Food Bioengineering

WILEY

REVIEW ARTICLE OPEN ACCESS

From Cell Line to Fillet: A Review of Biological and Engineering Strategies in Cultivated Seafood

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Received: 11 December 2025 | **Revised:** 5 May 2026 | **Accepted:** 12 May 2026

Funding: Australian Economic Accelerator Ignite, Grant/Award Number: IG240100362; James Cook University Postgraduate Research Scholarship, Grant/Award Number: 1

Keywords: bioreactors | cultivated seafood | scaffolds | suspension culture

ABSTRACT

Due to the increasing world population, traditional commercial sources of protein will soon be insufficient to meet global nutritional demands. To address this and other anthropological effects, including carbon emissions, land and freshwater usage and overfishing associated with traditional agriculture, aquaculture and wild-catch fisheries, cultivated meats have been proposed as a novel protein source, rather than animal slaughter. Currently, despite significant investment, the cultivated seafood industry is floundering to scale production. This is due to technological failures to adapt cells to suspension for integration into bioreactors, lack of appropriate scaffold materials and scalable techniques to support eventual product formation. To overcome these issues, it is crucial for the industry to choose methodologies and materials that are tailored to species-specific cells to compensate for differences in the sensitivity and behaviour of cells within different bioreactor systems. Moreover, for regulatory approval and consumer acceptance, appropriate materials and edibility are required for selecting scaffolds. Ultimately, the cultivated seafood industry must address the current limitations in production efficiency to become a viable alternative food source. To do so, the industry should focus on using the recent advancements from both industry and academia including methods and technologies in tissue engineering and the adaption of cells to suspension. This review focuses on cultivated seafood as an alternative to aquaculture and wild-catch fisheries and discusses the bottlenecks and potential solutions for the industry to upscale production.

1 | Introduction

The growing global population, coupled with increasing consumer demand for high-quality seafood, has placed significant pressure on legal fisheries, leading to stricter regulations and requirement for sustainable practices in seafood production. One potential solution to these challenges is the emergence of novel seafood production methods, such as cellular aquaculture, which aim to alleviate pressures on existing aquaculture and fisheries while promoting sustainability, preventing food shortages and mitigating the climate crisis (Trace et al. 2024).

Abbreviations: ALB, Airlift bioreactor; ANZFSC, Australian New Zealand Food Standards Code; BM, Basement membrane; CAM, Cell adhesion molecule; CHO, Chinese hamster ovary; CIB1, Calcium and integrin binding protein; COMP, Cartilage oligomeric matrix protein; CTM, cultivated terrestrial meat; DGC, Dystrophin-glycoprotein complex; EDTA, Ethylenediaminetetraacetic acid; EFSA, European Food Safety Authority; FBS, Foetal bovine serum; FDA, Food and Drug Administration; FSANZ, Food Standards Australia New Zealand; RWV, Rotary wall vessel; SFA, Singapore Food Administration; STB, Stirred tank bioreactor; USDA-FSIS, United States Department of Agriculture – Food Safety and Inspection Services; *Zic1*, Zic family member 1.

In addition to addressing supply chain and ecological pressures, cultivated seafood also presents a promising opportunity to reduce exposure to contaminants such as microplastics and heavy metals, which are increasingly found in wild-caught seafood (Traylor et al. 2024). Although a promising alternative, the industry of cultivated seafood still faces many challenges regarding scaling production and efficiently forming three-dimensional (3D) products.

Typically, the cultivated food industry adheres to a well-established production workflow, which can be broadly divided into four key stages: (i) cell harvesting and characterisation; (ii) cell expansion; (iii) cell maturation and (iv) scaffold seeding and the fabrication of 3D tissue constructs (Reiss et al. 2021). While this framework has been extensively adopted, cultivated seafood faces a series of unique challenges that distinguish it from cultivated terrestrial meat (CTM).

These challenges are most pronounced in cell expansion, scaffold integration and 3D tissue formation stages, where current methodologies often fail to support large-scale production for cultivated food (see Figure 1). In comparison, for CTM it is established that multiple cell lines and media formulations are available, and that the organisation of muscle fibres and texture of products are more simplified than cultivated seafood. The specific challenges unique to cultivated seafood include the scarcity of seafood-specific cell lines, affordable and sustainable cell culture media that support marine myoblasts, and complex microstructures to facilitate the development of textures mimicking fish meat flakiness and softness. Ongoing research and development efforts by a range of companies and academic institutions are focussing on mitigating these limitations across aquatic species, as recently discussed (Trace et al. 2024).

Several methodologies are currently under investigation to improve the expansion of established cell lines in cultivated seafood production. One approach involves adapting adherent cells to suspension cultures, thereby enabling the use of bioreactors to facilitate large-scale cell growth (proliferation) (Bilodeau 2024). Another strategy focuses on the optimisation of cell culture media to reduce production costs and enhance proliferation rates. This often includes the substitution of foetal bovine serum (FBS) with species-specific growth factors to better support the targeted cell types (Lee et al. 2022). While some companies have reported successful continuous cell proliferation, the subsequent integration of scaffolds and the formation of the final 3D tissue continues to present significant challenges. Currently, there is no consensus on the most effective methodology for 3D product formation across both cultivated seafood and meat industries. Conflicting approaches exist, with some groups pursuing scaffold-free techniques, while others relying heavily on scaffold-based systems adapted to specific tissue architecture (Tanaka et al. 2022). Additionally, the use of artificial intelligence (AI) and machine learning (ML) has growing interest in the field for optimising cell lines, culture conditions and key production stages. Nonetheless, this review will not include an analysis on computational methods involving AI and ML, as recently published (Ng and Tan 2025; Nikkhah et al. 2023).

This review aims to evaluate current tools and methodologies developed to address persistent bottlenecks in cell expansion, scaffold integration and 3D tissue formation within the cultivated seafood sector. Through critically examining recent innovations and challenges across these domains, we present future strategies for achieving scalable and structurally realistic cultivated seafood products. This work differs from previous reviews with a specific focus on seafood, with an integrated discussion of biology and engineering strategies currently employed in the cellular aquaculture sector, with their respective production bottlenecks.

2 | Cell Sourcing, Harvesting and Characterisation

Cell sourcing for marine species for cultivated seafood remains limited in comparison to CTM. Myoblasts are of most interest in the cultivated seafood sector, as they form myotubes and mature into muscle fibres, which seafood is primarily composed. Commercial cell production companies such as the American Type Culture Collection and CellBase, currently only offer three cell lines from marine muscle tissues, and just one are myoblast cells (CellBase 2026). Hence, the only commercially available myoblast cell line remains unauthenticated and uncharacterised, creating a critical research gap and inadvertently becoming the first bottleneck in the field. This leave researchers and industry to source and establish their own cells from target species. Moreover, developing cell lines require extensive characterisation before their sale and use by industry. Myoblast characterisation involves the assessment of proliferation, differentiation and morphology, using live cell analysis systems, staining and probing for myogenic markers such as MyoD1, myogenin, myomaker, pax 7 and Myf5 (García de la serrana et al. 2014; Long et al. 2023). Furthermore, cell lines can vary significantly depending on species, age, sex and location of the original tissue source. Typically, the epaxial muscles of fish fingerlings are used to extract cells, as the fish are still young enough to contain sufficient muscle satellite cells and presents the most muscle tissue (Zhu et al. 2014). Table 1 summarises the use of cells in the cultivated seafood industry, specific for fish, describing species targeted, the tissues and cell types isolated.

3 | Media Optimisation for Cultivated Seafood

Media formulation plays a crucial role in cell proliferation, differentiation and can significantly impact production costs of cultivated seafood. FBS is a main contributing factor to increased costs, as typical media formulas include 5%–20% FBS. Not only is FBS costly, but the sourcing of serum from unborn livestock can be considered unsustainable for the cultivated seafood industry, which aims to detach itself from a reliance on agricultural products. However, to substitute the use of FBS, several growth factors, hormones, proteins and amino acids are required for adequate cell expansion and proliferation. A 2022 study examined the replacement of FBS in media for embryonic stem cells of zebrafish, with low-cost natural sources such as, insects, plant, fungi, algae and marine invertebrates. The study concluded that most of these sources could decrease the use of serum up to 90%, however, they could completely replace the use of serum (Batish 2022). Serum-free media has been defined

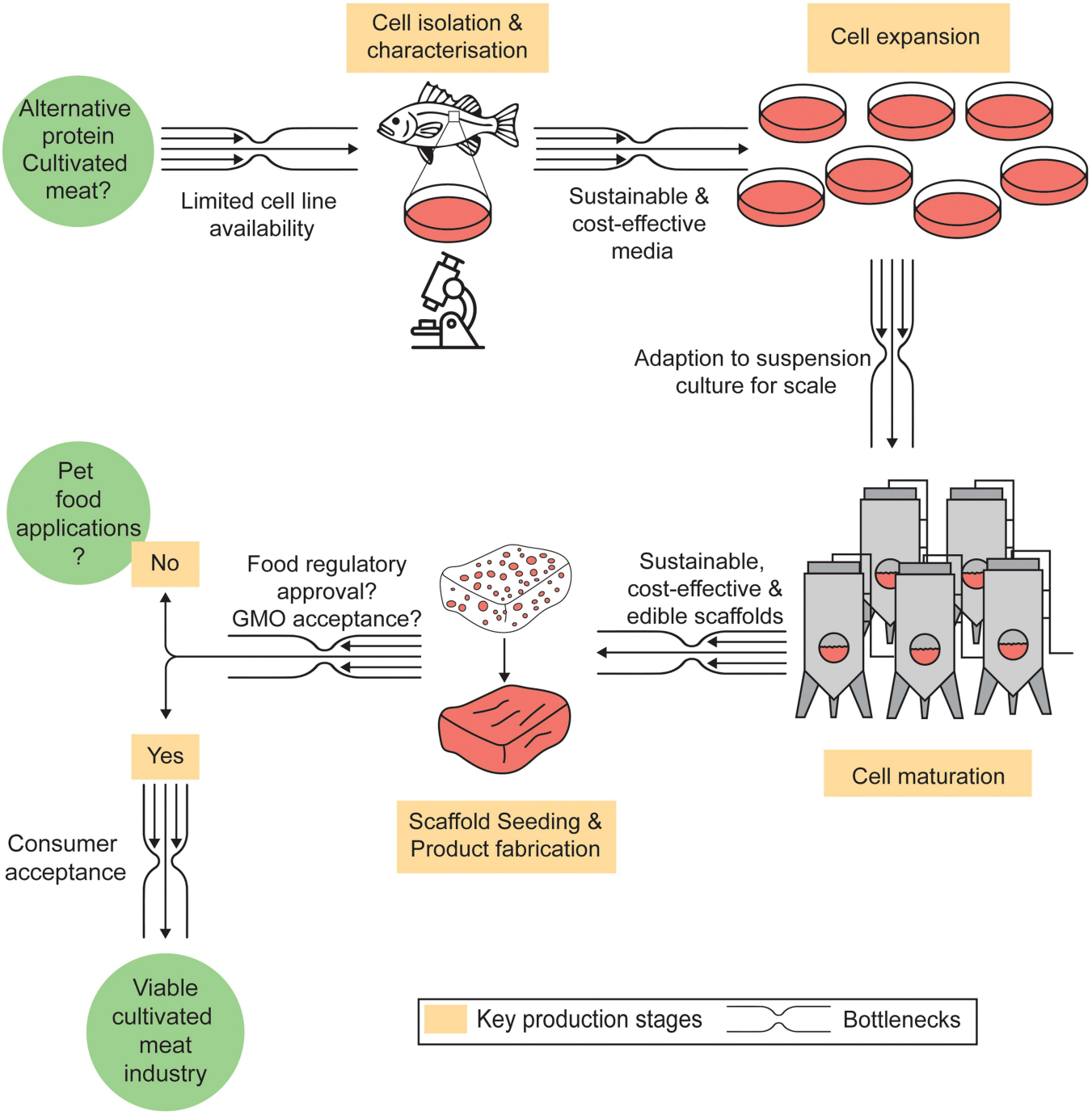

FIGURE 1 | Bottlenecks of the cultivated seafood workflow. Bottlenecks of the cultivated seafood industry are illustrated and prevent efficiency of each key production stage (yellow). These hurdles include limited cell line availability; sustainable and cost-effective media; adaption to suspension culture; sustainable, cost-effective and edible scaffolds; food regulatory approval and acceptance of genetic modified organisms (GMO); and consumer acceptance. In the absence of human consumption approval, the industry may make products for pet food applications.

for bovine cells, and is known as beefy-9 (Stout et al. 2022), beefy-R (Stout et al. 2023) and Tri-basal 2.0+ (Skrivergaard et al. 2023). However, serum-free media for marine cell lines remains limited. Such media has been defined for RTgill-W1 (epithelial [EGF]) cells (Jozef et al. 2025), but none have yet been described for marine muscle cells. EGF cell culture media differs from muscle cells in that require different growth factors, such as EGF, keratinocyte (KGF) and hepatocyte (HGF) growth factors; whereas muscle cells require at least insulin (IGF), fibroblast (FGF2), EGF and transferrin (Lee, Yun, et al. 2024). This suggests that serum-free media can be defined for fish myoblasts when key proteins and growth factors are present.

4 | Suspension Versus Adherent Culture

The mode of cell culture plays an important role in determining the scalability and efficiency of cultivated seafood production, as each approach presents distinct advantages and limitations for supporting the proliferation and differentiation of aquatic

TABLE 1 | Fish cells reported for use in cultivated seafood.

Species	Tissue sourced	Cell types isolated	References
Rainbow trout	Gill	Epithelial cells*	American Type Culture Collection (2026)
	Skeletal muscle (white)	Muscle satellite cells Adipose-derived stem cells	Li et al. (2025)
Atlantic Mackerel	Skeletal Muscle (white)	Skeletal muscle cells, adipocyte-like cells	Saad et al. (2023)
European Sea Bass	Skeletal Muscle (white)	Primary myoblasts	García-Pérez et al. (2025)
Brown-marbled grouper	Skeletal muscle (white)	Immortalised muscle stem cell	Xue et al. (2024)
Salmon	Skeletal muscle	Muscle satellite cells	Wei et al. (2025)
Marbled Goby	Skeletal Muscle	Immortalised myoblasts*	CellBase (2026)

*Commercially available cell lines.

muscle and fat cell lines. Broadly, there are two main modes of cell culture, adherent and suspension (faCellitate 2022). Adherent cell culture comprises cells that require attachment to a surface, typically culture-treated plastic or extracellular matrix (ECM) substrates such as Matrigel, to grow and differentiate (Bellani et al. 2020). In contrast, suspension cell culture allows cells to grow freely in liquid media without the need for surface attachment (faCellitate 2022). The choice between these two modes is particularly relevant in cellular aquaculture, where scaling adherent-dependent cells, such as fish myoblasts, presents a major bottleneck. Through adapting adherent cells to suspension culture systems, one could significantly enhance production efficiency, but this process introduces additional biological and engineering challenges. This section will explore the respective advantages and limitations of adherent and suspension culture systems, with a focus on their implications for large-scale cell line expansion in the context of cultivated seafood.

Adherent cell culture is widely used in early-stage research due to its ability to closely mimic local tissue environments, though it presents significant challenges in terms of scalability and cost (Bilodeau 2024). Most cells extracted from animals to produce cultivated foods, such as primary muscle cells, mesenchymal stem cells or induced pluripotent stem cells, are anchorage-dependent. These cells require physical attachment to a substrate or ECM to proliferate and differentiate. This is because many of their signalling cascades rely on cell-cell or cell-matrix interactions, which are essential for promoting cell survival and cellular functions necessary for cultivated food production (Bilodeau 2024). Adherent culture vessels are advantageous in that they provide a surface that facilitates these interactions and can be customised to specific applications through coatings with ECM-like substances such as hydrogels (Caliari and Burdick 2016). Additionally, adherent systems allow for visual monitoring of cells, an important feature for observing phenotypic changes during proliferation and passaging, which provides insights into cell health and function before scaled-up growth (Bilodeau 2024).

However, one major limitation of relying on adherent cultures is that the adherent culture vessel eventually becomes a bottleneck for scaling production. Specifically, the limited surface area of one-use plasticware and the extensive labour required for the large-scale cultivation of adherent cell lines becomes both impractical and wasteful, and hence counterproductive to the mission of the cultivated food sector (Bellani et al. 2020; Bilodeau 2024). Moreover, introducing the use of adherent cell lines introduces additional technical and financial barriers to scaling, as these cells inherently require cell-cell or cell-matrix interactions. To circumvent these problems, incorporating adherent cell lines into bioreactors or similar suspension-based systems is currently the most effective strategy for scaling production. This necessitates the use of microcarriers, which are spherical, bead-like structures that provide a support matrix for adherent cells within suspension cultures (Chen et al. 2020). These structures are made from biocompatible materials that incorporate into the 3D structure and are edible (Bodiou et al. 2020).

Suspension culture uses cells that are compatible with bioreactors and thus more suited for large-scale production as compared to adherent cultures. Flasks can be used for small-scale suspension cultures, however, bioreactors are essential for commercial-scale operations (Bilodeau 2024). Bioreactors facilitate automation and are better suited to handling high-volume production, which will be discussed in detail later in the review. Despite these advantages, not all cell types grow naturally in suspension, and many including aquatic muscle and fat cells, require adaptation (Kuppusamy et al. 2020). Some studies have demonstrated that adherent cells can be successfully adapted for growth in suspension, nonetheless, this process carries the risk of altered phenotypes, and diminished proliferation or differentiation capacity. As a result, extensive media optimisation may be required to maintain desired cell traits adding another layer of complexity to the already challenging task of scaling up production (Gomez Romero and Boyle 2023).

There are methods that have been successfully applied to adapt anchorage-dependent aquatic cells to suspension culture, these include serial passaging, genetic modification and surface coating removal and in some cases, cells have been shown to spontaneously adapt to suspension culture (Zheng et al. 2024).

4.1 | Spontaneous Adaptation to Nonadherent Culture

In a recent study (Zheng et al. 2024), Eel skin FGF2s were shown to autonomously adapt to suspension culture at later passages (greater than passage 50). This study examined the contribution of FBS concentration, cell density and temperature in controlling cell suspension and concluded that these cells were interchangeable between adherent and suspension modes of growth, and that this was dependent on the growth conditions tested. Importantly, no noticeable impact on cell behaviour or viability was noted in cells adapted to suspension growth, however, suspension cells exhibited increased proliferation rates when compared to adherent cells. Although Eel skin FGF2s may not be a relevant cell line for the cultivated seafood industry, the study raises the question of whether other cell lines, such as muscle and fat cells, from different aquatic species are able to undergo the same changes at higher passages. This natural adaptation to suspension culture contrasts with more deliberate strategies being pursued in the cultivated meat sector. For example, some entities, such as Vow Foods Pty Ltd, are potentially adapting traditionally adherent cell types for suspension culture through genetic modification.

4.2 | Genetic Modification Adaption to Suspension Culture

A recently published patent by Vow Foods reported that transcriptome analysis of quail FGF2s cultured in both adherent and suspension conditions revealed over 1400 differentially expressed genes, with 572 genes enriched in suspension-adapted cells (Ryall et al. 2025). Among these, the transcription factor, Zic family member 1 (*ZIC1*), was identified as a key inhibitor of suspension growth. The study demonstrated that suppression or inactivation of *ZIC1*, through targeted mutation or deletion, enabled anchorage-independent growth across multiple cell lines and species. However, the patent does not disclose whether disrupting the *ZIC1* gene resulted in phenotype changes, cell behaviour, proliferation or cell viability. There are other potential targets that may promote cell viability in cell suspension culture, such as integrin-linked kinase, pyruvate dehydrogenase kinase and multiple additional transcription factors, signalling kinases, cell cycle regulators, caspases and cell adhesion factors (Riquelme-Guzmán et al. 2024).

Given *ZIC1* is highly conserved across species, including aquatic organisms, these findings suggest that disrupting this gene could be an applicable strategy for adapting fish cells to suspension culture. However, the use of genetically modified materials will most likely pose challenges for consumer acceptance, but may have potential in the pet food industry. Depending on the extent of public resistance, alternative non-genetic approaches may be necessary to ensure market viability for human consumption (Hwang and Nam 2021). Some non-genetic approaches to suspension adaption include serial passaging and surface coating removal.

4.3 | Nongenetic modified organism (GMO) Adaption to Nonadherent Culture

Although muscle and fat cells are fundamentally adherent cells, they do have the ability to transition to suspension cultures, however, this can vary significantly depending on the species and cell line being used. Some cells demonstrate a high degree of substrate dependency, making direct adaptation to suspension culture challenging. To overcome this, microcarriers are often employed, where they serve as an intermediate scaffold that bridges the gap between traditional 2D adherent culture and full suspension systems (Bodiou et al. 2020).

Microcarriers are small beads (typically 100–300 μm in diameter) that provide an anchorage surface for adherent cells in suspension cultures (Chen et al. 2020). They significantly increase the available surface area for cell attachment, enabling higher cell densities in a given volume (Kulus et al. 2023). In the context of cultivated foods, microcarriers are particularly advantageous. Once sufficient cell expansion has occurred, the microcarriers can be removed to facilitate either the formation of 3D tissue-like structures, where cells are aggregated without a scaffold or the gradual adaptation to true suspension, where cells continue to proliferate without the need for attachment surfaces (Derakhti et al. 2019). Removal of microcarriers is typically achieved through enzymatic digestion with agents such as trypsin or Ethylenediaminetetraacetic acid (EDTA) (Derakhti et al. 2019). This process must be carefully controlled to preserve cell viability and functionality, especially if the cells are intended for downstream differentiation into structured food products (Lordon et al. 2024). Additionally, where microcarriers are included in suspension cultures, bioreactor systems design must ensure even suspension of the carriers through proper agitation, without causing aggregation or excessive shear stress. Stirred tank bioreactors (STBs) are often used for microcarrier-based systems due to their robust mixing capabilities, though shear stress conditions must still be optimised as mentioned later in this review (Kulus et al. 2023).

Alternatively, some cell types can naturally adapt to suspension culture through sequential passaging and gradual reduction of FBS from the media. A well-known example of this is Chinese Hamster Ovary (CHO) cells, which are commonly used for the expression and purification of recombinant proteins (Jukić et al. 2016). This method is relevant to the cultivated food sector, particularly for species where similar adaptation strategies might be employed. However, several important considerations must be addressed. Firstly, CHO cells are immortalised and proliferate indefinitely, and this may not be the case for primary cells from aquatic species (Kraemer et al. 1986). Secondly, the cells must remain viable in serum-free media and/or require the addition of specific growth factors to sustain viability and proliferation. Thirdly, once adapted to suspension the cells must maintain their differentiation capacity, and this is essential for forming structured food products. If we consider fish cell lines, a recent study has demonstrated successful adaptation of barramundi (Asian Sea Bass; *Lates calcarifer*) myoblasts to suspension culture using low-adhesion plates and constant media movement. This dynamic environment enabled the formation of 3D spheroid structures, mimicking seafood-like tissue clumps through natural cell aggregation (Mithra et al. 2025). However, the authors employed media containing serum throughout and did not test differentiation capacity of the spheroid structures, so the utility of this approach for fish cells remains to be further validated.

Ultimately, while multiple methods exist for adapting cells to suspension culture, the optimal approach will depend on the

cell type and species. For cultivated seafood, transitioning to suspension culture is critical for enabling scalability, reducing costs and enhancing energy efficiency. Nevertheless, this introduces new technical challenges, including the need for bioreactors capable of supporting large-scale suspension cell culture.

5 | Bioreactor Integration

Bioreactors are vessels designed to support biological reactions, typically involving living cells or microorganisms (Khan 2022). These systems have long been used in the food and beverage industry, particularly for fermentation processes such as brewing alcohol and large-scale dairy production (Sen et al. 2017). Due to their ability to maintain biologically active environments through controlling physical parameters, regulating nutrient supply, managing mixing, agitation and maintaining sterility (Chaudhry 2024), bioreactors are being adapted to scale up the production of cell lines for cultivated seafood.

5.1 | Principles of Bioreactor Operation

Important considerations for popular bioreactor systems in the cultivated seafood industry are displayed in Figure 2. Principles, including hydrodynamics and agitation mechanisms, shear stress, mass transfer and bioprocesses are key to ensuring functional and scalable bioreactor performance.

Hydrodynamics refers to the behaviour of the fluid flow within the bioreactor and directly influences the transport of nutrients, gases and waste products, as well as cell suspension and distribution (de Lamotte et al. 2017). Different bioreactor designs, like stirred-tank bioreactors (STBs), airlift bioreactors (ALBs) and rotating wall vessels (RWVs), induce varied flow patterns. STBs create turbulent flows, ALBs use bubbles for circulation and RWVs generate low-shear laminar flow (de Lamotte et al. 2017; Drochon et al. 2022; Escamilla Silva and Mendoza-Martínez 2013). RWVs offer gentler mixing but are less scalable. ALBs are ideal for sensitive cultures, but their mass transfer is less efficient than STBs. Proper hydrodynamic conditions ensure homogeneous mixing without causing damage to cells, microcarriers or scaffolds. Poor control of flow dynamics can result in cell sedimentation, nutrient gradients or scaffold deformation, resulting in reduced overall efficiency (Vivek et al. 2022). Simultaneously, the hydrodynamics of the bioreactor is affected by the agitation used to mix the culture medium (Kulus et al. 2023). For example, impellers of STBs are effective for large-scale mixing, but at high speeds cause foaming, resulting in loss of metabolites and nutrients for the cells (de Jesus et al. 2017). Conversely, systems like RWVs offer gentler mixing but are limited in scalability (Urtti 2024).

Shear stress from fluid movement can harm delicate cells such as stem or muscle cells, making bioreactor design crucial for preserving cell viability and ensuring adequate mixing (Pajčin

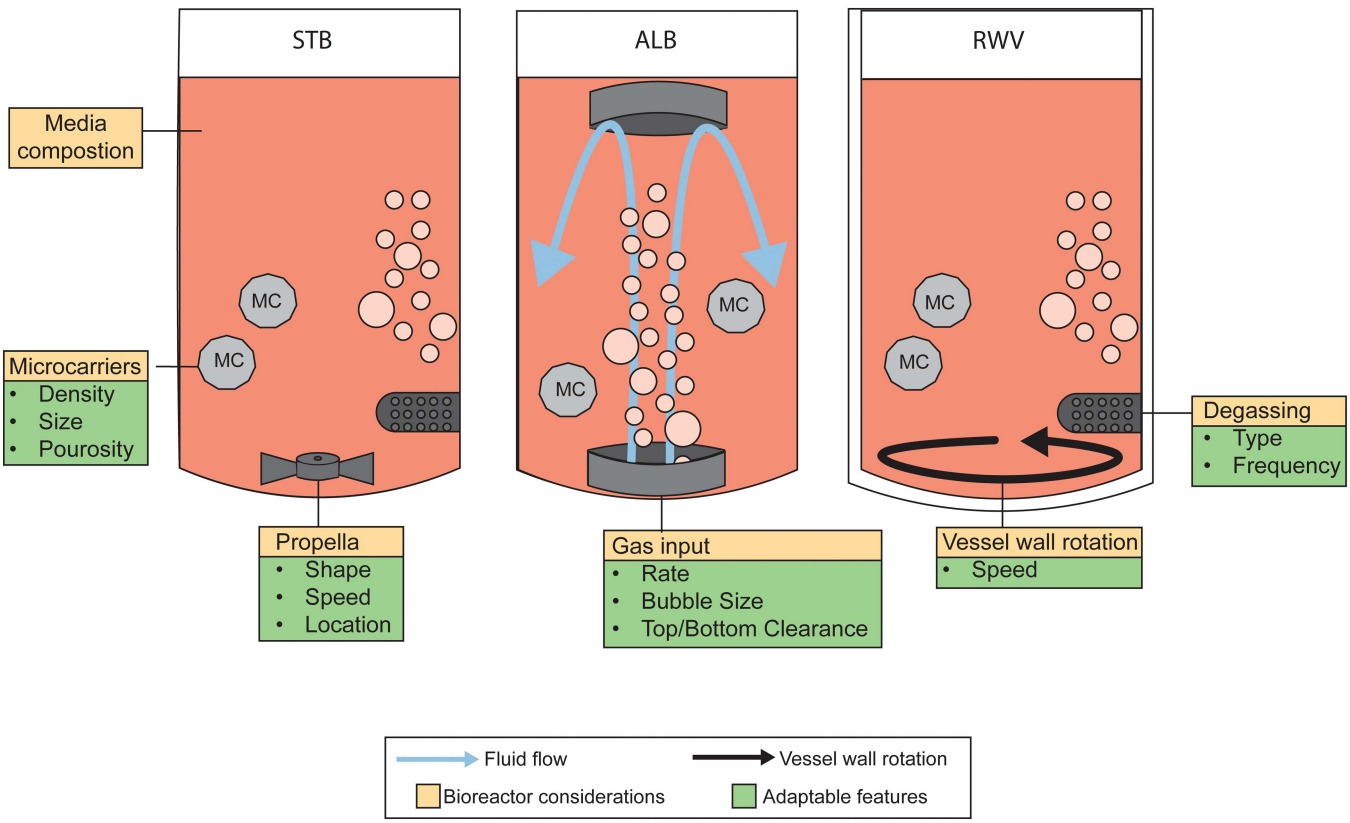

FIGURE 2 | Important variables for bioreactor design and cultivated seafood applications. Stirred tank bioreactors (STB), airlift bioreactors (ALB) and rotating wall vessels (RWV) all require important considerations when optimising conditions for different cell types and species. Important considerations are highlighted in yellow, with their adaptable features bellow in green.

et al. 2022). In general, low-shear systems like ALBs and RWVs are preferred for sensitive cultures to prevent morphology changes caused by shear stress in cells and cell surfaces that facilitate interactions, especially during the early stages of proliferation or tissue formation (Drochon et al. 2022). Moreover, shear stress levels can vary based on the design, as discussed in the comparative study of ALBs and STBs (de Jesus et al. 2017). STBs exhibit higher amounts of shear stress mainly due to the rotational speed, increased cell contact with the bioreactor wall, and radial flow. The different flow patterns associated with STBs are illustrated in Figure 3. In large-scale systems where ALB and RWV may not be appropriate, STB can be used at reduced stirring speeds and by installing propellers that promote axial flow to minimise shear stress.

Mass transfer, particularly oxygen, is vital for cell viability, especially in high-density cultures where demand exceeds supply. Most bioreactors enhance gas transfer by sparging (gas removal systems), surface and media aeration or through using oxygen-enriched media (Nickel et al. 2024). Importantly, controlling the levels of oxygen is challenging due to its low solubility in aqueous media, however STBs are advantageous in that they improve diffusion via mechanical disruption of bubbles (Al-Mashhadani et al. 2015; de Jesus et al. 2017; Vendruscolo et al. 2012). STBs facilitate high gas holdup, which in turn facilitates increased mass transfer (Achinas et al. 2022). Additionally, insufficient nutrient availability can influence the texture, colour and nutritional profile of the final seafood product, all of which are essential for consumer acceptance (Lambert et al. 2024; Negrete B et al. 2024; Pajčin et al. 2022). Thus, bioreactor design not only impacts productivity but also the quality of the final consumer product.

Bioreactors also differ in their operation modes: batch, continuous and fed batch (hybrid). Batch operations are simple but limited by the accumulation of toxic metabolic by-products, while continuous systems allow for longer culture durations and consistent cell growth, making them ideal for scalability (Reiss et al. 2021; Yasu 2024). Continuous systems, such as perfusion cultures can reduce the amount of waste by recycling the harvested media, to which higher cell densities can be achieved, however, their complexity and contamination risks will need to managed (Yang et al. 2019).

Hybrid systems, that combine batch and continuous modes are the most commonly used in cultivated seafood production due to the balance of benefits (Kulus et al. 2023). Despite this, a comparative study assessed the economics of each operational mode and concluded that continuous modes were the most cost-effective due to the requirement of fewer bioreactor tanks and thus a reduced operational footprint. However, the overall risks and benefits associated with each operational mode must be considered when finalising bioreactor choice, as costs associated with decontamination of bioreactors can be considerable (Yang et al. 2019).

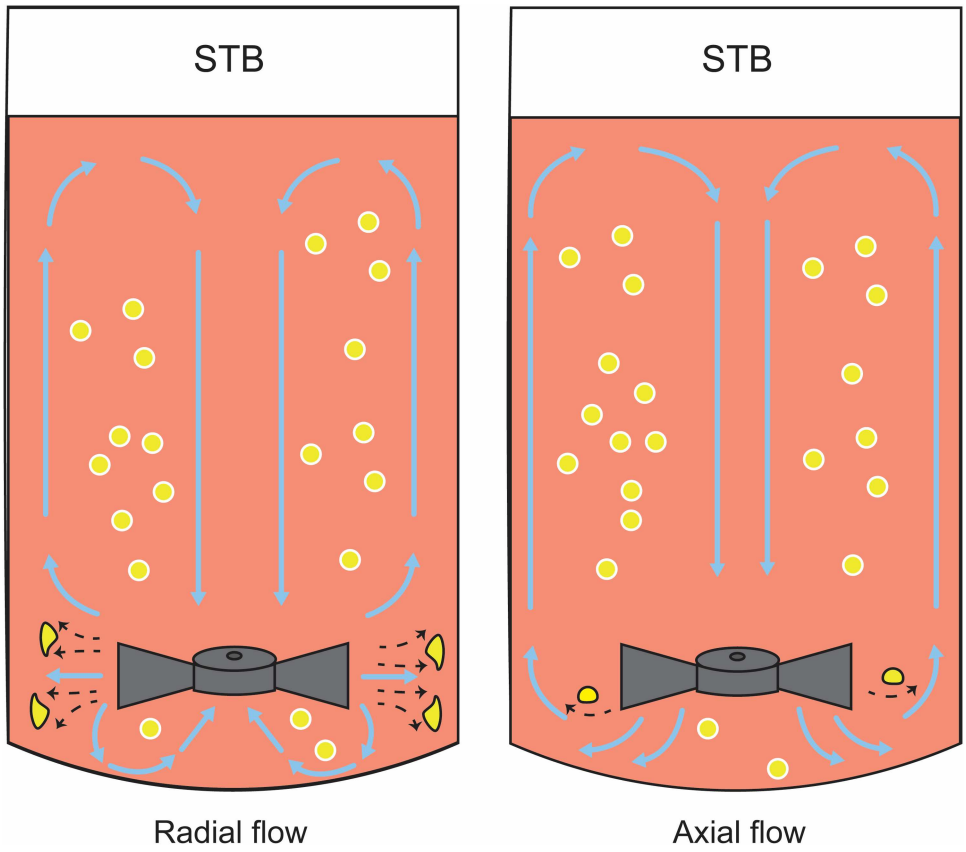

FIGURE 3 | Fluid flow pattern in radial and axial stirred tank bioreactor (STB) design. Blue arrows indicated fluid movement. Radial flow (left) causes fluid to flow in the direction of the radius of rotation. Axial flow (right) causes fluid flow in the direction of the axis of the agitator. Black dashed arrows indicate shear forces on cells (yellow).

5.2 | Implications for Cultivated Seafood

The operational principles and design of bioreactors carry significant implications for the successful scale-up and commercialisation of cultivated seafood. In comparison to terrestrial species, aquatic organisms present a unique set of biological and engineering challenges that influence bioreactor selection, optimisation and downstream processing, and these we will consider.

Cell lines derived from fish and other marine species typically exhibit different growth characteristics compared to mammalian cells. For example, many fish species are poikilothermic, meaning they thrive at lower temperatures, which may reduce energy costs for heating but may also reduce cell proliferation rates (Rossi and Messina 2014). Aquatic cell lines may also be more suited to bioreactor systems, as many species inhabit hypoxic environments, making the cells more resilient against inadequate oxygen transfer (Goswami et al. 2024; Rossi and Messina 2014). Additionally, fish myoblasts and other muscle precursor cells are often more sensitive to shear stress, making low-shear environments essential for maintaining cell viability and function during scale-up (Kulus et al. 2023).

Given the nature of aquatic cells, ALB or RWV bioreactor systems may be better suited than conventional STB designs, especially during early-stage proliferation. However, ALB systems, while providing suitable low-shear environments, may not maintain long-term sterility as effectively as closed-loop stirred systems, posing risks during extended periods of cell culture (Waler 2024). Marine and aquatic environments are often associated with higher microbial diversity, making contamination a critical concern in cultivated seafood production. Hence, once cells become robust, STBs systems may be employed to maintain long-term sterility and proliferation.

Moreover, selecting the appropriate bioreactor system also directly impacts the cost-efficiency and environmental footprint of cultivated seafood. Systems that operate at lower temperatures, maintain continuous cultures and support serum-free and defined media can lower costs and improve sustainability. In addition, innovations in energy-efficient mixing, oxygen delivery, and waste management will be crucial for reducing operating costs and making cultivated seafood competitive with conventional seafood products (Palladino et al. 2024).

In summary, in the context of cultivated seafood, bioreactor design is not a one-size-fits-all decision. It must be designed to the specific needs of aquatic cell types, production goals and consumer expectations. Understanding and applying bioreactor characteristics, such as shear stress control, oxygen transfer and sterility, will be key to enabling efficient, scalable and high-quality production of cultivated seafood products. A summary of the advantages and disadvantages, as well as the potential applications for each bioreactor type in cultivated seafood is provided in Table 2.

6 | Cultivated Seafood Tissue Engineering

Unlike simple cell cultures, tissue-engineered constructs must mimic the complex architecture, mechanical and sensory properties of native muscle and fat tissues, qualities that are essential for consumer acceptance and marketing (Engler et al. 2007). For seafood, this includes not only muscle fibres but also fat distribution, moisture content and fibrous or flaky textures specific to species like salmon, tuna and whitefish (Listrat et al. 2016). Central to this process is the use of scaffolds designed to replicate aspects of the natural ECM, supporting cell adhesion organisation, communication and growth (Banavar et al. 2024). In view of cultivated seafood, scaffolds are essential structural elements that guide the formation of three-dimensional tissues, offering mechanical support and facilitating the development of muscle, fat and connective tissue analogues (Nurul Alam et al. 2024). To achieve this, scaffolds must meet a set of interrelated biological, material and engineering criteria tailored to aquatic species. Scaffold design and material selection must therefore consider biocompatibility, edibility, mechanical strength, porosity and scalability, all of which pose unique challenges in the context of aquatic species (Feng et al. 2024). Creating engineered tissues allows producers to move beyond unstructured products, such as fish cakes or patties, toward more complex fillet-like or sashimi-grade seafood. This shift is vital for improving consumer acceptance, meeting nutritional expectations and to compete with traditional seafood in high-value markets.

TABLE 2 | Summary table of bioreactor types, applications, advantages and disadvantages.

Bioreactor type	Maximum cell density	Shear stress	Scalability	Suitability for scaffold-free	Cost/Energy efficient	Notes/Trade-offs
Stirred-Tank Bioreactor (STB)	High	High	High	Moderate	Moderate	Well established; good mixing and oxygen transfer; may experience foaming issues (Mithra et al. 2025; Ryall et al. 2025)
Airlift Bioreactor (ALB)	Moderate	Low	Moderate	Good	High (energy efficient)	Good mixing and oxygen transfer; short term sterility issues (Escamilla Silva and Mendoza-Martínez 2013; Urtti 2024)
Rotary Wall Vessel (RWV)	Low–Moderate	Low	Low	Excellent	Moderate	Relatively low shear stress; Ideal for scaffold-free approach; Rotation may affect scaffold adhesion (Drochon et al. 2022)

As the field matures, scaffold-free approaches have emerged as promising alternatives. These systems encourage cell self-assembly into tissues without external structural support and may offer advantages in biological realism and production efficiency, though they often lack precise architectural control (Goswami et al. 2024). This section explores the criteria for scaffold selection, common scaffold materials and fabrication techniques, scaffold-free strategies and recent innovations specific to cultivated seafood.

6.1 | Seafood-Specific Tissue Engineering Challenges

Cultivated seafood presents a distinct set of tissue engineering challenges compared to terrestrial meat, largely due to biological and structural differences inherent in aquatic species (Rossi and Messina 2014). One primary consideration is muscle texture and fibre alignment. Fish muscle is typically softer, less dense and has a lower degree of collagen cross-linking than mammalian muscle, which influences both mechanical properties and mouthfeel of the final product (Listrat et al. 2016; Rossi and Messina 2014). Additionally, moisture retention is a key factor in seafood tissue engineering. Fish tissues generally have a higher water content than land-based meats, which may affect the choice of scaffold composition. This elevated moisture content can also impact cell and scaffold interactions, necessitating more absorbent or hydrogel-based materials to prevent tissue collapse or dehydration (Wang et al. 2023).

Intramuscular fat distribution is another critical feature of seafood, as many fish species, such as salmon or tuna, derive much of their characteristic flavour and texture from specific fat marbling patterns (Kuppusamy et al. 2020; Lambert et al. 2024). Accurately mimicking these patterns in vitro is essential for consumer acceptance and sensory replication. This requires either co-culturing adipocytes alongside muscle cells or developing biomaterial systems that spatially guide lipid accumulation (Kuppusamy et al. 2020).

Moreover, temperature sensitivity distinguishes aquatic cell culture from traditional terrestrial meat cultivation. Most fish species thrive at lower culture temperatures (e.g., 18°C–28°C), which can significantly affect hydrogel gelation kinetics, bioreactor design and material behaviour during tissue maturation. For instance, gelatin-based scaffolds that perform well at mammalian body temperatures may require reformulation to remain stable and functional at lower incubation temperatures (Fonkwe et al. 2003). Taken together, these species-specific factors necessitate adapting tissue engineering strategies for cultivated seafood.

6.2 | Cultivated Scaffold Selection Criteria

Firstly, scaffolds must be biocompatible, allowing for robust cell adhesion, survival and proliferation, without eliciting cytotoxic or immunogenic responses. Materials such as marine collagen, alginate and gelatin have been shown to support fish myoblast viability while mimicking components of native ECM (Joyce et al. 2024). Edibility is another critical requirement, particularly given that they will be ingested as food. Ideally, scaffolds should be fully edible and safe for human consumption or easily removable during postprocessing. Edible materials such as fish gelatin, alginate or chitosan have demonstrated promise in seafood applications, aligning with emerging food safety regulations and consumer acceptance criteria (Ong et al. 2021).

Scaffolds must also be mechanically set to replicate the firmness, elasticity and tensile strength of native seafood tissues. For instance, scaffolds for species such as salmon or tuna should reflect the characteristic flaky, soft muscle architecture, while those for shellfish may require stiffer matrices (Rossi and Messina 2014). Achieving this involves modifying polymer blends or crosslinking density in hydrogels to match the biomechanical demands of the target tissue (Joyce et al. 2024). The porosity and internal architecture of scaffolds are equally essential. Highly porous structures facilitate diffusion of nutrients, oxygen and metabolic waste and promote uniform cell infiltration across the 3D matrix (Feng et al. 2024).

From a commercial perspective, the scalability and cost-effectiveness are nonnegotiable. Materials must be abundant, affordable and compatible with automated or high-throughput production systems, such as extrusion or 3D bioprinting (Liu, Zhang et al. 2022). This is important for ensuring that cultivated seafood can eventually compete with conventional seafood in both price and availability. Finally, species specificity must be considered when designing scaffolds. Different aquatic species may respond uniquely to various scaffold materials due to differences in cell adhesion molecules, growth factor requirements and ECM composition. For example, collagen derived from cold-water fish may better support salmon cells, while chitosan from crustacean shells could be advantageous for cultivating shrimp or lobster analogues (Joyce et al. 2024). Together, these criteria underline the complex nature of scaffold development in cultivated seafood, where the disciplines of materials science, marine biology, molecular biology and food engineering must converge to create viable and consumer-acceptable alternatives to wild-caught or farmed seafood.

6.3 | Myoblast-Matrix Adhesion in Scaffold Design

Given the important role of scaffolds in cultivated food, it is important to consider the role of cells adhesion molecules (CAMs) that mediate cell-cell and cell-matrix interactions, as they could be used to modulate the production process. Myoblasts express CAMs and include cadherins, integrins, selectins and the immunoglobulin superfamily of adhesion molecules (IgCAMs) (Taylor et al. 2022). For tissue engineering, scaffold design should parallel the adhesion of tissue basement membranes (BM), that supply structural support and adhesion for muscle and other cell types. The BM is primarily composed of laminin and type IV collagen that localise to the basal lamina and reticular lamina, respectively. The basal lamina is the inner layer of the BM and interacts with the sarcolemma through transmembrane protein complexes, such as the dystrophin-glycoprotein complex (DGC) and integrins interacting with various laminins (Csapo et al. 2020).

Integrins facilitate bidirectional cellular signalling, that is termed 'inside-out' and 'outside-in' signalling. Inside-out signalling refers to when intracellular proteins, such as talin or kindlin attach to the integrin causing a conformation change and promote binding to external laminin-2 (Boppart and Mahmassani 2019). In myoblasts, integrin α7β1 is the primary receptor for laminin and has demonstrated affinity for laminin-1 and laminin-2 (Grounds et al. 2005). Additionally, fibronectin can also bind to various integrins through outside-in signalling to increase clustering of the integrins through focal adhesion complexes and affinity for other ECM proteins (Boppart and Mahmassani 2019). Fibronectin binds the Arg-Gly-Asp sequence of the integrin, whilst the heparan sulphate regions of the protein binds to syndecans present on the membrane, resulting in a high-affinity conformation (Benito-Jardón et al. 2020). In humans, Integrin α7β1 can also interact with additional extracellular proteins, cartilage oligomeric matrix protein (COMP) (Raines and Bornfeldt 2010) and calcium and integrin binding protein (CIB1) (Huang et al. 2012). The DGC provides structural attachment between the intracellular contractile proteins and the ECM, but in contrast to integrins, incorporates dystrophin and associated proteins to fulfil muscle-specific functions, such as mechanotransduction and the maintenance of tissue integrity (Csapo et al. 2020). Thus, when designing scaffolds for cultivated seafood applications, the materials should mimic that of the native ECM to facilitate cell adhesion, tissue growth and final appearance. Common scaffold materials that do so, include marine collagen, chitosan and alginate (Ciriza et al. 2021; Iyer et al. 2015; Park et al. 2025). Alternatively, cell inclusion, on protein scaffolds, that express CAMs can also be used to enhance attachment, proliferation and differentiation of myoblasts and contribute to more structural and functional tissues.

6.4 | Common Scaffold Materials and Fabrication Techniques

Scaffold materials and fabrication methods have been investigated for engineering muscle and fat tissues in cultivated seafood. These biomaterials are categorised into natural and synthetic scaffolds, each paired with specific manufacturing strategies to recreate the desired structure, texture and functionality of fish-derived tissues.

Natural materials such as alginate, fish gelatin, marine collagen and chitosan are derived from seaweed, fish processing by-products and crustacean shells, respectively (Joyce et al. 2024). They offer exceptional biocompatibility, edibility and extracellular-mimicking properties, making them favourable for cell adhesion and differentiation (Jana et al. 2024; Kang et al. 2025). For instance, fish gelatin combined with alginate enhances printability and mechanical strength required for muscle tissue constructs (Maihemuti et al. 2023). Synthetic materials, however, including polylactic acid (PLA), polylactic acid-co-glycolic acid (PLGA) and polycaprolactone (PCL), provide precise mechanical tunability and controlled degradation (Seibert et al. 2025). A summary of key materials used in scaffold production and their advantages and limitations are listed in Table 3.

Several fabrication techniques have been explored for producing scaffolds for cultivated seafood, each with distinct advantages and challenges. Electrospinning uses high voltage to form structures with micro- to nanometre diameters (Guzman-Puyol et al. 2016). A charged polymer is ejected from a spinneret, usually a metallic needle and syringe, towards a conductive material, and the polymer stretches and decreases in diameter, whilst solidifying, before reaching the conductive material, forming a network of solid fibres (Abdulhussain et al. 2023). This method promotes cell adhesion and alignment, however, often lacks control of fibre formation (Santos et al. 2024; Smith and Mele 2021). Key advantages of electrospinning include a high surface area to volume ratio, that supports high cell densities and that the fibre arrangement can be either random or aligned. However, this method provides limited thickness for 3D constructs and difficulty to embed live cells during formation (Santos et al. 2024). A recent study highlights the effectiveness of electrospun fibres in cultivated seafood, using microalgae-rich nanofibers, to produce a prototype fish fillet that demonstrated myoseptum throughout the product (Marques, Pereira, et al. 2025). This breakthrough is crucial for cultivated seafood, considering this scaffold structure effectively mimics the appearance of traditional fish fillets, that are necessary for consumer acceptance.

Another technique, freeze-drying, allows sufficient nutrient transfer to cells adhered to scaffolds and has been used to form porous and printable scaffolds matching seafood tissue textures (Liu, Lau, et al. 2022). Freeze drying incorporates tissues which are decellularised, leaving behind the established ECM (Sheridan et al. 2013). These matrices are then exposed to cycles of freezing and drying to produce a 3D structure for scaffold use. Although the use of decellularised ECM will mimic seafood textures and structures, the scaffold product may be brittle and lacks flexibility resulting in disrupted fibres, causing heterogeneous pore sizes and an inconsistent final product (Collins et al. 2021). Freeze-dried scaffolds are more advantageous than electrospinning as they provide much more spatial control, however, this method has not yet been applied to cultivated seafood. One study has developed a scaffold via freeze-drying and discovered that the advantage of aligned scaffolds guided cells for specific attachment, proliferation and differentiation, to result in structures that closely resembled the native 3D environment of meat tissues (Xia et al. 2025). Seafood has a significantly different microenvironment in comparison to terrestrial meats, such as higher water content, shorter muscle fibres and less connective tissue, that may affect the ability to apply freeze-drying methods for cellular aquaculture (Listrat et al. 2016).

Alternatively, 3D bioprinting is a promising method to produce scaffolds for cultivated seafood. It involves the combinatory use of bioinks (materials, cells, bioactive molecules) and technology, such as laser-assisted bioprinting, extrusion printing and inkjet printing (Liu, Zhang, et al. 2022). Extrusion printing is the most common type of technology used for bioprinting, which entails the squeezing of bioinks through a nozzle that are continuously and accurately placed to form specific pore sizes, and mimick specific tissue types (Daly et al. 2021). Inkjet and laser-assisted bioprinting place bioinks in droplets, where the bioink is cured to form 3D products (Li et al. 2020). Laser-assisted bioprinting differs from inkjet, as it places droplets through the use of bubble formation, rather than direct droplet placement.

TABLE 3 | Summary of common scaffold materials used for cultivated seafood.

Scaffold material	Source	Type	Potential industry application	Limitations	Advantages
Alginate	Brown seaweed (e.g., *Laminaria* spp.)	Natural	Fish muscle cells (e.g., black sea bream)	• High melting temperature for removal • Poor cell adhesion	• Supports fish cell growth in 3D constructs (Lee, Jeong, et al. 2024; Marques, Jabouille, et al. 2025; Seo et al. 2023).
Chitosan	Crustacean shells (shrimp, crab)	Natural	Fish muscle constructs (e.g., black sea bream)	• Slow gelation rate	• Promotes adhesion • antimicrobial (Assis et al. 2024; Liu et al. 2024).
Fish gelatin	Fish skin/by-products	Natural	Salmon, black sea bream	• Undefined and inconsistent • Loss of native ECM organisation • Low stability • Acid-soluble	• High biocompatibility • High water solubility • Thermally reversible gelation (Jana et al. 2024).
Marine collagen	Fish skin, scales, bones	Natural	Tuna, salmon, black sea bream	• Acid-soluble	• High biological relevance (Assis et al. 2024; Liu, Zhang et al. 2022).
Decellularised Fish Matrix (dECM)	Whole fish tissue	Natural	Species-matched (e.g., salmon ECM for salmon cells)	• Limited printability	• Mimics native ECM; supports adhesion & differentiation (Kang et al. 2025; Lee, Jeong, et al. 2024).
GelMA (methacrylated gelatin)	Modified gelatin	Semi-synthetic	Fish cell bioprinting	• Low cell adhesion and proliferation	• Tuneable stiffness; suitable for extrusion-based bioprinting (Kim et al. 2024).
PLGA	Petroleum-derived synthetic polymer	Synthetic	Fish muscle constructs	• Low cell adhesion and proliferation	• Biodegradable • mechanical control but may require removal • high strength and rigidity (Ghafouri Azar et al. 2023).
Silk fibroin	Silkworm cocoons or recombinant production	Natural	Emerging use for muscle scaffolds	• Poor shape fidelity; • Limited rigidity	• High mechanical strength; edible in some forms (O'Brien 2011).

Recent studies have demonstrated the feasibility of 3D printing fish and seafood analogues using protein and polysaccharide-based food inks, providing insight into material systems relevant for seafood scaffold design. Soy protein-based inks have been employed for microscale 3D printing of fish analogues, where shear-thinning behaviour and gelation enabled the formation of aligned structures resembling fish muscle fibres (Shi et al. 2023). Similarly, algal protein-based inks have been developed to produce sustainable 3D-printed fish analogues with favourable printability and nutritional profiles (Alasibi et al. 2024). Fish-derived materials have also been explored, including salmon sashimi analogues printed using fish protein inks that demonstrated appropriate printing fidelity, texture and nutritional value (Tan and Ng 2025), and salmon fillet materials where printability was enhanced via high-pressure and postprinting enzymatic crosslinking using transglutaminase (Tay et al. 2023).

Across these studies, proteins such as soy, algal and fish-derived proteins act as primary structural components, while polysaccharides and enzymatic crosslinkers are used to modulate flexibility, printability and postprinting stability. Although these systems were developed for acellular fish analogue products, they highlight edible, biologically relevant material combinations that may assist in cultivated seafood scaffold design. However, material selection must be evaluated beyond printability alone. Synthetic polymers commonly used in biomedical 3D printing, such as PLGA, provide mechanical strength and stability but would face significant regulatory barriers for consumable seafood products, in addition to potential incompatibility with fish cell physiology. In contrast, natural and marine-derived materials, including decellularised fish extracellular matrices, marine collagen, alginate and chitosan, offer advantages in edibility, biocompatibility and biochemical similarity to native fish tissues, though they often require blending or crosslinking to improve printability, resistance to enzyme degradation and structural integrity (Jin et al. 2023). Overall, while advances in 3D bioprinting and food-based fish analogue printing show strong potential for cultivated seafood, careful optimisation of printing methods and material selection remains essential for producing structured products such as fish fillets.

Beyond traditional tissue fabrication techniques, hybrid approaches that incorporate a limited number of cultured animal cells into largely acellular or plant-based scaffolds have been explored as a strategy to enhance flavour while reducing overall cell requirements (Zhou et al. 2025). Conceptually, such strategies could offer a cost-effective route for flavour enhancement in cultivated seafood, however, current implementations primarily target volatile aroma generation and do not address the broader tissue engineering challenges specific to seafood, including species-specific myogenic differentiation, spatial organisation of muscle fibres and maturation of fish muscle tissue. In addition, the flavour, texture and biochemical composition of seafood differ substantially from those of terrestrial meat, limiting the direct transferability of agricultural-cell-based aroma systems to cultivated fish products. Hybrid strategies developed for cultivated meat also typically rely on meat analogues designed to replicate the sensory properties of terrestrial animal products, which are poorly aligned with the structural and sensory requirements of seafood. For instance, mycelium has been incorporated as a meat analogue in cultivated meat systems (Seo et al. 2023); however, replicating fish texture and flavour is likely to require a more complex combination of ingredients. Potential components that may resemble fish texture include soy, wheat and legumes, while flavour enhancement may be achieved using marine-derived ingredients such as algae, seaweed and nori to impart characteristic saline and umami notes (Appiani et al. 2025; Coleman et al. 2022).

6.5 | Scaffold-Free Approaches

Scaffold-free tissue engineering is an emerging process for the development of cultivated seafood that relies on the intrinsic self-organisation capacity of cells to form 3D tissue constructs, without the need for exogenous biomaterials. This method aims to mimic natural tissue architecture and function through cellular self-assembly, which may improve cell differentiation and tissue functionality (Alblawi et al. 2020). This is particularly valuable for replicating the fine muscle textures and flavour profiles of marine species.

A variety of scaffold-free engineering techniques have been explored in the context of cultivated seafood including cell sheet technology, spheroid and organoid formation and the use of magnetic forces. Cell sheet technology involves the culture of confluent monolayers of cells that can be detached and layered or folded to create stratified tissues (Thummarati et al. 2023). This approach preserves cell–cell junctions and native ECM components, providing structural and functional fidelity. Spheroid and organoid formation exploit the natural ability of cells to aggregate in suspension, forming spherical tissue-like microstructures (Mukhopadhyay and De 2022). These structures can model tissue-specific morphology and are commonly used for muscle and adipose tissue development (Mithra et al. 2025). The use of magnetic forces utilises external physical forces to guide cell positioning and assembly (Hu et al. 2023). In such a system, the cells are suspended and manipulated into complex geometries using magnetic nanoparticles, enabling scaffold-free 3D patterning without surface adhesion.

Scaffold-free systems offer important benefits for cultivated seafood production, such as regulatory simplicity whilst enhancing cell-cell interaction. Avoiding scaffold materials, whether natural or synthetic, simplifies the approval process, particularly for food-grade products. Regulatory challenges related to scaffold removal, safety and residuals are evaded with scaffold-free methods.

Despite these advantages, scaffold-free methods present several technical barriers such as limitations involving mechanical strength, scalability and spatial control. Without a supporting matrix, scaffold-free tissues often lack sufficient mechanical strength and structural integrity (Fasciano et al. 2024). This presents a challenge for recreating larger or more structured products, such as fish fillets. Techniques such as spheroid formation and cell sheet stacking are also difficult to automate and integrate into industrial-scale bioprocessing pipelines, making scaling production difficult (Tanaka et al. 2022). Ultimately, these limitations may affect product uniformity and textural

mimicry, particularly for complex seafood tissues like layered muscle or fatty fish belly cuts (Lee and Yang 2019).

Currently, scaffold-free strategies are best suited for unstructured seafood products, such as minced fish and seafood spreads, or early-stage proof-of-concept models that do not require precise architecture. As these technologies mature, scaffold-free approaches could play a crucial role in reducing cost, improving regulatory compliance and enhancing the biological realism of cultivated seafood.

6.6 | Current Research and Industry Examples

Ongoing advancements in both academia and industry are driving innovation in scaffold development and tissue engineering strategies tailored specifically for cultivated seafood. These efforts are increasingly focused on overcoming species-specific challenges such as texture, temperature sensitivity and biocompatibility, while ensuring scalability and consumer safety.

In the cultivated seafood industry, there have been mixed successes. An example is Shiok Meats, a former biotechnology company based in Singapore, which focused on the development of crustacean-specific scaffolds for the cultivation of shrimp and lobster meat. Their work involved optimising biomaterials that mimic the ECM environments of shellfish, supporting cell proliferation and tissue maturation at lower incubation temperatures appropriate for crustacean species (World Intellectual Property Organisation 2022). However, they were unable to achieve production scale with crustacean stem cells or attract further investment and the company merged with Umami Bioworks in March 2024.

In contrast, BlueNalu, a US-based cultivated seafood company, adopted scaffold-free methodologies for species such as the yellowtail amberjack (John 2019). Their platform leverages three-dimensional cell aggregation and self-assembly to create structured muscle tissue without the use of exogenous scaffolds. This approach simplifies regulatory hurdles while promoting tissue architecture that closely mimics the flaky texture characteristic of many finfish species. BluNalu raised a series B round of USD $33.5 million investment in 2023 and has partnered with Nomad foods, the European owners of the Birds Eye fish brand (Watson 2023).

Another industry example includes Wildtype, a US-based cultivated seafood company, focusing on sashimi-grade salmon. Wildtype has raised more than $123 million from multiple investors, making the start-up one of the better-funded organisations in the cultivated seafood sector (Watson 2025). This company is the first to have a cultured food product accepted to sell in the United States, with the FDA stating that Wildtype's salmon is as safe as comparable foods (Hartman 2025; Watson 2025). The scaffolding used in these products are plant-based and undergo rinsing and quality checks as would conventional food products, making the final products safe for human consumption (Hartman 2025).

In academia, innovations in 3D bioprinting are showing promise for generating structured seafood constructs, including layered assemblies of muscle and fat tissues that aim to replicate the anatomical complexity of natural fish fillets (Alblawi et al. 2020; Liu, Zhang, et al. 2022), offering a pathway towards high-fidelity replication of traditional seafood products in both structure and taste (Soleymani et al. 2024). Collectively, these efforts highlight the diversity of approaches pursued to engineer seafood-specific tissues, each contributing unique insights toward scalable, realistic and safe cultivated seafood production.

7 | Critical Challenges of Cultivated Seafood

Cultivated seafood presents a promising alternative to conventional fisheries and aquaculture; however, its commercialisation remains constrained by a series of biological, engineering and regulatory challenges. At the cellular level, robust cell sourcing, harvesting and characterisation remain foundational hurdles. The establishment of stable, well-characterised fish cell lines capable of long-term proliferation and differentiation are complicated by species-specific physiology, limited availability of characterised primary tissues and cells, and incomplete understanding of fish muscle development. These challenges are furthered by the need to adapt anchorage-dependent seafood cells to suspension culture systems suitable for large-scale production, while maintaining genetic stability, differentiation potential and product consistency.

Beyond cell line development, the successful scale-up of cultivated seafood depends on effective bioprocess integration. Bioprocessing and scale-up represent additional bottlenecks. The integration of seafood cells into scalable bioreactor systems requires optimisation of media formulations, oxygen transfer, shear stress tolerance and metabolic control under conditions that differ substantially from mammalian cell culture.

Downstream, scaffold design and tissue engineering pose distinct challenges for cultivated seafood due to the structural complexity of fish muscle. While advances in 3D bioprinting, hybrid scaffolds and food-based analogue materials offer promising pathways, achieving appropriate texture, spatial organisation and tissue maturation in an edible and scalable format remains unresolved.

Regulatory approval represents a major determinant of market entry for cultivated seafood. Regulatory frameworks for cultivated foods are still emerging and vary by location. At present, cultivated seafood has received regulatory acceptance in a limited number of regions, including Singapore and the United States. In Singapore, the Singapore Food Agency (SFA) approved GOOD Meat's cultivated chicken in 2020 and Vow's cultivated quail in 2024, establishing a regulatory precedent for cultivated foods (Johnson and Monaco 2025). The SFA strictly prohibits production, importation, distribution and sale of novel foods such as cultivated meat in Singapore, unless the SFA has granted premarket approval.

In the United States, the FDA completed a premarket safety review in June 2025 and authorised Wildtype's cultivated salmon, making it the first cultivated seafood product approved for sale in the United States (Bear-McGuinness 2026). The FDA process mainly focuses on early stages of production including

cell sourcing and tissue cultivation and maturation; however, later processes are assessed by the USDA-FSIS. Despite this regulatory pathway in the United States, several states have enforced bans and restrictions on cultivated foods, further complicating the potential of cultivated foods reaching market (Johnson and Monaco 2025).

Australia and New Zealand have also recently allowed the sale and consumption of cultivated foods, to Vow's cultivated quail in June 2025. These regulatory bodies include the ANZFSC and FSANZ, where cultivated foods are considered novel foods, however, depending on the application, can also be considered as food additives, processing aids, nutritive substances or foods produced using gene technology (Johnson and Monaco 2025). These regulatory bodies have proposed changes to the regulations so that premarket approval will be required, and that new standards be implicated, especially with regard to labelling requirements, production and processing requirements, applicable to cultivated foods. This will be so that cultivated foods will have a designated regulatory framework, rather than relying on the novel food frameworks in Australia and New Zealand (Food Standards Australia New Zealand 2026).

Generally, approval requires demonstration of: (i) food safety and absence of harmful contaminants, (ii) reproducible and controlled manufacturing processes, (iii) nutritional equivalence to conventional seafood and (iv) compliance with labelling and traceability standards. In contrast, many other regions lack clear regulatory pathways, creating uncertainty for developers and investors. For broader consumer acceptance and regulatory approval, cultivated seafood products must continue to meet stringent standards for consistency and alignment with local food regulations and cultural expectations, highlighting the importance of integrating regulatory considerations early in product development (Good Food Institute 2026). An example of consideration for the regulatory framework throughout production may include the exclusion of genetic modifications and/or use of synthetic materials, to assist in regulatory processes and eligible for the wider market.

Overall, while substantial progress has been made across cell biology, bioprocessing and scaffold engineering, cultivated seafood remains an interdisciplinary challenge that demands optimisation of processes across the production pipeline. Addressing these critical barriers, in particularly cell scalability, tissue structuring, cost reduction and regulatory clarity, will be essential to enable the transition of cultivated seafood from proof-of-concept to commercially viable and widely accepted food products.

7.1 | Future Directions and Considerations

As the field of cultivated seafood continues to evolve, future developments in tissue engineering are expected to address current limitations by combining structural innovation, regulatory alignment and economic feasibility. Central to this progression is the advancement of hybrid tissue engineering systems, which integrate minimal scaffold supports with scaffold-free tissue zones (Chen and Kawazoe 2023). These hybrid systems would balance the architectural control provided by scaffolds with the enhanced biological performance associated with self-assembling cell cultures. Such designs may improve construct integrity while reducing concerns related to regulatory hurdles. Another key area of focus is the integration of scaffold technologies with bioreactor systems, particularly suspension and perfusion-based platforms. For large-scale production, scaffolds must be engineered to be compatible with mechanical agitation, fluid flow and nutrient diffusion without compromising cell viability or tissue morphology (Khan et al. 2024). Materials with tuneable degradation profiles, enhanced shear resistance and increased oxygen permeability are likely to be prioritised to ensure compatibility with dynamic culture environments.

From a regulatory standpoint, the selection of scaffold and bioreactor-compatible materials must align with food-grade and clean-label standards. Regulatory bodies such as the EFSA (European Food Safety Authority), the FDA (Food and Drug Administration) and FSANZ (Food Standards Australia New Zealand) will require thorough assessments of edibility, digestibility, chemical safety and residue risk, which may limit the use of certain synthetic polymers, crosslinking agents or non-food-certified microcarriers unless proven safe for consumption. Sustainability and cost-efficiency are also central considerations. Scaffold and bioreactor components derived from marine by-products (e.g., fish skin, algae, crustacean shells) or agricultural waste streams (e.g., mycelium, cellulose) offer promising routes to reduce both environmental impact and production costs. These materials align with circular economy principles while maintaining functional suitability for supporting tissue growth and enabling scalability.

Moreover, the scalability of cultivated seafood will depend heavily on innovations in bioreactor design and suspension culture optimisation. Current STB and ALB systems offer viable routes for anchorage-independent cell expansion, yet ongoing research is needed to reduce shear stress, increase cell density and improve mass transfer efficiency for sensitive marine species. Novel bioreactor platforms may incorporate oscillatory flow, low-shear impellers or microcarrier-free aggregates to accommodate both cell proliferation and differentiation stages of growth (Rasche 2024). Integration of real-time sensing and automation technologies will also be critical to maintaining consistent culture conditions at industrial scale (Lim et al. 2019).

Finally, emerging research into smart and responsive scaffolds, such as materials that degrade in response to enzymatic activity or alter stiffness during culture, could guide cell differentiation, tissue maturation and nutrient delivery over time. Similarly, bioreactor systems equipped with feedback-controlled perfusion or tuneable environmental parameters could be used to trigger phenotypic maturation in fish muscle or fat tissues. These dynamic systems may play a critical role in producing more biomimetic, nutrient-rich and high-quality seafood analogues, particularly for structured products such as fish fillets and shellfish muscle (Lim et al. 2019). In summary, the future of cultivated seafood will likely involve solving the current bottlenecks of production through the convergence of biomaterial innovation, bioprocess engineering and regulatory foresight, with the overarching goal of producing structured, safe and sustainable seafood alternatives at industrial scale.

Author Contributions

Angela Trace: conceptualisation, software, visualisation, writing – review and editing, writing – original draft. **Miriam Wankell:** writing – review and editing. **Craig McFarlane:** supervision, funding acquisition, visualisation, writing – review and editing. **Lionel Hebbard:** supervision, funding acquisition, visualisation; writing – review and editing.

Acknowledgments

The study was supported by an Australian Economic Accelerator Ignite Grant IG240100362 (Lionel Hebbard and Craig McFarlane) and a James Cook University Postgraduate Research Scholarship (Angela Trace).

Ethics Statement

The study in this article did not involve any trials on humans or animals.

Conflicts of Interest

The authors Angela Trace and Miriam Wankell declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Craig McFarlane and Lionel Hebbard are co-founders of Infinite Bioworks, that pursues commercial work in cultivated meat.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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