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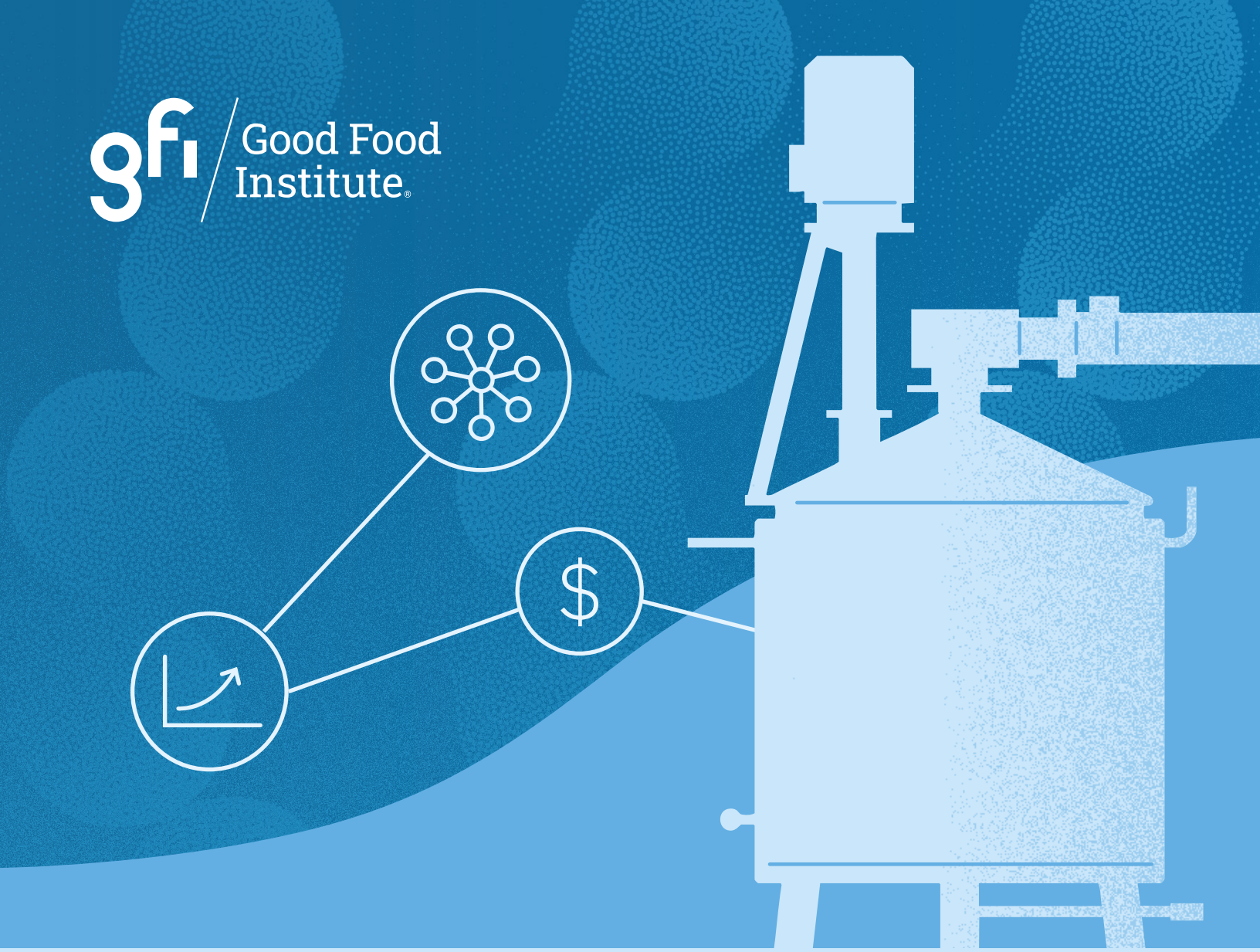

TECHNICAL SUMMARY

Optimizing cultivated meat techno-economics:

Cell growth modeling review and recommendations

Authors

Faraz Harsini, MSc, PhD, DipACLM,
lead bioprocessing scientist

Elliot Swartz, PhD*,
senior principal cultivated meat scientist

Bert Frohlich, PhD,
BioFarm Designs

*Corresponding author: elliots@gfi.org

Supplement to:

This report summarizes the key findings and research recommendations of the full technical report for this study, "Optimizing cultivated meat techno-economics: Cell growth modeling review and recommendations." The full technical report and supplemental data are available for download at gfi.org.

Acknowledgments

The authors would like to acknowledge and thank the following technical advisory committee members for their valuable guidance on study design and ecosystem relevance, and critical review of the modeling framework:

KC Carswell, PhD, independent consultant

Karen A. McDonald, PhD, professor emerita, Department of Chemical Engineering, University of California, Davis

James Ryall, PhD, life sciences and biotech consultant, honorary research fellow at The University of Melbourne

Minliang Yang, PhD, North Carolina State University

Project management: Amanda Bess, PhD
Graphic design and copy edit: Emily Hennegan, Kelli Cromsigt, Tara Foss
Cover illustration credit: dnbr/Adobe Stock; modified by The Good Food Institute

Suggested citation: Harsini, F., B. Frohlich, and E. Swartz. Technical summary for optimizing cultivated meat techno-economics: Cell growth modeling review and recommendations. Washington D.C.: Good Food Institute. 2025. https://doi.org/10.62468/ohpu7135

About the Good Food Institute

The Good Food Institute is a nonprofit think tank working to make the global food system better for the planet, people, and animals. Alongside scientists, businesses, and policymakers, GFI's teams focus on making plant-based, fermentation-enabled, and cultivated meat delicious, affordable, and accessible. Powered by philanthropy, GFI is an international network of organizations advancing alternative proteins as an essential solution needed to meet the world's climate, global health, food security, and biodiversity goals.

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Table of Contents

Introduction

Cultivated meat (CM) offers a promising path to produce meat with fewer resource demands compared to conventional animal agriculture, supporting a more environmentally sustainable and resilient protein supply. However, the path to cost-effective production at scale is still uncertain. Although many companies are working toward commercial products, the public data that support process modeling, investment planning, or infrastructure decisions remain limited.

Techno-economic models (TEMs) combine mathematical models of the underlying biological and physical (or physicochemical) processes with analysis of key financial parameters to evaluate the performance and economics of a given technology. Most CM TEMs rely on simplified assumptions, such as fixed cell growth rates, static metabolism, and homogeneous bioreactor conditions, and data from stirred-tank reactors and cell lines developed for biopharma applications. These models, therefore, may not reflect the behavior of other cell types, processes, and bioreactor designs being pursued for CM production, such as perfusion bioreactors, or muscle and fat cells used in CM processes. The lack of relevant data, combined with simplified assumptions, collectively limits the utility and accuracy of current TEMs.

This report summarizes the key findings and recommendations of a study conducted by the Good Food Institute and BioFarm Designs to lay the groundwork for more robust, adaptable, and realistic modeling approaches to guide process development, cost estimation, and research priorities. To achieve this, we defined an overarching performance-to-cost modeling framework for future bioprocess optimization. Within the performance model, we developed mathematical equations governing cell growth, and performed a literature review of the key cell growth parameters in these equations. The literature review serves as a foundational resource for the field and a systematic guide for CM researchers to understand the types of experiments to perform, data to collect, and how these data plug into models that inform scale-up and optimization of commercial processes.

The performance model includes three connected parts: the cell growth model, the bioreactor environment model, and the bioreactor system model. This study focused solely on developing the cell growth component of that broader framework. Future work will expand on this study by modeling the bioreactor environment and system-level dynamics. Together, these components will support more accurate predictions of performance over time, help evaluate trade-offs across different bioprocess strategies, and incorporate dynamic biological responses such as stress and adaptation. This stepwise approach aims to support the design of scalable and cost-effective CM processes. All model components will need validation through iterative experimentation to create a feedback loop between data and modeling that improves accuracy and decision-making.

Key findings of the study

Overall, we found that critical data such as cellular dry mass and composition, concentration thresholds of inhibitory metabolites, and substrate consumption rates for CM-relevant cell lines are generally missing from the public domain. These data are needed to predict growth and yield, which are key to predicting cost. Without them, current models are less accurate and less useful. We strongly encourage more measuring and reporting of these parameters, which can occur in the peer-reviewed literature or, in the case of industry, by anonymous submission to third parties such as GFI.

Other key gaps highlighted throughout the study include the need for dynamic measurements of nutrient uptake and waste production over time, as well as experimental validation of energetics-based models. Energetics models emerged in our literature review as a promising approach to capture the shifting metabolic demands of cells over time, especially under changing environmental conditions, because they account for energy carriers like ATP and NADH. Better data on how pH, osmolality, and metabolite buildup affect muscle and fat cells used in CM are also needed. Closing these gaps will help improve TEMs and accelerate progress in cost-effective and scalable CM bioprocess development.

Study approach and industry engagement

We defined an empirical and dynamic approach to modeling cell growth that accommodates the prediction of bioreactor volumetric productivity, optimization of feeding strategies and bioreactor operating modes, and evaluation of heterogeneous conditions and trade-offs influencing overall performance. We then set out to determine whether sufficient data were available to support this approach (Figure 1).

In addition to an extensive literature review, we surveyed the industry and spoke directly with companies to gather experimental information. Many companies were hesitant to share performance data, especially around growth rates or media usage. However, some were willing to share simpler parameters like cell size. These inputs helped us test how well previous TEMs aligned with experimental reality.

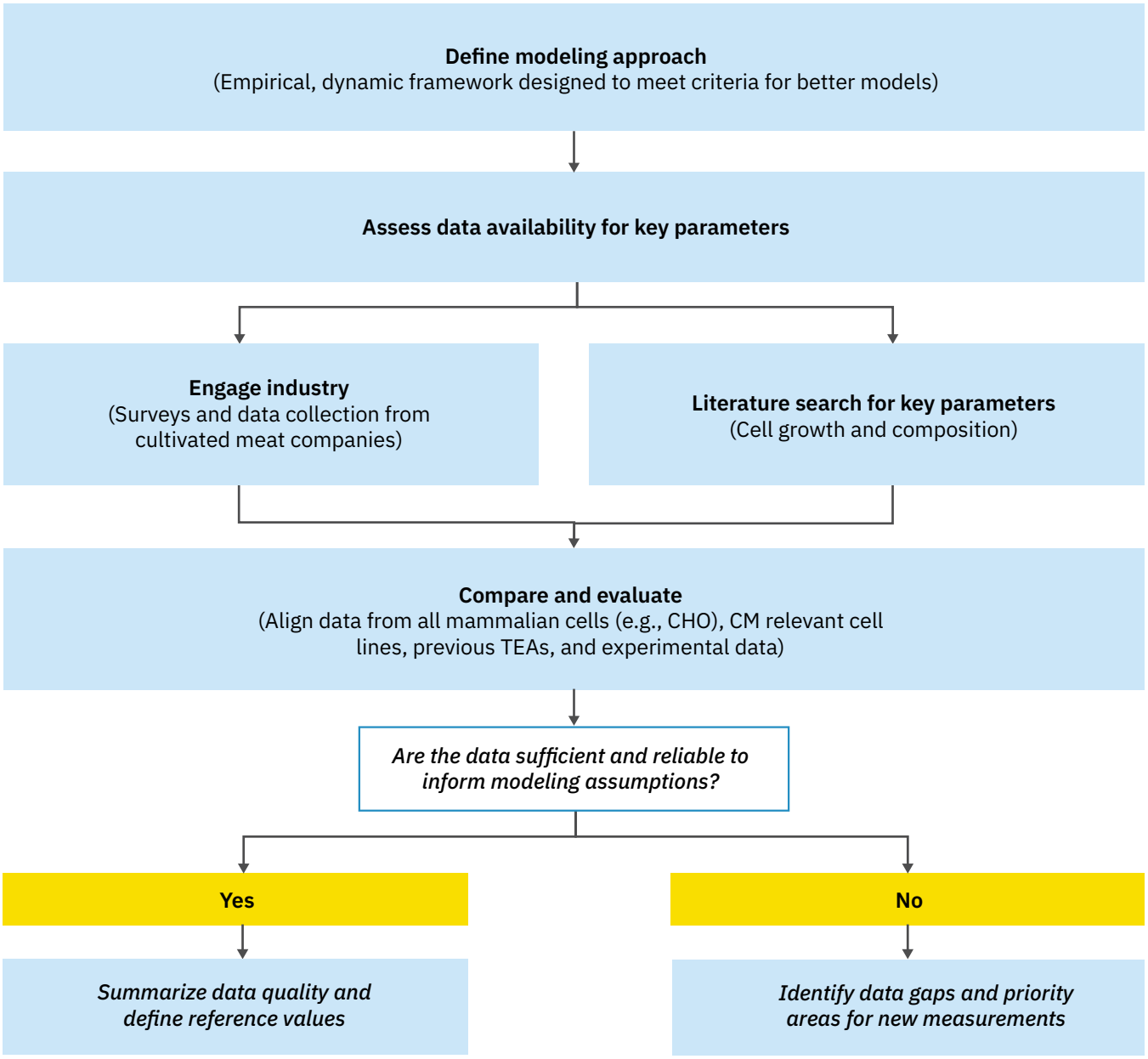

Figure 1: Flow diagram summarizing the scope and approach of the study

Study report organization

The full study report consists of four sections that outline the development and assessment of an improved cell growth and performance-to-cost modeling framework for CM production.

Section 1 describes the performance modeling framework, which is structured in three nested components: a cell growth model, a bioreactor environment model, and a bioreactor system model (Figure 2). It explains the rationale for focusing first on cell growth as the core driver of productivity before layering on bioreactor and system-level considerations, which will be the focus of separate studies.

Section 2 describes the cell growth model, outlining the mathematical equations and modeling approaches to simulate cell proliferation, differentiation, death, nutrient consumption, metabolite formation, and inhibition. It explains options for modeling these processes, including empirical equations and structured energetics-based models.

Section 3 provides a critical review of the data available to define each parameter required by the modeling approaches in Section 2. It evaluates the strength and consistency of existing evidence, highlights areas where assumptions rely on limited information, and identifies specific gaps that researchers must address to build reliable models.

Section 4 examines the big picture and broader challenges in modeling CM cell growth, including the limitations of current approaches described in Section 2 and the data gaps identified in Section 3. It explores opportunities to improve modeling frameworks and outlines directions for developing more robust and adaptable tools.

Results by section

Section 1: Performance modeling framework

Section 1 introduced the performance modeling framework for CM production that separates the system into three nested components: the cell growth model, the bioreactor environment model, and the bioreactor system model (Figure 2). This structure allows each part of the process to be evaluated or refined independently, which makes it possible to see how cell growth, the bioreactor environment, and system-level components each contribute to overall performance and cost.

In Section 1, we described why the cell growth model is the first focus, since it determines the biological limits of volumetric productivity and influences all other parts of the system. The framework also presents the concept of a performance-to-cost ratio (PCR) to compare process strategies at different levels, from the bioreactor alone to the overall manufacturing facility. The cost model is described as a separate component that uses the same specifications as those given to the cell and bioreactor component models to calculate operating and capital costs, which are then combined with the performance model output to estimate the PCR.

At a high level, this framework provides a clear way to organize modeling inputs and facilitates adaptation of models as better information becomes available. It also offers structure to the mathematical approaches in Section 2 and the evaluation of the quality and consistency of supporting data in Section 3.

Key challenges and data gaps

- Lack of standard methods to measure and report performance parameters. The field lacks a widely adopted framework for defining volumetric productivity, yields, or cost contributions in a way that enables consistent comparison across processes or designs. As a result, researchers must invest significant effort to normalize data for cross-study comparisons.
- Limited analysis of PCRs and cost trade-offs, with a narrow scope of process designs and scales. There are few examples of studies that compare PCRs across different process designs and scales or incorporate the broader cost trade-offs needed to understand how these designs perform in practice. Existing TEMs have largely focused on a narrow range of process designs and scales, which leaves significant gaps in process and cost data. This limits the ability to fully explore alternative designs or optimize performance across diverse facility types.

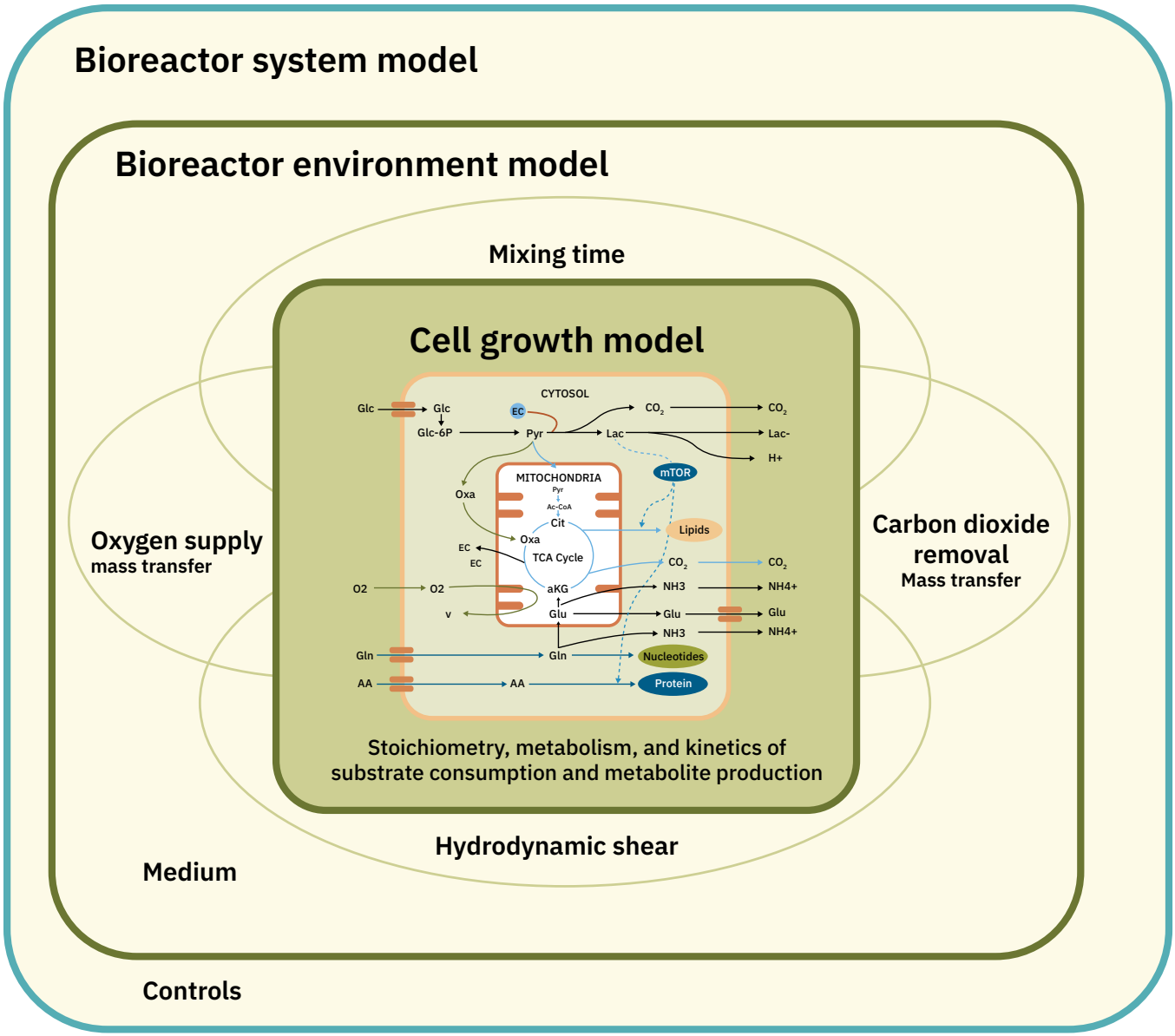

Figure 2: Overview schematic of the performance model, consisting of three individual component models.

Section 2: Cell growth model framework

Section 2 described the cell growth model and the mathematical framework to simulate how cells proliferate, consume nutrients, and release waste over time. This framework includes a set of empirical equations that describe growth and death rates, volumetric productivity, substrate consumption, byproduct formation, inhibition effects, and the influence of environmental factors such as temperature and pH. We began with the cell growth model because it defines the biological limits of productivity and directly shapes the inputs to all other parts of the system. Also, prior TEMs often used fixed growth rates and static assumptions, which may not capture complex dynamic biological behavior.

The section also described why it is important to include factors such as substrate limitation, inhibition by waste products, and maintenance energy requirements in the model. It also noted that common single-parameter inhibition models can misrepresent growth at extreme inhibitor concentrations, since they do not predict full arrest and may overestimate effects at very low or very high levels.

More accurate representations may require multiparameter or threshold-based models that incorporate IC50 and IC100 values to capture both gradual inhibition and complete growth arrest. Maintenance metabolism refers to the baseline consumption of energy and nutrients required to keep cells alive even when they are not actively dividing. This is different from growth-associated metabolism, which relates to biomass accumulation. Including maintenance terms is important because failing to account for them can lead to overestimating yields and underestimating nutrient demand, especially in slower-growing cultures or phases when cells are not proliferating.

This modeling approach is not without its own set of limitations. Simulating the coordinated metabolism of key substrates glucose and glutamine, and the interaction effects and feedback loops related to their byproducts, lactate and ammonia, is not trivial. To manage this, we proposed models based on ATP and overall energy balance, which serve as the underlying foundation for the principal anabolic and catabolic processes of the cell. These models treat ATP and NADH demand as internal variables that link substrate consumption to energy production and growth.

Energetics-based models help address challenges by describing how cells balance energy requirements across different pathways and by predicting how productivity and nutrient demands evolve over time. We noted that while this modeling strategy had been proposed and demonstrated in earlier research on mammalian cells, it has not yet been widely applied to CM. Structured energetics models may offer advantages, especially in more complex fed-batch or perfusion systems.

At a high level, this section hypothesizes that while simpler empirical models may be adequate for some scenarios, capturing dynamic changes in metabolism and environmental stress will likely require more detailed approaches based on structured energetics models.

Key challenges

- Selecting a modeling approach for CM that balances ease of use, prediction, flexibility, data availability, and complexity. It is highly unlikely that any single model can satisfy all future needs as CM technology continues to develop, particularly with the anticipated variety of CM products. Rather than a single tool, the mathematical models presented in the study report should be viewed as a toolbox from which to select the appropriate tool.
- Dynamic instead of static assumptions. Prior TEMs use fixed stoichiometries, static growth rates, and homogenous mixing assumptions. Section 2 emphasizes the need for models that incorporate dynamic growth behavior, substrate availability, and metabolite accumulation to better reflect cell growth and bioreactor performance.
- Capturing multifactor interactions. The combined effects of temperature, pH, shear, nutrient availability, and inhibitory byproducts strongly influence growth and viability. Incorporating these interactions in a way that improves predictions without making the model overly complex remains a key challenge.

Section 3: Cell growth model parameter critical review and data gaps

Section 3 reviewed published literature and industry data gathered for this project to assess what is known about key parameters used in the modeling framework described in Section 2. We evaluated the extent to which the available data, based strongly on biopharma cell lines, can serve as a starting point for modeling CM-relevant cells. Most of the review focuses on steady-state relationships between nutrients, metabolites, and growth or inhibition rates, though we also reviewed and included some studies on response times and environmental factors.

The subsections correspond to the main components of the growth model outlined in Section 2, including cell size and composition (3.2), proliferation and differentiation kinetics (3.3), inhibition by metabolic byproducts (3.4), and stoichiometry of substrate use and byproduct formation (3.5).

Section 3.2: Cell size, mass, and composition

In subsection 3.2, we reviewed available data on cell size, water content, dry mass, and biomass composition because understanding and measuring cell mass and composition are crucial to accurately model biomass production and the productivity of CM processes. One of the main problems we identified is that much of the modeling literature relies on assumptions or back-calculated estimates of cell mass rather than direct measurements. For instance, many studies estimate cell mass from diameter and assumed density, but our findings show this approach is unreliable because measured dry mass often does not correlate well with size. Literature and survey data revealed that reported water content varies widely, from about 70% up to nearly 90%, due to differences in sampling and measurement methods. These inconsistencies can lead to significant overestimation or underestimation of total biomass and productivity.

Similarly, while dry mass data are essential for comparing studies and normalizing yields, most of the available measurements come from Chinese Hamster Ovary (CHO) cells, not the cell types most relevant to CM. Standardized measurements of dry mass and composition across different species, growth phases, and production conditions are urgently needed, since variability in these parameters can have a large impact on model predictions of nutrient demands, byproduct generation, and cost.

Having size and composition for CM-relevant cells is especially important because muscle and adipose cells differ significantly from standard biopharma models. For example, CM processes may involve cells in one or more stages, such as myoblasts, myocytes, myotubes, and myofibers. These cells can have vastly different diameters and biomass characteristics depending on their stage of maturation. Muscle cells are unique in that they fuse during differentiation and are among the few tissues that form multinucleated structures when mature, adding further complexity. To model their growth accurately, measured data specific to these cell types are essential.

We also compared published composition estimates in CHO cells. Older sources reported roughly 70% protein in CHO cells, while more recent studies in CHO lines found closer to 46% protein, with higher percentages of lipids and other components. Composition varied with growth rate and cell cycle stage, which affected yields and nutrient requirements.

Overall, we found no consistent standards for measuring or reporting cell mass and composition, with very limited data on CM-relevant cells grown in defined media.

Key data gaps

- Lack of reliable dry mass, size, and composition measurements for CM-relevant cell types.
- Limited understanding of how the growth phase, cell cycle, and differentiation affect mass gain and composition.
- No standardized protocols for measuring and reporting these parameters.

Section 3.3: Kinetics of cell proliferation and differentiation

In subsection 3.3, we reviewed how growth rate and doubling time vary across conditions and how differentiation affects biomass accumulation. A main finding is that cell growth rates are not fixed traits but can change substantially with nutrient levels, temperature, pH, oxygen, and other cell culture conditions. Relying on static growth rates from small cultures can misrepresent performance in bioreactors.

While intrinsic biological limits likely exist for growth rates, they are poorly defined. The fastest doubling times found in the literature range from 4–8 hours in some T cells and hamster lines, but most CM-relevant cell lines are expected to fall between 12 and 24 hours after process optimization. This range provides a useful reference for modeling, but more data in actual bioreactor environments are needed to validate it.

Temperature is a parameter with a significant impact on growth. Higher temperatures can accelerate growth, but also raise the chance of stress and protein misfolding. As cultures get denser, oxygen limits can change the optimal temperature. Overall, the optimal temperature in a bioreactor can be a moving target, and robust models alongside lessons from biopharma can help determine whether adjusting temperature during culture improves yields.

Similarly, pH has complex, nonlinear effects. The few studies that exist suggest growth rates often follow a bell-shaped curve across pH. However, quantitative models are lacking, and most data are from mouse and human cells rather than CM-relevant lines. In large-scale cultures, pH can change due to CO_2 and lactate accumulation, and adjusting pH can change other parameters such as osmolality, which further complicates mathematical modeling of the role of pH.

We also examined the kinetics of differentiation, which most previous TEMs have ignored. Industry survey data show most companies expect to include this step, which often lasts several days. Our review found that mass gain starts quickly but slows over time, so assuming constant growth can overestimate yields and hide trade-offs between longer culture and declining productivity. To address this, we developed a saturation-based model that accounts for decelerating growth and changes in composition as cells mature. While fat differentiation mainly involves lipid accumulation, muscle cells fuse and deposit extracellular proteins, making modeling more complex. More experimental data on mass gain and composition changes during muscle, fat, and fibroblast differentiation are needed to validate these models and inform future iterations.

We also reviewed how oxygen, glucose, and glutamine levels affect cell growth and death, since these are the main substrates that fuel metabolism in culture. To support modeling, we identified and, where possible, derived Monod half-saturation constants (Ks) for oxygen, glucose, and glutamine from datasets where growth rate was measured at varying substrate concentrations.

While mammalian cells are highly efficient at extracting oxygen, both low and high oxygen levels can reduce growth or increase cell death. For glucose and glutamine, sensitivity to depletion varied widely across studies. Differences in methods, media, and cell types likely explain this inconsistency. We found limited datasets measuring growth and death rates together across nutrient gradients, which makes it difficult to define clear thresholds. More controlled experiments in CM-relevant cell lines to improve models and set realistic targets for bioreactor feeding strategies are needed.

At a high level, this subsection showed that specific growth rate, doubling time, and differentiation mass gain are all dynamic traits shaped by environmental conditions and cell type. Static assumptions are unlikely to capture the real performance envelope for CM processes.

Key data gaps

- Most data come from small-scale, adherent cultures. More measurements are needed in suspension or perfusion systems that resemble manufacturing environments.
- We have limited quantitative data on how temperature and pH influence kinetics for CM-relevant cell lines.
- Few studies have measured biomass accumulation rates and compositional changes during muscle and fat differentiation. Standardized methods to quantify these dynamics are lacking.
- No TEMs have included detailed modeling of the differentiation stage, and models that compare productivity and cost under different timelines are needed.

Section 3.4: Kinetics of metabolite-induced growth inhibition and cytotoxic death

In subsection 3.4, we reviewed how the buildup of lactate, ammonia, osmolality, and dissolved CO_2 affects growth and viability. Most available data come from CHO and hybridoma cell lines, but differences in experimental conditions, such as the use of serum, lead to inconsistent results. Such variability limits the usefulness of published findings for modeling CM-relevant cell lines.

As part of this review, we calculated IC50 values for key metabolites by fitting dose-response data from the literature. This included lactate (9 studies, ~11 data points) and ammonia (11 studies, ~20 data points). For dissolved CO_2 and osmolality, fewer datasets were available, but we derived representative IC50 estimates from the limited studies.

For lactate, we found that although many have long considered it a major inhibitor, its effects involve more than simply crossing a fixed threshold. Cell growth declines progressively as lactate rises, and sensitivity differs across cell lines and culture modes. For example, some studies showed that gradual accumulation is less toxic than sudden spikes. Data suggest that fitting dose-response curves with a two-parameter model captures behavior more comprehensively, but almost none of this work was done with muscle or fat cells used in CM.

Ammonia was more consistently toxic, often reducing growth at much lower concentrations than lactate. The literature shows a clear pH dependency, with higher pH increasing cell sensitivity to ammonia. However, studies mostly used bolus additions in serum-containing media, and very few tested the effects of ammonia in continuous cultures or CM-relevant cell types.

Osmolality is another important parameter, linked to other variables such as pH. Higher osmolality can slow growth, and it often rises in tandem with lactate and ammonia accumulation. The available data showed a roughly linear decline in growth as osmolality exceeded normal levels. But again, since nearly all this work was done in CHO cultures, it is unclear the extent to which it applies to CM systems.

For dissolved CO_2, we observed that excess accumulation can also inhibit growth through intracellular acidification, but distinguishing CO_2's direct impact from pH and osmolality effects is tricky. Some studies tried to isolate these factors, but the results were still variable. It was surprising how little quantitative information we were able to find to approximate clear thresholds for tolerable CO_2 levels in muscle or adipose cells, given how critical CO_2 control is in large-scale culture.

This subsection of our study report showed that metabolite inhibition is complex and influenced by many interacting factors. Some studies have shown that cells can be adapted to tolerate higher metabolite concentrations over time. For example, CHO cells have been engineered or conditioned to reduce lactate production or even start consuming lactate in later culture stages. Similar strategies, like adjusting glucose feeding or using alternative substrates, have been used to improve energy efficiency and limit byproduct buildup. Researchers could eventually apply these strategies in CM processes to help define more realistic bounds and parameter values for future models. Although existing knowledge offers useful ranges, its variability and focus on non-CM cell lines require cautious application.

Key challenges and data gaps

- Limited data on metabolite inhibition in CM-relevant muscle and fat cells.
- Few studies measured gradual accumulation effects or adaptation over time.
- Lack of standardized methods to separate osmolality, pH, and metabolite toxicity.
- More controlled experiments are needed using CM-relevant muscle and fat cells, particularly studies that measure gradual metabolite accumulation under defined, serum-free conditions and that isolate the individual effects of pH, osmolality, and metabolite toxicity.

Section 3.5: Stoichiometry of cell growth, substrate consumption, and metabolite production

In subsection 3.5, we reviewed how cells use and transform key nutrients and how these stoichiometric relationships impact productivity and waste formation. Our main motivation was to test the common TEM assumption that yields of substrates and byproducts are fixed and scale linearly with growth rate. We found that this simplification often does not hold, since yield factors can change depending on oxygen availability, substrate concentration, growth phase, and culture conditions.

Oxygen

For oxygen metabolism, studies in hybridoma cells showed that when dissolved oxygen (DO) drops below ~1% of air saturation, cells switch from oxidative phosphorylation to glycolysis and glutaminolysis to maintain ATP, which increases glucose and glutamine uptake and boosts lactate and ammonia production. We found surprisingly few datasets linking oxygen consumption rates directly to growth rates. Most studies rely on constant estimates or narrow ranges. This is a limitation for CM modeling, as oxygen transfer is an important parameter, especially when highly concentrated (dense) cultures are desirable in CM production.

Key challenges and data gaps

- Very low DO (<0.5% air saturation) and very high DO (>10% air saturation) both negatively affect metabolism and culture performance, but precise optimal targets are unclear.
- There is insufficient data on oxygen maintenance requirements and cell-line-specific responses to oxygen limitation.
- Oxygen transfer remains a likely bottleneck in high-density cultures and needs better characterization in bioreactor systems.
- There is limited quantitative data correlating oxygen uptake rates with growth, especially for CM-relevant cells.

Glucose

Glucose metabolism data were more available, and most studies agreed that faster growth increases glucose uptake and lactate production.

Figure 3 illustrates findings from our literature review, including data compiled from prior TEMs, showing how glucose consumption scales with growth rate.

Reported specific consumption rates typically ranged from 8 to 18 mmol/gDCW/day, and the estimated range of feed conversion ratios for glucose roughly spans 1.6 to 3.6 g Glc/g DCW. However, the variability in consumption rates was large, especially at low growth rates or in small-scale cultures. Some data indicated that yield coefficients drop at higher growth rates, meaning cells use glucose less efficiently. This could have big implications for CM processes aiming for high productivity. We also found evidence that restricting glucose below 1 mM can lead to dramatically increased biomass yields and decreased lactate production, a strategy already used in biopharma.

Key challenges and data gaps

- The Warburg Effect can be engineered or at least partially mitigated. Reducing lactate: glucose ratios toward 0.5 by shifting cells toward more efficient oxidative metabolism can be a promising strategy.
- Data for glucose consumption and maintenance requirements are scattered, and glucose consumption during differentiation is largely absent. There is a need for controlled experiments in CM-relevant cell lines.
- Measuring dry cell weight across different cell lines is critical to accurately assess the relationship between glucose consumption and growth rate.

Glutamine

Glutamine metabolism showed similar variability to glucose. Most of the data for glutamine consumption rates range between 0.5 and 7 mmol/gDCW/day, which corresponds to a feed conversion ratio of 0.4 to 0.65 g Gln/g DCW. Most studies indicated that glutamine yields are more efficient at low concentrations, while higher glutamine supply increases ammonia production, leading to growth inhibition. Interestingly, the data did not show a consistent maintenance requirement for glutamine, and in some cases, apparent yields were flat or even negative. This likely reflects glutamine's partial substitutability with glucose and the complex interactions among amino acids in the medium.

Key challenges and data gaps

- No clear maintenance requirement could be established for glutamine, likely due to partial substitutability with glucose and contributions from other amino acids as energy or nitrogen sources.
- Restricting glutamine below ~0.3 mM can lead to increased apparent biomass yields and may reduce its contribution to media costs.
- Lactate formation is strongly influenced by residual glutamine concentration as well as glucose, which contributes to variability in biomass yields.
- Spontaneous degradation of glutamine in media should be mitigated in manufacturing and accounted for in metabolic models.

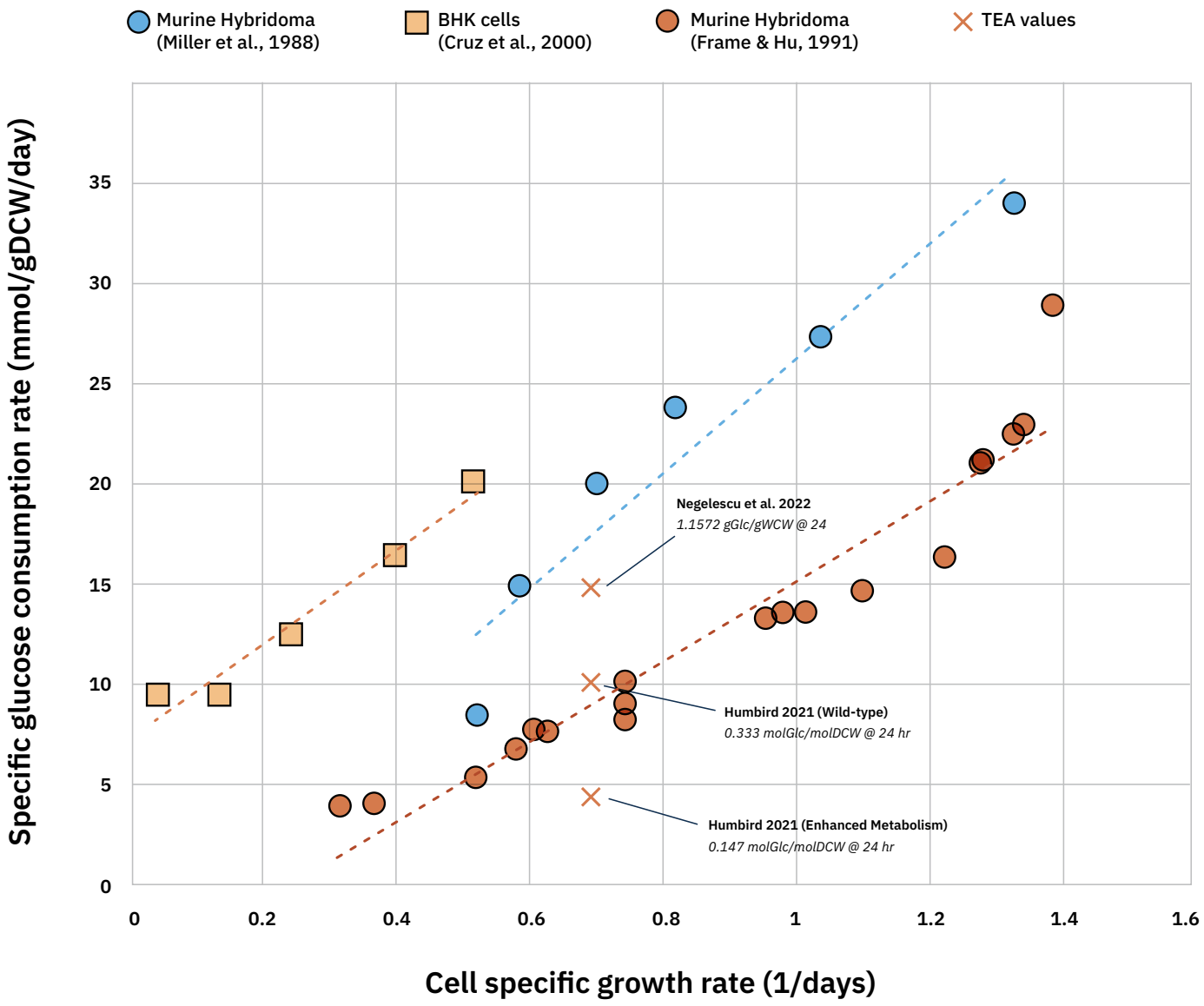

Figure 3: Example of findings from the study report, showing how glucose consumption increases with growth rate across different cell lines and studies. The Y-intercept for the lines theoretically corresponds to the maintenance requirement for glucose.

Lactate and ammonia

We also looked at how lactate and ammonia accumulation can alter metabolism. Data from hybridoma and CHO lines showed that high lactate can suppress its own production, while elevated ammonium shifts glutamine metabolism toward alanine. Adapted cell lines demonstrated dramatically reduced lactate output and better tolerance, which suggests targeted adaptation could improve CM performance. However, nearly all data came from biopharma cell lines, with little published on muscle or fat cells used in CM.

Limited work has quantified how lactate and ammonium accumulations dynamically reshape metabolism over time.

Key challenges and data gaps

- Most data on lactate and ammonia effects come from CHO and hybridoma cells; little is known for CM-relevant muscle or fat cells.
- There is limited characterization of adaptive responses (e.g., reduced lactate production, improved tolerance) in CM-relevant cells.
- There is a need for a better understanding of how lactate and ammonia accumulation cross-regulate glucose and glutamine metabolism in CM production settings.

ATP

Several studies calculated ATP production and consumption to better explain how cells meet their energy needs under different conditions. They show that growth-associated ATP yield stays fairly consistent across mammalian cell types, while maintenance makes up a large share of total energy use, especially at low growth rates. The total ATP required to support cell growth under normal conditions, when normalized to dry biomass, is approximately 8 gDCW/mol ATP consumed. However, the maintenance energy demand is not fixed, and can fluctuate and become the dominant energy sink in non-proliferating or slow-growing conditions.

Changes in growth rate also affect cell size and mass, which in turn influence apparent yields, and experiments with alternative carbon sources found that overall ATP demand stays steady even as cells shift between glycolysis and oxidative phosphorylation.

Other studies linked NADH production to oxygen levels, showing that low oxygen limits glutamine oxidation and alters ATP generation through the TCA cycle. Therefore, using energy-based models that account for both growth-associated and maintenance requirements could provide a more accurate approach than relying only on fixed substrate-to-biomass ratios.

Key challenges and data gaps

- There is limited quantitative data on growth-associated versus maintenance -associated ATP requirements for CM-relevant cells.
- Few studies link ATP and NADH balance to process conditions (e.g., oxygen, substrate levels) in CM cells.
- There is a need for energy-based models tailored to CM that capture both maintenance and growth energy demands instead of fixed stoichiometric assumptions.

At a high level, Section 3 showed that stoichiometric parameters are not static, but are shaped by nutrient availability, oxygen, pH, and even process design. Using a single fixed yield for each substrate in TEMs risks masking tradeoffs between productivity and efficiency. The most consistent pattern was that low oxygen and high glucose drive inefficient glycolytic metabolism with high lactate yields, while restricting glucose and improving oxygen delivery can shift cells toward more efficient oxidative metabolism.

Section 4. Challenges and opportunities for cell growth modeling

In Section 4 of the study report, we reflected on the results and described why no single model will be enough to predict CM production performance. Different products and processes will need tailored approaches, since proliferating cells in suspension and differentiating cells on scaffolds have very different requirements. The literature shows that animal cells typically consume glucose and glutamine inefficiently, producing lots of lactate and ammonia. This raises doubts that wild-type metabolism and standard substrates can ever deliver commercially viable yields without adaptation and optimization.

Some studies have tested alternative feedstocks such as pyruvate and alpha-ketoglutarate to reduce waste, but evaluating these options will require models that can account for their effects on both productivity and cost. Current TEMs rely on static assumptions and binary thresholds that do not reflect how cells gradually shift metabolism under stress. Much of the data also comes from CHO and hybridoma lines in ideal lab settings, with limited information for CM-relevant cells.

Section 4 additionally compared empirical, structured, and hybrid models. Figure 4 compares these model types in terms of their mathematical complexity and computational demands. Empirical models offer simplicity, but can become messy when too many variables interact. Structured models, which account for intracellular energy carriers like ATP and NADH, are better suited to describing metabolic behavior.

Accounting for intracellular energy pools allows structured models to capture how cells coordinate glucose and glutamine utilization, respond to changes in oxygen and pH, and adjust metabolic pathways under stress or adaptation. Therefore, structured energetics models may handle complex feedback inhibition and metabolic control mechanisms that empirical models cannot represent without complicated equations. Thus, energetics models may be especially valuable for predicting the effects of alternative substrates, feeding strategies, or genetic modifications on both productivity and waste generation in CM processes. In addition, segregated and hybrid models that combine mechanistic equations with AI can help simulate gradients, adaptation, and complex dynamics in large bioreactors.

Better modeling will be crucial not just to predict yields but to weigh cost trade-offs, optimize feeding strategies, and guide bioreactor design. Combining modeling with AI offers a chance to accelerate parameter estimation and improve TEMs with more realistic assumptions about metabolism and adaptation. AI can also streamline experiments needed to determine model parameter values.

Cell growth model levels of complexity

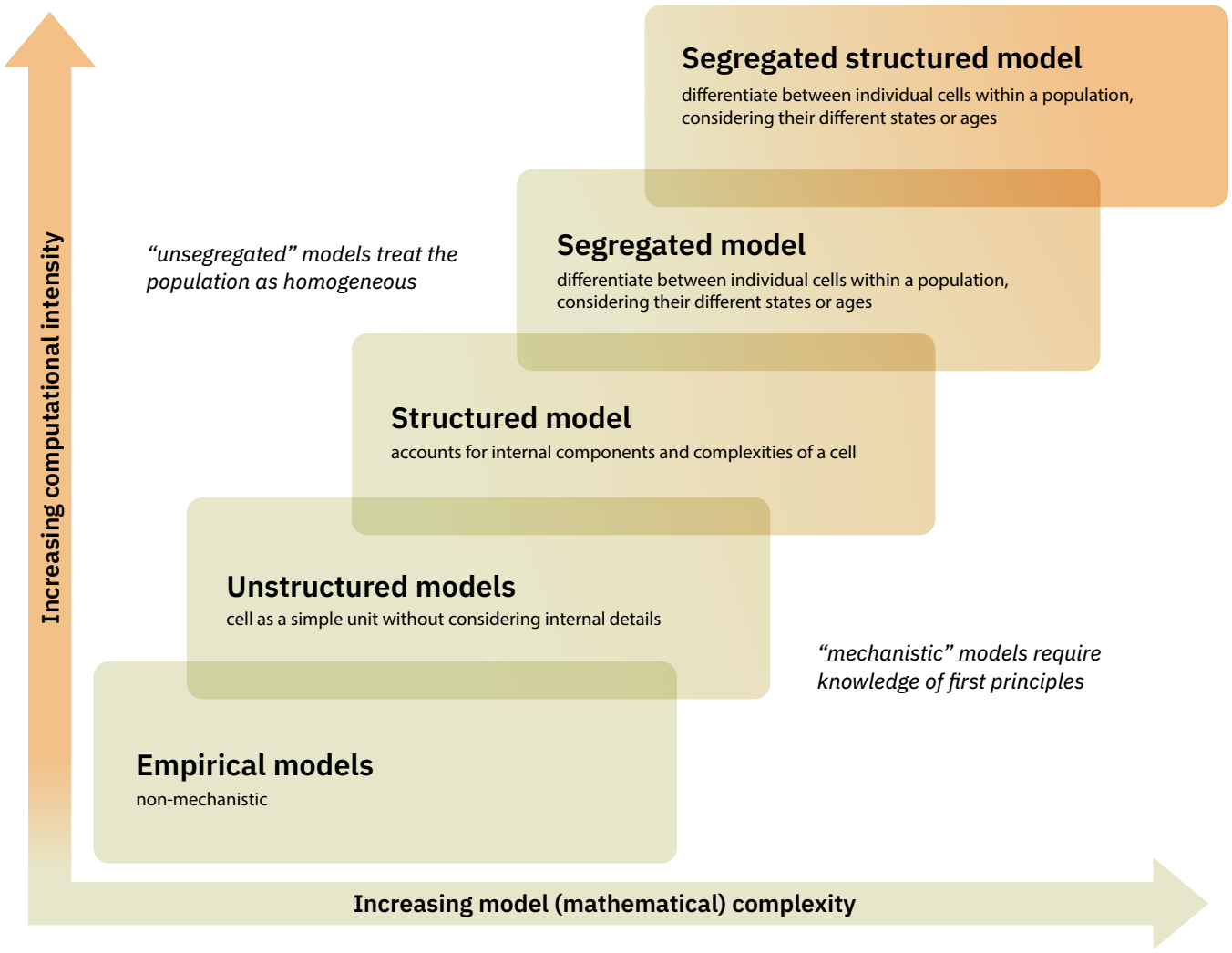

Figure 4: Comparison of common biological model types by their mathematical complexity and computational intensity. Empirical models are simpler but limited in scope, while structured, segregated, and hybrid models incorporate intracellular processes or population heterogeneity, increasing their complexity and predictive capability. The structured vs. unstructured distinction describes the level of intracellular detail, while the segregated vs. unsegregated distinction refers to whether individual cell variation is included. A segregated model can be applied on top of structured or unstructured models.

Calls to action

Our study identified critical gaps in data and modeling that stand in the way of higher-utility CM TEMs. Addressing these gaps will require action from researchers, CM companies, and academic groups working in cell culture, bioprocessing, and modeling. In the full study report, we highlighted many foundational studies that helped characterize our understanding of cell growth and metabolism in animal cells. We encourage researchers to replicate these studies using CM-relevant cell lines, focusing on generating and publishing data for the following aspects.

Publish dry mass, size, and composition measurements for CM-relevant cells

Collect standardized measurements of dry cell mass, size, and macromolecular composition (protein, lipids, carbohydrates, nucleic acids) for proliferating and differentiating muscle and adipose cells. Many models rely on back-calculated estimates from CHO cells that likely do not represent muscle or fat cells. This is critical because accurate and standardized measurements of dry mass and composition values are needed to improve accuracy in predicting yields and nutrient demands.

Generate time-series data on growth, nutrient consumption, and waste accumulation

Move beyond single-point or steady-state averages by collecting dynamic datasets that track cell growth, substrate uptake, and metabolite production over time. Future experiments should include fed-batch, perfusion, or continuous processes to better represent manufacturing conditions for CM, as most existing datasets are limited to steady-state or batch processes. Dynamic measurements are essential for building models that can simulate processes more accurately, identifying points where metabolism limits growth or productivity, and optimizing feeding and control strategies.

Report maintenance metabolism and energetics parameters

Measure and report both growth-associated and non-growth-associated substrate consumption and energy use (e.g., ATP, NADH). These parameters are critical for correcting overestimated yields and improving modeling accuracy. Without these data, models may overstate productivity and underestimate costs, leading to poorer process design decisions. Collecting these measurements will also provide the essential inputs needed for developing energetics models.

Develop energetics models to capture metabolic flexibility

Build and validate models based on ATP and NADH, which could allow these models to incorporate how cells reallocate energy and adjust metabolic pathways under stress, oxygen limitation, metabolite buildup, or adaptation. These models may enable better prediction of cell performance and more informed process optimization.

Quantify inhibition effects in CM-relevant lines

Generate dose-response curves for lactate, ammonia, CO_2, and osmolality in muscle and adipose cells to determine IC50 or IC100 values and inhibition exponents used in models. Use controlled experiments to mimic production-scale conditions and define realistic and more relevant inhibitory thresholds. This is vital for determining safe operating windows, designing better bioprocesses for CM, and preventing growth-limiting metabolite accumulation during scale-up.

Share industry data

Share basic parameters like IC50 values, biomass yields, uptake rates, and metabolite levels in formats that protect proprietary information. This can be done through peer-reviewed publications or anonymized submissions to neutral third parties or GFI. Sharing even basic nonproprietary data can accelerate progress across the field by improving model accuracy and reducing redundant experiments.

Explore alternative substrates and feeding strategies

Study the potential of substrates such as pyruvate and alpha-ketoglutarate to reduce lactate and ammonia accumulation. Test feeding regimes, such as low-residual glucose or glutamine, to improve efficiency, and report how these changes impact both costs and productivity. Optimized and alternative feeding regimes are important for identifying strategies that balance growth performance with lower waste production and more cost-effective media use.

Integrate AI and machine learning into model development

Combine mechanistic and structured models with AI to accelerate parameter estimation, improve predictive power, and optimize process design. Hybrid approaches can help identify key drivers of cost and performance, incorporate new experimental data, and support faster development of scalable, cost-effective CM bioprocesses.

Lastly, more work is also needed to model the impact of adapting cells to tolerate high metabolite concentrations, to understand how bioreactor design drives gradients and transients, and how genetic modifications could improve yields. These areas all have direct implications for modeling and will help the field build more predictive frameworks that go beyond static, oversimplified assumptions.