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Opinion on Biofilms as Production Systems

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In the 21st century, applied biology must embrace quantitative and scalable approaches to effectively support a sustainable circular economy. Given the significant pressures posed by climate change, we can reasonably expect a growing interest in innovative biotechnological production methods. Market trends already reflect this shift. For instance, in a study by Philp et al. in (2013), it was reported that while the market for chemical products grew by a factor of only 1.2, the biotechnology market expanded by a remarkable factor of 10.3. Although the chemical industry remains dominant, these trends persist, with the biotechnology sector projected to experience a compound annual growth rate of 11.1% (Philp et al. 2013). This rapid evolution in production conditions necessitates the exploration of methods for generating substantial amounts of bulk and fine chemicals through biotechnology.

Despite the chemical industry's diversity in production processes, biotechnology predominantly relies on a single reactor system—the stirred tank reactor—operated with various organisms under different conditions (Noorman 2011; Meyer et al. 2017; Schirmer et al. 2021). This reactor system has been extensively utilised at large scales, particularly in the biofuel sector (Weiler et al. 2024). While research continues to enhance the understanding of fluid dynamics in these systems, especially as their geometry becomes more complex, it can be said that stirred tank reactors, primarily used for industrial antibiotic production since the 1940s and 1950s, are well understood (Bud 1993; Demain et al. 2017).

In these stirred tank reactors, we utilise whole cell biocatalysts as individual planktonic entities. However, it is noteworthy that most microorganisms naturally grow as biofilms (Flemming and Wuertz 2019). Consequently, utilising microorganisms in a production environment that diverges from their natural growth form may not be optimal. This might be analogous to how human productivity would differ if we were required to work in social isolation or within a social framework. Still the production methods we employ do not necessarily need to mimic the natural growth form of microorganisms, provided they can achieve efficient production under optimal conditions. This raises the question of whether opportunities exist for alternative operational regimes beyond stirred tank reactors, including the potential for biofilms as effective production systems.

Effective bioprocessing involves multiple factors: (I) price and quality of feedstock, (II) energy and material costs, (III) process control capabilities, (IV) volumetric productivity and achievable titers, (V) ease of product separation from fermentation broth, (VI) feasibility of continuous processes and (VII) at least in some cases genetic stability of biocatalysts. While feedstock prices will similarly affect stirred tank and biofilm-based systems, the remaining factors necessitate thorough evaluation when comparing these approaches.

Several reasons explain the long-standing dominance of stirred tank reactors in biotechnology, despite some inherent drawbacks. These reactors are relatively straightforward to control, particularly in well-mixed environments where pH, biocatalyst concentration and substrate/product concentrations are uniform. However, uniformity may become less attainable as systems scale up. Additionally, the reactor volume aligns closely with the reaction volume, providing an advantage over biofilm systems. Decades of experience in stirred tank reactor operation, along with advanced models, inform our understanding of potential process developments, especially regarding gas transfer in oxic or gas fermentation systems.

The question arises whether reactor systems that focus more on the biofilm growth form might be better or at least similarly suited for specific production processes. Or in other words what intrinsic advantages do biofilms offer due to their unique growth structure (Figure 1)?

Biofilms consist of interconnected organisms adherent to a surface called substratum, or grouped as clusters or flocks, bound by an extracellular polymeric matrix primarily made up of sugar polymers, DNA and protein. This matrix not only serves as a binding agent but also influences substrate and product diffusion and can absorb substances due to its generally negative charge. The combination of this extracellular matrix and the typically lower growth kinetics of biofilm microorganisms confers enhanced robustness against potentially toxic substances or substrates. From a process development perspective, this implies that substrates could be introduced at higher concentrations, potentially allowing for increased product titers while reducing the need to dilute the substrate with water. Moreover, the adherent growth form of biofilms facilitates faster product separation from biocatalysts, enabling the realisation of plug-flow operations (Philipp et al. 2023).

The adherence of cells also results in exceptionally high biomass densities; when considering only the biofilm volume, these can exceed those achieved in planktonic systems. However, the necessity of including a substratum in the reactor volume means that the advantages of higher biocatalyst densities will require engineering solutions to maximise surface area while maintaining a controllable fluid dynamic regime.

In biofilm systems, the biocatalysts operate under more stable conditions compared to stirred tank reactors. While microbial activity in biofilms may lead to steep concentration gradients of substrates and products, a stable environment is achieved when the system operates as plug flow, allowing evolutionary pressures to favour organisms with advantageous traits. This evolutionary adaptation is particularly beneficial if a catabolic end product is the desired product of the biotechnological process, such as in methanogenesis or acetogenesis. Still, many processes are dependent on genetically engineered organisms and on genetic adjustments that often decrease organism fitness; thus, genetic stability becomes crucial. Developing strains that can consistently produce targeted end products without disruption from mutations and genetic drift is a significant challenge in biotechnology (Rugbjerg et al. 2018). Biofilms present unique opportunities, as reports indicate a decoupling of growth and productivity within them, allowing for lower growth rates and, consequently, reduced mutation frequency by genetic drift. This might result in a slower spread of advantageous mutations throughout the community, leading to the formation of distinct subpopulations (Lewis 2001; Stewart and Franklin 2008). Additionally, intermittent removal of biomass from nutrient-rich biofilm peripheries might further mitigate the risk of mutation-driven instability. Unlike planktonic systems, biofilms offer the potential to manage biomass age, making it easier to separate new from old cells and thereby remove cells that will be characterised with a higher number of mutations compared to the previous generation. Along these lines, studies suggest that biofilm systems may enhance the heterologous production of enzymes and demonstrate improved plasmid stability and copy number compared to planktonic systems (Soares et al. 2022).

Nevertheless, biofilm systems face inherent challenges, such as the requirement for a substratum. This necessity can compromise reactor space, reducing the potential productive volume. Balancing this disadvantage with the benefits of higher biocatalyst concentrations and wider substrate utilisation is critical. Still, exceptionally high substratum surface-to-reactor volume ratios were already established. Packed bed systems, for example anaerobic filters and upflow anaerobic sludge blankets have shown surface areas of 400–800 m^2 per cubic meter (Kongjan et al. 2019). Such ratios have been replicated with biofilm carriers in rotating drum reactors, where a threefold increase of highest achieved ethanol titre and volumetric productivity, as reported by the cited authors Shen et al. was observed compared to continuous stirred tank reactors (Shen et al. 2017). The necessary substratum surface area can be leveraged as a process advantage if its activity is a requirement for the process. So-called active substrata are primarily utilised in gas fermentation

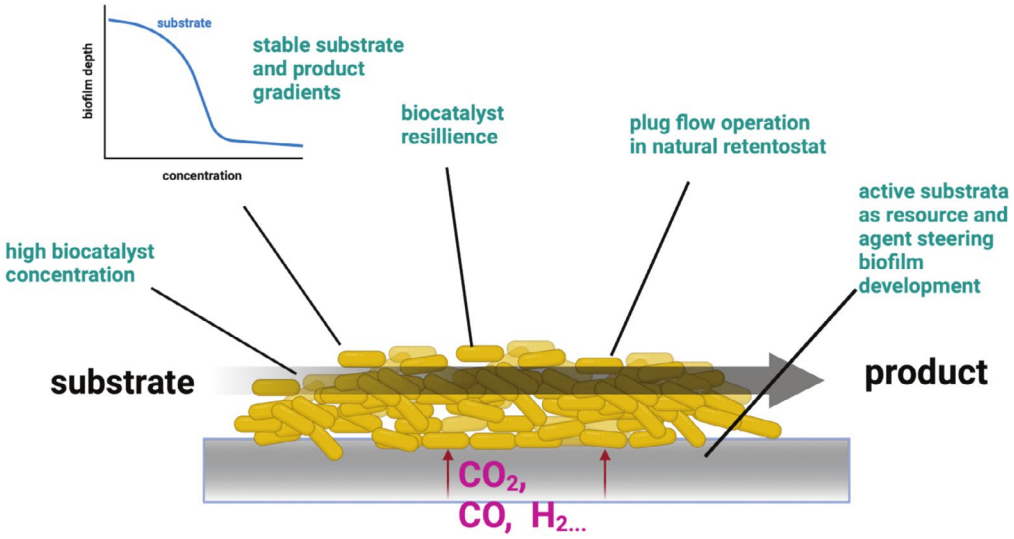

FIGURE 1 | Overview of the potential benefits of processes using biofilm systems.

systems, as substitutes for conventional aeration or in bioelectrochemical systems, where an anode and/or cathode drives or enables a biofilm-based process (Rittmann 2018). In membrane biofilm reactors, the objective is to deplete the gas supplied through a membrane while it diffuses through the biofilm. This setup eliminates the need for the gas to be dissolved in the medium before uptake by microorganisms, which can significantly enhance process rates, especially for gases with limited solubility such as H_2, CO and O_2. Comparable surface-to-volume ratios of 400–800 m^2/m^3 have also been achieved in membrane biofilm reactors (Gross et al. 2010, 2013; Renaudie et al. 2021). However, the cost of these membranes remains a significant factor, suggesting that their current use in white biotechnology processes is predominantly limited to high-value products. It will be interesting to observe whether this may change in the future due to decreasing membrane prices or economic incentives for biobased production processes.

In bioelectrochemical systems, even higher surface areas can be realised; the porosity of conductive biofilm carriers has resulted in surface areas ranging from 220,000 to 380,000 m^2/m^3 (equating to 100–200 m^2/m^3 when considering only the spherical carrier without porosity) (Liu and Lee 2022). While anode-driven microbial fuel cells and microbial electrolysis cells are gradually making headway into the water treatment sector, as evidenced by a growing number of startups and larger installations, cathodic systems have also demonstrated comparable production rates to conventional gas fermentation, along with an expanding portfolio of products for the biotechnology market (Jourdin et al. 2018; Rominger et al. 2025; Boto et al. 2023).

Nevertheless, while available data indicates a promising future for biofilm-driven processes in biotechnology, several challenges must be addressed. As the surface area in reactors increases, maintaining a predictable fluid dynamic regime becomes increasingly complex, raising the risk of dead zones within the reactor. Additionally, we have yet to develop reactor systems or technologies in white biotechnology that allow for continuous trimming of biofilms to a desired thickness. As a solution, some biofilm carriers have been engineered for wastewater applications with cavities designed to remove excess biofilm through constant collisions of the carriers in moving bed bioreactor setups (di Biase et al. 2019). Lastly, it is essential for all reactor types to operate for extended periods under axenic conditions if applications in white biotechnology are to be realised. This challenge remains unresolved for all types of biofilm reactors. Furthermore, achieving sufficient biofilm densities and substratum coverage will take time, highlighting the need for technologies capable of accelerating biofilm growth.

Overall, our aspiration for the future should be to diversify biotechnological production methods, establishing a more robust foundation to meet anticipated demand. Historical examples in biology and applied biology reveal that relying solely on well-established technologies may not always be optimal. A notable illustration is Craig Venter, who transformed the field of genomics by introducing novel sequencing methods and challenging traditional approaches to sequencing the human genome. His efforts culminated in a race that, despite initial scepticism from many, ended with a tie or in favour of Venter. Dedicated biofilm research centres, as well as collaborative research hubs, have already been established in several countries, including the United States, United Kingdom, Singapore and Germany. It will be exciting to observe how this area of bioengineering develops in the future and the role these collaborative research activities may play in driving transformational processes.

Author Contributions

Carmen Mandel: writing – original draft, visualization. **Miriam Edel:** writing – review and editing, conceptualization. **Johannes Gescher:** conceptualization, project administration, resources, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

Boto, S. T., B. Bardl, F. Harnisch, and M. A. Rosenbaum. 2023. "Microbial Electrosynthesis With *Clostridium ljungdahlii* Benefits From Hydrogen Electron Mediation and Permits a Greater Variety of Products." *Green Chemistry* 25: 4375–4386.

Bud, R. 1993. *The Uses of Life: A History of Biotechnology*. Cambridge University Press.

Demain, A. L., E. J. Vandamme, J. Collins, and K. Buchholz. 2017. "History of Industrial Biotechnology." In *Industrial Biotechnology*, 1–84. John Wiley & Sons, Ltd.

di Biase, A., M. S. Kowalski, T. R. Devlin, and J. A. Oleszkiewicz. 2019. "Moving Bed Biofilm Reactor Technology in Municipal Wastewater Treatment: A Review." *Journal of Environmental Management* 247: 849–866.

Flemming, H.-C., and S. Wuertz. 2019. "Bacteria and Archaea on Earth and Their Abundance in Biofilms." *Nature Reviews. Microbiology* 17: 247–260.

Gross, R., K. Buehler, and A. Schmid. 2013. "Engineered Catalytic Biofilms for Continuous Large Scale Production of n-Octanol and (S)-Styrene Oxide." *Biotechnology and Bioengineering* 110: 424–436.

Gross, R., K. Lang, K. Bühler, and A. Schmid. 2010. "Characterization of a Biofilm Membrane Reactor and Its Prospects for Fine Chemical Synthesis." *Biotechnology and Bioengineering* 105: 705–717.

Jourdin, L., S. M. T. Raes, C. J. N. Buisman, and D. P. B. T. B. Strik. 2018. "Critical Biofilm Growth Throughout Unmodified Carbon Felts Allows Continuous Bioelectrochemical Chain Elongation From CO_2 up to Caproate at High Current Density." *Frontiers in Energy Research* 6: 7.

Kongjan, P., S. Inchan, S. Chanthong, R. Jariyaboon, A. Reungsang, and S. O-Thong. 2019. "Hydrogen Production From Xylose by Moderate Thermophilic Mixed Cultures Using Granules and Biofilm Up-Flow Anaerobic Reactors." *International Journal of Hydrogen Energy* 44: 3317–3324.

Lewis, K. 2001. "Riddle of Biofilm Resistance." *Antimicrobial Agents and Chemotherapy* 45: 999–1007.

Liu, S.-H., and K.-Y. Lee. 2022. "Performance of a Packed-Bed Anode Bio-Electrochemical Reactor for Power Generation and for Removal of Gaseous Acetone." *Journal of Environmental Management* 314: 115062.

Meyer, H., W. Minas, and D. Schmidhalter. 2017. "Industrial-Scale Fermentation." In *Industrial Biotechnology*, edited by C. Wittmann and J. C. Liao, 1–53. Wiley.

Noorman, H. 2011. "An Industrial Perspective on Bioreactor Scale-Down: What We Can Learn From Combined Large-Scale Bioprocess and Model Fluid Studies." *Biotechnology Journal* 6: 934–943.

Philipp, L.-A., K. Bühler, R. Ulber, and J. Gescher. 2023. "Beneficial Applications of Biofilms." *Nature Reviews. Microbiology* 22: 276–290.

Philp, J. C., R. J. Ritchie, and J. E. M. Allan. 2013. "Biobased Chemicals: The Convergence of Green Chemistry With Industrial Biotechnology." *Trends in Biotechnology* 31: 219–222.

Renaudie, M., C. Dumas, S. Vuilleumier, and B. Ernst. 2021. "Biohydrogen Production in a Continuous Liquid/Gas Hollow Fiber Membrane Bioreactor: Efficient Retention of Hydrogen Producing Bacteria via Granule and Biofilm Formation." *Bioresource Technology* 319: 124203.

Rittmann, B. E. 2018. "Biofilms, Active Substrata, and Me." *Water Research* 132: 135–145.

Rominger, L., M. Hackbarth, T. Jung, et al. 2025. "Efficiency and Process Development for Microbial Biomass Production Using Oxic Bioelectrosynthesis." *Trends in Biotechnology* 43: 673–695.

Rugbjerg, P., K. Sarup-Lytzen, M. Nagy, and M. O. A. Sommer. 2018. "Synthetic Addiction Extends the Productive Life Time of Engineered *Escherichia coli* Populations." *Proceedings of the National Academy of Sciences* 115: 2347–2352.

Schirmer, C., R. W. Maschke, R. Pörtner, and D. Eibl. 2021. "An Overview of Drive Systems and Sealing Types in Stirred Bioreactors Used in Biotechnological Processes." *Applied Microbiology and Biotechnology* 105: 2225–2242.

Shen, Y., R. C. Brown, and Z. Wen. 2017. "Syngas Fermentation by *Clostridium carboxidivorans* P7 in a Horizontal Rotating Packed Bed Biofilm Reactor With Enhanced Ethanol Production." *Applied Energy* 187: 585–594.

Soares, A., L. C. Gomes, G. A. Monteiro, and F. J. Mergulhão. 2022. "Hydrodynamic Effects on Biofilm Development and Recombi-nant Protein Expression." *Microorganisms* 10, no. 5: 931. https://doi.org/10.3390/microorganisms10050931.

Stewart, P. S., and M. J. Franklin. 2008. "Physiological Heterogeneity in Biofilms." *Nature Reviews. Microbiology* 6: 199–210.

Weiler, J., M. Edel, and J. Gescher. 2024. "Biofilms for Production of Chemicals and Energy." *Annual Review of Chemical and Biomolecular Engineering* 15: 361–387.