penetration, mixing, cellular response heterogeneity, equipment design, and the stability of the engineered response. Other external actuators would require equivalent analysis of delivery uniformity and response dynamics.

The proposed architecture therefore permits metabolic intervention only after four questions are addressed: whether the relevant state is sufficiently observable, whether the proposed actuator can change that state with adequate specificity, whether sensing and actuation occur within a useful response time, and whether the relationship remains valid in the intended host, product, bioreactor, and scale. Failure of any condition should reduce decision authority rather than force optimization. This rule is an original proposed boundary and requires prospective perturbation, calibration, and transferability testing.

Control of expression, folding, and modification

Recombinant-protein output cannot be represented adequately by transcription or translation rate alone. Productive expression depends on folding capacity, aggregation control, proteolysis, secretion, and the ability of the host to absorb biosynthetic stress without losing viability or product integrity [13].

Stress-responsive regulation provides one route toward conditional proteostasis control. Feedback modulation of the unfolded-protein response demonstrates that cellular stress signals can be connected to interventions intended to preserve production capacity [14]. Such feedback remains dependent on the host, product, sensor range, and intervention dynamics.

Secretory-pathway engineering further illustrates the coupling between productivity and product quality. Multiplex modification of secretome functions can influence recombinant-protein production and purity simultaneously [15]. The direction of benefit cannot be presumed for another construct, cell line, or process without product-specific evidence.

Expression, folding, stress adaptation, and secretion therefore cannot be treated as independent control variables [13-15]. The proposed architecture represents them as a coupled proteostasis state. Intervention is permitted only when increased expression does not produce unacceptable aggregation, degradation, impurity, modification, or stress-related consequences.

Yield and productivity optimization

Dynamic metabolic control includes staged, continuous, and population-level strategies, each involving trade-offs among titer, rate, yield, productivity, burden, and response stability [16]. Yield is therefore treated as one objective within a constrained manufacturing system rather than as the controller's overriding target.

Iterative systems engineering can combine measurements, modeling, and experimental modification to identify bottlenecks across successive production cycles [17]. This supports evidence-guided improvement, but iterative learning should not be confused with autonomous online control or assumed to transfer between hosts and products.

Automation and machine learning can accelerate exploration of a predefined production-design space [18]. Their conclusions remain conditional on the sampled domain, encoded objective, measurement quality, and available interventions. Extrapolation beyond that domain should reduce decision authority rather than increase it.

The proposed controller accepts a yield- or productivity-enhancing action only when predefined quality, biosafety, stability, and robustness conditions remain satisfied. Yield optimization is thus subordinate to constraint preservation. **Table 1** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in programmable biomanufacturing cells with evidence-bounded control over metabolic state.

Table 1. Definitions, components, relationships, and intended uses in Programmable Biomanufacturing Cells with Evidence-Bounded Control over Metabolic State.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Metabolic-state sensing	Static pathway settings may become unsuitable during cultivation	Metabolites, population state, extracellular analytics, process signals	**Proposed:** combine multiple signals rather than treat one proxy as complete state	Earlier detection of state deviation	Sensor specificity, calibration, response time, perturbation evidence [10]	Partial observability, cross-reactivity, delayed response	A measured proxy does not establish complete metabolic state
Metabolic intervention	Production and growth demands compete	Flux state, growth phase, burden, actuator availability	**Proposed:** intervene only when state and actuator relationships are sufficiently supported	Conditional redirection of resources	Host- and pathway-specific intervention studies [11]	Off-target flux changes, instability	Control evidence is not automatically transferable
External actuation	Intracellular sensing may be insufficient or slow	Light or other controllable process inputs	**Proposed:** use bounded external signals where delivery is demonstrably uniform	Temporal separation of growth and production	Delivery, penetration, response-homogeneity, and scale testing [12]	Non-uniform exposure, scale dependence	Laboratory actuation does not establish manufacturing-scale controllability
Expression and folding	High expression can exceed proteostasis capacity	Translation load, folding capacity, aggregation, degradation	**Proposed:** treat expression and folding as a coupled state	Reduced mismatch between expression and functional product formation	Product- and host-specific proteostasis evidence [13]	Aggregation, degradation, cellular stress	More protein does not necessarily mean more acceptable product
Stress-responsive feedback	Cellular stress may emerge after induction	Stress reporters, unfolded-protein response, viability	**Proposed:** restrict or redirect expression when validated stress conditions occur	Preservation of productive cellular function	Prospective feedback and perturbation testing [14]	Sensor saturation, maladaptive feedback	No universal stress threshold is implied
Secretome and modification control	Secretion and host-derived impurities affect quality	Secretory capacity, host-cell proteins, modification machinery	**Proposed:** coordinate secretion interventions with quality monitoring	Joint consideration of productivity and purity	Product-specific secretome evidence [15]	New impurities, altered modifications	Improvement in one product does not establish general benefit
Yield and productivity policy	Single-objective maximization can violate other requirements	Titer, rate, yield, burden, quality, stability	**Proposed:** biosafety and quality constraints veto yield-only actions	Bounded multi-objective optimization	Comparative dynamic-control evaluation [16]	Objective conflict, controller oscillation	Simultaneous maximization is not assumed

Iterative learning	Bottlenecks may not be identifiable from one experiment	Omics, process measurements, models, experimental outcomes	**Proposed:** update hypotheses and interventions through traceable cycles	More informative engineering decisions	Reproducible model–experiment cycles [17]	Spurious attribution, context dependence	Iterative improvement is not online autonomy
Algorithmic optimization	Design spaces may be too large for manual exploration	Training data, objective function, intervention space	**Proposed:** limit recommendations to validated domains	Faster bounded search	External validation, calibration, domain-shift analysis [18]	Overfitting, objective misspecification	Model output does not by itself authorize intervention

Product-quality and heterogeneity constraints

Biomanufacturing hosts differ in metabolic, secretory, and processing characteristics. Multi-omics comparisons of CHO parental hosts demonstrate cell-line-specific variation in traits relevant to growth, secretion, and bioprocess behavior [19]. Host identity must therefore remain part of the controller's evidence domain.

Product quality may also be affected by specific host-cell proteins. Targeted CHO engineering has reduced a defined host-cell-protein-mediated degradation mechanism and improved a corresponding monoclonal-antibody quality attribute [20]. This supports mechanism-specific intervention, not generalized deletion of host functions.

Process conditions can alter glycosylation, but reported relationships vary across products, cell lines, analytical definitions, and cultivation contexts [21]. A process parameter should therefore be treated as a reliable quality-control variable only after its effect on the intended critical quality attribute has been established.

The architecture treats quality as a distribution rather than a single mean value. Glycoforms, aggregates, fragments, charge variants, impurities, and other relevant attributes may become heterogeneous even when average productivity appears acceptable. The proposed controller does not replace analytical release testing or established pharmaceutical quality systems.

Robustness across bioreactor and manufacturing scales

Large bioreactors contain spatial and temporal gradients in oxygen, substrate, pH, metabolites, temperature, and hydrodynamic exposure. Cells consequently experience fluctuating environmental histories that are not reproduced by an idealized well-mixed laboratory culture [22].

Scale-down systems can reproduce selected large-scale disturbances. Multicompartment bioreactors have been used to expose CHO cells to controlled fluctuations intended to mimic particular large-scale effects [23]. Such systems support targeted validation but do not establish complete equivalence with manufacturing equipment.

Scale robustness is defined here as preservation of acceptable sensing, estimation, intervention, product quality, and cellular stability under relevant process-domain changes. A controller calibrated at one scale should not retain unchanged confidence when mixing, transport, gradients, or exposure frequencies move outside its evaluated domain.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for programmable biomanufacturing cells with evidence-bounded control over metabolic state.

Table 2. Testable propositions, evidence requirements, and validation criteria for Programmable Biomanufacturing Cells with Evidence-Bounded Control over Metabolic State.

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Context declaration	Define host, product, CQAs, process, equipment, and scale	Manufacturing specifications enter the evidence register	Constrains every downstream model and intervention	Variables and operating domain are explicitly documented	Missing or ambiguous domain definition	Process and product experts define the admissible context	No control claim outside the declared domain
Sensor layer	Measure intracellular, extracellular, and	Signals move to state estimation	Provides observations but not direct authority	Specificity, repeatability, latency, and	Drift, saturation, missing signals	Experimental teams qualify sensors under perturbation	An unqualified signal cannot authorize action

	equipment states			range are demonstrated			
State estimator	Infer decision-relevant biological and process state	Multiple observations are integrated	Communicates estimates and uncertainty to the evidence layer	Calibration and prediction error remain acceptable under tested perturbations	Latent confounding or incorrect state attribution	Model developers and biologists challenge inferred mechanisms	Prediction is not equivalent to causal understanding
Evidence register	Record provenance, domain validity, calibration, and uncertainty	Evidence accompanies every estimate and recommendation	Restricts policy authority	Supporting data are traceable and relevant to the current context	Stale, incomparable, or non-transferable evidence	Quality and scientific reviewers audit evidence lineage	Missing provenance requires non-action or escalation
Constraint-aware policy	Select among permitted interventions	Qualified state information enters a hierarchical decision rule	Biosafety and CQAs constrain robustness and yield objectives	Comparative testing shows acceptable behavior under conflicts	Yield-only optimization or unstable switching	Multidisciplinary governance defines veto conditions	Policy logic remains proposed until prospectively validated
Product-quality monitoring	Detect CQA and heterogeneity changes	Analytical outcomes return to estimation and policy layers	Can veto metabolic or process intervention	Product-specific analytical methods detect relevant changes [19]	Unobserved or delayed quality drift	Analytical and quality teams define and verify CQAs	The architecture does not replace release testing
Mechanism-specific quality intervention	Correct a supported host- or process-derived failure	Defined intervention modifies a known mechanism	Requires outcome monitoring and reversibility assessment	The targeted mechanism and product consequence are reproduced [20]	New impurities or compensatory host effects	Experimental teams verify mechanism and off-target consequences	Evidence for one mechanism does not authorize broad engineering
Scale-transfer layer	Represent gradients and process-domain change	Scale and equipment information modify model confidence	Interacts with state estimation and fallback	Relevant gradients and exposure histories are characterized [22]	Hidden domain shift	Process engineers design scale-down and transfer studies	Confidence must decrease outside evaluated scale conditions
Scale-down validation	Challenge the architecture with selected large-scale disturbances	Controlled fluctuations test sensing and intervention	Supplies transfer evidence to the register	Selected large-scale effects are reproduced and responses remain acceptable [23]	Incomplete mimicry or misleading equivalence	Engineers define what is and is not represented	Scale-down success is not complete manufacturing validation

Evidence thresholds and fail-safe control

Production strains can acquire diverse genetic errors during prolonged operation, including changes that reduce pathway activity or improve cellular fitness at the expense of production [24]. Genetic stability must therefore be monitored as a dynamic manufacturing property rather than assumed from an initial genotype.

Burden-responsive feedback demonstrates that a measurable cellular signal can restrict excessive heterologous expression [25]. This provides a mechanistic example of fail-safe regulation, but the reporter, response range, and acceptable burden state remain host- and construct-specific.

An evidence threshold is proposed as the minimum combination of provenance, domain relevance, calibration, uncertainty characterization, reversibility, and consequence monitoring required before an intervention is

permitted. Failure to meet that threshold should produce non-action, additional testing, human escalation, or return to a previously supported operating condition.

Gradient exposure, incomplete scale representation, and genetic instability constitute distinct robustness failure modes that require separate evaluation [22-24]. A fail-safe mechanism should specify its trigger, permissible fallback, recovery conditions, and consequences of false activation or non-activation. No universal numerical threshold is proposed.

Validation, biosafety, and governance

Biocontainment performance cannot be judged solely by initial function. Rationally designed microbial kill switches have been evaluated for evolutionary stability and escape, illustrating the need to challenge containment mechanisms over relevant durations and conditions [26].

Governance requirements extend beyond technical performance. Deployment of genetically engineered microbes raises questions concerning monitoring, responsibility, environmental interaction, institutional authority, and public legitimacy [27]. Contained pharmaceutical manufacturing differs from environmental release, but accountability and oversight remain necessary.

Validation should progress from individual sensors and actuators to integrated perturbation testing, product-specific analytical verification, scale-down evaluation, pilot or manufacturing-relevant operation, longitudinal stability, containment challenge, and governance review. Advancement would indicate accumulation of relevant evidence, not automatic regulatory acceptance.

Human responsibility remains explicit throughout the architecture. Qualified personnel define objectives, critical quality attributes, evidence domains, intervention permissions, fallback conditions, and escalation routes. Automated components may assist measurement, estimation, and bounded selection, but they do not assume independent scientific, quality, or regulatory accountability.

Limitations and research priorities

The architecture is principally framed around living production cells. Cell-free biomanufacturing removes some cellular constraints but introduces distinct limitations involving resource regeneration, component stability, reaction duration, scale, and economics [28]. Its sensing and control variables would therefore require separate definition.

A limited world model may also fail because biotechnology data are sparse, noisy, imbalanced, unstable, or poorly matched to the intended decision. Machine-learning performance depends on suitable data design, validation, calibration, and analysis rather than algorithmic complexity alone [29]. Model confidence must not substitute for external evidence.

Research priorities include multimodal state observability, causal intervention testing, product-specific quality feedback, longitudinal genetic-stability monitoring, scale-aware calibration, uncertainty-sensitive control, whole-cell versus cell-free comparison, fail-safe challenge testing, and governance evaluation. Each should be assessed with predeclared failure criteria rather than only favorable production outcomes.

Figure 2 presents the original conceptual synthesis for evidence-bounded optimization across yield, quality, and robustness, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

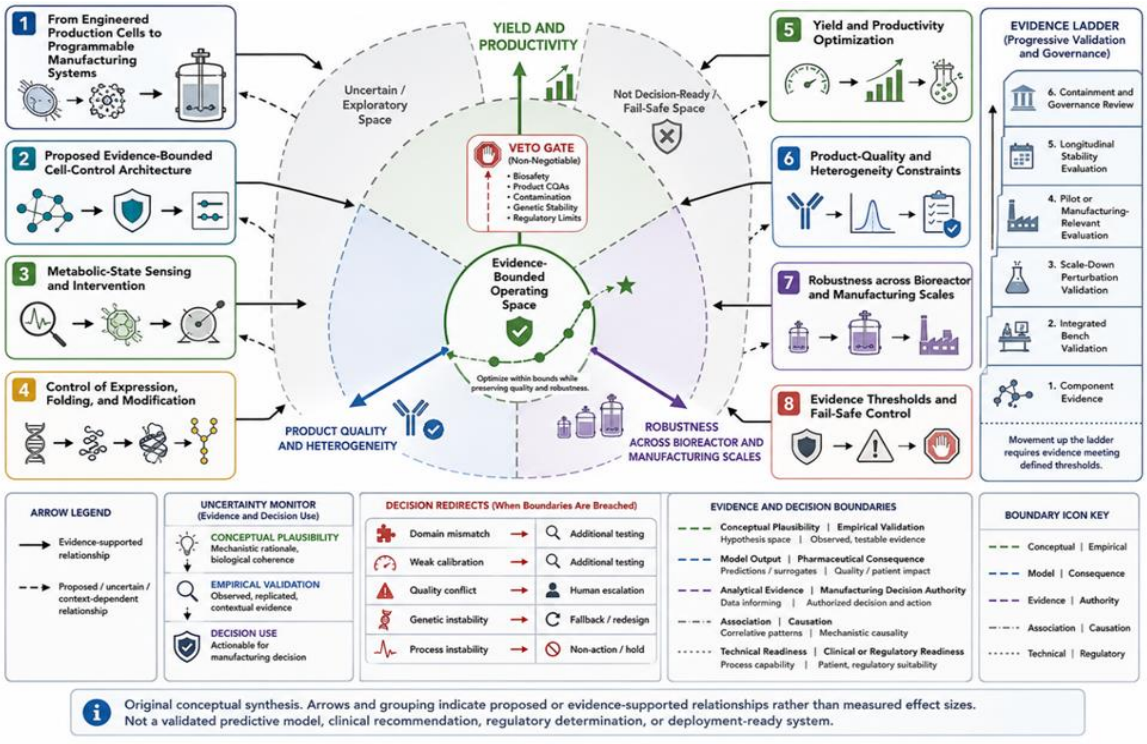

Figure 2. Evidence-Bounded Optimization across Yield, Quality, and Robustness

The figure is an original conceptual synthesis developed for "Programmable Biomanufacturing Cells with Evidence-Bounded Control over Metabolic State, Product Quality, Yield, and Process Robustness across Manufacturing Scales." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

CONCLUSION

Programmable biomanufacturing requires more than engineered production capacity or an unconstrained optimizer. The proposed evidence-bounded architecture integrates state sensing, limited state estimation, evidence qualification, hierarchical decision rules, biological and process intervention, quality monitoring, scale-awareness, and fail-safe control. Its central contribution is to make decision authority conditional on evidence, product quality, biosafety, robustness, and declared manufacturing context. The architecture remains an original conceptual synthesis requiring component-level, integrated, product-specific, scale-relevant, longitudinal, containment, and governance validation before any manufacturing decision use can be justified.

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REFERENCES

1. Voigt CA. Synthetic biology 2020–2030: six commercially-available products that are changing our world. Nat Commun. 2020;11(1):6379. doi:10.1038/s41467-020-20122-2
2. Lee SY, Kim HU, Chae TU, Cho JS, Kim JW, Shin JH, et al. A comprehensive metabolic map for production of bio-based chemicals. Nat Catal. 2019;2(1):18-33. doi:10.1038/s41929-018-0212-4
3. Kim GB, Kim HR, Lee SY. Comprehensive evaluation of the capacities of microbial cell factories. Nat Commun. 2025;16(1):2869. doi:10.1038/s41467-025-58227-1

4. Bachhav B, de Rossi J, Llanos CD, Segatori L. Cell factory engineering: Challenges and opportunities for synthetic biology applications. Biotechnol Bioeng. 2023;120(9):2441-59. doi:10.1002/bit.28365
5. Orsi E, Claassens NJ, Nikel PI, Lindner SN. Growth-coupled selection of synthetic modules to accelerate cell factory development. Nat Commun. 2021;12(1):5295. doi:10.1038/s41467-021-25665-6
6. Brooks SM, Alper HS. Applications, challenges, and needs for employing synthetic biology beyond the lab. Nat Commun. 2021;12(1):1390. doi:10.1038/s41467-021-21740-0
7. Carbonell P, Jervis AJ, Robinson CJ, Yan C, Dunstan M, Swainston N, et al. An automated Design-Build-Test-Learn pipeline for enhanced microbial production of fine chemicals. Commun Biol. 2018;1:66. doi:10.1038/s42003-018-0076-9
8. HamediRad M, Chao R, Weisberg S, Lian J, Sinha S, Zhao H. Towards a fully automated algorithm driven platform for biosystems design. Nat Commun. 2019;10(1):5150. doi:10.1038/s41467-019-13189-z
9. Yuan S, Xu V, Muddana C, Sureshkumar P, Tang YJ. From design-build-test-learn cycles to AI-driven digital twins for bioprocess scale-up in the Genesis Mission era. Curr Opin Biotechnol. 2026;100:103516. doi:10.1016/j.copbio.2026.103516
10. Gupta A, Reizman IMB, Reisch CR, Prather KLJ. Dynamic regulation of metabolic flux in engineered bacteria using a pathway-independent quorum-sensing circuit. Nat Biotechnol. 2017;35(3):273-9. doi:10.1038/nbt.3796
11. Xu X, Li X, Liu Y, Zhu YL, Li J, Du G, et al. Pyruvate-responsive genetic circuits for dynamic control of central metabolism. Nat Chem Biol. 2020;16(11):1261-8. doi:10.1038/s41589-020-0637-3
12. Zhao EM, Zhang Y, Mehl J, Park H, Lalwani MA, Toettcher JE, et al. Optogenetic regulation of engineered cellular metabolism for microbial chemical production. Nature. 2018;555(7698):683-7. doi:10.1038/nature26141
13. Rong Y, Jensen SI, Lindorff-Larsen K, Nielsen AT. Folding of heterologous proteins in bacterial cell factories: Cellular mechanisms and engineering strategies. Biotechnol Adv. 2023;63:108079. doi:10.1016/j.biotechadv.2022.108079
14. Barrios D, Bachhav B, Carlos-Alcalde W, Llanos CD, Zhou W, Segatori L. Feedback-responsive cell factories for dynamic modulation of the unfolded protein response. Nat Commun. 2025;16(1):4106. doi:10.1038/s41467-025-58994-x
15. Kol S, Ley D, Wulff T, Decker M, Arnsdorf J, Schoffelen S, et al. Multiplex secretome engineering enhances recombinant protein production and purity. Nat Commun. 2020;11(1):1908. doi:10.1038/s41467-020-15866-w
16. Hartline CJ, Schmitz AC, Han Y, Zhang F. Dynamic control in metabolic engineering: Theories, tools, and applications. Metab Eng. 2021;63:126-40. doi:10.1016/j.ymben.2020.08.015
17. Eng T, Banerjee D, Menasalvas J, Chen Y, Gin J, Choudhary H, et al. Maximizing microbial bioproduction from sustainable carbon sources using iterative systems engineering. Cell Rep. 2023;42(9):113087. doi:10.1016/j.celrep.2023.113087
18. Carruthers DN, Kinnunen PC, Li Y, Chen Y, Gin JW, Yunus IS, et al. Automation and machine learning drive rapid optimization of isoprenol production in Pseudomonas putida. Nat Commun. 2025;16(1):11489. doi:10.1038/s41467-025-66304-8
19. Lakshmanan M, Kok YJ, Lee AP, Kyriakopoulos S, Lim HL, Teo G, et al. Multi-omics profiling of CHO parental hosts reveals cell line-specific variations in bioprocessing traits. Biotechnol Bioeng. 2019;116(9):2117-29. doi:10.1002/bit.27014
20. Dovgan T, Golghalyani V, Zurlo F, Hatton D, Lindo V, Turner R, et al. Targeted CHO cell engineering approaches can reduce HCP-related enzymatic degradation and improve mAb product quality. Biotechnol Bioeng. 2021;118(10):3821-31. doi:10.1002/bit.27857
21. Bravo-Venegas J, Rodriguez-Siza J, Vergara M, Torres M, Dickson A, Toledo JR, et al. Impact of process parameters on IgG glycosylation in CHO systems: A comprehensive quantitative analysis. MAbs. 2026;18(1):2643039. doi:10.1080/19420862.2026.2643039
22. Nadal-Rey G, McClure DD, Kavanagh JM, Cornelissen S, Fletcher DF, Gernaey KV. Understanding gradients in industrial bioreactors. Biotechnol Adv. 2021;46:107660. doi:10.1016/j.biotechadv.2020.107660
23. Gaugler L, Hofmann S, Schlüter M, Takors R. Mimicking CHO large-scale effects in the single multicompartment bioreactor: A new approach to access scale-up behavior. Biotechnol Bioeng. 2024;121(4):1244-56. doi:10.1002/bit.28647

24. Rugbjerg P, Myling-Petersen N, Porse A, Sarup-Lytzen K, Sommer MOA. Diverse genetic error modes constrain large-scale bio-based production. Nat Commun. 2018;9(1):787. doi:10.1038/s41467-018-03232-w
25. Ceroni F, Boo A, Furini S, Gorochowski TE, Borkowski O, Ladak YN, et al. Burden-driven feedback control of gene expression. Nat Methods. 2018;15(5):387-93. doi:10.1038/nmeth.4635
26. Stirling F, Bitzan L, O'Keefe S, Redfield E, Oliver JWK, Way J, et al. Rational design of evolutionarily stable microbial kill switches. Mol Cell. 2017;68(4):686-97.e3. doi:10.1016/j.molcel.2017.10.033
27. Brewer AM, George DR, Frow EK. Emerging governance considerations for the deployment of genetically engineered microbes. Curr Opin Microbiol. 2026;89:102685. doi:10.1016/j.mib.2025.102685
28. Rasor BJ, Vögeli B, Landwehr GM, Bogart JW, Karim AS, Jewett MC. Toward sustainable, cell-free biomanufacturing. Curr Opin Biotechnol. 2021;69:136-44. doi:10.1016/j.copbio.2020.12.012
29. Mey F, Clauwaert J, Van Huffel K, Waegeman W, De Mey M. Improving the performance of machine learning models for biotechnology: The quest for deus ex machina. Biotechnol Adv. 2021;53:107858. doi:10.1016/j.biotechadv.2021.107858