Techno-Economic Modelling and Assessment of Cultivated Meat: Impact of Production Bioreactor Scale

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Abstract

Increases in global meat demands cannot be sustainably met with current methods of livestock farming, which has a substantial impact on greenhouse gas emissions, land use, and water consumption. Cultivated meat is a rapidly advancing technology that produces meat products by proliferating and differentiating animal stem cells in large bioreactors, avoiding conventional live-animal farming. While many companies are working in this area, there is a lack of existing infrastructure and experience at commercial scale, resulting in many technical bottlenecks such as scale-up of cell fermentation and media availability and costs. In this study, we evaluate theoretical cultivated beef production facilities with the goal of envisioning an industry with multiple facilities to produce in total 100,000,000 kg of cultured beef per year or ~0.14% of the annual global beef production. Using the computer-aided process design software, SuperPro Designer®, facilities are modelled to create a comprehensive techno-economic analysis (TEA) to highlight improvements that can lower the cost of such a production system and allow cultivated meat products to be competitive. Three facility scenarios are presented with different sized production reactors; 42,000 L stirred tank bioreactor (STR) with a base case cost of goods sold (COGS) of $30.4/kg, 210,000 L STR with a COGS of $20.8/kg, and 260,000 L airlift reactor (ALR) with a COGS of $13.0/kg.

This study outlines how advances in scaled up bioreactors and decreased media costs are necessary for commercialization of cultured meat products.

Keywords

Cultivated meat, cultured meat, cell-based meat, process and production facility modelling, techno-economic analysis, mammalian cell culture, large-scale model

Abbreviations

TEA, Techno-economic analysis; CM, cultivated meat; GHG, greenhouse gas; USP, United States Pharmacopeia; STR, stirred-tank reactor; ALR, air-lift reactor; CAPEX, capital expenditures; OPEX, operating expenditures; COGS, cost of goods sold; CHO, Chinese hamster ovary cells; OUR, oxygen uptake rate; OTR, oxygen transfer rate; SS, stainless steel

1. Introduction

1.1 Challenges with conventional meat production

There is an increase in global meat demand due to an increase in population and income. Since 1961, total meat production has more than quadrupled (Ritchie & Roser, 2019). Globally, the most produced and consumed meat types are poultry, pork, and beef, and the total annual meat production is estimated at 328 million metric tons or 3.28×10^{11} kg as of 2020, with an expected 14% increase in production by 2030, coinciding with an 11% global population increase (OCED-FAO, 2021). There are significant challenges to meeting the global population's nutritional needs and food preferences while also meeting environmental goals and supporting animal welfare.

The environmental sustainability of conventional meat production is an often-explored issue. In recent years, global greenhouse gas (GHG) emissions from meat production make up 54% of all agriculture-based emissions on a CO_2-equivalent basis (OCED-FAO, 2021), and the agriculture economic sector (including crops, livestock, and land use) makes up around 17% of all global GHG emissions (FAO, 2020). Looking at GHG emissions data in terms of kilograms of carbon dioxide equivalents (kg CO_2eq) generated per kilogram of food product, beef meat tops all foods with 99.5 kg CO_2 eq/kg meat (Poore & Nemecek, 2018). Looking at resource usage, the dry mass of animal feed required to produce one kilogram of edible beef product is 25 kg (Alexander et al., 2016), and there is a need for comparison of such environmental and resource metrics across different food production technologies. These simple statistics make it clear that a new method of food production is needed, one that is more efficient and capable of sustaining the growing population while also avoiding deleterious environmental effects.

1.2 Opportunities for alternative protein and cultivated meat products

In recent years, there has been growth in the investment and development of alternative proteins; sources of protein from plants, algae, and filamentous fungi have been developed into meat-like products. (Here we refer to plant-based meat, eggs, and dairy products that are designed to mimic the consumption experience of the non-plant-based products) (Ignaszewski, 2021). This is an active area of research with several success stories in large-scale commercialization, including Beyond Meat, Impossible Foods, and Quorn. Environmental and life cycle assessments (LCA) show that when looking at the global warming potential, aquatic eutrophication, and land use, alternative protein products perform better than currently conventional beef products, with the exception of microalgae-based production (Barzee et al., 2022).

Another strategy for meat production that is gaining attention recently is cultivated meat or cultured meat, abbreviated as CM in this study. This technology consists of growing animal cells *in vitro*, beginning with a proliferation stage in cell-culture bioreactors, and then differentiating the cells into muscle, fat, and connective tissue, and possibly growing them or 3-D printing them on edible scaffolds, to replicate a meat texture without any livestock rearing or animal slaughtering. CM products could increase the market slice of alternative protein "meat" foods since CM products have the potential to more closely replicate the appearance, taste, texture, and nutritional profile of any meat type, including beef, chicken, and fish. There are also claims of increased resource use efficiency (Thavamani et al., 2020) and the potential to create "designer foods" with novel nutritional, flavor, and/or organoleptic profiles. Nonetheless, techno-economic models and analyses are needed at this stage to identify the most promising biomanufacturing paradigms and to indicate where research and engineering efforts are most likely to reduce manufacturing costs, capital costs, and environmental impacts.

Much of the early development of CM was based on mammalian cell culture technology implemented in the biopharmaceutical industry, which is fundamentally different than the food industry from both a scale and economic perspective. In particular, production scales and profit margins are very different – mammalian biologic drug products are made in small volumes and sold at high prices whereas food products are made in much larger volumes and sold at much lower prices. The mammalian cell culture industry has a typical throughput of ~0.1-1 tons/year (Li et al., 2020; Oosterhuis, 2018) compared to a global beef production of ~6 x 10^7 tons/year (Knight et al., 2022). Compared to the ~\$$10^3$-$10^4$/kg prices of typical mammalian cell therapeutic products (Li et al., 2020; Oosterhuis, 2018), the average export price of U.S. bulk processed beef in 2021 was \$8.95/kg and the average wholesale price of choice grade beef in the U.S. was ~\$9.35/kg (USDA, 2022; USTR, 2022)(Market Insider, 2022; USDA, 2022). So, in order to be directly competitive with beef, CM products, or at least the cost of production, must drop to a level below \$9/kg meat.

1.3 Existing techno-economic analysis (TEA) research for CM production

TEAs are computer-based simulations of manufacturing facilities (real or conceptual designs) based on mathematical models for mass and energy balances for each unit operation and utilizing necessary biological, engineering, and cost assumptions. TEAs are often used at the conceptual design stage to evaluate the economic feasibility of alternative facility designs, identify economic and environmental "hot spots", and focus research and development efforts on process steps that reduce manufacturing costs, capital expenditures, and environmental impacts. Such a model and its corresponding economic outputs can give the scientific community a benchmark of how this technology could play out in the path towards commercialization of a product. In the context of a CM TEA, biomanufacturing production models could utilize any cell type, although recently

104 published TEAs have focused on bovine cells considering the aforementioned challenges
105 associated with conventional beef production.
106 There are several published TEAs, which we summarize here to provide context for the TEA
107 presented in this study. One TEA model was created and published in 2020 by Risner et al with
108 detailed assumptions and scenarios, primarily modelled in Python and was limited to the
109 production bioreactors and associated costs (Risner et al., 2020). A 20 m^3 food-grade stirred tank
110 bioreactor was modelled (without a seed train, medium preparation, or downstream processing),
111 and multiple reactors were combined to reach a target production of 121,000,000 kg of cultured
112 beef per year, which is ~1% of the United States market for beef. The medium used was Essential
113 8^{TM}, an animal-free, or serum-free, medium with over 50 components. The prices of these
114 components were taken from a Good Food Institute (GFI) report which used vendor prices,
115 resulting in an exorbitant media cost of ~$377/L (Specht, 2020). The base case scenario required
116 5,205 x 20 m^3 bioreactors and a unit production cost of ~$4 x 10^5 per kg to account for operating
117 costs and amortized capital expenses. In the best-case scenario presented, very optimistic technical
118 and cost assumptions are implemented, including an inexpensive medium price of $0.24/L,
119 extremely high cell density, efficient glucose/media consumption, significantly increased cell
120 growth rate, and a significantly decreased differentiation time. This ambitious scenario results in
121 only 50 x 20 m^3 bioreactors needed and a price of ~$2/kg of CM (Risner et al., 2020). The platform
122 can be found on the following website: https://acbmcostcalculator.ucdavis.edu/.
123 Another TEA report released in 2020 by Humbird illustrates several striking points on the
124 scientific and engineering challenges of large-scale CM production (Humbird, 2020, 2021).
125 Furthermore, there is extensive analysis on the technical and economic design aspects of modelling
126 a single CM facility, which in this study add up to meet an industry goal of 100,000,000 kg of beef

per year. This TEA is primarily modelled in Excel, and presents overviews of model results for two scenarios of production reactor operating modes: a fed-batch case and a perfusion case. These models include a seed train along with media tanks, media and equipment sterilization, and a disk-stacked centrifuge for concentrating the cells. For the medium cost, rather than rely on current vendor prices with production volumes that don't align with required amounts, the author used actual price-volume data of commercial amino acids and recombinant proteins produced via microbial and mammalian cell fermentation (Arbige & Pitcher, 1989; BCCResearch, 2017; Gotham et al., 2018; IHS Markit, 2019; Kelley, 2009; Sanchez et al., 2017). The compiled data for amino acids and proteins and their corresponding logarithmic correlations were used in order to estimate what a media component's price would be at the required annual volume. The equations are reproduced below with Equation 1 representing the amino acid quantity-price correlation and Equation 2 representing the protein quantity-price correlation.

$$\log\left(Price\left[\frac{\$}{kg}\right]\right) = -0.563\ log\left(Production\ Volume\left[\frac{MT}{y}\right]\right) + 3.65 \qquad \text{Equation 1}$$

$$\log\left(Price\left[\frac{\$}{kg}\right]\right) = -0.861\ log\left(Production\ Volume\left[\frac{MT}{y}\right]\right) + 4.90 \qquad \text{Equation 2}$$

The amino acid data includes data from the production of cysteine, tryptophan, glycine, phenylalanine, glutamine, threonine, methionine, and lysine. The protein data includes the production of monoclonal antibody, chymosin, pectinase, glucose isomerase, protease, and amylase. Furthermore, Humbird also included scenarios where the amino acid requirements are replaced by a soy hydrolysate, further reducing costs. For perfusion operation, 96 bioreactors each with sizes of 2 m^3 are required, and the cost of production is \$51/kg beef with the defined medium and about \$15.5/kg beef for the hydrolysate medium (Humbird, 2020).

Finally, in early 2021 a TEA report commissioned by GFI was prepared by CE Delft researchers (Vergeer et al., 2021). This report is not based on a publicly available model, but rather it presents

results that are based on data from sixteen companies either developing CM products or active in the supply chain. The production scale of this model is smaller than the other TEAs by an order of magnitude, 10,000,000 kg meat/yr. Seed reactors are modelled with stirred tank reactors leading up to multiple production reactors, which are 2,000 L perfusion reactors, and media component prices are taken from Alibaba, individual suppliers, and literature. The base case results are based on current technological abilities, but several scenarios are presented which show how technological innovations could bring down the COGS. The base case scenario with current technology is based on a range of data with varying media usage and component prices, resulting in a range of COGS from $149/kg to $22,422/kg. The scenario with the most technological advancement, including extremely low media costs, reduced capital expenditures, higher cell density, shorter production run time, and larger cell volume, results in a COGS of $5.66/kg (Vergeer et al., 2021).

These published TEAs have been restricted to maximum CM bioreactor volumes of 20 m^3 and larger-scale production bioreactors will likely be required for the CM industry to reach economies of scale. Food ingredients have been typically produced in much larger production systems with reactors up to 100-1,000 m^3 (Li et al., 2020). In a recent publication by Li et al, the authors make a case, based on computational fluid dynamics (CFD) studies, that mammalian cells could be grown in airlift bioreactors at a much larger-scale, up to 300 m^3. The authors designed a 300 m^3 , 13.75 m tall airlift reactor with air sparging creating a circular flow of liquid, which avoids moving parts like impellers and creates a more homogeneous shear stress distribution. Using CHO cell data in conjunction with the designed reactor, a fluid dynamics simulation was performed to study the effects on mammalian cell growth on microcarriers and cell viability. It was found that a cell density of at least 2 x 10^8 cells/mL and an oxygen uptake rate (OUR) of 9.2 mol/m^3/s could be

supported by this bioreactor configuration (Li et al., 2020). There is also progress in addition to conceptual large-scale bioreactor designs as the company GOOD Meat has announced beginning construction of 10 new bioreactors for cultivated chicken and beef, each reactor with a capacity of 250,000 L (Carrington, 2022). Another source of inspiration for exploring large-scale ALR is the 155 m^3 reactors used by Quorn™ to produce large amounts of mycoprotein™ meat substitute (Moore et al., 2020).

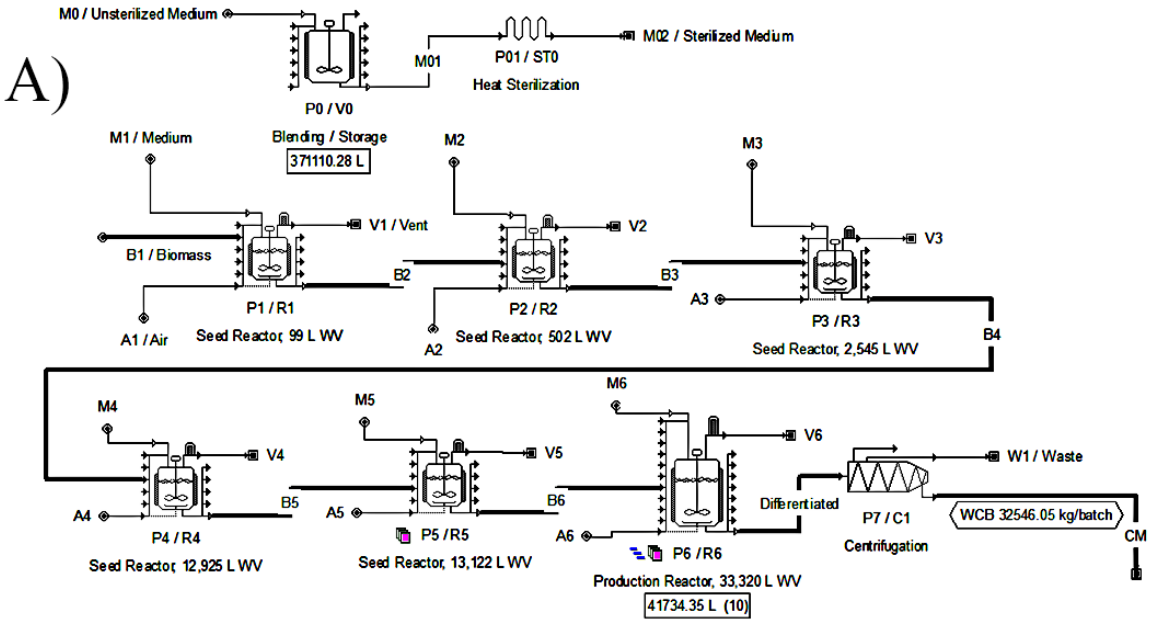
To build off of this work and explore the possibility of much larger-scale bioreactors for CM production, we present three novel TEA models for production of 100,000,000 kg of unstructured beef per year using SuperPro Designer® with assumptions informed by CM researchers in the UC Davis Cultivated Meat Consortium (CMC). The target 100,000,000 kg of cultivated unstructured beef per year is in line with previous TEA studies, and this amount is approximately the equivalent of one slaughterhouse in the U.S., or 0.16% of global beef production (Knight et al., 2022). We compare three scenarios with different production bioreactor volumes and bioreactor types: ~42,000 L stirred tank bioreactor (STR), ~210,000 L STR, and 260,000 L airlift bioreactor (ALR), all operating in batch mode. In each scenario we include the seed train, medium preparation tanks, medium and equipment sterilization, and partial downstream processing using a decanter centrifuge, and we use the correlations provided by Humbird et al (2020) to estimate costs of defined medium at scale.

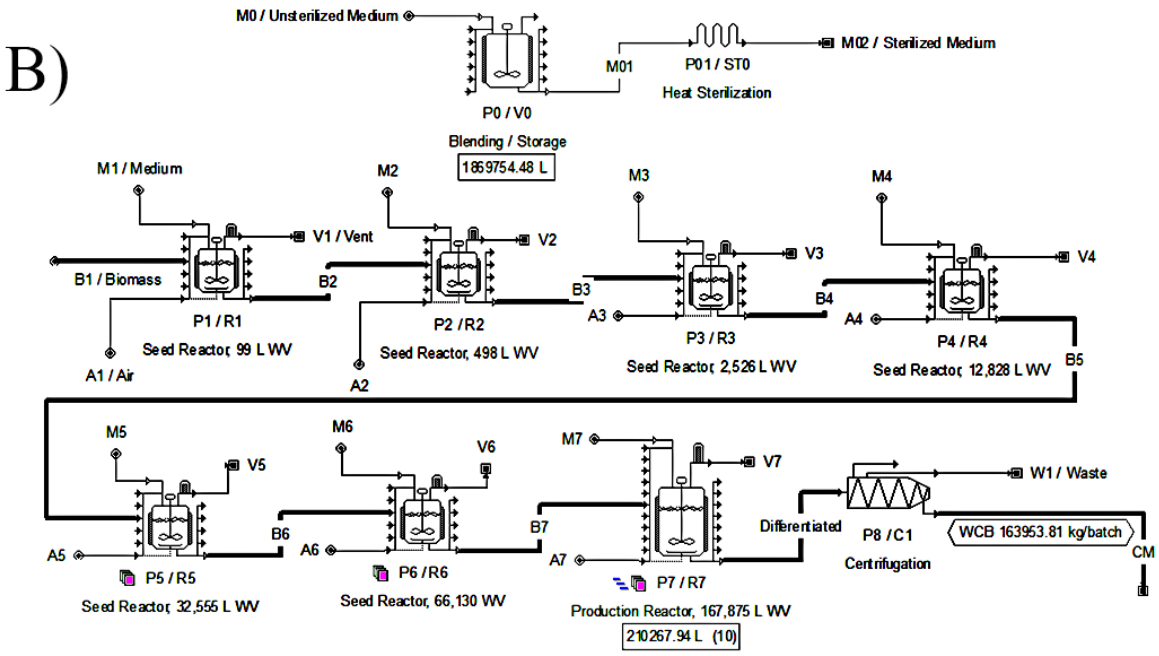
2. Materials & Methods

2.1 Model overview

This analysis was performed by designing facility models using a process simulation tool, SuperPro Designer® Version 12 Build 3 Special Build 2101 (Intelligen, Inc.). The models in this work are publicly available at https://mcdonald-nandi.ech.ucdavis.edu/tools/techno-economics/. A

free trial download of SuperPro Designer (https://www.intelligen.com/download/) can be used to view the models, run the simulations, and change process parameters/assumptions (although changes cannot be saved). The process flow diagram for the model facilities can be seen in Figure 1, each consisting of a seed train, the production bioreactor, and a simple decanting centrifuge for concentrating the cell mass.





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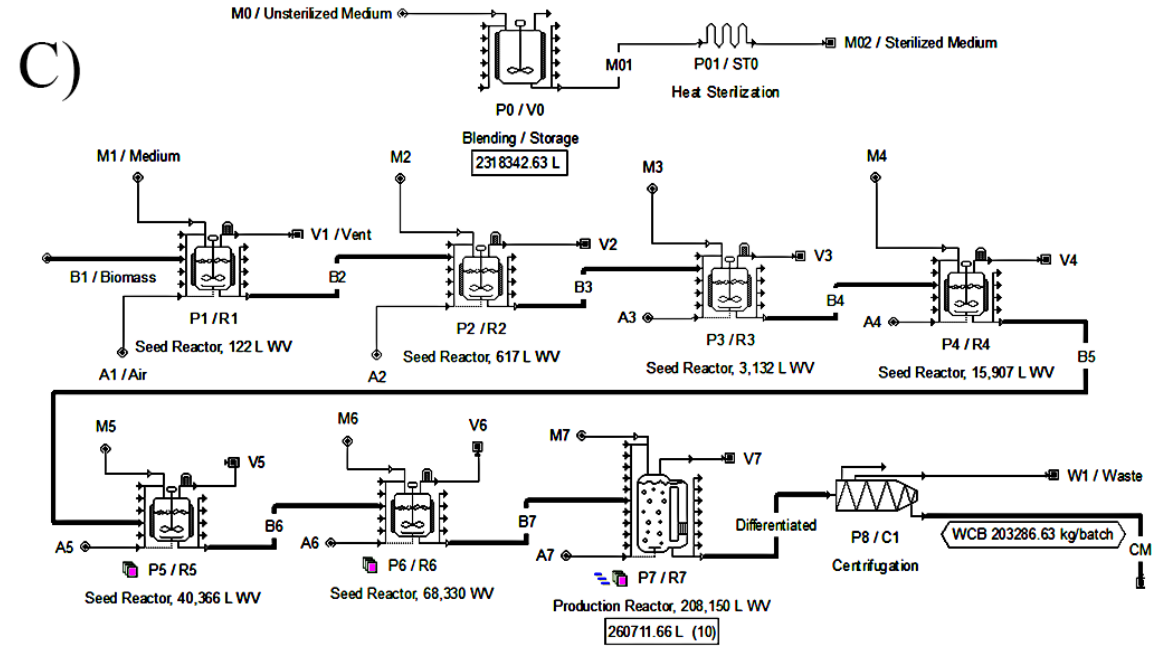

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204 **Figure 1**: Process flow diagrams of A) 42K L STR production bioreactor; B) 210K L STR

205 production bioreactor; C) 260K L ALR production bioreactor.

206 **2.2 Basic biological assumptions**

At each fermentation step in the seed train, it was assumed that cells multiplied by a factor of 5, typical of large-scale mammalian cell culture fermentations. Thus, each step takes nearly 54 hours based on the base case assumption of a 23-hour doubling time (specific growth rate $\mu = 0.03\ hr^{-1}$) as measured at the lab scale. Each fermentation step starts at 20 g fresh weight per L (g FW/L) and finishes at 100 g FW/L, a density which is close to the higher-end of densities typically seen in mammalian cell culture and in simulations (Humbird, 2020; Jagschies & Łacki, 2018). Fresh weight is assumed to be composed of 30% dry cell mass and water (Humbird, 2020). The hydrated cell mass for bovine stem cells was assumed to be the average for mammalian cells, 3×10^{-9} g FW/cell with a 17.7 μm diameter (Humbird, 2020), so the final cell density at each fermentation step is 3.3×10^{7} cells/mL. Finally, differentiation time was set to 10 days for the base case.

2.2.1 Media and stoichiometry assumptions

For the base case, a medium specifically prepared for bovine satellite cells (BSCs) was used. This serum-free medium is called Beefy-9 by the authors, and it is inspired from B8 medium used for human induced pluripotent stem cells (hiPSCs) with the basal medium being DMEM/F12 (Stout et al., 2022). Even though Beefy-9 medium was used for the base case, one can easily change the medium composition (a "stock mixture" in SuperPro Designer®) once individual components are registered in the pure component database. Although differentiation medium is likely to have an altered composition, these changes were neglected in the analysis, assuming that the difference in the cost between the two media types would be minor. The use of antibiotics in the medium was neglected because of the additional cost and need to prevent antibiotics in the environment; it is assumed that sterile design and aseptic operations are sufficient to maintain aseptic operation. The volume of fresh medium needed for each reactor is determined using the initial cell concentration of 20 g FW/L and a 20% inoculation ratio (ratio of biomass inoculum volume from the prior step

to final working volume in the subsequent step). For the sake of simplicity, the stoichiometry equation used was based on a mass factor of media required to yield the necessary final biomass concentration of 100 g FW/L at the end of each growth step. Based on enhanced metabolism, the yield of oxygen to carbon dioxide in the stoichiometry is set to 1.2 as a molar ratio, as reported in literature (Humbird, 2020).

Using the concentrations in Beefy-9, a total yearly quantity of each media component was calculated. The cost of glucose was set to $0.44 per pound in line with recent 2022 global sugar prices, which are very high by historical standards (USDA ERS, 2022). Unit prices for each amino acid and protein were approximated from the quantity-price correlations of Equations 1 and 2 using the calculated yearly quantity demanded. With regards to the vitamins, salts, lipids, and other components, there were no such correlations available so prices were approximated with bulk prices listed online using alibaba.com, made-in-china.com, or fischersci.com. Usually, these sites provided a price range for bulk or food-grade products and reasonable judgement was used to estimate the price from those ranges for the needed demand. For example, there is a required yearly quantity demanded for sodium selenite of about 20 kg, but since the exact bulk order amount could not be found a listed range of $18-$50/kg for an order of 1 kg of sodium selenite was used (Alibaba.com, 2022). Since the required quantity demanded is larger than 1 kg, $18/kg, the lower bound of the listed price range, was used. Table S1 in the Supplementary Materials shows each component of Beefy-9 and the corresponding concentration, yearly quantity demanded for the model, and different cost metrics. The components other than glucose, amino acids, and proteins were collectively found to consist of a mere ~0.17% of total media costs, so these were left out of the model, leaving a calculated media cost of ~$1.0/L.

2.3 Engineering assumptions

Each bioreactor is assumed to be made of food-grade 304 stainless steel (SS) material, rather than the pharmaceutical grade 316 SS material, and each reactor is an ASME pressure vessel since between fermentations it will be steam sterilized using a steam-in-place (SIP) system. A differentiation step was assumed to occur in the production bioreactor at the end of the batch fermentation step. Each CM facility produces enough biomass leading up to the final step to simultaneously fill ten production bioreactors. This number was chosen so that seven of these reactors would hold cells differentiating in muscle cells, two would differentiate cells to fat cells, and one would differentiate into connective tissue to approximately replicate a meat-like composition of 70% muscle, 20% fat, and 10% connective tissue. The final step of the process is a decanting centrifuge with 2% losses to remove most of the water and media components, resulting in a product that is about 97% FW meat tissue, 3% water, and less than 0.02% impurities. This model neglects some additional downstream steps that might occur to make a finished final product with the desired taste and texture, including dewatering, drying, filtering, extraction of compounds, chopping, texturizing, flavoring, and packaging and labeling (Allan et al., 2019; Barzee et al., 2022).

Detailed calculations were made to ensure that the oxygen transfer rates (OTR), 12.8 mmol O_2/L/hr for STRs and 13.5 mmol O_2/L/hr for the ALR, were sufficient to meet the cellular oxygen uptake rate (OUR) of about 10.3 mmol O_2/L/hr, which is based on the maximum cell concentration of 100 g FW/L. This calculated OUR is on the same order of magnitude as measured OURs of individual mammalian cells; 0.6-4.2 mmol/hr/L for mouse embryonic stem cells and 1.0-7.1 mmol/hr/L for CHO cells (Super et al., 2016). Also, the entire volume of media utilized was steam sterilized using high temperature short time (HTST) sterilization. It was sized assuming a maximum of 1 contamination per 50 years. Before each fermentation, reactors have a steam-in-place (SIP) cycle

and after fermentation there is a clean-in-place (CIP) cycle. Additional information and detailed calculations can be found in the Supplementary Materials.

The pricing of bioreactors was carefully chosen to represent food-grade based reactor setups, rather than pharma-grade. The textbook *Plant Food Economics* has cost data for common food-based stirred tank reactors, and a correlation relating price to bioreactor sizes (using a power exponent of 0.6) was used to price the STRs in this model using a base price of $300,000 for a 20 m^3 STR (Maroulis & Saravacos, 2008). This method was also used to price the ALR from a listed price of $174,300 for a 190 m^3 ALR in a publication led by the Swiss chemical processing company, Sulzer Chemtech, Ltd. (Zuber et al., 1997). The following equation is the form of these price-volume correlations.

$$C_2 = C_1(^{A_2}/_{A_1})^{0.6} \quad \text{Equation 3}$$

In Equation 3, C_2 is the cost for equipment with "size" A_2, C_1 is the cost for equipment with "size" A_1, and A_1 and A_2 can be attributes like reactor volume, filter area, etc. In the case of adjusting prices to the current year based on inflation, linear ratios of inflation indices are used, specifically the Chemical Engineering Plant Cost Index, CEPCI, was used (Access Intelligence, 2021; Yong, n.d.).

3. Results & Discussion

3.1 Scenario analysis overview

At the start of each seed train there is about 2-2.5 kg of FW biomass entering the first reactor. For the first case (42K L STR), there are six fermentation steps, including the main production reactor which is 41,734 L with a final working volume of 33,320 L. The other two scenarios at larger-scales have an extra step for a total of 7 fermentations. The STR is 210,268 L with a working volume of 167,875 L and the ALR is 260,712 L with a working volume of 208,148 L. In each

299 case, the production bioreactor is the main scheduling bottleneck due to the differentiation time.
300 So, it was decided to stagger that step, or have extra sets of equipment, thus lowering the cycle
301 time or the time between the start of two consecutive batches. This allows for more batches to be
302 run in a year and creates an overall more productive facility. Scheduling can be visualized in Figure
303 S1 in the Supplementary Materials. For each scenario, there are 5 staggered sets of the 10
304 production reactors, meaning 5 x 10, or 50 production bioreactors. Although 50 large production
305 reactors per facility is unusually high, this model indicates what might be possible for this industry.
306 This setup of staggered equipment in fact has the lowest COGS compared to other setups, as
307 demonstrated by Table S5 in the Supplementary Materials. Table 2 shows the basic scheduling
308 and throughput results. Each facility was sized so that the throughput per batch and thus the
309 throughput per facility per year would be close to a whole number that can be multiplied by a
310 certain number of facilities to reach the industry goal of 100,000,000 kg of CM per year.
311 **Table 2**: Scheduling and throughput parameters for each of the three facility sizes and how the
312 facility sizes add up in an industry to meet the 100 million kg of CM product.

	Production Bioreactor Scale (L)		
	42 K STR	210 K STR	260 K ALR
Facility Parameters			
Annual Operating Time (days)	330	330	330
Batch Time (days)	24.0	26.3	26.3
Cycle Time (days)	2.5	2.5	2.5
Batches Per Year	123	123	123
Throughput per batch (thousand kg)	32.5	163	203

Throughput per facility (million kg/yr)	4	20	25
Industry Parameter			
Number of Facilities	25	5	4
Total Number of Production Bioreactors	1,250	250	200
Total media flow (L/yr)	1.03×10^9	1.03×10^9	1.03×10^9

As expected, the number of facilities required drops as the production reactor size increases. It is difficult to predict exactly how facilities will be designed and sized, but this scenario analysis shows the expected trend that with increasing bioreactor size there will be fewer facilities and fewer bioreactors necessary to replace a portion of existing slaughterhouses that produce conventional meat. In Table 3, one can clearly see that the economics favor larger reactors. Note that depreciation would not be included in cash flow based profitability analysis such as discounted cash flow rate of return calculation.

Table 3: Breakdown of CAPEX and OPEX for each facility type and corresponding industry, and the COGS with and without depreciation.

Economic Parameter	42 K STR	210 K STR	260 K ALR
CAPEX per facility ($ million)	431	1,158	352
OPEX per facility ($ million per yr)	122	420	325
CAPEX for 100,000,000 kg industry ($ million)	10,770	5,789	1,408
OPEX for 100,000,000 kg industry ($ million per yr)	3,043	2,098	1,301
COGS with depreciation ($/kg)	30.4	20.8	13.0
COGS without depreciation ($/kg)	20.8	15.7	11.8

Comparing the smaller scale 42K reactor scenario to the larger 210K STR, we see that although the CAPEX and OPEX per facility increases with increasing reactor size, when looking at the entire industry these parameters actually decrease at larger-scales because there are fewer facilities needed. With COGS ($/kg) calculated as OPEX ($/yr) divided by total production (kg/yr), we see that COGS clearly decreases with increasing production reactor size. Looking at the third scenario with the ALR, the COGS further decreases because of the larger size, but another difference between this case and the STR cases is the much lower CAPEX due to the more efficient and cheaper airlift configuration. There are significant cost advantages with ALR, largely in part due to the absence of moving parts like impellers for agitation, and there are other advantages such as low shearing effects (Wang & Zhong, 2007). In order to determine which reactor type is best for mammalian cells at large scales, more studies need to be performed and tested, including more computational fluid dynamics studies as previously mentioned (Li et al., 2020).

3.2 Overall operating costs

Figure 2 demonstrates how certain categories make up this OPEX in each scenario. Total material costs remain similar across all three scales, but they make up an increasing percentage of total OPEX. The main differences in OPEX are caused by the facility dependent costs. Larger production bioreactors result in fewer facilities and fewer bioreactors needed, thus lowering total facility related costs. We see drops in waste and labor as fewer facilities are needed, but overall, they play a minor role in OPEX. Since materials make up a significant portion of the OPEX, it is necessary to look at the breakdown of materials in Figure 3. In Figure 3, we see that media costs make up 94% of the materials cost in the first scenario, and 98% in the larger-scale scenarios. This change is due to the decrease in acid, base, and water usage from the fewer cleaning and sterilization operations at larger scales.

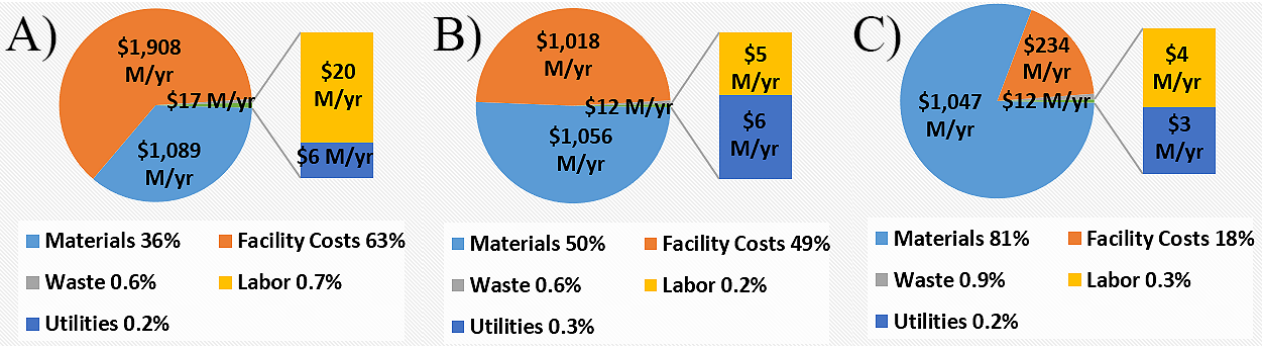

Figure 2: Breakdown of industry annual operating costs (millions $/yr) for each of the three facility sizes: a) 42K L STR, b) 210K L STR, and c) 260K L ALR. Facility dependent costs are associated with the capital expenses and they include maintenance, depreciation, insurance, taxes, and factory expenses.

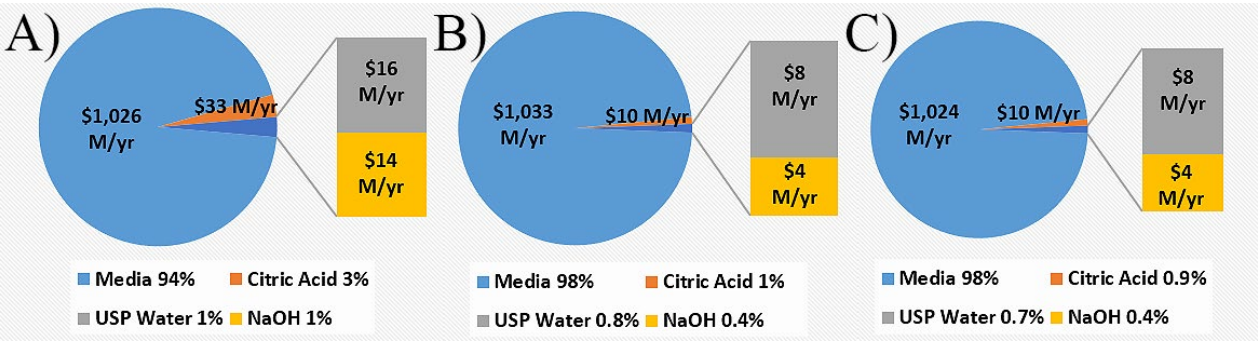

Figure 3: Breakdown of total industry raw materials costs (millions $/yr) for each of the three facility sizes: a) 42K L STR, b) 210K L STR, and c) 260K L ALR

3.3 Media cost sensitivity

The analysis presented thus far makes it clear that other than the CAPEX and other facility costs, a major bottleneck is the media cost, which makes up ~34% of the OPEX in the 42K L STR scenario, ~49% of the OPEX in the 210K L STR scenario, and ~79% of the OPEX in the 260K L ALR scenario. Even using prices from scaled up demand-price correlations, the media cost at $1/L

is still a major cost contributor. Changing the media cost allows for a useful sensitivity analysis shown in Figure 5.

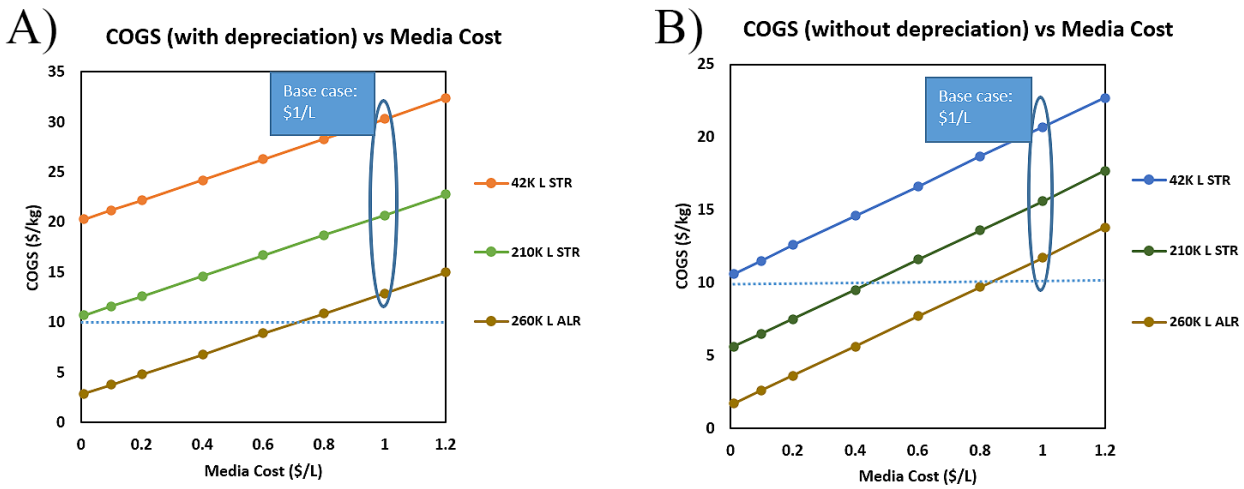

Figure 5: Sensitivity analysis of COGS vs media cost for each of the three scenarios, both a) with depreciation and b) without depreciation. A horizontal dotted line is added at $10/kg to aid in visualizing the target range for a competitive COGS, ~$0/kg-$10/kg.

As mentioned in the introduction, in order to be competitive with conventional meat products, cultivated meat must at least have a COGS comparable to wholesale beef prices, about $9/kg or less. We can see from Figure 5 that the first scenario, the smaller scale 42K L reactor, struggles to reach that $9/kg target even with no media costs. The 210K L STR reactor reaches under $10/kg COGS only when neglecting depreciation and when the media cost is less than or equal to ~$0.45/L. Finally, the 260K L ALR reaches the target range when the media cost drops to about $0.7/L or $0.8/L.

These are merely future projections, and it is uncertain where the industry stands with current technology, either with bioreactor scale-up, media costs, or other issues. However, it is clear that many processes, namely those producing media components, much be massively scaled up. Media prices of $377/L were used in previous studies (Specht, 2020), and Figure 6 makes it clear that

using any prices based on small or lab scales, even an optimistic $16/L with in-house production of growth factors (Stout et al., 2022), results in uncompetitive economics. Figure 6 shows that it is only once media prices approach $1/L or less that CM products have a chance to be competitive with conventional meat products, although there are certainly commercial opportunities for specialized products that could command higher selling prices.

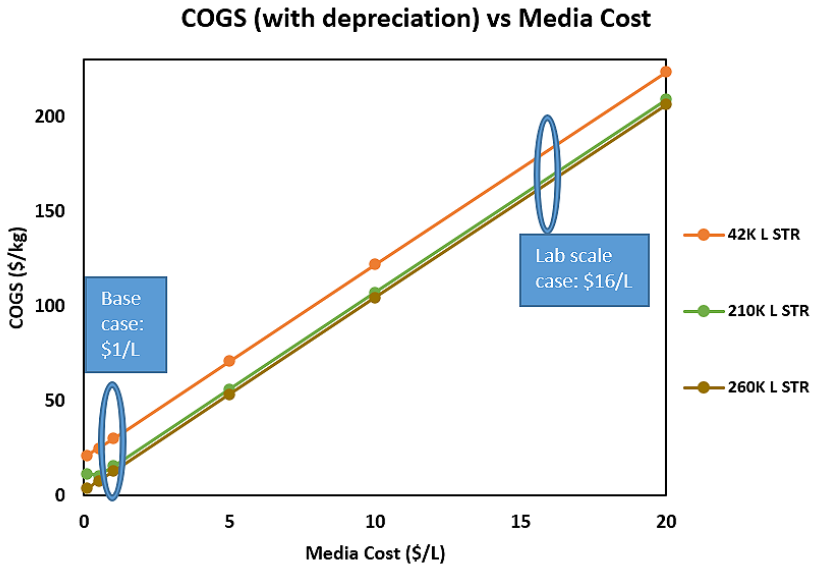

Figure 6: Sensitivity analysis of COGS vs media cost for each of the three scenarios, both with and without depreciation, extrapolated out to lab scale media prices.

To further highlight just how sensitive the cost of production is to the media costs, we can visualize the effects of media costs compared to other effects. Consider the best scenario with the ALR production reactor of 260 K L ALR. Figure 7 shows that reductions in the media cost have a more significant effect on COGS than reductions in the doubling time.

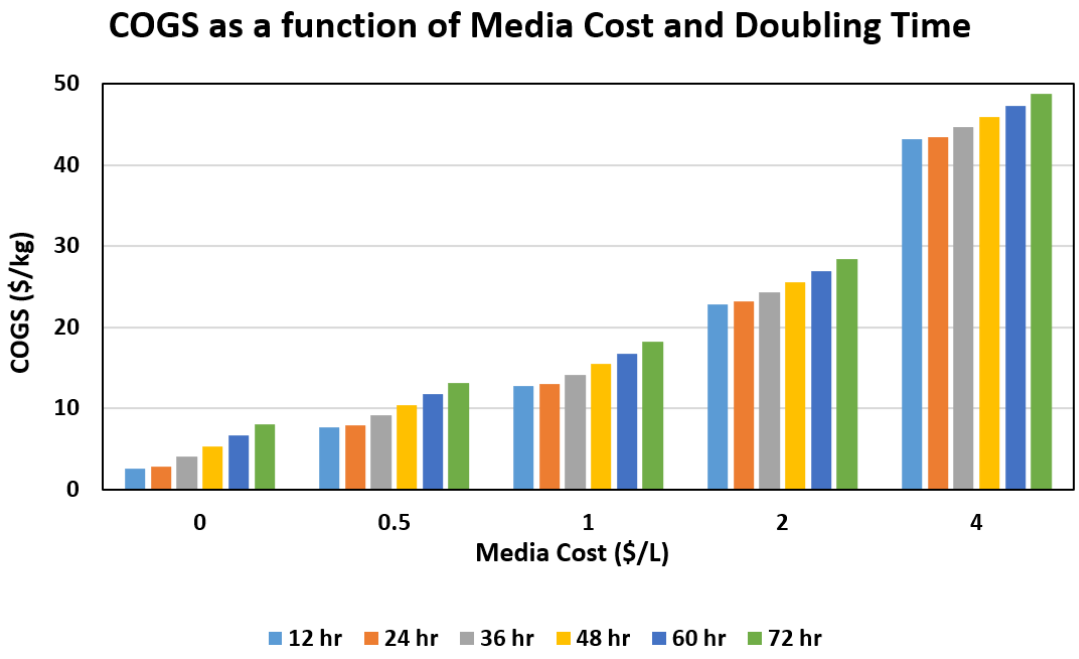

Figure 7: In the 260K L scenario, COGS is displayed as a combined effect of media costs ($/L), represented by the x-axis, and cell growth rate in doubling time (hr), represented by each color category in the legend.

At higher media costs such as $4/L, a six-fold reduction in the doubling time from 72 hours to 12 hours reduces the COGS only by about $5.5/kg, but halving the media cost can reduce the COGS by about $20/kg. It is only around $1/L when a six-fold reduction in the doubling time results in a similar effect on COGS as halving the media costs. With no media costs and a 12-hour cell doubling time, the COGS gets to $2.5/kg. Thus, biological improvements are still necessary, but the current pressing challenge is finding a cheap and efficient source of media to reach that regime of less than $1/L media in order to quickly reach an economical cost of production.

3.3.1 Production scale-up of media components

In addition to looking at a collective media cost, it is also useful to break it down into costs of individual components as shown in Figure 8.

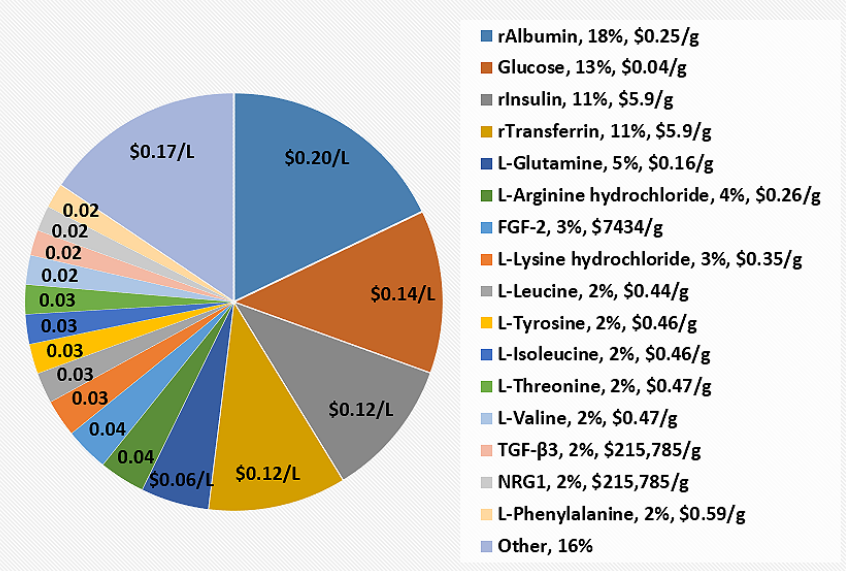

Figure 8: Breakdown of media cost by component. In the pie chart, the costs per L media are stated, and in the legend the percent's of media cost and individual costs per g of the component are stated.

Among the top four most costly media components for this model are recombinantly produced proteins: albumin, insulin, and transferrin. To visualize the state of scaling up these components, consider recombinant transferrin as an example. This TEA model requires ~20,500 kg of transferrin yearly, but based on personal communication and the $14 million global market for transferrin in 2020 (Marketandresearch.biz, 2021), it was estimated that the total global production capacity of transferrin is only 200-300 kg. Evidently, even outside of scaling up mammalian cell culture, there is much infrastructure to be built in order to meet the necessary media demands of a CM industry.

One can expect that there will be creative solutions technically and economically. CM companies may decide to produce protein media components in-house rather than rely on purchases from other companies. Furthermore, many components could be taken from the same source rather than

419 relying on individual production of each and blending all individual components together. One
420 could conceive of a process where a plant recombinantly produces one or more protein media
421 components, and the plant biomass could also be used as a hydrolysate providing the amino acids
422 components.

423 **3. Conclusions and Future Work**

424 As outlined in the introduction, there are multiple challenges with conventional meat production,
425 particularly beef production. Notably, there are several resource inefficiencies and damaging
426 environmental effects. Beef production requires 25 kg of dry feed mass to produce 1 kg of meat
427 and it releases 99.5 kg CO_2eq/kg meat (Alexander et al., 2016; Poore & Nemecek, 2018). Our
428 models show that not including water or cleaning solutions, only about 5 kg feed is required to
429 produce 1 kg of meat and only 0.1 kg CO_2eq/kg meat is released from the actual fermentation
430 process. Therefore, such advantages of CM must also be taken into account when assessing the
431 future viability and success of this technology.

432 The existing published TEAs on CM give a rough estimate of future CM economic viability.
433 However, they are limited in that they assume a maximum mammalian cell culture bioreactor scale
434 of 20 m^3, and they do not dive deeper into the sensitivity of media costs and possible solutions.
435 Results from these TEA studies display a wide and uncertain range of COGS, from thousands of
436 dollars per kg to a few dollars per kg in the most idealistic scenarios (Humbird, 2020; Risner et
437 al., 2020; Vergeer et al., 2021). This TEA study portrays the effects of a much-needed scale-up of
438 cell culture bioreactors combined with low media costs. At a base case of $1/L for an estimated
439 future media price, CM facilities with 42K L stirred tank production bioreactors have a COGS of
440 $30.4/kg, facilities with 210K L stirred tank production bioreactors result in a COGS of $20.8/kg,
441 and finally facilities with 260K L airlift production bioreactors have a COGS as low as $13.0/kg,

all including depreciation. As the reactor scale increases, production becomes more efficient, facility costs decrease as fewer reactors are needed, and economic profitability becomes most dependent on media costs.

Initially, CM products will likely engage the market as high cost, low volume products before advances are made to significantly lower the OPEX. For the large-scale airlift production reactor, the COGS becomes competitive with a value under $10/kg when the media costs drop below ~$0.75/L. Further decreases in COGS for this model could be made if optimized ALRs are used for the entire seed train, and it is possible that some innovative reactor configuration or operation is developed to further maximize efficiency. Nevertheless, a pressing goal for the CM industry is securing a cheap source of media or working to scale up the infrastructure and production for media components. Then, at such low media costs, improvements in biology such as growth rate can have more significant effects on the economic outputs. A future iteration of this TEA study will explore multiple sensitivity analyses to test other biological assumptions such as biomass yield, cell density, and differentiation time. TEA model inputs and outputs can also be used to analyze the process mass intensity, energy consumption, and environmental, health, and safety impact of the designed facilities to assess sustainability and environmental impact (Biwer & Heinzle, 2004; Budzinski et al., 2019). These metrics can be compared with traditional animal-based meat production. SuperPro Designer® can also be integrated with Crystal Ball (Oracle, Inc) Monte Carlo simulation capabilities with a COM library for uncertainty quantification. So, a future analysis would consist of assigning a probabilistic distribution for each parameter to generate economic output distributions based on projected parameter uncertainty distributions. As CM research advances, this model can be easily modified to incorporate improved assumptions, thus informing both academic and industrial CM development of bottlenecks to commercialization.

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